Multi-center clinical evaluation of the Access AMH assay to determine AMH levels in reproductive age women during normal menstrual cycles

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Abstract

Background AMH is widely used for assessing ovarian reserve, and it is particularly convenient, because it is thought to have minimal variability throughout the menstrual cycle. However, studies assessing the stability of AMH over the menstrual cycle have been conflicting.

Purpose The purpose of this study is to determine whether AMH levels vary across the normal menstrual cycle.

Design A multi-center, prospective cohort study conducted at three US centers.

Methods Fifty females with regular menstrual cycles aged 18–45 underwent serial venipuncture every 3–5 days starting in the early follicular phase and lasting up to 10 collections. AMH was tested using the Access 2 immunoassay system.

Results Age-adjusted mixed-effect models utilizing data from 384 samples from 50 subjects demonstrated a within subject standard deviation of 0.81 (95% CI 0.75–0.88) with a coefficient of variation of 23.8% across the menstrual cycle and between subject standard deviation of 2.56 (95% CI 2.13–3.21) with a coefficient of variation of 75.1%. Intra-class correlation (ICC) of AMH across the menstrual cycle was 0.91.

Conclusion Overall, AMH levels, using the automated Access AMH assay, appear to be relatively stable across the menstrual cycle. Fluctuations, if any, appear to be small, and therefore, clinicians may advise patients to have AMH levels drawn at any time in the cycle.

Keywords Ovarian reserve · AMH · Menstrual cycle · Intra-cycle variability · Anti-Mullerian hormone · Endocrinology · Access AMH

Introduction

AMH is a product of granulosa cells of primordial follicles that have undergone initial recruitment and is thought to reflect the size of the ovarian follicular reserve [1]. Serum AMH

levels decline with age [2, 3] and were previously shown to reach undetectable levels approximately 5 years before the final menstrual period [4]. More recent findings show that AMH is measureable in perimenopausal women up to menopause [5] and that AMH levels have been found to help predict the final menstrual period in late reproductive age women [6, 7]. AMH has also been studied extensively in infertile women pursuing assisted reproductive technologies. In this population, AMH helps to predict response to ovarian stimulation and is routinely used to tailor IVF stimulation regimens [8, 9]. Moreover, given the high correlation with antral follicle counts, AMH has been identified as a potential surrogate marker for polycystic ovary morphology in diagnosing polycystic ovary syndrome (PCOS) [1, 10].

One of the advantages of AMH as compared to other measures of ovarian reserve, such as inhibin B or follicle-stimulating hormone (FSH), is that it is thought to have

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minimal within menstrual cycle variation [10]. However, studies assessing the stability of AMH over the menstrual cycle have been conflicting. The degree of daily AMH variability across the normal menstrual cycle is essential for understanding and interpreting AMH assay results and for fostering standardization and better cross comparison between individual AMH test results. This is particularly important, since AMH levels are now widely used in clinical practice to counsel women about their reproductive health. The purpose of this study is to determine whether or not AMH levels vary significantly across the normal menstrual cycle.

Methods

Study population and design

This is a multi-center, prospective cohort study conducted at three centers in the USA (site 3 University of Pennsylvania; site 1 Beckman, Carlsbad, CA; and site 2 Beckman, Chaska, MN). Females between the ages of 18 to 45 years with regular menstrual cycles (21 to 35 days) and both ovaries were included. Women were excluded if they had a confirmed or suspected pregnancy, a previous diagnosis of PCOS, history of ovarian surgery (oophorectomy, ovarian cystectomy), or exposure to cytotoxic therapy (chemotherapy or pelvic radiotherapy). In addition, women who had a history of short-term (< 1 year) hormonal contraceptive use could not enroll until more than 1 month since the last use had elapsed. Women who had a history of long-term (≥ 1 year) hormonal contraceptive use could not enroll until more than 3 months since the last use. Woman who had taken hormone therapy for any other indication aside from contraception could not enroll until more than 6 months had elapsed since the last use. IRB approval was obtained at each site, and informed consent was obtained from all participants prior to enrollment.

Study visits and data collection

Participants completed a baseline demographic questionnaire and underwent serial venipuncture to collect serum and plasma. Visits were scheduled every Monday and Thursday, starting on approximately the second to fourth day of the menstrual cycle, and subsequently repeated every 3 to 5 days lasting up to a maximum of 10 collections (the average was 7 to 8 draws per subject).

