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Age-specific serum anti-Müllerian hormone concentration in Japanese women and its usefulness as a predictor of the ovarian response

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Abstract

Purpose: To compare the ovarian response predictive ability of anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), and estradiol (E2) and to determine the age-specific distribution of serum AMH concentrations of Japanese women.

Methods: This was a multicenter (four-site), observational, analytic, cross-sectional Japanese study consisting of two parts: Study 1 (the prediction of the ovarian response of 236 participants who were undergoing controlled ovarian stimulation [COS]) and Study 2 (the distribution of the AMH concentration with an assay of 417 healthy women who were aged 20-49 years and who had normal menstrual cycles).

Results: The AMH had a significantly higher predictive value for the normal and high responders than FSH and E2 as a stronger correlation between the ovarian response and AMH was observed than for FSH and E2. The serum AMH concentration decreased proportionally with age.

Conclusion: The AMH concentration correlated well with the oocyte count in the patients who were undergoing COS for in vitro fertilization and was shown to predict the risk of ovarian hyperstimulation syndrome among these patients.

KEYWORDS

anti-Müllerian hormone, Japanese, oocyte retrieval, ovarian reserve, ovulation induction

1 | INTRODUCTION

Potentially related factors to low fertility in Japan include a decrease in marriage rates, delay in marrying, deferring childbearing to later years, and improved access to contraception.[1] These factors have resulted from demographic and socioeconomic changes, as well as medical advancements in past decades, which have affected the role of women in society. Furthermore, postponing childbearing to the biological age limit has resulted in an increase in the need for, and seeking of, infertility treatments, including assisted reproductive techniques.[1-3]

Currently, in order to achieve better reproductive outcomes with assisted reproductive techniques, such as in vitro fertilization (IVF), controlled ovarian stimulation (COS) is used for the induction of multiple follicular development.[4] Variations in the ovarian response to hormonal stimulation are considerably large; thus, selecting individualized COS protocols is of great importance.[4,5] Such individualized COS protocols can reduce the risk of ovarian hyperstimulation in women that might have an excessive response. Additionally, individualized COS protocols can lead to improved outcomes in women with a poor ovarian response.[6]

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic condition that results from COS. The conditions that are associated with

a higher risk of OHSS are a young age, low body weight, polycystic ovary syndrome (PCOS), higher doses of exogenous gonadotropins, high absolute serum estradiol (E2) levels or a rate of increase in E2, and previous episodes of OHSS.[7] It is important to predict and prevent OHSS as the associated morbidity can be severe. Furthermore, improper management can result in severe sequelae.[8] In severe OHSS cases, renal failure leads to decreased urine volume, followed by respiratory and circulatory failure. Life-threatening thrombosis also can develop with the progression of OHSS. Therefore, the prediction of OHSS recently has gained considerable importance among IVF specialists.

Previously, anti-Müllerian hormone (AMH) has been identified as a predictor of OHSS.[5,9,10] Anti-Müllerian hormone is a protein that belongs to the transforming growth factor-β family. In men, AMH is secreted by the Sertoli cells in the testes during embryogenesis and plays a significant role in sexual differentiation, particularly in inhibiting the development of the Müllerian ducts.[11] In women, AMH is produced by the granulosa cells of the pre-antral and small antral follicles during the early stages of follicular recruitment. Its production decreases with follicular growth.[12] With aging, the circulating AMH levels decrease, until its production eventually ceases during menopause.[13]

The serum AMH level indicates the number of pre-antral and small antral follicles and it is useful to assess the reserve capacity of the ovaries.[14,15] The use of AMH levels to predict OHSS leads to decreased risks of treatment-related complications, thereby leading to safer, more efficient infertility treatment. The efficacy of AMH as a measure of ovarian reserve is well known; thus, its use in several clinical settings, including infertility treatment, has become widespread.[10]

The distribution of AMH levels in healthy Japanese women has yet to be reported. Additionally, assessments of the relationship between the retrieved oocyte count and AMH levels are scarce in this population. This study aimed to assess AMH as a predictor of the ovarian response during COS and to determine the age-specific distribution of AMH levels in healthy Japanese women.

2 | MATERIALS AND METHODS

2.1 | Study design and treatment

This was a multicenter (four-site), observational, analytic Japanese study consisting of two parts; namely, Study 1 and Study 2. Study 1 was a retrospective, cross-sectional study and consisted of the evaluation of the ovarian response prediction during COS by using the Elecsys® AMH Plus assay (Roche Diagnostics International, Ltd., Rotkreuz, Switzerland). This part of the study was conducted at Asada Ladies Clinic and IVF Namba Clinic between December, 2014 and March, 2016. Study 2 was a prospective study and consisted of determining the distribution of the AMH concentration levels (measured using the Elecsys® AMH Plus assay) of 417 healthy Japanese women. This part of the study was conducted at Tokushima University Hospital, Asada Ladies Clinic, and Yamaguchi University Hospital between May, 2014 and May, 2015.

