

Random anti-Müllerian hormone (AMH) is a predictor of ovarian response in women with elevated baseline early follicular follicle-stimulating hormone levels

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Objective: To investigate the utility of random anti-Müllerian hormone (AMH) in assessing ovarian response among women with diminished ovarian reserve (DOR) diagnosed by elevated early follicular-phase FSH levels.

Design: Retrospective study.

Setting: Academic and academically affiliated assisted reproductive technology (ART) programs.

Patient(s): Seventy-three women undergoing ART with elevated early follicular FSH levels.

Intervention(s): None.

Main Outcome Measure(s): Number of oocytes retrieved during ART cycle, number of day 3 embryos, and cycle cancellation and clinical pregnancy rates.

Result(s): Random AMH levels were strongly correlated with the number of oocytes retrieved during an ART cycle among women with elevated FSH ($r = 0.55$). Women with elevated FSH who had a random serum AMH level of 0.6 ng/mL or higher had twice the number of oocytes retrieved (11 ± 1.3 vs. 5.6 ± 0.6), a greater number of day 3 embryos (5.7 ± 0.9 vs. 3 ± 0.5), and approximately a third of the cycle cancellation rate (14% vs. 41%) compared with women with a random serum AMH below 0.6 ng/mL. The clinical pregnancy rate was also higher among women with a random serum AMH ≥ 0.6 ng/mL (28% vs. 14%), however, the difference was not statistically significant.

Conclusion(s): A random serum AMH level is useful in setting expectations for ART prognosis in women with elevated early follicular-phase serum FSH levels. (Fertil Steril® 2011; ■:■-■. ©2011 by American Society for Reproductive Medicine.)

Key Words: Anti-Müllerian hormone, ART, Müllerian inhibiting substance, diminished ovarian reserve, elevated FSH levels, ovarian response

Diminished ovarian reserve (DOR) due to aging or other yet unknown conditions is one of the most common causes of infertility and is the fastest growing infertility problem according to 2008 Society for Assisted Reproductive Technologies data (1, 2). In 2003, DOR was designated as the third leading cause of infertility, with approximately 10% of all infertile couples being diagnosed with DOR. However, between 2003 and 2008, the number of infertile couples diagnosed with DOR increased 40%, accounting for 14% of all infertility diagnoses, second only to male factor infertility. DOR is associated with both decreased number and quality of oocytes retrieved during an assisted reproductive technology (ART) cycle, as evidenced by decreased clinical pregnancy rates (3, 4). DOR is the result of the normal aging process. However, it may also result from genetic, autoimmune, or iatrogenic conditions, or it may be idiopathic. Genetically, women with the FMR1 mutation have a 20%–30% chance of having this

condition (5). In addition, autoimmune endocrinopathies, radiation therapy, or pelvic surgery may also lead to DOR (4, 6, 7). In clinical practice, DOR is most often diagnosed by elevated serum FSH levels on day 2 or 3 of the menstrual cycle (baseline). However, an antral follicle count fewer than five per ovary, low ovarian volume, low inhibin B levels, fewer than five oocytes retrieved during an ART cycle, and low anti-Müllerian hormone (AMH) levels are all used to define DOR (3).

AMH is a dimeric glycoprotein belonging to the transforming growth factor beta (TGF β) family and closely related to inhibin and activin. AMH inhibits the development of the Müllerian ducts in the male fetus (8). It is secreted by the Sertoli cells in males and the granulosa cells in postpubertal females (9). In females, AMH controls the development of primary follicles by inhibiting further recruitment of other follicles during folliculogenesis (10). Serum AMH levels decrease gradually with age, and the levels become undetectable after menopause (11). It is the earliest marker of diminishing ovarian reserve, with relatively minimal intra- and intercycle variation, and its serum levels decrease well before any increase in baseline FSH (3). In clinical practice, serum AMH level has been shown to be one of the best predictors of the number of oocytes retrieved during an ART cycle (12–14). Recently, it has been reported that AMH can also predict the pregnancy outcome (15). However, the utility of obtaining a random serum AMH level in infertile women with elevated baseline FSH levels has not been established.

In this retrospective study, we examined the value of random AMH levels in women with DOR, as defined by elevated baseline

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early follicular serum FSH levels. We hypothesized that among women with elevated early follicular serum FSH levels, there is a subset of women who have higher random AMH levels and better ART outcomes than those with lower AMH levels.

MATERIALS AND METHODS

We collected data from 73 consecutive women undergoing IVF who had elevated baseline early follicular FSH levels who attended Montefiore Institute for Reproductive Medicine and Health and Genesis Fertility and Reproductive Medicine between September 2007 and July 2010. The study was approved by the Institutional Review Board of both institutions.

