Antimüllerian hormone in gonadotropin releasing-hormone antagonist cycles: prediction of ovarian response and cumulative treatment outcome in good-prognosis patients

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Objective: To assess the relationships between serum antimüllerian hormone (AMH) and ovarian response and treatment outcomes in good-prognosis patients undergoing controlled ovarian stimulation using a gonadotropin-releasing hormone (GnRH) antagonist protocol.
Design: Secondary analysis of data prospectively collected in a randomized, assessor-blind trial comparing two different gonadotropin preparations with respect to ongoing pregnancy rate.
Setting: Twenty-five centers in seven countries.
Patient(s): 749 women, aged 21 to 34 years, with primary diagnosis of infertility being unexplained infertility or mild male factor infertility and with serum follicle-stimulating hormone (FSH) level 1–12 IU/L and antral follicle count (AFC) ≥ 10.
Intervention(s): Controlled ovarian stimulation with highly purified human menopausal gonadotropin (hphMG) or recombinant FSH in a GnRH antagonist cycle with compulsory single-blastocyst transfer and potential subsequent 1-year cryopreserved blastocyst replacement in natural cycles.
Main Outcome Measure(s): Relationships between AMH at start of stimulation and ovarian response and treatment outcome.
Result(s): Serum AMH concentration was strongly correlated with oocyte yield: AMH accounted for 85%, FSH for 14%, and inhibin B and AFC for $<1\%$ each of the explained variation in oocyte yield. Also, AMH showed a high accuracy for the prediction of poor (≤ 3 oocytes) and high response (≥ 15 oocytes), which was statistically significantly better than basal FSH, AFC, or inhibin B. AMH was statistically significantly positively associated with ongoing pregnancy rate in the fresh cycle as well as with the 1-year cumulative ongoing pregnancy and live-birth rates.
Conclusion(s): There is a positive relationship between AMH and oocyte yield in GnRH antagonist cycles, and AMH is the best predictor for identifying patients with poor and high ovarian response. The positive association between AMH and cumulative live-birth rates after fresh and cryopreserved cycles reflects the availability of more oocytes/blastocysts, not higher quality.
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Key Words: Antimüllerian hormone, GnRH antagonist, live birth, ovarian response, pregnancy

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The circulating concentration of antimüllerian hormone (AMH) has been demonstrated to be a reliable surrogate marker for the functional ovarian follicle reserve (1, 2). In assisted reproductive technology (ART), serum AMH has been shown to be a better endocrine indicator of a patient's follicular response to controlled ovarian stimulation (COS) with gonadotropins than the basal levels of follicle-stimulating hormone (FSH), estradiol, inhibin B, or the woman's age (3–8). Also, AMH has been claimed to possess at least the same level of accuracy as the antral follicle count (AFC) for the prediction of poor (9) and excessive (10) response. In addition, a high serum concentration of AMH before the start of COS has been shown to be associated with increased risk of developing ovarian hyperstimulation syndrome (OHSS) (6, 11, 12). As with other ovarian reserve tests, AMH has not proven to be a good predictor of embryo quality or pregnancy in COS cycles, suggesting that AMH is a marker of quantitative rather than qualitative aspects of the ovarian reserve (2, 3, 10, 12, 13).

The value of serum AMH in predicting ovarian response to COS and cycle outcome has, however, overwhelmingly been studied in patients down-regulated with a gonadotropin-releasing hormone (GnRH) agonist in a long protocol. Only a few studies have specifically addressed the value of AMH measurements in GnRH antagonist cycles (14–16), and few published reports address the association between the basal serum AMH level and ovarian response, embryo quality, or pregnancy/live-birth rates in GnRH antagonist regimens. It remains to be confirmed that AMH is an important predictive marker of response to COS in a manner similar to that of a GnRH agonist protocol in patients treated with a GnRH antagonist.

Recently, it was demonstrated that the nature of the relationship between AMH and oocyte retrieval below or above the stimulation target differed when using different types of gonadotropin preparations—that is, recombinant FSH or highly purified human menopausal gonadotropin (hphMG, menotropin)—in the long GnRH agonist protocol (3). Hence, the type of gonadotropin preparation should be taken into consideration when evaluating the predictive value of AMH in GnRH antagonist cycles.

We evaluated the relationship between serum AMH and ovarian response and treatment outcome in patients undergoing COS with either hphMG or recombinant FSH using a GnRH antagonist protocol. The results were compared with those of other markers of ovarian reserve.

MATERIALS AND METHODS

This study is a secondary analysis of data prospectively collected in a randomized, open-label, assessor-blind, parallel-groups, multicenter trial. The trial compared ongoing pregnancy rates in patients undergoing in vitro fertilization (IVF) after stimulation with hphMG (Menopur; Ferring Pharmaceuticals) or recombinant FSH (follitropin beta, Puregon; MSD) following a GnRH antagonist protocol after collection of evidence of functional ovarian reserve. The trial was performed in accordance with the declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and local regulatory requirements. The trial protocol was approved by both the local regulatory authorities and the independent ethics committees covering all participating centers. Written informed consent was provided by all patients before any trial-related examinations were initiated. The trial design, population, methods, conduct, and results were described previously elsewhere (17).

Trial Population

Eligible patients were women between the ages of 21 and 34 years, and the primary diagnosis for treatment of unexplained infertility or mild male factor infertility. Further inclusion criteria were serum FSH concentration between 1 and 12 IU/L and AFC ≥ 10 measured within the last 12 months, a body mass index (BMI) of 18 to 25 kg/m^2, and regular menstrual cycles of 24 to 35 days. Women with polycystic ovaries, endometriosis stages I to IV, or poor response in a previous cycle were excluded.

Treatment Regimen

The starting gonadotropin dosage was fixed at 150 IU for the first 5 days and adjusted according to ovarian response from day 6 when the GnRH antagonist (ganirelix acetate, Orgalutran; MSD) was initiated at a daily dose of 0.25 mg and continued throughout the gonadotropin treatment period. A single injection of 250 μg of human chorionic gonadotropin (hCG, choriogonadotropin alpha, Ovitrelle; Merck Serono) was administered when three follicles of ≥ 17 mm were observed. Oocyte retrieval took place 36 ± 2 hours after the hCG administration. All oocytes retrieved were fertilized by intracytoplasmic sperm injection (ICSI). Fertilization was assessed 19 ± 1 hours after insemination, and embryos with two pronuclei were cultured individually.