Blood specimens were collected and processed in a standard fashion, centrifuged, and aliquoted into 1-mL cryovials within 24 h of venipuncture and stored at -20 or colder (see [Appendix](#)). Samples were shipped, frozen, and then tested for AMH, β -hCG, LH, FSH, estradiol, and progesterone after a single thaw cycle. Acceptable AMH test results were defined

as those that were collected, handled, and stored correctly and that passed calibration and QC results without instrument or testing errors. Subjects providing the clinical information and blood sample(s) with acceptable AMH test results were deemed evaluable. Subjects failing to provide more than one blood sample in a 7-day period were deemed non-evaluable. There were three enrolled subjects (of 53 total) who were not included in the final analyses, one identified as ineligible for having an irregular menstrual cycle, and two subjects who withdrew and did not provide the required specimens per the protocol.

Study staff involved in participant enrollment and consenting was blinded to all test results, and the testing site was blinded to the clinical information associated with each subject.

Laboratory assays

Assays for β -hCG, LH, FSH, estradiol, and progesterone were performed with commercially available tests from Beckman Coulter per the manufacturer's instructions. AMH was tested using the Access AMH assay with kit calibrators and quality control materials on the Access 2 immunoassay system at a single test site (Beckman Coulter, Chaska, MN). Test volume was 0.02 mL per replicate in addition to system volume requirements. Specimens were tested in duplicate, and the first replicate was used for data analyses. The median %coefficient of variation (CV) between replicates was 0.94% with 95% of duplicates having %CVs less than 2.85%. No samples were excluded due to high CVs between replicates. The Access AMH assay has a linear range up to 24 ng/mL with total imprecision from 2.4 to 5.2% and with a reported limit of detection of 0.01 ng/mL [11].

Statistical analysis

A priori, it was determined that at least 50 normally cycling women should be enrolled in order to provide stable estimates of within subject and between subject variability. Each site aimed to enroll approximately equal numbers of subjects. Baseline characteristics were summarized for the study population with all sites combined. Age-adjusted mixed-effect models were constructed to estimate within subject variability and intra-class correlation (ICC) across the menstrual cycle, which included estimation of variance components and calculation of confidence interval of variance components. The dependent variable was AMH, the random effect variable was the subject, and the fixed effect variables were age and day of cycle. A two-tailed p value of less than 0.05 was considered statically significant. All statistical analyses were performed by BCI using SAS version 9.4.

Results

Fifty participants with a total of 384 samples were enrolled in this study and were considered evaluable. Sites 1, 2, and 3 enrolled 12, 20, and 18 subjects, respectively. Mean age of all subjects, and for sites 1, 2, and 3, was 34.7, 38.4, 32.4, and 34.5, respectively. The mean AMH was 3.4 ng/mL and ranged from 0 to 15.1 ng/mL. Baseline measures of hormones are shown in Table 1. Figure 1 demonstrates the distribution of AMH values which is noted to be skewed to the right. The two subjects with elevated AMH were not identified as having PCOS per the eligibility criteria. Age-adjusted mixed-effect models utilizing data from 384 samples from 50 subjects demonstrated a within subject standard deviation of 0.81 (95% CI 0.75–0.88) and within subject coefficient of variation of 23.8% across the menstrual cycle. In contrast, models demonstrated a between subject standard deviation of 2.56 (95% CI

2.13–3.21) and an expected high between subject coefficient of variation of 75.1%. ICC of AMH across the menstrual cycle was 0.91, and the ICC was decreased slightly to 0.88 when the two subjects with elevated mean AMH levels were removed. The model also explored the relationship between AMH, age and the day of the menstrual cycle, and age, but not cycle day, which was significantly associated with AMH levels (age: $p < 0.001$; cycle day: $p = 0.46$). Overall, median AMH values did not vary significantly across the menstrual cycle (Fig. 2) and AMH values across each cycle are shown for comparison (Fig. 3). Age was negatively correlated with mean AMH across menstrual cycle per subject (Fig. 4). The repeated AMH results across the menstrual cycle of all eligible subjects enrolled in this study are shown in Fig. 5, with results displayed in order of increasing median AMH values. Younger individuals (21 to 30 years) are observed to have higher median AMH values indicated by the increased number of individuals falling in the young age group (21 to 30 years) as median AMH values of individuals going up from left to right. In addition, individuals with high median AMH concentrations (above 3 ng/mL) are observed to have higher absolute individual variability indicated by their relatively wider ranges of AMH results. There was a slight drop of AMH values observed during the ovulation period (day 13 to 16).