2.2 | Participants

2.2.1 | Study 1

Women who were planning to undergo COS were eligible for the study if they were aged between 20 and 45 years, had a >0.8 mL serum blood sample available for analysis (taken during a previous clinical visit) that was collected within 2-4 days from the beginning of their menstrual period, they were planning to undergo COS by either a gonadotropin-releasing hormone (GnRH) antagonist protocol or a short or long GnRH agonist protocol, the presence of both ovaries had been confirmed by transvaginal echography, and if they had provided written informed consent to participate in the study.

The main exclusion criteria were as follows: PCOS; ovarian abnormalities (eg, an ovarian cyst sized >2 cm, confirmed by transvaginal echography); hydrosalpinx; endometriosis; a history of ovarian surgery within 6 months prior to the beginning of the study; metabolic or endocrine diseases (diabetes, thyroid disease, Cushing's syndrome etc.); administration of the combined oral contraceptive pill <60 days from the beginning of the study; hormone treatment within the last 21 days with clomiphene, aromatase inhibitor, gonadotropin (all types), estrogen receptor inhibitor, tamoxifen, or a GnRH agonist or GnRH antagonist; malignant tumor; patients undergoing radiotherapy or chemotherapy; drug addiction or alcoholism; patients who had joined the clinical study within the last 90 days of the study; patients taking medications for which COS is contraindicated; a positive pregnancy test; COS from the clomiphene administration method; and individuals who were judged by the investigator as unfit to participate in the study.

2.2.2 | Study 2

The AMH concentration tends to decrease with age and it is measured before beginning infertility treatment in routine clinical practice. Therefore, it was aimed to determine the distribution of the AMH concentration in healthy women by age group. For this, a 3 year layer was set for women who were aged 30-44 years and a 5 year layer was set for women who were aged 20-29 years and >45 years, with a total of eight layers for the total sample population. The study targeted 50 patients for each layer, yielding a sample size of 400 (8 × 50) participants.

Women aged between 20 and 49 years, with a normal menstrual cycle duration (defined as 25-38 days, according to the guideline from the Japan Society of Obstetrics and Gynecology[16]), who clearly recalled the date of their last period, had a body mass index (BMI) ranging between 19 and 30 kg/m^2, and whose AMH and other hormone levels were measured were eligible for enrollment.

The exclusion criteria were as follows: PCOS; patients with ovarian abnormalities; endometriosis; a history of ovarian surgery, diabetes, thyroid disease, metabolic, or endocrine disease (eg, adrenal gland disease); hormone treatment or the combined oral contraceptive pill within 90 days of the beginning of the study); a history of anticancer or immunosuppressive drug use; and participants whose concentrations of thyroid-stimulating hormone (TSH) and free thyroxine (FT4) were outside of the reference range.

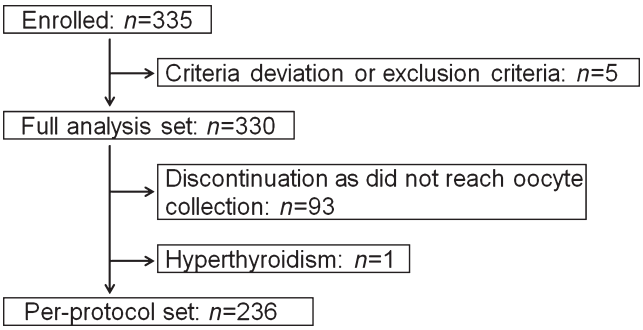

FIGURE 1 Patient disposition (per-analysis sets)

2.3 | Study reagents and assays

During Study 1, the levels of AMH, luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, E2, progesterone (P4), testosterone, TSH, and FT4 were measured in the serum that had been obtained within 2-4 days after the beginning of the menstrual period. The reagents that were used for the measurement of AMH are described in detail elsewhere.[17] All the other serum markers were measured with an electro-chemiluminescence immunoassay on an automated analyzer (cobas; Roche Diagnostics International, Ltd.). The GnRH antagonist protocol or GnRH agonist long or short protocol was used for COS. From day 3 of the menstrual period, the patients underwent the administration of 225 IU or 300 IU of FSH and/or human menopausal gonadotrophin. The growth of the follicles was monitored by the E2, FSH, and LH levels and by an ultrasound examination. The dose was adjusted if necessary in order to obtain mature oocytes. The presence of the mature follicles was confirmed and oocyte retrieval was performed 36 hours after triggering oocyte maturation with human chorionic gonadotrophin or with a gonadotrophin-releasing hormone agonist.

TABLE 1 Demographic and clinical characteristics of the participants in Study 1 (n = 236)

Variable	Median	Interquartile range
Age (years)	36	33-39
Height (cm)	160.0	156.0-162.4
Weight (kg)	51.2	48.0-55.0
Body mass index (kg/m^2)	20.1	19.1-21.8
Mature oocytes (N)	13	7-19
MII oocytes (N)	11	7-19
Retrieved oocytes (N)	14	9-23
Elecsys AMH (ng/mL)	2.38	1.47-3.75
LH (mIU/mL)	4.80	3.71-6.09
FSH (mIU/mL)	7.08	6.11-8.75
E2 (pg/mL)	40.7	30.4-54.4
P4 (ng/mL)	0.384	0.260-0.502

AMH, anti-Müllerian hormone; E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; MII, metaphase II; P4, progesterone.