On day 5 (120 ± 2 hours) after insemination, the blastocyst quality was assessed using the grading system of Gardner and Schoolcraft (18), and a single blastocyst of the best quality was transferred. Remaining blastocysts were cryopreserved individually by vitrification. A serum β-hCG test was performed 13 to 15 days after blastocyst transfer. Clinical and ongoing pregnancy was confirmed by transvaginal ultrasound at 5 to 6 and 10 to 11 weeks, respectively, after transfer. A patient with no ongoing pregnancy at the end of the stimulated cycle/trial period and with surplus cryopreserved blastocysts could undergo cryopreserved replacement cycles within 1 year of the patient's start of treatment, with compulsory single-blastocyst transfer in a natural cycle on day 7 after the luteinizing hormone (LH) peak. All patients with an established ongoing pregnancy in a fresh or cryopreserved cycle were observed until delivery.

Endocrine Assays and Antral Follicle Count

Circulating concentrations of AMH, inhibin B, FSH, LH, estradiol, and progesterone were analyzed in the serum samples collected on stimulation day 1 before the start of stimulation. The serum samples were analyzed at a central laboratory (Laboratory for Clinical Research, Kiel, Germany).

Concentrations of AMH (1 ng/mL = 7.14 pmol/L; Gen 2 ELISA; ref. no. A79765; Beckmann-Coulter) and inhibin B were analyzed by an enzyme-linked immunosorbent assay (ELISA). Levels of FSH, LH, estradiol, and progesterone were analyzed by an electrochemiluminescence immunoassay (ECLIA; Roche Diagnostics). The assays used for AMH, inhibin B, FSH, LH, estradiol, and progesterone had a sensitivity of 0.57 pmol/L, 2.6 ng/L, 0.10 IU/L, 0.10 IU/L, 18.4 pmol/L, 0.095 nmol/L, respectively, and an intra-assay and interassay imprecision (% coefficient of variation) of 5.7 and 4.6, 10.8 and 11.4, 2.0 and 3.8, 2.1 and 1.6, 2.9 and 5.6, and 5.9 and 7.2, respectively. The AFC was defined as the total number of follicles in both ovaries on stimulation day 1 before the start of stimulation (days 2 to 3 of the natural cycle) with a diameter between 2 and 10 mm as measured by transvaginal ultrasound by local clinic sonographers.

Statistical Analysis

All analyses were based on the intention-to-treat population. Continuous data are presented as median and interquartile range (IQR), and categorical data are presented as frequencies and percentages. The ovarian response categories were defined according to the number of oocytes retrieved: poor ($\leq$3 or cancellation due to poor response), low (4–7), appropriate (8–14), high (15–19), and excessive response ($\geq$20 or cancellation due to excessive response). The correlations between baseline variables and oocytes retrieved were evaluated using Spearman's rank correlation coefficient. Subjects were grouped according to AMH quartiles and selected variables of interest summarized within each quartile, overall and by treatment group. Differences between AMH quartiles were evaluated overall using the nonparametric Kruskal-Wallis test for continuous data, and categorical data were evaluated using the chi-square test or Fisher's exact test.

A regression modeling approach using log-AMH as covariate and treatment as factor was used to test for linear trend and differences between treatment groups. Continuous data were analyzed using general linear models in which the endocrine parameters were log-transformed. Categorical data were analyzed using generalized linear models with canonical link functions as follows: binary data (logistic regression models); ordinal data (proportional odd models); count data (Poisson models allowing for overdispersion); and fractions (binomial regression models allowing for overdispersion).

The ability of selected baseline characteristics to predict poor or high response was evaluated using receiver operating characteristic (ROC) curves. The area under the curve (AUC) was compared using the method described by DeLong et al. (19). Optimal cutoff points were determined by the combination of specificity and sensitivity closest to the optimal.

RESULTS

The study included 749 women, and the primary treatment diagnosis was mild male factor infertility (61%) or unexplained infertility (39%), as reported in Devroey et al. (17). The hphMG (n = 374) and recombinant FSH (n = 375) treatment groups were similar with respect to demographics, baseline characteristics, and serum hormone concentrations at start of stimulation (Supplemental Table 1, available online).

Markers of Baseline Ovarian Reserve

In this study population of young women (median [interquartile range]: 31 [29, 32] years), a small ($r = -0.20$) but statistically significant ($P<.001$) inverse correlation was observed between age and AMH at start of stimulation (Table 1). The serum AMH concentration before stimulation correlated moderately with AFC ($r = 0.48$), and the correlation coefficients between AMH and serum concentrations of FSH and inhibin B at start of stimulation were relatively lower ($r = -0.32$ and $r = 0.20$, respectively). Also, AFC was weakly correlated with FSH ($r = -0.19$) (see Table 1).

Oocyte retrieval was performed for 97% of the patients in each treatment group. The median number [and interquartile range] of oocytes retrieved was statistically significantly ($P<.001$) higher in the recombinant FSH group compared with the hphMG group: 9 [6, 14] versus 8 [5, 12]. For both groups, AMH was more strongly correlated with the oocyte yield than were FSH, AFC, and inhibin B (hphMG: $r = 0.52$, -0.36, 0.33, and 0.17, respectively; recombinant FSH: $r = 0.59$, -0.38, 0.35, and 0.12, respectively) (see Table 1). Also, AMH displayed a higher potential for distinguishing between different ovarian response categories when compared with FSH and inhibin B (Fig. 1). A multiple regression model revealed that AMH ($P<.001$) and FSH ($P<.001$) were statistically significant predictors of the number of oocytes retrieved, but AFC ($P=.125$) and inhibin B ($P=.706$) were not. In this combined model, AMH accounted for 85%, FSH for 14%, and inhibin B and AFC for <1% each of the explained variation in oocyte yield.

We performed ROC curve analyses to assess the predictive values of AMH, FSH, inhibin B, and AFC for the estimation of ovarian response (Fig. 2). For both treatment groups, AMH showed a high accuracy for the prediction of poor and high response: hphMG, AUC = 0.779 (95% confidence interval [CI], 0.742–0.816 and 0.765 (95% CI, 0.738–0.791); and recombinant FSH, AUC = 0.897 (95% CI, 0.861–0.935) and 0.813 (95% CI, 0.787–0.839). The AMH cutoff values for prediction of poor response were 13 pmol/L (sensitivity 66%, specificity 80%) for hphMG stimulation, and 12 pmol/L (sensitivity 92%, specificity 83%) for recombinant FSH stimulation. The AMH cutoff values for prediction of high response were 28 pmol/L (sensitivity 78%, specificity 67%) for hphMG stimulation and 31 pmol/L (sensitivity 76%, specificity 74%) for recombinant FSH stimulation.

Compared with AMH, the AUC values of AFC and inhibin B for prediction of poor as well as high response were statistically significantly ($P<.001$) lower in both treatment groups. The AUC values of FSH for prediction of poor and high response were also statistically significantly lower compared with those of AMH ($P=.012$ and .009, respectively). When including both AMH and FSH for prediction of poor or high response, the AUC values were not statistically significantly higher compared with those obtained with AMH only: poor

TABLE 1

Correlations between markers of ovarian reserve and ovarian response.