Random serum AMH levels for each woman, unrelated to the day of the menstrual cycle, were measured at Reprosourc (Woburn, MA) (16). All women with elevated serum baseline FSH above 10 IU/L were enrolled. Baseline FSH levels were measured on day 2 or 3 of the cycle. Seventy-three women were divided into two groups according to their AMH levels (cutoff 0.6 ng/mL). Unpublished data from our center demonstrated that having seven or more oocytes retrieved during an ART cycle predicted pregnancy outcome and that an AMH cutoff of 0.6 ng/mL or above had the best sensitivity and specificity to predict seven or more oocytes retrieved (see Results). All women underwent controlled ovarian hyperstimulation with recombinant FSH or highly purified hMG. Prevention of premature ovulation was achieved with either GnRH agonist down-regulation or antagonist suppression. The percentages of women receiving recombinant FSH or hMG and GnRH agonist and antagonist down-regulation were similar in all groups. Ovulation was induced with highly purified or recombinant hCG. For canceled cycles, the number of oocytes and embryos were considered as missing and not zero.

Statistics

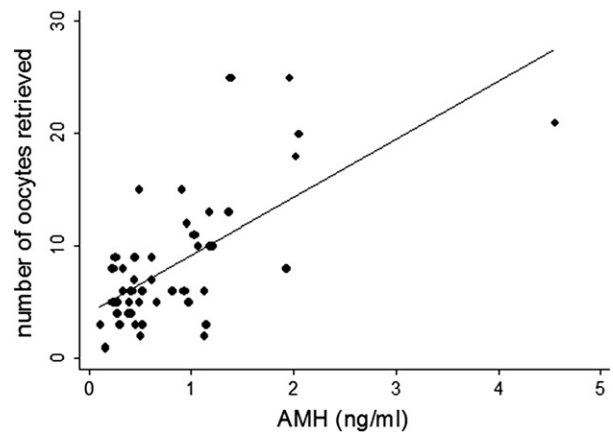
Data are presented as mean \pm SEM. Student's *t*-test and χ^2 -test were used to test the differences between groups, for continuous and categorical data, respectively. When conditions of normality were not met, Mann-Whitney *U*-test was used. Spearman rank correlation was used to test the association between groups. Sensitivity analysis was performed to determine a cutoff level for AMH that predicted seven or more oocytes retrieved during an ART cycle. All statistical tests were done using STATA software. $P < .05$ was considered statistically significant.

RESULTS

As in women with normal ovarian reserve, AMH was significantly associated with the number of oocytes retrieved among women with DOR ($r = 0.55$, $P < .0001$; Fig. 1). Our preliminary findings demonstrated that having seven or more oocytes retrieved during an ART cycle improved pregnancy outcome, even though there was no difference in pregnancy outcome if seven versus more than seven oocytes were retrieved (unpublished data). We noted that an AMH cutoff ≥ 0.6 ng/mL was associated with the greatest sensitivity (70%) and specificity (70%) to predict seven or more oocytes retrieved (Fig. 2). The demographic and cycle characteristics of women grouped according to their AMH levels are shown in Table 1. Women with an AMH level below 0.6 ng/mL had similar age, baseline FSH, and body mass index compared with women with an AMH greater than or equal to 0.6 ng/mL. However, women with an AMH level of 0.6 ng/mL or above had greater antral follicle counts (10 ± 0.4 vs. 7 ± 0.4 ; $P < .0001$), greater peak serum E_2 levels ($2,715 \pm 245$ pg/mL vs. $1,336 \pm 150$ pg/mL; $P < .0001$), twice the number of oocytes retrieved (11 ± 1.3 vs. 5.6 ± 0.6 ; $P = .0004$), and a greater number of day 3 embryos (5.7 ± 0.9 vs. 3 ± 0.5 ; $P = .03$). The cycle cancellation rate was almost 3 times lower in women with an AMH greater than or equal to 0.6 ng/mL (14% vs. 41%; $P = .02$), while the clinical pregnancy rate was higher (28% vs. 14%) but not statistically significant ($P = .1$).

FIGURE 1

AMH is significantly correlated to the number of oocytes retrieved among women with DOR ($r = 0.55$, $P < .0001$).



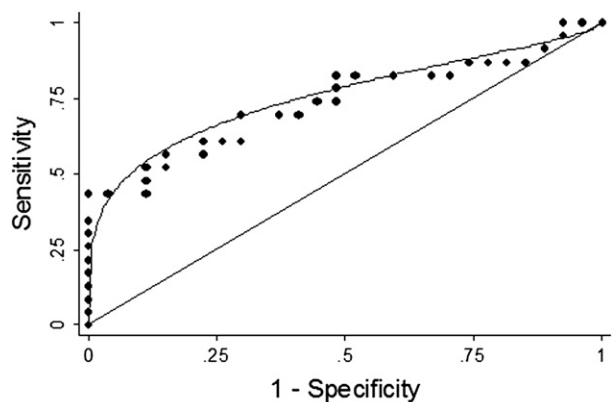
Buyuk. AMH and diminished ovarian reserve. *Fertil Steril* 2011.