2.4 | Endpoints

2.4.1 | Study 1

The primary endpoint of Study 1 was the correlation of the AMH concentration with the oocyte count. A regression analysis was performed in order to determine if AMH was significantly and strongly associated with the oocyte count (response variable: oocyte count; explanatory variables: age, AMH, LH, FSH, E2, and P4).

The Guideline of the European Society of Human Reproduction and Embryology[18] was used and the patients were grouped as "poor" responders (P-arm: less than three oocytes), "normal" responders (N-arm: 4-14 oocytes), and "high" responders (H-arm: >15 oocytes). The receiver operating characteristic (ROC) curves were plotted in order to assess the P-arm and N-arm, N-arm, and H-arm by AMH, FSH, and E2. The area under the curve (AUC) also was compared for each parameter to determine whether AMH was superior to the other parameters regarding the predictive ability of the oocyte count.

The secondary endpoints were as follows: an assessment of the correlation of the AMH, FSH, and E2 concentrations with the oocyte count and an assessment of whether the correlation with AMH was the strongest among the studied markers.

2.4.2 | Study 2

The primary endpoint of Study 2 was to investigate the distribution of the AMH concentration for each age group in order to create a correlation chart of age and AMH concentration.

2.5 | Ethics and study oversight

This study was carried out according to the Declaration of Helsinki, as well as the Japanese laws and regulatory requirements. All the participants, or their legally acceptable representatives, provided written informed consent prior to entering the study. The protocol,

TABLE 2 Demographic and clinical characteristics of the participants in Study 2 (n = 417)

Variable	Median	Interquartile range
Age (years)	36	30-41
Height (cm)	158.5	154.8-162.0
Weight (kg)	52.6	48.9-56.0
Body mass index (kg/m^2)	20.7	19.5-22.3
AMH (ng/mL)	2.42	1.15-4.77
LH (mIU/mL)	5.84	3.83-8.50
FSH (mIU/mL)	6.04	4.38-7.71
E2 (pg/mL)	80.5	49.2-153.6
P4 (ng/mL)	0.483	0.307-3.890

AMH, anti-Müllerian hormone; E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; P4, progesterone.

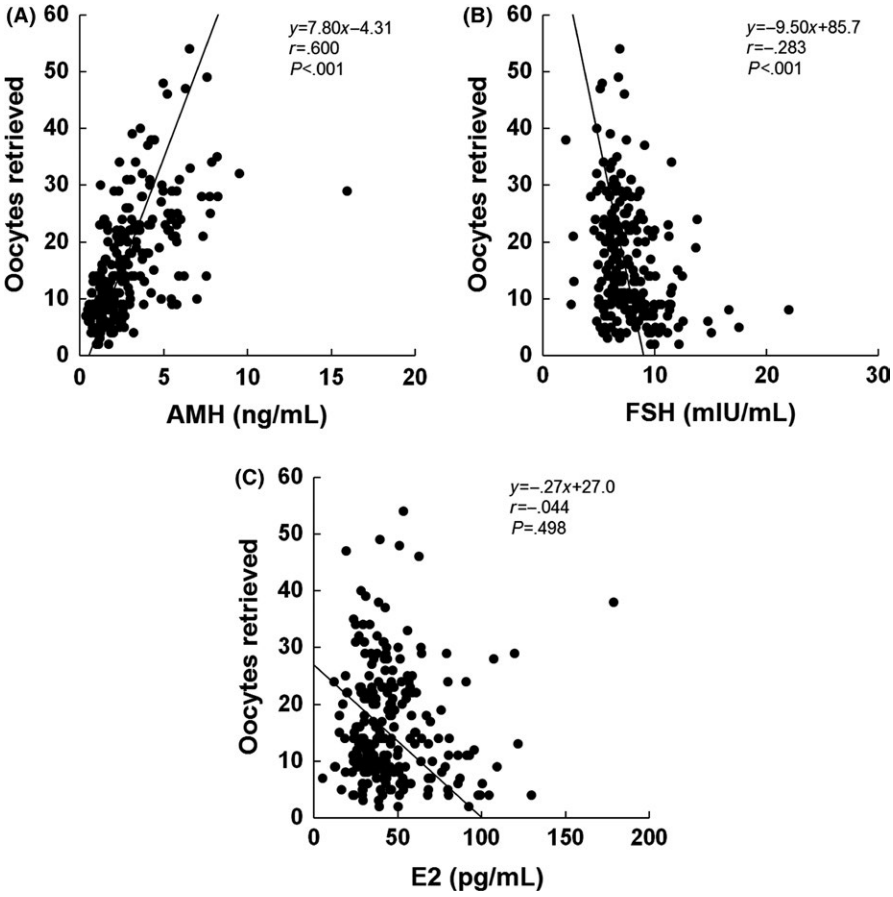

FIGURE 2 Relationships between (A) anti-Müllerian hormone (AMH), (B) follicle-stimulating hormone (FSH), and (C) estradiol (E2) by the number of retrieved oocytes