	Age	AMH[a]	FSH[a]	Inhibin B[a]	AFC[a]
AMH					
All	−0.20 (−0.27, −0.13)				
hphMG	−0.14 (−0.24, −0.04)				
rFSH	−0.26 (−0.35, −0.16)				
FSH					
All	0.10 (0.03, 0.18)	−0.32 (−0.39, −0.26)[b]			
hphMG	0.05 (−0.05, 0.15)	−0.32 (−0.41, −0.23)[b]			
rFSH	0.16 (0.05, 0.25)	−0.32 (−0.41, −0.23)[b]			
Inhibin B					
All	0.01 (−0.06, 0.08)	0.20 (0.13, 0.27)	−0.10 (−0.17, −0.03)		
hphMG	0.04 (−0.06, 0.14)	0.27 (0.17, 0.36)	−0.17 (−0.26, −0.07)		
rFSH	−0.02 (−0.12, 0.08)	0.14 (0.04, 0.24)	−0.04 (−0.14, 0.06)		
AFC					
All	−0.20 (−0.27, −0.13)	0.48 (0.42, 0.53)[b]	−0.19 (−0.26, −0.12)	0.09 (0.02, 0.17)	
hphMG	−0.17 (−0.26, −0.07)	0.47 (0.39, 0.55)[b]	−0.19 (−0.29, −0.10)	0.16 (0.06, 0.26)	
rFSH	−0.24 (−0.33, −0.14)	0.49 (0.41, 0.56)[b]	−0.18 (−0.28, −0.08)	0.03 (−0.07, 0.13)	
Oocytes retrieved					
All	−0.17 (−0.24, −0.10)	0.55 (0.50, 0.60)[b]	−0.37 (−0.43, −0.31)[b]	0.14 (0.07, 0.21)	0.34 (0.27, 0.40)[b]
hphMG	−0.10 (−0.20, 0.01)	0.52 (0.44, 0.59)[b]	−0.36 (−0.44, −0.26)[b]	0.17 (0.07, 0.27)	0.33 (0.24, 0.42)[b]
rFSH	−0.22 (−0.31, −0.12)	0.59 (0.52, 0.65)[b]	−0.38 (−0.47, −0.29)[b]	0.12 (0.01, 0.22)	0.35 (0.26, 0.44)[b]

Note: Numbers are Spearman's rank correlation coefficient, *r* (95% confidence interval). AFC = antral follicle count; AMH = antimüllerian hormone; FSH = follicle-stimulating hormone; rFSH = recombinant follicle-stimulating hormone; hphMG = highly purified human menopausal gonadotropin; OHSS = ovarian hyperstimulation syndrome.

[a] Stimulation day 1 (cycle day 2–3).

[b] $r > 0.30$ (or $r < -0.30$) and $P < .001$.

Arce. AMH, oocytes, and cumulative live births. Fertil Steril 2013.

response 0.820 (95% CI, 0.766–0.874) versus 0.818 (95% CI, 0.762–0.874), $P=.774$; and excessive response 0.815 (95% CI, 0.781–0.848) versus 0.792 (95% CI, 0.756–0.828), $P=.081$.

Baseline Characteristics, Stimulation Characteristics, and Ovarian Response According to AMH Quartiles

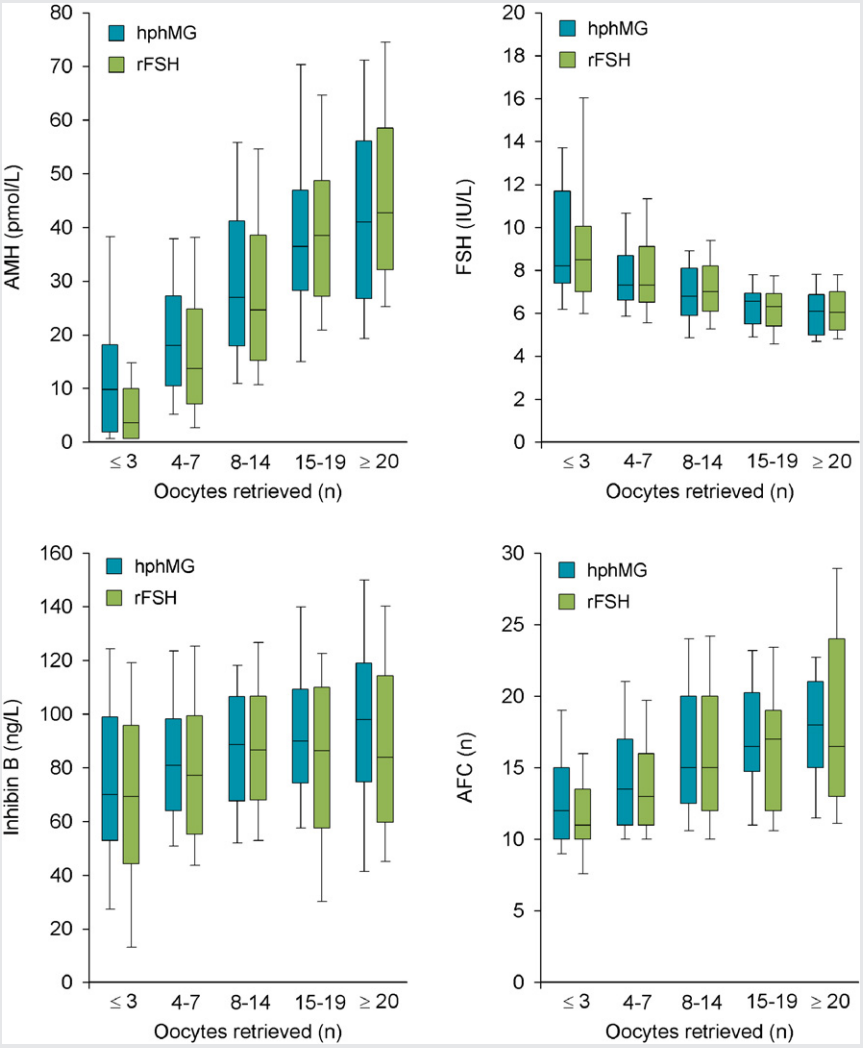
The patient population was stratified according to the 25th, 50th, and 75th percentiles of the serum AMH concentration at start of stimulation. Statistically significant differences among the AMH quartiles were noticed for most of the baseline and stimulation characteristics, ovarian response variables, and the blastocyst quality for the overall study population and for each treatment group (Table 2).