Table 1 Patient characteristics

Characteristic		All
Site	Site 1	12 (24)
	Site 2	20 (40)
	Site 3	18 (36)
Age	Mean $\pm$ SD	34.7 $\pm$ 6.6
	Median (range)	35.5 (24.0–45.0)
Race	Asian	7 (14.0)
	Black	3 (6.0)
	Pacific Islander	1 (2.0)
	White	38 (76.0)
	More than one race	1 (2.0)
Ethnicity	Hispanic or Latino	5 (10.0)
	Not Hispanic or Latino	44 (88.0)
	Unknown	1 (2.0)
BMI ¹	Mean $\pm$ SD	26.1 $\pm$ 4.5
	Median (range)	25.3 (18.5–37.4)
Smoking ²	Current	1 (3.3)
	Never	22 (73.3)
	Past	7 (23.3)
No. of visits	Mean $\pm$ SD	7.7 $\pm$ 1.2
	Median (range)	7.5 (5.0–10.0)
AMH (ng/mL)	Mean $\pm$ SD	3.4 $\pm$ 3.0
	Median (range)	2.5 (0.1–15.1)
Baseline E2 (pg/mL)	Mean $\pm$ SD	42.6 $\pm$ 25.8
	Median (range)	37.1 (0.0–110.8)
Baseline hFSH (mIU/mL)	Mean $\pm$ SD	16.6 $\pm$ 62.7
	Median (range)	6.6 (2.1–449.9)
Baseline hLH (mIU/mL)	Mean $\pm$ SD	16.9 $\pm$ 83.4
	Median (range)	4.5 (0.6–594.7)

¹ BMI missing for 18 patients enrolled at site 3

² Smoking status missing for 20 patients enrolled at site 2

Discussion

AMH has become a popular measure of ovarian reserve for counseling women about reproductive health. AMH is strongly correlated with age and can predict response to ovarian stimulation. In particular, AMH levels are valuable to optimize clinical protocols and gonadotropin dosing for ovarian stimulation among women seeking conception through assisted reproduction. This test is thought to be more convenient than testing follicle-stimulating hormone or inhibin B, because it is less variable throughout the menstrual cycle and therefore can be obtained at any time in the cycle. However, data have been limited in this area and are difficult to interpret given historical differences in assays used. The aim of this study was to determine if levels of AMH, using the automated Access AMH assay, varied across the menstrual cycle.

In the current study, serial AMH measurements were found to be stable across the menstrual cycle in a population of healthy reproductive age women. These results are similar to several other studies [12–15]. For example, a study of 44 fertile, regularly cycling females found AMH levels to be stable over the menstrual cycle [16]. Another study of 20 healthy regularly menstruating women also showed no significant fluctuation in AMH [13].

However, several other studies have reported that levels of AMH do vary across the menstrual cycle [2, 14, 17–21]. The

Fig. 1 Distribution of mean AMH values per subject

largest report described a prospective cohort study conducted in 259 regularly menstruating women between the ages of 18–

Fig. 2 Median AMH values across menstrual cycle. Boxplot of AMH values across different days of menstrual cycle utilizing data from 384 samples from 50 subjects is showing that median AMH values did not vary significantly across the menstrual cycle

Fig. 3 Individual AMH values across the menstrual cycle for all subjects

44 years in which AMH was measured with the Beckman Coulter Gen 2 assay up to eight times during the menstrual cycle. They reported that levels of AMH were the highest

Fig. 4 Mean AMH values by age per subject. Scatter plot of mean AMH values vs age per subject utilizing 50 eligible subjects is showing that mean AMH values were negatively correlated with age. A fitted line with slope = -0.2466 generated by simple linear regression is showing the same trend