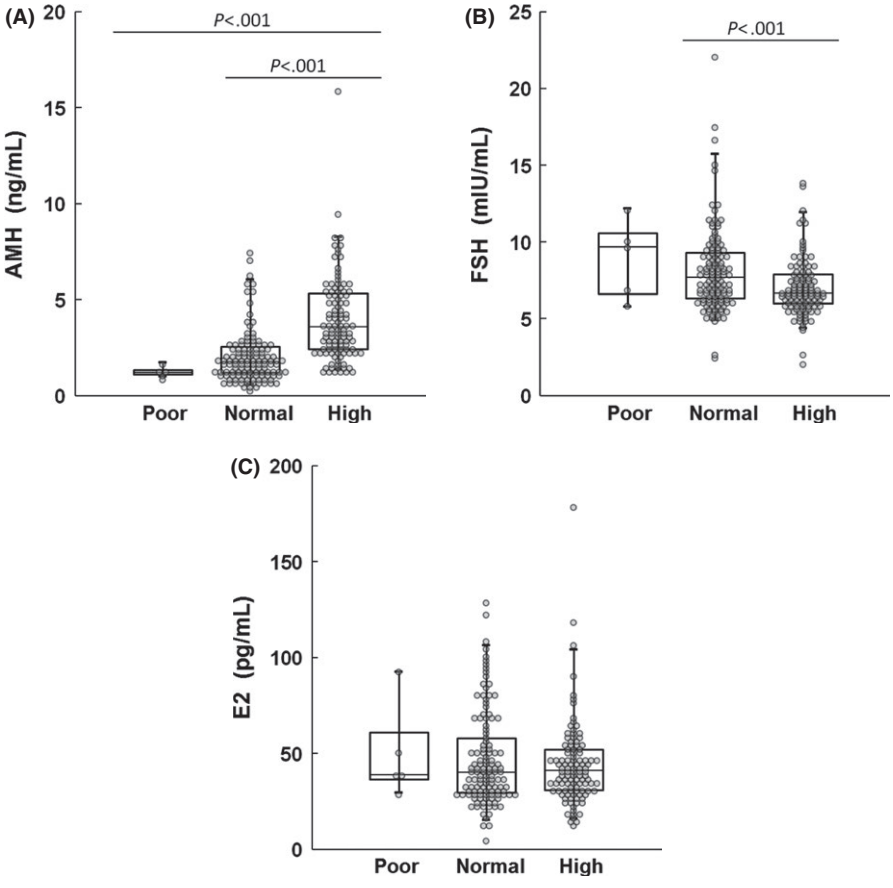

FIGURE 3 Box and whisker plot for (A) anti-Müllerian hormone (AMH), (B) follicle-stimulating hormone (FSH), and (C) estradiol (E2) in patients within each group divided by the number of oocytes retrieved. Poor ≤3 (n = 5); normal = 4-14 (n = 123); high ≥15 (n = 108). The *P*-values refer to the *t* tests of the means of each group

amendments, and informed consent form were approved by the institutional review board or independent ethics committee at each site prior to the study's commencement.

