Does the time interval between antimüllerian hormone serum sampling and initiation of ovarian stimulation affect its predictive ability in in vitro fertilization–intracytoplasmic sperm injection cycles with a gonadotropin-releasing hormone antagonist? A retrospective single-center study

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Objective: To investigate whether the time interval between serum antimüllerian hormone (AMH) sampling and initiation of ovarian stimulation for in vitro fertilization–intracytoplasmic sperm injection (IVF-ICSI) may affect the predictive ability of the marker for low and excessive ovarian response.

Design: Retrospective cohort study.

Setting: University-based tertiary center.

Patient(s): Five hundred and forty women with AMH values measured before their first IVF-ICSI cycle.

Intervention(s): Eligible patients treated with 150–225 IU recombinant follicle-stimulating hormone (FSH) in a gonadotropin-releasing hormone (GnRH) antagonist protocol.

Main Outcome Measure(s): Predictive ability of AMH for low and excessive ovarian response in relation to the time interval between serum AMH sampling and initiation of ovarian stimulation for IVF-ICSI.

Result(s): All patients had their AMH concentration measured up to 12 months before initiation of stimulation. The level of AMH demonstrated a statistically significant positive correlation with number of oocytes retrieved. The time interval between AMH measurement and initiation of stimulation had no influence on this correlation. The area under the receiver operator characteristic curve (ROC AUC) of

AMH was high for both poor (0.72) and excessive response (0.80). The ROC regression analysis demonstrated that the time interval from sampling did not affect the performance of either poor response or excessive response prediction.

Conclusion(s): A time interval up to 12 months between AMH serum sampling and initiation of ovarian stimulation does not appear to affect the correlation between AMH level and the number of oocytes retrieved and the predictive ability of AMH to identify women at risk of low or excessive ovarian response. (Fertil Steril® 2013;100:438–44. ©2013 by American Society for Reproductive Medicine.)

Key Words: AMH, AMH variability, excessive responders, OHSS, ovarian response, poor responder, stimulation, time interval

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Antimüllerian hormone (AMH) is increasingly being established as the serum biomarker of choice for predicting ovarian response to stimulation during in vitro fertilization–intracytoplasmic sperm injection (IVF-ICSI) cycles (1). Several large cohorts using long-course gonadotropin-releasing hormone (GnRH) agonist stimulation protocols have shown a strong correlation of AMH with the number of oocytes retrieved, with a very high predictive ability for poor and excessive ovarian response, equivalent to that of the antral follicle count (AFC) (2–4). Even when the analyses are restricted to cycles that have used GnRH antagonist–based strategies, with the inherent differences in follicular recruitment, these strong associations persist (1).

Given the ability of AMH to predict both a poor and excessive ovarian response, using AMH to tailor ovarian stimulation has been proposed by several investigators (5–7). The ability of AMH to accurately identify women at risk of ovarian hyperstimulation syndrome (OHSS) is potentially its greatest utility, as we now have a variety of techniques available to us to reduce or completely eliminate the risk of this potentially fatal complication (8–10). Initial studies using an AMH stratified approach to individualize treatment have demonstrated a significant reduction in OHSS (6) while not compromising live-birth rates (11).

However, as the use of AMH has become more common, when it is measured in the fertility workup has also changed. In the initial studies, AMH was primarily assessed during the menstrual cycle immediately preceding the cycle of ovarian stimulation (4, 12, 13). However, now AMH is increasingly measured much earlier, during the initial fertility workup and even by primary care physicians before referral to specialist services. In fertility centers, this assessment frequently takes place significantly earlier than the initiation of ovarian stimulation. This delay may be even be more pronounced in centers that have a high volume of patients, or when the initial plan is intrauterine insemination, with ensuing IVF-ICSI in case of treatment failure.