In the group consisting of all patients with AMH <25th percentile, a large proportion (44%) had a gonadotropin-dose increase on stimulation day 6; despite this, cycle cancellation due to poor response occurred most frequently (6%) in this quartile. In the two middle quartiles (25th–50th and 50th–75th percentiles), the majority (75%) of patients maintained the initial dose on day 6 of stimulation, and less than 1% of the cycles were canceled due to poor response. In the AMH >75th percentile, interventions due to excessive ovarian response and early moderate/severe OHSS occurred at the highest frequency: 10% and 4%, respectively. The median number of oocytes retrieved statistically significantly increased ($P<.001$) across the AMH quartiles, from 5 [4, 7] in the <25th percentile to 12 [9, 17] oocytes in the >75th percentile. Both the proportion of patients with blastocysts available for transfer in the fresh cycle (from 71% to 86%; $P<.001$) and the number of blastocysts (from 1 [0, 2] to 3 [1, 6]; $P<.001$) statistically significantly increased across the AMH quartiles, but there was no difference between the quartiles in the number of blastocysts available for transfer when adjusting for the number of oocytes retrieved ($P=.937$). The total number of cryopreserved blastocysts ($P<.001$) and number of cryopreserved blastocysts per oocyte retrieved ($P=.004$) as well as the proportion of patients with cryopreserved blastocysts available for transfer in a subsequent cycle ($P<.001$) statistically significantly increased across the AMH quartiles. In relation to AMH, statistically significant differences were observed between the hphMG and recombinant FSH groups for several stimulation characteristics and ovarian response variables, as detailed in Table 2.

Outcome According to AMH Concentrations/Categories

The ROC analyses indicated that AMH was not an absolute predictor of ongoing pregnancy in the fresh cycle with either gonadotropin (hphMG: AUC = 0.573 [95% CI, 0.542–0.604]; recombinant FSH: AUC = 0.476 [95% CI, 0.445–0.507]). Nevertheless, taking the whole patient population, a statistically significant ($P=.038$) association between the AMH concentration and the ongoing pregnancy rate in the fresh cycle was recorded, and a similar trend, although borderline statistically significant ($P=.085$), was also noted for the relation between AMH and live-birth rate in the fresh cycle (see Table 2). When comparing patients with AMH above and below the 50th percentile, both the ongoing pregnancy rate (32% vs. 23%, $P=.006$) and live-birth rate (31% vs. 23%, $P=.022$) in the fresh cycle were statistically significantly increased in patients with high AMH levels. Also, statistically

FIGURE 1



Box and whisker plots for antimüllerian hormone (AMH), follicle-stimulating hormone (FSH), inhibin B, and antral follicle count (AFC) at start of stimulation in patients with various numbers of oocytes retrieved after stimulation with highly purified human menopausal gonadotropin (hphMG) or recombinant FSH in a gonadotropin-releasing hormone (GnRH) antagonist protocol. Values are median (*lines*), 25th–75th percentile (*boxes*), and 10th–90th percentile (*whiskers*). hphMG: ≤3 (n = 47), 4–7 (n = 124), 8–14 (n = 145), 15–19 (n = 38), ≥ 20 (n = 18); recombinant FSH: ≤3 (n = 25), 4–7 (n = 112), 8–14 (n = 147), 15–19 (n = 55), ≥ 20 (n = 30).

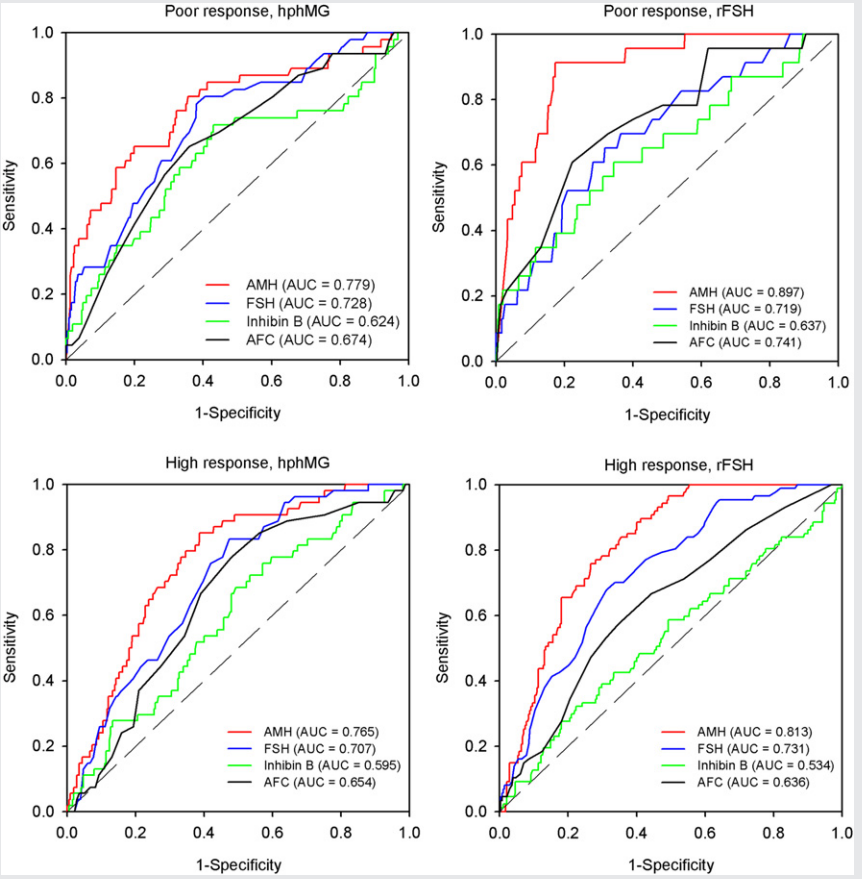
Arce. AMH, oocytes, and cumulative live births. Fertil Steril 2013.

significantly higher ongoing pregnancy and live-birth rates in the fresh cycle were observed for the hphMG-treated patients in the two highest quartiles compared with the two lowest quartiles (35% and 34% vs. 23% and 23%, $P=.007$ and $P=.013$, respectively).

Among the recombinant FSH-treated patients, there was no statistically significant increase in pregnancy or live-birth rates in the fresh cycle in the two highest AMH quartiles compared with the two lowest (29% and 27% vs. 24% and 24%, $P=.236$ and $P=.462$, respectively) due to an apparent reduction in pregnancy and live-birth rates in the fresh cycle in the highest quartile.

A total of 222 patients (107 for hphMG and 115 for recombinant FSH) underwent up to 6 cryopreserved replacement cycles, for a total of 355 cycles and an average of 1.6 ± 0.9 in the hphMG group and 1.6 ± 1.0 in the recombinant FSH group. No pregnancies were achieved after the third cryopreserved cycle. In the cryopreserved cycles, the ongoing pregnancy and live-birth rates per started stimulation cycle statistically significantly increased ($P<.022$) across the AMH quartiles, from 8% in the <25th percentile to 15% in the >75th percentile (see Table 2), reflecting the statistically significant ($P<.001$) relationship between AMH and number of cryopreserved blastocysts. Nevertheless, the ongoing pregnancy and live-birth rates per blastocyst transferred in cryopreserved cycles were not statistically significantly ($P=.195$) different between the AMH quartiles nor increased with the AMH quartiles (30%, 18%, 30%, and 25% in quartiles 1, 2, 3, and 4, respectively; identical percentages for ongoing pregnancy and live-birth rates).