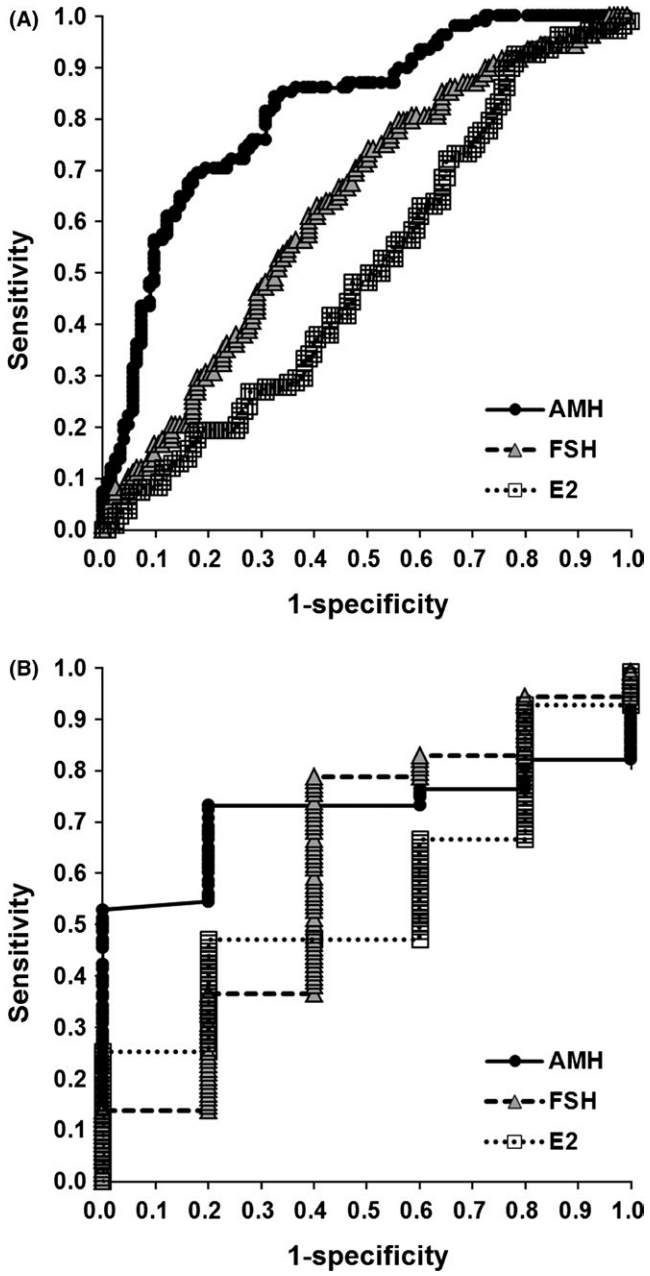

FIGURE 4 Receiver operating characteristic curve analysis showing the predictive value of anti-Müllerian hormone (AMH) for the estimation of high responders (≥15 oocytes retrieved). A, Prediction of a normal and a high response. The area under the curve (AUC) of the receiver operating characteristic curve for the N-arm, compared to the H-arm, was 0.818 (95% confidence interval, CI: .763-.872, $P < .001$) for AMH, 0.632 (95% CI: 0.560-0.703, $P = .001$) for follicle-stimulating hormone (FSH), and .512 (95% CI: 0.437-0.587, $P = .757$) for estradiol (E2). B, Prediction of a poor and a normal response. The AUC of the receiver operating characteristic curve for the P-arm, compared to the N-arm, was .717 (95% CI: 0.607-0.827, $P = .101$) for AMH, .613 (95% CI: 0.338-0.888, $P = .338$) for FSH, and 0.558 (95% CI: 0.349-0.767, $P = .662$) for E2

2.6 | Statistical methods

All the statistical analyses were performed by using IBM SPSS Statistics for Windows (v. 19; IBM Corporation, Armonk, NY, USA) and SAS (v. 9.2; SAS Institute, Cary, NC, USA). The distribution of the response variables and explanatory variables was confirmed by non-parametric tests (one-sample Kolmogorov-Smirnov test) and the data normalization was performed by power transformation. The explanatory variables were selected after confirming the possible factors of multicollinearity from the correlation matrix. A regression analysis was performed by using these explanatory variables and a stepwise model was used to establish correlations with the response variables. The AUC values of the plotted ROC curves (significance test [null hypothesis: AUC = 0.5]) were compared. Also calculated and compared were the correlation coefficients. All the tests were two-sided, with an alpha level of 5%.

3 | RESULTS

3.1 | Demographic and clinical characteristics of the participants

In Study 1, 335 participants were enrolled, 330 were included in the full analysis set, and 236 participants who were undergoing COS were included in the per-protocol set (an oocyte count was performed) (Figure 1). Five participants were excluded because they met the exclusion criteria, while 93 participants discontinued for the following reasons: their oocyte retrieval failed, pregnancy was achieved by other methods, the patient's decision, or the oocyte collection used clomiphene. One participant was excluded as she was diagnosed with hyperthyroidism, based on her TSH and FT4 levels. Finally, 236 participants who were undergoing COS were analyzed in Study 1 and 417 healthy participants were analyzed in Study 2.

The participants in Study 1 had a median (range) age of 36 (33-39) years, a median (range) BMI of 20.1 (19.1-21.8) kg/m^2, median

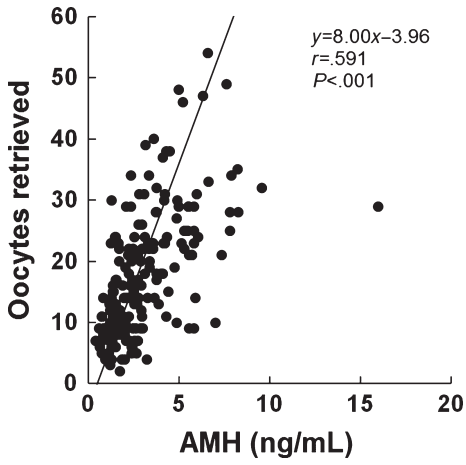

FIGURE 5 Relationship between anti-Müllerian hormone (AMH) and the number of retrieved oocytes

(range) AMH concentration of 2.38 (1.47-3.75) ng/mL, and median number of retrieved oocytes was 14 (9-23) (Table 1). The participants in Study 2 had a median (range) age of 36 (30-41) years, median (range) BMI of 20.7 (19.5-22.3) kg/m^2, and median AMH concentration of 2.42 (1.15-4.77) ng/mL (Table 2).

3.2 | Correlation of anti-Müllerian hormone, follicle-stimulating hormone, and estradiol with the oocyte count

Based on the correlation coefficient (r = .600), there was an intermediate positive correlation between the AMH level and the oocyte count (Figure 2). There was a weak negative correlation (r = −.283) between the FSH level and the oocyte count. There was no correlation between the E2 level and the oocyte count (P = .498).

3.3 | Predictive ability of the ovarian response by anti-Müllerian hormone

Regarding the ovarian response, the predictive ability of AMH was statistically significant (P < .001), except between the P+N-arms (Figure 3). The predictive ability of FSH was only significant (P < .001) between the N+H-arms. The predictive ability of E2 did not reach statistical significance, which was determined by calculating the

TABLE 3 Summary of the regression analysis results

		All items		After conducting the stepwise model	
Variable	N	Standardized partial regression coefficient	*P*-value	Standardized partial regression coefficient	*P*-value
AMH	236	.569	<.001	.587	<.001
Age	236	−.129	.018	−.129	.017
LH	236	−.047	.392	–	–
FSH	236	−.076	.197	–	–
E2	236	−.018	.723	–	–
P4	236	−.014	.784	–	–

AMH, anti-Müllerian hormone; E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; P4, progesterone.