Given that serum AMH levels decline with age (14, 15), and that this decline may be as much as 15% per annum (16), a key question is whether the interval between AMH serum measurement and initiation of stimulation may adversely affect the performance of AMH for predicting ovarian response. To address this question, we have examined in a large, single-center cohort study of women undergoing their first IVF cycle whether the time interval between serum AMH sampling and initiation of ovarian stimulation affects the correlation of AMH and oocyte yield. More importantly, we also assessed whether a delay of up to 12 months affects the ability of AMH to predict both poor and excessive ovarian response.

MATERIALS AND METHODS

Institutional review board approval was obtained for the current study (B.U.N. 143201111492), and all patients gave written authorization at the time of treatment for the future use of their clinical data. The eligible cohort were all consecutive patients who fulfilled the following criteria: [1] having at least 2 years of infertility, [2] undergoing their first IVF-ICSI attempt from 2010–2011, [3] being treated with a fixed GnRH antagonist protocol followed by recombinant follicle-stimulating hormone (FSH), and [4] having AMH values tested in our laboratory with the Immunotech Beckman Coulter AMH enzyme-linked immunosorbent assay (ELISA) kit during the preliminary fertility workup at their first consultation.

Antimüllerian Hormone Measurement

Serum AMH samples were obtained during the initial fertility workup. Samples were 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 the 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 has demonstrated stable intra-assay and interassay coefficients of variation of <9.5% and a functional sensitivity of 0.35 ng/mL. All values are presented in ng/ml (to convert to pmol/L multiply by 7.14).

Interval between AMH Serum Sample and Initiation of Stimulation

The time interval between AMH measurement and initiation of stimulation was calculated in days. This time interval was calculated by taking into account the exact date of AMH sampling and the first day or initiation of stimulation and was analyzed as a continuous outcome. No restriction was applied regarding this time interval, and all patients who had an AMH serum sample before stimulation were considered eligible, regardless of the duration of this interval.

Treatment Plan

Patients received subcutaneous injections of 150–225 IU of recombinant FSH from cycle day 2 onward, with initiation of a GnRH antagonist 0.25mg/day from day 7 of the cycle. The gonadotropin starting dose was adapted based on the patients' body mass index (BMI) and age, and was determined by the individual treating physicians. Ovulation triggering was accomplished with 10,000 IU of human chorionic gonadotropin (hCG) as soon as three follicles of 17 mm size were observed via transvaginal ultrasound scan. Patients who were at risk of developing OHSS were triggered with either 5,000 IU hCG or with a bolus of GnRH agonist (0.2 mg of Decapeptyl; Ipsen).

Oocyte pickup was planned for 36 hours after triggering, and embryo transfer was performed on days 3 or 5. The luteal phase support consisted of 600 mg of vaginal micronized progesterone (Utrogestan; Besins) with or without the addition of estradiol. In cycles triggered with a GnRH agonist, modified luteal phase support was provided with 1,500 IU of hCG 1 hour after oocyte pickup.

In cases of monofollicular development, rescue intrauterine insemination was performed. If there was no evidence of follicular development, the treatment cycle was canceled. In both cases, this cycle was included in our analysis, and the number of oocytes was considered to be 0.

Given the wide diversity of definitions for poor ovarian responders (17), we decided to use the threshold of <4 oocytes retrieved to define poor ovarian response, in accordance with the Bologna consensus statement definition (18). Use of this definition may also be helpful for future comparisons and for facilitating combined analyses in the future (19). Excessive responders were considered to be the women with >20 oocytes retrieved at OPU, in accordance with previous trials evaluating the predictive ability of AMH in infertile patients (6).

Statistical Analysis

The Spearman rank correlation coefficient (ρ) was calculated to assess the correlation between potential predictive factors and the number of cumulus-oocyte complexes (COCs) retrieved. Receiver operator characteristic (ROC) curves were constructed, and the area under the ROC curve (ROC AUC) was calculated to assess the predictive ability of AMH for low and excessive ovarian responders.