FIGURE 2



Receiver operating characteristic (ROC) curve analysis showing the predictive values of antimüllerian (AMH), follicle-stimulating hormone (FSH), inhibin B, and antral follicle count (AFC) at start of stimulation for estimation of poor ovarian response (≤3 oocytes retrieved or cycle cancellation due to poor response) and high response (≥15 oocytes retrieved or cycle cancellation due to excessive response), respectively, after controlled ovarian stimulation in patients treated with highly purified human menopausal gonadotropin (hphMG) or recombinant FSH in a gonadotropin-releasing hormone (GnRH) antagonist protocol. The diagonal line is the reference line of no discrimination (area under the curve = 0.5).

Arce. AMH, oocytes, and cumulative live births. Fertil Steril 2013.

The cumulative (i.e., combined fresh and cryopreserved cycles) rates of ongoing pregnancy ($P<.001$) and live-birth ($P<.001$) were positively associated with the AMH concentration at the start of stimulation. In both treatment groups, higher outcome rates were observed among patients with AMH >50th percentile compared with the patients with AMH ≤50th percentile. Respectively, the ongoing pregnancy rates were for hphMG, 50% versus 31% ($P<.001$); and recombinant FSH, 46% versus 33% ($P=.010$). The live-birth rates were for hphMG, 49% vs. 31% ($P<.001$); and recombinant FSH, 43% vs. 33% ($P=.030$). Including age in the logistic regression analyses showed that this potential confounding variable had no statistically significant impact on the pregnancy and live-birth rates, neither in fresh nor in cumulative cycles (data not shown).

DISCUSSION

The results of this study showed that the AMH concentration at start of stimulation is predictive of the ovarian response in good-prognosis patients undergoing COS in a GnRH antagonist cycle. This finding is in line with numerous previous studies in patients following a long GnRH agonist protocol (1–8). The correlation between AMH and the number of oocytes retrieved was superior to those for other hormonal markers of the ovarian reserve (i.e., FSH and inhibin B), as previously shown elsewhere for the long GnRH agonist protocol (2). The ROC analyses indicated that the basal serum AMH concentration was a better predictor of poor as well as high ovarian response than FSH or inhibin B in cycles controlled with a GnRH antagonist. This observation was independent of the type of gonadotropin preparation used for stimulation.

It should be noted that the relative differences in AMH values between patients with few and many oocytes retrieved were larger than the interindividual differences of the other markers of ovarian reserve, including AFC. In our study, the measurements of AMH and AFC were performed on the same day: the first day of stimulation just before

gonadotropin exposure. Hence, the moderate correlation of 0.48 between AMH and AFC suggests either that these two markers of ovarian reserve represent somewhat different follicle cohorts or that there is an influence of the variability of these assessments. The usefulness of AFC as a predictor of ovarian response has primarily been established in single-center investigations rather than in multicenter studies, which suggests sonographer-dependent variability. Although single-center studies have indicated that early-follicular phase AFC and AMH show similar correlations to the number of oocytes retrieved (9, 10, 20), we found that AMH better correlated with the ovarian response than AFC, reproducing the findings of earlier multicenter trials (3, 15).

Our finding that patients with an AMH level below the 25th percentile had statistically significantly fewer oocytes retrieved after COS than the patients in the other AMH quartiles emphasizes the current view that low oocyte yield is mainly a sign of diminished ovarian reserve (9, 21, 22) and, to a lesser extent, of gonadotropin underdosing. The alternative explanation that follicles in these patients were less sensitive to FSH was not supported by the evidence, which showed that the duration of stimulation, and therefore the FSH-mediated growth rate, was not longer in the patients with low AMH values.

The potential disadvantages of assigning all patients to a nonindividualized dose regimen for the first 5 days, irrespective of a large interindividual variability of basal serum AMH levels, were evident. This conventional approach resulted in an initial inadequate follicular response in one-fourth of the total study population, as measured by transvaginal ultrasound on stimulation day 6. Because the patients with a "required" gonadotropin-dose increase on day 6 were distinguished by a lower basal AMH concentration compared with the patients who had no need for a dose adjustment during stimulation, it can be hypothesized that an increase of their starting dose beyond 150 IU may have resulted in a higher ovarian response for some of these patients and, possibly, reduced cycle cancellation rates without an increased risk of OHSS. However, a couple of studies in patients defined as low responders based on a low AMH or AFC before starting the first COS cycle did not report improvements in the number of oocytes retrieved or the pregnancy rates by increasing the starting gonadotropin doses (23, 24).

Prospective (25) and retrospective (26) studies have indicated potential benefits of using AMH to individualize treatment strategies for COS. In the large prospective (but not randomized) study by Nelson et al. (25), a reduction in the incidence of underresponse and overresponse to stimulation was observed when assigning patients with low or high AMH levels to the GnRH antagonist protocol, with high and low gonadotropin doses, respectively, while assigning the patients with normal AMH levels to the long GnRH agonist protocol. These findings were recently supported in a large retrospective study by Yates et al. (26), who reported that embryo transfer, pregnancy, and live-birth rates per cycle started increased significantly when using stratified COS protocols that were tailored to individual AMH levels as compared with conventional nonindividualized stimulation, although the patients with very low AMH levels were excluded. Large prospective, randomized, controlled trials to evaluate the potential clinical benefits of individual treatment strategies for patients undergoing their first IVF/ICSI cycle are needed before any firm conclusions can be drawn in relation to AMH-based individual dosing algorithms.

Although the cutoff values of AMH for prediction of low or high ovarian response were quite similar between the treatment groups, there were some differences in the clinical response in each AMH quartile depending on the type of gonadotropin. Treatment with hphMG was associated with a somewhat lower oocyte yield in patients with a medium or high AMH value at start of stimulation compared with recombinant FSH treatment. Consequently, the occurrence of a high ovarian response ($\geq$ 15 oocytes retrieved) and preventive interventions or OHSS treatment among patients with higher basal AMH values was more common in the recombinant FSH group than in the hphMG group. Despite a larger oocyte yield among the recombinant FSH-treated patients with AMH above the 75th percentile, apparently lower ongoing pregnancy and live-birth rates in the fresh cycle were observed in the recombinant FSH group, which influenced the cumulative ongoing pregnancy and live-birth rates in that group.