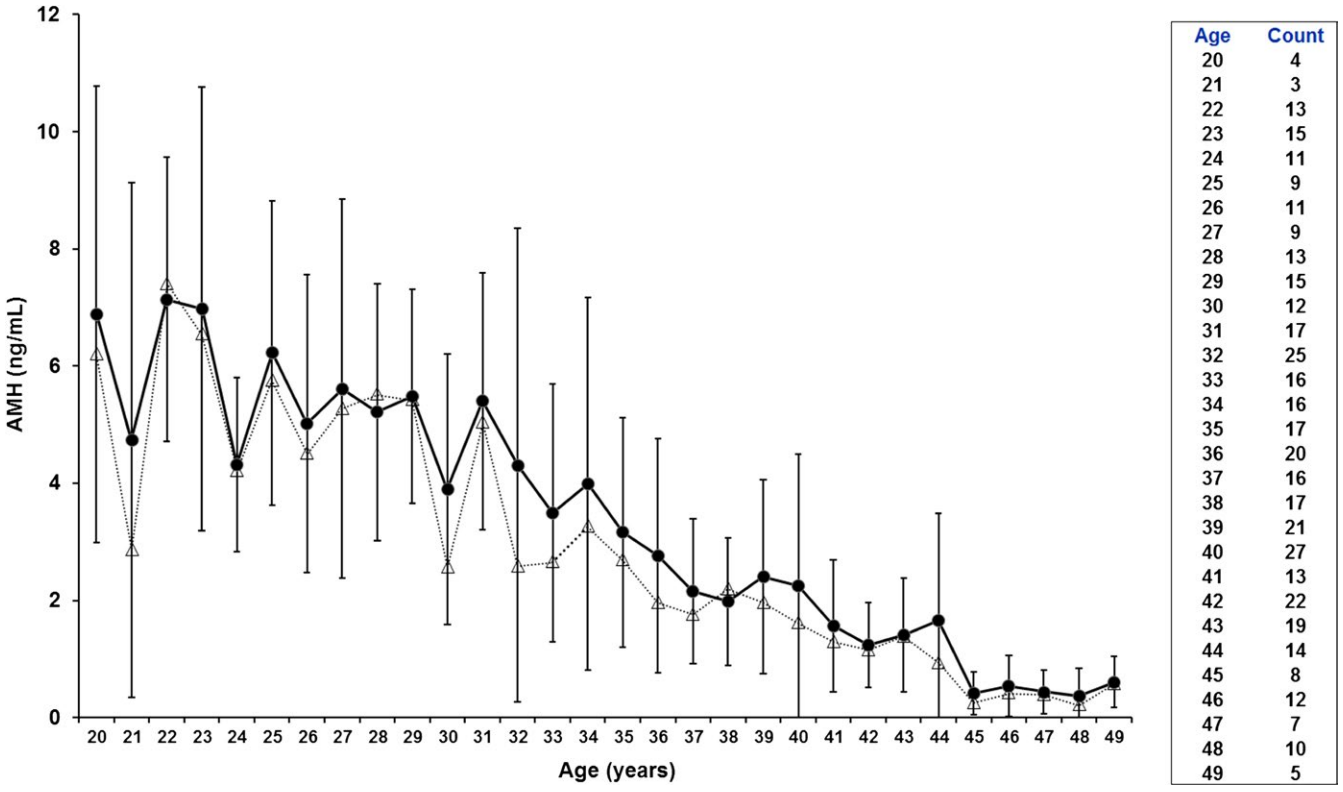

FIGURE 6 Age-specific anti-Müllerian hormone (AMH) concentrations. (●) Mean ± standard deviation; (△) median

asymptote *P*-value of the AUC in case the null hypothesis was .5 (significance level of .05).

Regarding the predictive ability of AMH of the ovarian response, based on a ROC curve analysis and comparison of the AUC values of each arm (Figure 4), AMH had a significantly (*P*<.001) higher predictive value for the normal and high responders, compared with FSH and E2, and a lower predictive value for the poor and normal responders, compared with FSH and E2. The FSH seemed to have a lower predictive value, compared with AMH, but a higher predictive value, compared with E2.

The AUC of AMH was .818 (95% CI: 0.763-0.872), with the highest precision in the N+H-arms. The AUC of AMH was clearly higher, compared with the other two parameters. The AMH yielded the highest ovarian response predictive ability. As the P-arm only included five patients, the AUC did not reach statistical significance; thus, the N+P-arm assessment was not sufficiently reliable.

Then, the H-arm (high risk of OHSS) was analyzed separately from the other arms (P- and N-arms). However, no significant difference was found when analyzing the N-arm, compared to the H-arm, and the P+N-arms, compared to the H-arm. The AUC of AMH was .824 (95% CI: 0.771-0.877, *P* < .001), indicating that AMH had a high predictive value of the ovarian response and OHSS, compared to FSH and E2.