To evaluate the effect of the time interval between AMH serum measurement and initiation of stimulation on the correlation of the marker with the number of oocytes retrieved, we calculated partial correlation coefficients for AMH and number of COCs after controlling for the time interval between AMH sampling and initiation of ovarian stimulation. This strategy was adopted to identify any potential effect of this interval on the correlation of the marker with the number of COCs. Partial correlation allows the correlation between the criterion (number of oocytes retrieved) and a predictor (AMH) after common variance with other predictors (time interval)

TABLE 1

Patient and stimulation characteristics overall and according to the level of ovarian response.

	All patients	Low responders	Normal responders	High responders
Patient characteristics, mean (SD)				
No. of patients	540	56	435	49
Age (y)*	31.9 (4.6)	33.1 (3.8)	31.9 (4.6)	29.5 (3.9)
BMI	23.9 (5.3)	24.2 (7.1)	23.9 (5.1)	24.2 (4.9)
Primary infertility cause, N (%)				
Male factor	314 (58)	27 (48)	253 (58)	34 (69)
Idiopathic	138 (26)	11 (20)	118 (27)	9 (19)
Tubal factor	49 (9)	8 (14)	38 (9)	3 (6)
Ovulatory	24 (4)	5 (9)	17 (4)	2 (4)
Endometriosis	13 (2)	8 (9)	7 (1)	1 (2)
Genetic (PGD)	2 (1)	–	2 (1)	–
Ovarian reserve markers, mean (SD)				
AMH (ng/L)*	4.1 (2.6)	2.7 (2.4)	3.9 (2.3)	7.2 (3.4)
Basal FSH (IU/L)*	6.9 (2.7)	8.9 (4.9)	6.8 (2.2)	5.3 (1.3)
Stimulation characteristics, mean (SD)				
Starting FSH dose (IU)*	168 (24)	171 (26)	168 (24)	159 (19)
Total FSH dose (IU)*	1,532 (667)	1,468 (475)	1,560 (717)	1,357 (217)
Duration of stimulation (d)*	8.9 (1.7)	8.4 (2.5)	9.0 (1.6)	8.8 (0.9)
No. of COCs*	11.0 (7.8)	1.6 (1.3)	10.2 (4.2)	28.9 (8.7)
Time interval between AMH sampling and initiation of stimulation, mo				
Mean (SD)	3.6 (2.7)	3.1 (2.0)	3.6 (2.8)	3.6 (2.8)
Median (IQR)	3 (2–5)	3 (2–4)	3 (2–5)	3 (2–5)
Distribution of patients according to the time interval between AMH sampling and initiation of stimulation, N (%)				
0–3 mo	347 (64)	38 (68)	277 (63)	32 (65)
3–6 mo	112 (21)	12 (21)	90 (21)	10 (20)
>6 mo	81 (15)	6 (11)	68 (16)	7 (15)

Note: AMH = antimüllerian hormone; BMI = body mass index; COCs = cumulus-oocyte complexes; FSH = follicle-stimulating hormone; IQR = interquartile range; PGD = preimplantation genetic diagnosis; SD = standard deviation.
* $P < .05$ for comparisons.

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has been removed from both the criterion and the predictor of interest.

Finally, we studied whether the accuracy of AMH in the prediction of low and excessive response was modified by this time interval. For this, we used the ROC regression model proposed by Pepe and Janes (20, 21). This model allows us to study the effect of the time interval between AMH serum sampling and initiation of stimulation on the classification accuracy of AMH. In this model, the AMH ROC curves for prediction of low and excessive responders are modeled as a function of the covariate "time interval between AMH serum sampling and initiation of stimulation." Following this approach, the regression coefficients were computed with adjustment for this time interval on the ROC curve between AMH and low or excessive ovarian response.

Correlation coefficients and ROC analysis were performed in SPSS 20.0 (SPSS, Inc.). The ROC regression analysis was performed in STATA 10 statistical software (StataCorp LP).