Our study showed no statistically significant differences in the number of available blastocysts on day 5 between the AMH quartiles when adjusting for the number of oocytes retrieved. This is in accordance with the poor predictive value for AMH as a marker of qualitative aspects of the ovarian reserve when using a GnRH agonist protocol (3, 7, 13, 27, 28). Although there was a statistically significant association between AMH and ongoing pregnancy in the fresh cycle in our study, the ROC analyses showed that AMH was not an absolute predictor of ongoing pregnancy in the fresh cycle, which is in agreement with several large studies of patients undergoing COS using a GnRH agonist protocol (1, 3, 21, 29). However, statistically significantly higher cumulative ongoing pregnancy and live-birth rates were observed with increasing AMH levels. This documents the importance of AMH in the cumulative outcome of a single stimulation cycle, even when evaluating mainly patients who are considered to have a good ovarian reserve. The logistic regression analysis indicated that the statistically significant positive association between AMH and outcome rates was most likely mediated through increased oocyte yields, and therefore more blastocysts available for fresh and cryopreserved cycles, rather than a direct association between AMH and oocyte/blastocyst quality. This conclusion is further strengthened by the observation that no statistically significant differences in pregnancy or live-birth rates per blastocyst transferred in cryopreserved cycles were observed between the AMH quartiles. Consequently, the analysis of combined fresh and cryopreserved cycles showed stronger associations between AMH and outcome than the analysis of fresh cycles alone.

Our study has shown that AMH predicts the number of oocytes retrieved in good-prognosis patients undergoing COS in a GnRH antagonist cycle. We found that AMH is a better predictor of poor and high ovarian response than basal FSH, inhibin B, or AFC. The value of AMH as a predictor of treatment outcome is clearly evident after combined

TABLE 2

Variables obtained at baseline, stimulation day 6, and end of stimulation as well as outcome variables grouped by AMH quartiles at start of stimulation.

	AMH quartiles[a]					
	Q1: <25th (<13 pmol/L)			Q2: 25th–50th (13–23 pmol/L)		
Variable	All (n = 185)	hphMG (n = 91)	rFSH (n = 94)	All (n = 189)	hphMG (n = 99)	rFSH (n = 90)
Start of stimulation						
AMH (pmol/L)	7 (3, 10)	7 (3, 10)	6 (2, 10)	17 (15, 21)	18 (15, 21)	17 (15, 20)
Age (y)	32 (30, 33)	32 (30, 33)	32 (30, 33)	31 (29, 32)	31 (29, 33)	31 (29, 32)
Age range (y)	21–34	21–34	22–34	22–34	22–34	23–34
BMI (kg/m^2)	21.9 (20.3, 23.9)	21.9 (20.3, 23.5)	21.9 (20.3, 24.2)	21.8 (20.3, 23.5)	21.6 (20.4, 23.3)	22.0 (20.0, 23.8)
FSH (IU/L)	7.9 (6.7, 9.7)	7.9 (6.8, 9.9)	8.1 (6.5, 9.6)	7.2 (6.2, 8.2)	7.2 (6.1, 8.3)	7.2 (6.4, 8.2)
Inhibin B (ng/L)	76 (55, 100)	72 (55, 100)	79 (55, 103)	81 (61, 97)	81 (59, 98)	82 (65, 97)
AFC (n)	11 (10, 14)	11 (10, 14)	12 (10, 14)	14 (12, 17)	14 (12, 17)	14 (11, 17)
Stimulation day 6						
Follicles ≥10 mm (n)	5 (3, 6)	5 (3, 7)	5 (3, 6)	7 (5, 9)	6 (4, 8)	7 (5, 9)
Estradiol (nmol/L)	2.1 (1.3, 2.9)	2.3 (1.4, 2.9)	1.8 (1.2, 2.7)	2.5 (1.7, 3.3)	2.3 (1.8, 3.2)	2.5 (1.7, 3.4)
Gonadotropin dose adjustment						
Decrease, n (%)	1 (1%)	1 (1%)	0 (0)	0 (0)	0 (0)	0 (0)
No change, n (%)	101 (56%)	47 (52%)	54 (59%)	139 (75%)	72 (74%)	67 (76%)
Increase, n (%)	79 (44%)	42 (47%)	37 (41%)	46 (25%)	25 (26%)	21 (24%)
Missing, n (%)	4 (2%)	1 (1%)	3 (3%)	4 (2%)	2 (2%)	2 (2%)
Gonadotropin dose (IU)	150 (150, 225)	150 (150, 225)	150 (150, 225)	150 (150, 150)	150 (150, 225)	150 (150, 150)
End of stimulation						
Treatment days (n)	8 (7, 9)	8 (7, 9)	8.5 (7, 9)	9 (8, 9)	9 (8, 9)	8 (8, 9)
Total gonadotropin dose (IU)	1,350 (1,125, 1,650)	1,350 (1,200, 1,650)	1,350 (1,050, 16,509)	1,350 (1,200, 1,500)	1,350 (1,200, 1,575)	1,350 (1,200, 1,500)
Cycle cancellation, n (%)	12 (6%)	5 (5%)	7 (7%)	2 (1%)	2 (2%)	0 (0)
Poor response, n (%)	12 (6%)	5 (5%)	7 (7%)	2 (1%)	2 (2%)	0 (0)
Excessive response, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Follicles ≥10 mm (n)	8 (6, 10)	8 (5, 11)	8 (6, 10)	12 (9, 14)	11 (9, 14)	12 (9, 15)
Progesterone (nmol/L)	2.4 (1.7, 3.1)	2.4 (1.6, 3.1)	2.4 (1.7, 3.1)	2.5 (1.9, 3.2)	2.4 (1.9, 3.0)	2.7 (2.0, 3.6)
Progesterone >4 nmol/L, n (%)	20 (12%)	11 (13%)	9 (11%)	20 (11%)	8 (8%)	12 (14%)
Early OHSS (moderate/severe), n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Interventions due to excessive ovarian response[b], n (%)	4 (2%)	1 (1%)	3 (3%)	4 (2%)	2 (2%)	2 (2%)
Outcome						
Oocyte retrieval, n (%)	170 (92%)	85 (93%)	85 (90%)	184 (97%)	96 (97%)	88 (98%)
Oocytes retrieved (n)	5 (4, 7)	5 (3, 8)	6 (4, 7)	8 (6, 11)	7 (5, 10)	9 (7, 12)
Patients with oocytes retrieved according to categories, n (%)						
≤3 oocytes	40 (24%)	24 (28%)	16 (19%)	10 (5%)	9 (9%)	1 (1%)
4–7	88 (52%)	38 (45%)	50 (59%)	76 (41%)	45 (47%)	31 (35%)
8–14	39 (23%)	20 (24%)	19 (22%)	84 (46%)	38 (40%)	46 (52%)
15–19	3 (2%)	3 (4%)	0 (0)	10 (5%)	2 (2%)	8 (9%)
≥20	0 (0)	0 (0)	0 (0)	4 (2%)	2 (2%)	2 (2%)
Blastocysts available, n (%)	131 (71%)	62 (68%)	69 (73%)	167 (88%)	86 (87%)	81 (90%)
Blastocysts (n)	1 (0, 2)	1 (0, 2)	1 (0, 2)	2 (1, 3)	1 (1, 3)	2 (1, 4)
Blastocysts (n)/oocytes retrieved (n), (%)	25% (13%, 43%)	25% (0, 40%)	25% (14%, 43%)	25% (13%, 41%)	26% (16%, 41%)	23% (11%, 41%)
Blastocyst transfer, n (%)	132 (71%)	62 (68%)	70[c] (74%)	168 (89%)	87[c] (88%)	81 (90%)
Blastocyst transfer for patients with oocytes retrieved, n (%)	132 (79%)	62 (73%)	70[c] (84%)	168 (91%)	87[c] (91%)	81 (92%)
Blastocysts cryopreserved, n (%)	79 (43%)	39 (43%)	40 (43%)	99 (52%)	49 (49%)	50 (56%)
Blastocysts cryopreserved (n)	0 (0, 1)	0 (0, 1)	0 (0, 1)	1 (0, 3)	0 (0, 2)	1 (0, 3)
Blastocysts cryopreserved (n)/oocytes retrieved (n), (%)	0 (0, 25%)	0 (0, 20%)	0 (0, 25%)	10% (0, 30%)	8% (0, 29%)	11% (0, 32%)
Fresh cycle						
Ongoing pregnancy, n (%)	45 (24%)	22 (24%)	23 (24%)	42 (22%)	21 (21%)	21 (23%)
Live birth, n (%)	45 (24%)	22 (24%)	23 (24%)	42 (22%)	21 (21%)	21 (23%)
Cryopreserved cycles						
Ongoing pregnancy, n (%)	14 (8%)	7 (8%)	7 (7%)	17 (9%)	8 (8%)	9 (10%)
Live birth, n (%)	14 (8%)	7 (8%)	7 (7%)	17 (9%)	8 (8%)	9 (10%)
Fresh + cryopreserved cycles						
Ongoing pregnancy, n (%)	59 (32%)	29 (32%)	30 (32%)	59 (31%)	29 (29%)	30 (33%)
Live birth, n (%)	59 (32%)	29 (32%)	30 (32%)	59 (31%)	29 (29%)	30 (33%)