3.4 | Regression analysis: Correlation of anti-Müllerian hormone with the oocyte count

A regression analysis was performed in order to evaluate the correlation of AMH with the oocyte count (response variable: oocyte count; explanatory variables: age, AMH, LH, FSH, E2, and P4 [primary endpoint]). The standardized partial regression coefficient of AMH was .569 (Table 3). A strong correlation between the AMH concentration and the ovarian response was found (Figure 5).

3.5 | Distribution of the anti-Müllerian hormone concentration

The age-specific distribution of AMH concentrations is shown in Figure 6. The single-year-specific median, mean, and standard deviation values are summarized in Table 4. Both the mean and median AMH concentrations decreased progressively with age. Five patients had an undetectable AMH concentration (<.01 ng/mL) and were aged ≥44 years. Figure 7 shows the median levels, 95% range (2.5-97.5th percentile value), and 25-75th percentile values of each age group. The AMH concentration decreased progressively by age group, with the highest median concentration (5.96 ng/mL) found among the women who were aged 20-24 years and the lowest median concentration (0.32 ng/mL) among the women who were aged 45-49 years (Table 5).

4 | DISCUSSION

This multicenter, observational, multipart study showed that AMH had the strongest and highly significant correlation with the oocyte count, compared with FSH and E2, especially among those patients who were classified as normal and high responders to COS for IVF. Among the patients who were undergoing COS, AMH yielded the highest ovarian response predictive ability.

Although several clinical trials have been conducted in the USA,[19] there is little information regarding potential ethnic differences in the serum AMH concentrations.[20-23] Additionally, the distribution of AMH concentrations has been reported previously, but the data were mainly obtained from patients with infertility, rather than from healthy controls.[24] As the distribution of AMH levels in healthy Japanese women had yet to be reported, this study aimed to address this particular knowledge gap in Japan. Data on the potentially useful

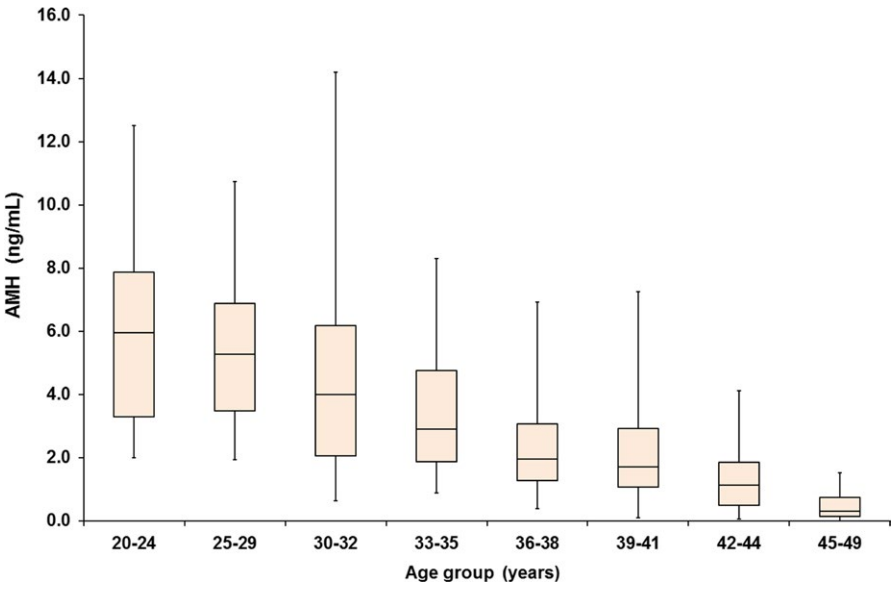

FIGURE 7 Anti-Müllerian hormone (AMH) concentration by age group. The values are the medians (lines), 25-75th percentiles (boxes), and 95% range (2.5-97.5th percentiles) (whiskers)

TABLE 4 Age-specific median, mean, and 1-specificity (1SD) for the serum anti-Müllerian hormone levels (ng/mL) of 417 healthy Japanese women who were enrolled at three centers between May, 2014 and May, 2015

Age (years)	N	Median	Mean	1SD
20	4	6.2	6.9	3.9
21	3	2.9	4.7	4.4
22	13	7.4	7.1	2.4
23	15	6.5	7.0	3.8
24	11	4.2	4.3	1.5
25	9	5.8	6.2	2.6
26	11	4.5	5.0	2.5
27	9	5.3	5.6	3.2
28	13	5.5	5.2	2.2
29	15	5.4	5.5	1.8
30	12	2.6	3.9	2.3
31	17	5.0	5.4	2.2
32	25	2.6	4.3	4.0
33	16	2.7	3.5	2.2
34	16	3.3	4.0	3.2
35	17	2.7	3.2	2.0
36	20	2.0	2.8	2.0
37	16	1.8	2.2	1.2
38	17	2.2	2.0	1.1
39	21	2.0	2.4	1.7
40	27	1.6	2.3	2.2
41	13	1.3	1.6	1.1
42	22	1.2	1.2	.7
43	19	1.4	1.4	1.0
44	14	.9	1.7	1.8
45	8	.2	.4	.4
46	12	.4	.5	.5
47	7	.4	.4	.4
48	10	.2	.4	.5
49	5	.6	.6	.4

predictors of the ovarian response have gained particular importance as the need for infertility treatment has been increasing in Japan. As far as the authors know, this study is the first to determine the age-specific distribution of the serum AMH concentration in healthy Japanese women with a normal menstrual cycle. As shown in other studies, the AMH concentration in Japanese women decreased progressively by age group. The results obtained in Study 2 will serve as preliminary data for the use of AMH in clinical practice in Japan as it was possible to evaluate the age-specific distribution of the AMH concentration in a relatively large population (417 Japanese participants) of women who were aged between 20 and 49 years with normal menstrual cycles.