RESULTS
Patient Population

In total, 540 patients were included in the analysis. The patients' characteristics (age, BMI), ovarian reserve markers (AMH, basal FSH), and ovarian stimulation characteristics for the whole cohort and also according to the level of ovarian response are presented in Table 1. The interval between AMH serum sampling and initiation of stimulation ranged from 0 to 12 months. This majority of the patients (64%) started their stimulation within 3 months of the AMH serum measurement, whereas in 81 (15%) patients this interval exceeded 6 months.

Prediction of Oocyte Yield

We found that AMH demonstrated a statistically significant positive correlation with the number of COCs (Spearman co-efficient; $\rho = 0.51$, $P<.0001$). In addition, basal FSH and age demonstrated a statistically significant negative correlation with the number of COCs ($\rho = -0.36$, $P<.0001$; and $\rho = -0.28$, $P<.0001$, respectively). The number of COCs demonstrated a weakly significant correlation with the gonadotropin starting dosage ($\rho = -0.15$, $P=.001$) and with the total amount of gonadotropin used ($\rho = -0.12$, $P=.005$). No statistically significant correlation was demonstrated for BMI, the time interval between AMH sampling and initiation of stimulation, or the duration of stimulation with the number of COCs.

The ability of AMH to predict the ovarian response category was assessed by constructing ROC curves. We found that AMH demonstrated a good predictive ability for both low ovarian response (ROC AUC = 0.72; 95% CI, 0.65–0.80) and excessive ovarian response, (ROC AUC = 0.80; 95% CI, 0.74–0.87), as seen in Figure 1. Both FSH level and age were associated with the ovarian response category; however, for both low and high ovarian response, the ROC AUC was lower than observed for AMH (data not shown).

Influence of the Time Interval between Serum AMH Sampling and Initiation of Stimulation on the Accuracy of AMH for Predicting Low and Excessive Ovarian Response

The time interval between AMH measurement and initiation of stimulation was not directly correlated with AMH values ($\rho = -0.05$, $P=.22$) or with the number of oocytes retrieved ($\rho = 0.01$, $P=.84$). Consistent with this, controlling for the time interval between AMH measurement and initiation of stimulation did not statistically significantly alter the correlation (partial coefficient of AMH with oocyte yield, $r = 0.53$, $P<.0001$).

The ROC regression analysis was performed to examine the effect of this time interval on the accuracy of AMH in

FIGURE 1
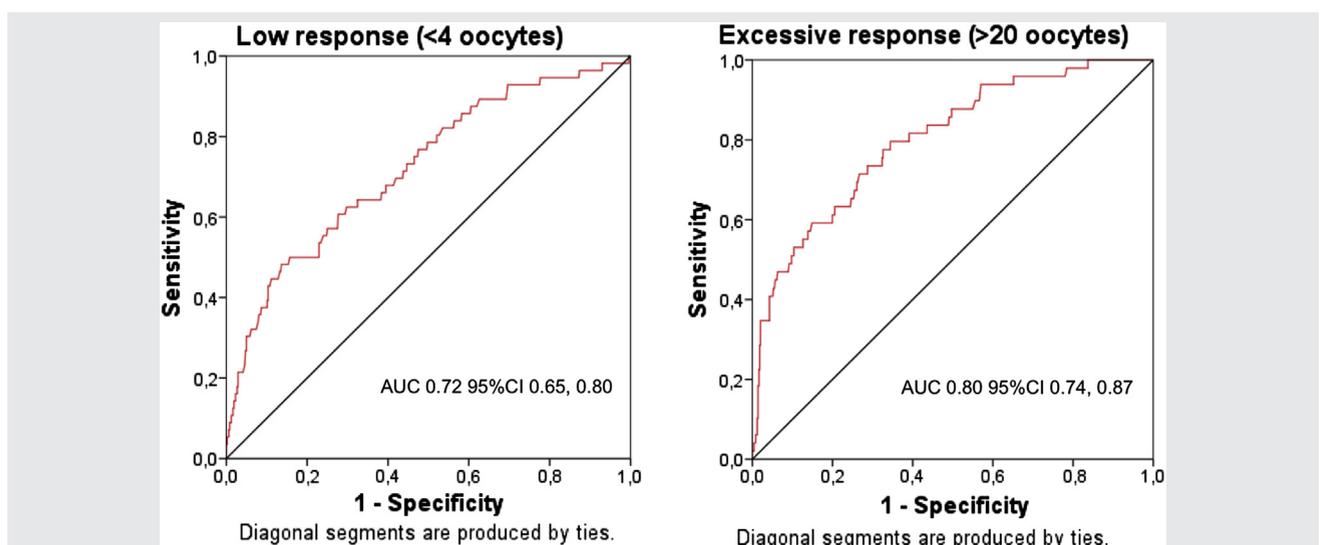
Receiver operator characteristic (ROC) curves for antimüllerian hormone (AMH) for the prediction of low and excessive ovarian responders.