DISCUSSION

DOR is a condition of decreased fertility owing to a reduction in the overall quantity and quality of the oocytes. It is associated with the greatest use of medications during IVF cycles and with the least successful outcomes (1, 17). In clinical practice, baseline early follicular serum FSH level is the most commonly used test to diagnose DOR. However, its value in determining cycle outcome is less informative compared with AMH (3). Low antral follicle count (less than five per ovary) at baseline, low ovarian volume (less than 2 mL), baseline serum E_2 above 80 pg/mL, and low serum inhibin levels are all associated with DOR (3, 6). However, like baseline FSH, their predictive value in determining cycle outcome is less useful when compared with AMH. AMH is a member of TGF β superfamily, with growing clinical significance in the diagnostic workup and precycle counseling of women with

FIGURE 2

Receiver operating curve curve analysis showing the relation between AMH and seven or more oocytes retrieved in women with elevated basal serum FSH.



Buyuk. AMH and diminished ovarian reserve. *Fertil Steril* 2011.

TABLE 1

Demographic characteristics and cycle outcomes of women with elevated early follicular-phase FSH levels as a function of random serum AMH levels.

	AMH <0.6 ng/mL (n = 44)	AMH ≥0.6 ng/mL (n = 29)	P value
Age	37.6 ± 0.8	36.8 ± 1	.1
Baseline FSH, IU/L	13.7 ± 0.5	13.5 ± 0.6	.24
AMH, ng/mL	0.3 ± 0.02	1.3 ± 0.1	<.0001
BMI, kg/m ²	25.6 ± 0.8	24.1 ± 1	.2
Other etiology for infertility (%):			
None	18 (41)	17 (59)	.1
Male	14 (32)	5 (17)	.2
Tubal	8 (18)	5 (17)	.9
Endometriosis	4 (9)	2 (7)	.7
Antral follicle count	7 ± 0.4	9.9 ± 0.4	<.0001
Total gonadotropin used, IU	6,017 ± 509	6,328 ± 473	.6
Maximum E ₂ , pg/mL	1,336 ± 150	2,715 ± 245	<.0001
Oocytes	5.6 ± 0.6	11.1 ± 1.3	.0004
Day 3 embryos	3 ± 0.5	5.7 ± 0.9	.03
Cycle cancellation, n (%)	18 (41)	4 (14)	.02
Clinical pregnancy, n (%)	6 (14)	8 (28)	.1

Buyuk. AMH and diminished ovarian reserve. *Fertil Steril* 2011.

infertility (12). Unlike FSH, its serum levels are relatively constant during the menstrual cycle (18). It is one of the best predictors of the number of oocytes retrieved during an ART cycle (12–14), and recent reports indicate that it may predict pregnancy outcome (15).

In this study, we sought to determine whether AMH would have any use in predicting the number of oocytes retrieved, the number of day 3 embryos, or cycle cancellation and clinical pregnancy rates among women with DOR as diagnosed with high baseline early follicular FSH levels. To our knowledge, this is the first study elucidating the value of AMH in predicting the cycle outcome among women with elevated baseline FSH levels. A similar study was recently published by Gleicher et al., where DOR was defined as abnormally high age-specific FSH and abnormally low age-specific AMH (19). The investigators reported that an AMH cutoff above 1.05 ng/mL predicted better delivery chances among women with DOR, although live births occurred even at undetectable AMH levels. However, the definition of DOR was different from the one that we used in our study, and timing of serum AMH levels in reference to menstrual cycle day was not specified.

Our data demonstrate that AMH is strongly associated with the number of oocytes retrieved among women with DOR. Moreover,

women with elevated FSH but a random serum AMH level of 0.6 ng/mL or above have a greater number of oocytes retrieved, a greater number of day 3 embryos, and lower cancellation rates compared with women with elevated FSH but lower AMH levels. Although the clinical pregnancy rate is also greater among women with elevated FSH but AMH of 0.6 ng/mL or above, the difference did not achieve statistical significance. Since AMH levels decrease before any appreciable increase in FSH levels (3), one would expect that AMH levels would be very low once FSH increases above 10 IU/L. However, our findings suggest that among women with DOR, there is a subgroup of women with relatively higher AMH levels who appear to have better outcomes with ART cycles. This subgroup may actually represent women with high FSH that fluctuates from cycle to cycle, compared with women with low AMH, who may have persistently elevated FSH.

These data suggest that women with elevated follicular FSH and random AMH levels above 0.6 ng/mL be counseled regarding a possible better prognosis during ART cycles than women with elevated early follicular FSH and a random AMH <0.6 ng/mL. Furthermore, women with elevated FSH and a low AMH level should be counseled regarding poor outcome with ART.

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