The currently available clinical data regarding AMH are growing as AMH is being recognized as a useful marker and predictor of the

TABLE 5 Age-specific median and interquartile range for the serum anti-Müllerian hormone levels (ng/mL) of 417 healthy Japanese women who were enrolled at three centers between May, 2014 and May, 2015 at a 3 year interval for those aged 30-44 years and a 5 year interval for those aged 20-29 years and >45 years

Age (years)	N	Median	Interquartile range
20-24	46	5.96	3.30-7.87
25-29	57	5.27	3.49-6.88
30-32	54	4.00	2.06-6.18
33-35	49	2.91	1.87-4.76
36-38	53	1.96	1.29-3.07
39-41	61	1.72	1.07-2.92
42-44	55	1.13	0.51-1.86
45-49	42	.32	0.15-0.74
Total	417	2.42	1.15-4.77

ovarian response.[5,6,9,10,13-15] As infertility treatments become more readily available to couples with infertility and reproductive issues worldwide, the accurate and safe assessment and prediction of the ovarian response have gained considerable importance. It is of particular importance to predict the risk of OHSS of patients who are considered as potentially high responders to COS because they are at higher risk of developing OHSS, which could be a severe and life-threatening condition. In the present study, AMH had a significantly ($P < .001$) higher predictive value for normal responders, compared to high responders, and poor + normal responders, compared to high responders, compared with the other evaluated parameters. In order to discriminate the high responders (high risk of OHSS) from the other arms (poor + normal), the other arms were analyzed separately. However, no significant difference was found when analyzing the normal responders, compared to the high responders, and the poor + normal responders, compared to the high responders. The reason for the lack of significant difference between the poor + normal responders and the high responders was the small number of patients in the P-arm. The P-arm consisted of only five patients, while the N-arm consisted of 123 patients. Furthermore, regarding the median AMH concentrations, those in the P-arm and N-arm were 1.20 and 1.74 ng/mL, respectively, compared with those in the H-arm (3.58 ng/mL). Finally, the AMH concentration varied widely among individuals. Up to 20% of the patients in the N-arm had a relatively low AMH concentration. Given the lower concentrations and few participants, the P+N-arms had little influence on the results; thus, there was not enough power to detect large differences.

One report indicated that the method of measuring the AMH concentration has not been standardized. Additionally, the need for assay-specific interpretation was emphasized as AMH concentrations can be remarkably different, depending on the assay system that is used for quantification.[25] Additionally, limitations across countries regarding the availability of equipment should be considered when standardizing such parameters. For instance, Gen II ELISA is not readily available in Japan;[24] thus, it is necessary to obtain data with other systems that are locally available.

Many studies have assessed the prediction of the ovarian response by the AMH concentration, but most of them quantified AMH by ELISA, which has been reported as a method that lacks precision.[5] In Study 1, the predictive ability of the ovarian response was assessed by an automatic immunoanalyzer system that uses electrochemiluminescence. According to the present analyses of the tested parameters, AMH showed the highest correlation (r = .66, intermediate positive correlation) with the ovarian response, while FSH and E2 were only weakly correlated (r = −.283, r = .044).

This study has several limitations. Regarding the assessment of the predictive ability of the ovarian response by AMH, the P-arm only included five patients, which precluded the researchers from finding significant differences; thus, the N+P-arm assessment was not sufficiently reliable. Although a lack of generalizability could be a limitation of this study, as patients from two centers only were included, the age-specific distribution of the AMH concentration was evaluated in a relatively large population (417 Japanese participants) of women who were aged between 20 and 49 years with normal menstrual cycles. The authors consider that because these AMH concentration data were collected from a relatively large number of women with such characteristics, these data will serve as a point of reference for future studies in Japan.

In conclusion, the mean serum AMH concentration decreased progressively with age. Additionally, the AMH concentration correlated well with the oocyte count in those patients who were undergoing COS for IVF. This study's results support the widespread use of AMH as a marker of the ovarian reserve and ovarian response, which also was shown to predict the risk of OHSS among the patients who were undergoing COS. Thus, quantifying the AMH concentration prior to selecting an individualized COS protocol will be useful for ensuring patients' safety and improved outcomes, not only in assisted reproductive techniques but also in fertility preservation after cancer treatment.[26,27]

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DISCLOSURES

Conflict of interest: Y. A., Y. M., and M. I. are members of the advisory board of Roche Diagnostics, K.K. The study was funded by Roche Diagnostics, K.K, Tokyo, Japan. *Human and Animal Rights*: All the procedures were followed in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all the patients to be included in the study. The protocol for the research project that included human participants was approved by the institutional review board or independent ethics committee at each site prior to the study's commencement. This article does not contain any study with animal participants that has been performed by any of the authors.

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