Fig. 5 AMH values across menstrual cycle per subject. Repeated AMH results across the menstrual cycle of all eligible subjects enrolled in this study are shown, with results displayed in order of increasing median AMH values. Each bar represents the range of AMH results for a given subject, with the purple star representing the median of AMH results and the color type representing the corresponding age group

during the mid-follicular phase, decreased around the time of ovulation and increased thereafter. Other studies have demonstrated a similar pattern of change over the cycle [17–20]. This pattern has been thought to reflect the function of AMH which is involved in regulation of follicular growth. Specifically, it inhibits the sensitivity of FSH in the growing follicles in the early follicular phase when levels are the highest. The development of a dominant follicle occurs when AMH levels decline. We also observed a slight drop of AMH values during the ovulation period (day 13 to 16), but this was not statistically significant. At least one study has demonstrated that observed fluctuations in AMH during the menstrual cycle do not appear to result from the use of different AMH assays [22]. And, while earlier studies may have been impacted by possible assay differences, the current automated AMH assay under investigation is not subject to complement interference and has low analytical variability across the assay range. Most importantly, several authors acknowledge that although statistically significant, the variability in AMH over a cycle is not large enough to warrant a change in current clinical practice to time AMH measurements to a specific cycle day/phase.

Clinical decisions can be made on AMH drawn on any day of the cycle [21, 22]. The current study supports this recommendation as well.

In the current study, AMH was found to be more variable across the cycle in women with high levels (> 3 ng/mL) compared to low levels. This finding is likely not attributable to assay variability because of the low analytical imprecision of the automated assay, and while this is an important observation, it would be unlikely to change clinical management since most cutoffs for classifying diminished ovarian reserve are much lower (e.g., < 1 ng/mL). Likewise, women with AMH levels of three or greater are usually considered at risk for brisk ovarian response [23]. While this has not been consistently reported, Randolph et al. also observed more variability in levels with high AMH values, with a more pronounced mid-follicular increase, mid-cycle decrease, and mid-luteal increase in AMH [20].

This study has several strengths. It is one of the larger studies to investigate AMH stability across the menstrual cycle and required frequent sampling over two menstrual cycles to capture consistent changes over time. Moreover, there was

strict adherence to sample collection, processing, and performance of the assays. Importantly, it is the first study to assess the consistency across the menstrual cycle with the automated Access AMH assay. Nonetheless, unmeasured differences in subject characteristics may have existed between the clinical sites which skewed the results. The ICC value may be overestimated to a small degree due to the possible inclusion of subjects with undiagnosed PCOS. In addition, our results are only applicable to a select group of menstruating females who were not seeking pregnancy and may not be generalizable to all patients.

In summary, AMH is widely used for counseling women about reproductive health. The current study found that AMH levels, using the automated Access AMH assay, appear to be relatively stable across the menstrual cycle. Fluctuations, if any, appear to be small and therefore clinicians may advise patients to have AMH levels drawn at any time in the cycle.

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Compliance with ethical standards

IRB approval was obtained at each site, and informed consent was obtained from all participants prior to enrollment.

Appendix

Specimen collection, preparation, storage, and transportation

The venipuncture procedure shall be performed in accordance with accepted equipment and techniques. The phlebotomist shall be experienced and trained as noted in CLSI Standard GP39-A6 and will adhere to universal precautions and utilize engineered sharps, decontamination, and disposal plans as explained in the SOPs or procedures and the exposure plans specific to each site (see section 8.1).

- At least one tube of serum and plasma will be drawn from each subject at each collection.
- Blood specimens should be collected in such a way as to avoid hemolysis.
- Allow serum samples to clot completely before centrifugation in a vertical, closure up position.
- Non-anticoagulated tubes containing gel or a clot activator should be stored in an upright position as soon as the mixing is complete.
- Pre-centrifugation serum/cells contact time is according to tube manufacturer's recommendations but no more than 2 h at room temperature. Clotting may be slowed

at cooler temperatures or if patient is on anticoagulant therapy.

- Keep tubes stoppered until centrifugation is complete.
- Pipet processed samples into 1-mL aliquots in cryovials within 24 h of venipuncture and store at -20°C or colder (-80°C preferred) until samples are shipped for testing.
- Instructions for sample shipping provided in Appendix A.

Specimens are collected and stored without any personally identifiable information. The tubes will be labeled with study identification numbers and the date of the draws. Some information that is important to this research such as age, ethnicity, health conditions, smoking history, weight, height, and the last menstrual period (LMP) date will be recorded on separate case report form (CRFs), but this information will not be enough to identify the subject in the research population. The blood draws will take place approximately every Monday and Thursday. The first sample collection event will take place at the second to fourth day of the menstrual cycle and will continue every 3 to 5 days lasting up to 10 collections.

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