Note: Continuous data are presented as median (interquartile range), and categorical data as frequency and percentage. AFC = antral follicle count; AMH = antimüllerian hormone; BMI = body mass index; rFSH = recombinant follicle-stimulating hormone; hphMG = highly purified human menopausal gonadotropin; OHSS = ovarian hyperstimulation syndrome.

[a] The AMH quartiles were defined for the total study population.
[b] Cycle cancellation, paracentesis, or albumin administration.
[c] One patient with transfer of a nonblastocyst is included.
[d] Kruskall-Wallis test.
[e] Chi-square test.
[f] Fisher's exact test.
[g] Logistic regression.
[h] Linear regression.
[i] Poisson regression.
[j] Binominal regression.

Arce. AMH, oocytes, and cumulative live births. Fertil Steril 2013.

TABLE 2

Continued.

AMH quartiles[a]						*P* value		
Q3: > 50th–75th (> 23–37 pmol/L)			Q4: > 75th (> 37 pmol/L)					
All (n = 187)	hphMG (n = 97)	rFSH (n = 90)	All (n = 188)	hphMG (n = 87)	rFSH (n = 101)	AMH quartile	AMH overall	AMH overall/ treatment
30 (26, 33)	30 (27, 33)	30 (25, 33)	49 (43, 62)	51 (44, 62)	48 (43, 59)	< .001[d]		
31 (29, 33)	31 (29, 33)	30.5 (29, 32)	30 (28, 32)	30 (28, 33)	30 (28, 31)	< .001[d]	< .001[h]	< .026[h]
21–34	21–34	23–34	22–34	22–34	23–34			
22.0 (20.4, 24.0)	22.3 (21.1, 24.1)	21.5 (20.3, 23.8)	21.8 (20.5, 23.5)	22.1 (21.0, 23.9)	21.6 (20.1, 23.0)	.744[d]	.530[h]	.192[h]
6.9 (6.0, 7.9)	6.9 (6.0, 7.8)	6.8 (6.0, 7.9)	6.5 (5.7, 7.6)	6.7 (5.6, 7.7)	6.4 (5.7, 7.5)	< .001[d]	< .001[h]	.303[h]
85 (66, 106)	88 (70, 108)	78 (63, 101)	91 (69, 116)	90 (73, 115)	93 (66, 118)	< .001[d]	< .001[h]	.244[h]
16 (12, 19)	16 (12, 19)	15 (12, 19)	18 (15, 22)	18 (15, 22)	18 (15, 22)	< .001[d]	< .001[i]	.706[i]
8 (5, 10)	7 (5, 9)	9 (5, 12)	9 (6, 12)	8 (4, 10)	10 (7, 14)	< .001[d]	< .001[i]	< .001[i]
2.9 (2.0, 3.8)	2.9 (1.9, 3.8)	2.9 (2.2, 3.9)	3.1 (1.9, 4.8)	2.4 (1.5, 4.2)	3.4 (2.4, 5.1)	< .001[d]	< .001[h]	.005[h]
						< .001[e]	< .001[g]	.018[g]
3 (2%)	1 (1%)	2 (2%)	8 (4%)	2 (2%)	6 (6%)			
140 (75%)	68 (71%)	72 (80%)	137 (73%)	61 (70%)	76 (75%)			
43 (23%)	27 (28%)	16 (18%)	43 (23%)	24 (28%)	19 (19%)			
1 (1%)	1 (1%)	0 (0)	0 (0)	0 (0)	0 (0)			
150 (150, 150)	150 (150, 225)	150 (150, 150)	150 (150, 150)	150 (150, 225)	150 (150, 150)	< .001[d]	< .001[h]	.013[h]
9 (8, 9)	9 (8, 10)	8 (8, 9)	9 (8, 10)	9 (8, 10)	9 (8, 9)	.002[d]	.017[i]	.015[i]
1,350 (1,200, 1,500)	1,350 (1,200, 1,575)	1,350 (1,200, 1,425)	1,350 (1,200, 1,500)	1,350 (1,200, 1,650)	1,350 (1,200, 1,500)	.845[d]	.244[h]	.001[h]
2 (2%)	1 (1%)	1 (1%)	1 (1%)	0 (0)	1 (1%)	< .001[f]		
1 (1%)	1 (1%)	0 (0)	0 (0)	0 (0)	0 (0)			
1 (1%)	0 (0)	1 (1%)	1 (1%)	0 (0)	1 (1%)			
14 (11, 18)	14 (11, 17)	15 (12, 18)	18 (14, 21)	17 (13, 20)	19 (15, 21)	< .001[d]	< .001[i]	.007[i]
2.7 (2.1, 3.4)	2.7 (2.1, 3.7)	2.6 (2.0, 3.2)	2.9 (2.1, 3.8)	2.8 (2.1, 3.9)	3.0 (2.1, 3.8)	< .001[d]	< .001[h]	.441[h]
22 (12%)	17 (18%)	5 (6%)	44 (24%)	21 (24%)	23 (23%)			
4 (2%)	3 (3%)	1 (1%)	8 (4%)	3 (3%)	5 (5%)			
8 (4%)	1 (1%)	7 (8%)	19 (10%)	7 (8%)	12 (12%)	.002[e]	.002[g]	.437[g]
185 (99%)	96 (99%)	89 (99%)	185 (98%)	85 (98%)	100 (99%)	.001[e]	< .001[g]	.960[g]
10 (7, 14)	10 (7, 13)	12 (8, 15)	12 (9, 17)	12 (8, 15)	14 (10, 19)	< .001[d]	< .001[i]	< .001[i]
						< .001[e]	< .001[g]	< .001[g]
2 (1%)	1 (1%)	1 (1%)	5 (3%)	5 (6%)	0 (0)			
46 (25%)	28 (29%)	18 (20%)	26 (14%)	13 (15%)	13 (13%)			
91 (49%)	47 (49%)	44 (49%)	78 (42%)	40 (47%)	38 (38%)			
32 (17%)	15 (16%)	17 (19%)	48 (26%)	18 (21%)	30 (30%)			