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prediction of ovarian response category. This ROC regression analysis demonstrated that the accuracy of AMH was not affected by the time interval for low ovarian response (regression coefficient −0.16 [95% CI, −0.49, 0.17], $P=.331$) or excessive response (regression coefficient 0.04 [95% CI, −0.36, 0.11], $P=.314$).

DISCUSSION

To our knowledge, this is the first study examining the effect of the time interval between AMH assessment and the initiation of ovarian stimulation for IVF-ICSI on the correlation between AMH values and oocyte yield, and on its predictive ability for low and excessive ovarian response. According to our results, an interval of up to 12 months does not appear to affect this correlation or compromise the predictive ability of AMH.

Previous studies have shown that in adults AMH progressively declines with age, mirroring the decline in primordial follicle counts (22). This rate of decline has been estimated to approximate 15% per annum (16), and an overall 34% of the variance of AMH can be attributed to age alone (23). A second level of time-dependent variation can be attributed to the day of the cycle and to which cycle AMH is measured in; these have been estimated at 17.4% (24) and 11% (25), respectively. Despite these potential sources of time-dependent variation, we did not demonstrate an adverse impact of the time interval between AMH serum sampling and ovarian stimulation on the correlation of the marker with the number of COCs, nor on its predictive ability for poor and excessive response.

Although early reports examining the intercycle variability of AMH within a period of three (26) or four consecutive menstrual cycles (24) concluded that this variability was small, others have suggested on reanalysis of their original data that the within-patient variability of circulating AMH is significant (27). Although variation in AMH level is likely given that it reflects the dynamic process of early follicular development, the extent of this variation reflects the basal AMH concentration. For example, women with a low AMH concentration may exhibit some fluctuation, but overall it will remain low; conversely, women with a high AMH concentration will exhibit greater variation, but their AMH values will generally remain high (28). Nonetheless, despite any fluctuation of AMH over time, the crucial point of interest is not whether AMH levels remain stable across cycles, but whether the level of ovarian response can be safely predicted even if a single AMH measurement was obtained much earlier than the initiation of treatment. Our study provides important reassuring information that this time interval appears to have no effect on the predictive ability of AMH for ovarian response. Thus, a single measurement of serum AMH levels within a period of 12 months before ovarian stimulation appears to be adequate to counsel patients for their outcome in a forthcoming ovarian stimulation cycle and may be safely used to tailor IVF-ICSI treatment based on AMH values obtained at the initial fertility workup.

A limitation of our study is its retrospective design. However, we have to acknowledge that designing such a study in a prospective manner would be difficult, given that the time of starting an IVF-ICSI cycle depends on both the convenience of the patient and the availability of the physician. Also, it may not be considered ethical to postpone initiation of treatment for infertile couples for a very long period to test this effect in a clinical trial.

In addition, although no AMH-guided treatment strategy had been adopted in our center at the time of the study, we cannot exclude individual physicians' behavior; they may have preferred to start with higher doses of gonadotropins in expected low responders and lower doses in expected excessive responders, based on the patients' characteristics (such as those of advanced age or with polycystic ovaries, respectively). According to our analysis, the excessive responders appeared to have had significantly lower starting FSH doses, which may actually reflect patient selection bias.