14 (8%)	5 (5%)	9 (10%)	28 (15%)	9 (11%)	19 (19%)			
164 (88%)	86 (89%)	78 (87%)	162 (86%)	73 (84%)	89 (88%)	< .001[e]	.008[g]	.376[g]
3 (1, 5)	2 (1, 4)	3 (1, 5)	3 (1, 6)	3 (1, 6)	3 (1, 6)	< .001[d]	< .001[i]	.063[i]
25% (11%, 43%)	24% (11%, 43%)	27% (11%, 43%)	25% (11%, 43%)	27% (12%, 43%)	22% (10%, 40%)	.937[d]	.346[j]	.705[j]
162 (87%)	84 (87%)	78[c] (87%)	159 (85%)	72 (83%)	87 (86%)	< .001[e]	< .001[g]	.264[g]
162 (88%)	84 (88%)	78[c] (88%)	159 (86%)	72 (85%)	87 (87%)	< .007[e]	< .032[g]	.164[g]
120 (64%)	58 (60%)	62 (69%)	122 (65%)	59 (68%)	63 (62%)	< .001[e]	< .001[g]	.505[g]
2 (0, 4)	1 (0, 4)	2 (0, 4)	2 (0, 5)	2 (0, 5)	2 (0, 5)	< .001[d]	< .001[i]	.072[i]
14% (0, 33%)	12% (0, 32%)	18% (0, 33%)	15% (0, 33%)	17% (0, 35%)	12% (0, 30%)	.004[d]	.075[j]	.751[j]
64 (34%)	34 (35%)	30 (33%)	57 (30%)	31 (36%)	26 (26%)	.037[e]	.038[g]	.519[g]
62 (33%)	33 (34%)	29 (32%)	53 (28%)	30 (34%)	23 (23%)	.088[e]	.085[g]	.413[g]
29 (16%)	14 (14%)	15 (17%)	29 (15%)	13 (15%)	16 (16%)	.022[e]	.004[g]	.566[g]
29 (16%)	14 (14%)	15 (17%)	29 (15%)	13 (15%)	16 (16%)			
93 (50%)	48 (49%)	45 (50%)	86 (46%)	44 (51%)	42 (42%)	< .001[e]	< .001[g]	.843[g]
91 (49%)	47 (48%)	44 (49%)	82 (44%)	43 (49%)	39 (39%)	< .001[e]	< .001[g]	.724[g]

Arce. AMH, oocytes, and cumulative live births. Fertil Steril 2013.

evaluation of the fresh and cryopreserved cycles. A high AMH level is associated with increased cumulative ongoing pregnancy and live-birth rates, which is in line with its ability to predict higher yields of oocytes and blastocyst availability. Our results also suggest that further examination of differential approaches or dosing regimens to ovarian stimulation determined by an individual's AMH level is warranted.

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SUPPLEMENTAL TABLE 1

Patient demographics, baseline characteristics, and serum endocrine concentrations at start of stimulation.

Variable	All (n = 749)	hphMG (n = 374)	rFSH (n = 375)
Baseline			
Age (y)	31 (29, 33)	31 (29, 33)	31 (29, 32)
Weight (kg)	60 (56, 64)	60 (56, 65)	60 (55, 64)
BMI (kg/m^2)	21.9 (20.4, 23.7)	22.1 (20.7, 23.7)	21.7 (20.2, 23.8)
Cycle length (d)	28 (28, 30)	28 (28, 30)	28 (28, 30)
Duration of infertility (y)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	2.5 (1.9, 4.0)
Primary reason for infertility			
Mild male factor, n (%)	457 (61%)	232 (62%)	225 (60%)
Unexplained, n (%)	292 (39%)	142 (38%)	150 (40%)
Day 1 of stimulation (cycle d 2–3)			
AMH (pmol/L)	23 (13, 37)	23 (13, 36)	24 (13, 39)
21–29 y	28 (17, 44); n = 239	28 (17, 43); n = 111	27 (17, 44); n = 128
30–34 y	21 (11, 34); n = 510	21 (11, 33); n = 263	20 (10, 36); n = 247
FSH (IU/L)	7.0 (6.1, 8.2)	7.1 (6.2, 8.2)	6.9 (6.0, 8.2)
Inhibin B (ng/L)	84 (64, 105)	85 (65, 105)	83 (59, 105)
LH (IU/L)	5.9 (4.6, 7.6)	5.9 (4.6, 7.8)	5.9 (4.6, 7.6)
Estradiol (nmol/L)	0.16 (0.13, 0.21)	0.16 (0.13, 0.21)	0.16 (0.13, 0.20)
Progesterone (nmol/L)	2.0 (1.5, 2.7)	2.0 (1.5, 2.6)	2.0 (1.5, 2.7)
AFC (n)	15 (12, 18)	15 (12, 18)	14 (11, 18)

Note: Continuous data are presented as median (interquartile range) and categorical data as frequency and percentage. AFC = antral follicle count; AMH = antimüllerian hormone; BMI = body mass index; FSH = follicle-stimulating hormone; rFSH = recombinant follicle-stimulating hormone; LH = luteinizing hormone; hphMG = highly purified human menopausal gonadotropin; OHSS = ovarian hyperstimulation syndrome.

Arce. AMH, oocytes, and cumulative live births. Fertil Steril 2013.