Another limitation of the study is the limited time interval between AMH sampling and initiation of stimulation. The change in AMH levels within 12 months might not be robust enough, even when used as a continuous variable as done here, to alter the prognostic classification of the patient, especially in the population analyzed in this study. This may also be the case due to the fact that only 15% of the study population (81 women) had an interval that exceeded 6 months. However, because of the lack of patients starting their treatment cycle at an interval greater than 12 months from the first AMH sample obtained, we were unable to test such intervals and cannot provide information on them. Nonetheless, we must acknowledge that all patients included in the current study represent a typical population in an IVF setting, with the majority of women expected to start stimulation within a short period from the initial assessment. Thus, ovarian stimulation for IVF-ICSI is highly unlikely to start at intervals greater than 12 months from the AMH serum sampling (at the time of the initial fertility workup), even in centers with a high volume of patients or even when intrauterine insemination is the initial treatment approach.

In addition, although our analysis shows that this interval does not affect the predictive ability of the biomarker in general, we cannot say whether that our results are applicable in other, specific patient categories. For example, in women of advanced age (e.g., who are older than 40 years years) with normal AMH values a long interval may indeed play an important role, particularly given the detrimental impact of age on the ovarian reserve (29). However, in our data set only 21 (3.9%) out of 540 patients were of advanced age (>40 years), and the mean interval between AMH sampling and initiation of stimulation was 4.4 months. Thus, although it may have been meaningful to examine whether this time interval had a clinically important effect in these women, our limited data set precluded testing such an effect. However, the likelihood of starting ovarian stimulation at longer intervals in older women is significantly reduced because of their accelerating decline in ovarian reserve and the overall detrimental effect of age on IVF success rates (30). In contrast, in women with a low ovarian reserve and low AMH values, the prediction of a low response cannot be thus compromised by time; it can be only reinforced by the physiologic reduction of the ovarian reserve, as the AMH value can only decline with age. Similarly, in women with polycystic ovaries, the

decline in AMH has been reported as only 8% per annum compared with 15% in the general population. Consequently, in a population of high responders with high AMH values, it would be difficult to claim that in a short period and in young women like the high responders of our study the ovarian reserve could have a decrease so rapid as to transform the patient into a poor responder unless new risk factors were involved.

An important consideration, is that although AMH is a statistically significant predictor of low and excessive response in this study, its accuracy is far from perfect. The rank correlation coefficient of 0.5 for the association between AMH and the number of oocytes retrieved indicates that ranked AMH values explain about 25% of the variability in COC rank. This finding suggests that there is ample room for additional explanatory variables, including aspects of the timing of AMH measurement that were not captured in this analysis. This is further highlighted by the performance of the biomarker for predicting low and excessive response in ROC curve analysis. As shown, although the AUC is reasonably large for both outcomes, the tradeoff between sensitivity and false-positive rate is far from optimal. For example, in both cases, to have a sensitivity of 50% or higher we would have to accept a false-positive rate of 20% or more, misclassifying one out of five normal responses. If the cutoff value of AMH were chosen to secure high specificity of the diagnosis, too many true cases would go unrecognized. This uncertainty prevents us from drawing definitive conclusions and highlights the need for additional confirmatory studies from other research groups.

In conclusion, allowing for the limitations we have described, our study suggests that serum AMH levels and the number of COCs after ovarian stimulation are strongly correlated, and AMH has a high predictive ability for poor and excessive ovarian response to stimulation. Its predictive ability does not appear to be affected by the time interval between AMH measurement and initiation of ovarian stimulation for IVF, implying that AMH-tailored ovarian stimulation may be safely implemented whenever a single serum AMH value is available, even up to 12 months before the expected date of initiation of stimulation. Given the widespread uptake of AMH in the workup of infertile couples, this type of confirmation examining the impact of more refined timing of AMH measurement is urgently required in large cohorts.

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