Age-specific serum anti-Müllerian hormone values for 17,120 women presenting to fertility centers within the United States

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Objective: To determine age-specific serum anti-Müllerian hormone (AMH) values for women presenting to U.S. fertility clinics.
Design: Retrospective study.
Setting: Single clinical reference laboratory.
Patient(s): A total of 17,120 women of reproductive age ranging from 24 to 50 years old.
Intervention(s): None.
Main Outcome Measure(s): Determination of single-year median and mean AMH values with SDs.
Result(s): Single-year-specific median, mean, and SD values are summarized in Table 1. Both median and mean AMH values decreased steadily in a manner highly correlated with advancing age. The average yearly decrease in the median serum AMH value was 0.2 ng/mL/year through age 35 and then diminished to 0.1 ng/mL/year after age 35. The rate of decline in mean AMH values was 0.2 ng/mL/year through age 40 and then diminished to 0.1 ng/mL/year thereafter.
Conclusion(s): Median and mean AMH levels decreased steadily with increasing age from 24 to 50 years of age. Such data may be of value to physicians and their patients who are considering reproductive options. (Fertil Steril® 2011;95:747–50. ©2011 by American Society for Reproductive Medicine.)

Key Words: Anti-Müllerian hormone, Müllerian inhibiting substance, AMH, MIS, ovarian reserve, age-specific values, reproductive aging, ovarian aging, reference values

As a woman ages there is a decline in the number of primordial follicles, accompanied by a concomitant decrease in serum concentration of anti-Müllerian hormone (AMH), also known as Müllerian inhibiting substance (MIS) (1, 2). Repeated clinical studies have demonstrated that serum AMH levels correlate strongly to antral follicle count and are more accurate than age and other conventional serum markers (FSH, E_2, inhibin B) in predicting preovulatory oocyte supply in response to ovulation induction (3–8). Relative to these conventional ovarian serum makers, AMH appears to vary significantly less throughout the menstrual cycle or with perturbations of the endocrine system (9–16). Furthermore, with respect to other methods of follicular supply assessment, AMH measurement has practical advantages, including less dependence upon operators and less intra- and intercycle variation, and analysis can be performed at a later time on stored blood (17).

Currently, serum AMH testing in women is often obtained during an initial clinical evaluation at a fertility center. However, there are no age-specific medians or means based upon large populations of women to use as a reference point. Age-specific reference values for AMH in women presenting for their initial fertility evaluation would provide a framework for expected values that could potentially improve discussions between patients and practitioners regarding expectations and consideration of treatment options for infertility. The objective of this study was to calculate age-specific serum AMH median and mean values with SDs from a large population of women of reproductive age who presented to multiple U.S. fertility centers for evaluation.

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MATERIALS AND METHODS

AMH measurements, determined at a single reference laboratory (ReproSource, Inc., Woburn, MA), were reviewed under Institutional Review Board approval (New England Institutional Review Board no. 10-094) in 17,120 randomly selected women ranging in age from 24 to 50 years old. Serum specimens were received from U.S. fertility centers located in 37 different states between 2007 and 2010. Each woman was represented only once in the set of 17,120 AMH values, which were used to determine median, mean, and SD at single-year intervals from 24 through 50 years of age. The laboratory-developed AMH assay was based on research-use-only materials and reagents from Beckman Coulter-DSL (Chaska, MN) and applied uniformly for all patient samples. Intra- and interassay coefficients of variation with serum controls were approximately 5%–9% and 7%–12%, respectively. Serum AMH values below the reported clinical level of detection (0.1 ng/mL) were treated as a zero value for analysis.

RESULTS

Single-year-specific median, mean, and SD values are summarized in Table 1. Both median and mean AMH values decreased steadily

TABLE 1

Age-specific median, mean, and SD for serum AMH levels (ng/mL) for 17,120 women in U.S. Fertility Centers, ages 24–50 at 1-year intervals.

Age	n	Median	Yearly average decrease	Mean	Yearly average decrease	1 SD	Yearly average decrease
24	228	3.4		4.1		3.0	
25	284	3.2		4.1		4.0	
26	366	3.2		4.2		3.9	
27	471	2.9		3.7		2.9	
28	587	2.8	−0.2	3.8	−0.2	4.7	−0.2
29	732	2.6		3.5		3.6	
30	867	2.4		3.2		3.2	
31	925	2.2	−0.2	3.1	−0.2	2.9	−0.2
32	865	1.8		2.5		2.3	
33	940	1.7		2.6		4.0	
34	1,019	1.6		2.3		2.3	
35	1,161	1.3		2.1		2.5	
36	1,097	1.2		1.8		2.0	
37	1,234	1.1		1.6		1.8	
38	1,233	0.9	−0.1	1.4	−0.2	1.9	−0.2
39	1,170	0.8		1.3		1.6	
40	1,088	0.7		1.1		1.3	
41	893	0.6		1.0		1.1	
42	664	0.5		0.9		1.2	
43	489	0.4	−0.1	0.7	−0.1	0.9	−0.1
44	323	0.3		0.6		1.2	
45	227	0.3		0.5		0.9	
46	115	0.2		0.4		0.6	
47	69	0.2		0.4		0.4	
48	41	0.0	−0.1	0.2	−0.1	0.3	−0.2
49	22	0.1		0.1		0.1	
50	10	0.0		0.0		0.0	

Note: AMH values were generated using a laboratory-developed test from a single laboratory using materials and reagents from the Beckman/DSL Generation I AMH system. Values from different laboratories may vary.

Seifer. Age-specific AMH values for U.S. clinics. Fertil Steril 2011.

in a manner highly correlated with advancing age (R^2>0.95 for linear relationship; R^2>0.99 for quadratic equation fit). For intervals of 5 years from age 26 through 50, the average yearly decrease in median, mean, and SDs are also shown. The average yearly decrease in the median serum AMH value was 0.2 ng/mL/year through age 35 and then diminished to 0.1 ng/mL/year after age 35. The rate of decline in mean AMH values was 0.2 ng/mL/year through age 40 and then diminished to 0.1 ng/mL/year thereafter. Graphical comparisons of AMH reference values as a function of age in 1-year intervals are summarized in Figure 1. The shape of the median and mean curves fit nicely with a linear decline (R^2>0.95 and >0.97, respectively), but better correlation was found with a line determined by the quadratic equation (R^2>0.99 for both).

Figure 2 shows the distribution of AMH values within representative single-year intervals (ages 27, 32, 35, and 40). All age groups showed skewed distributions of AMH values not following the standard bell-shaped curve found in the normal or Gaussian distribution, with the skew increasing with age.

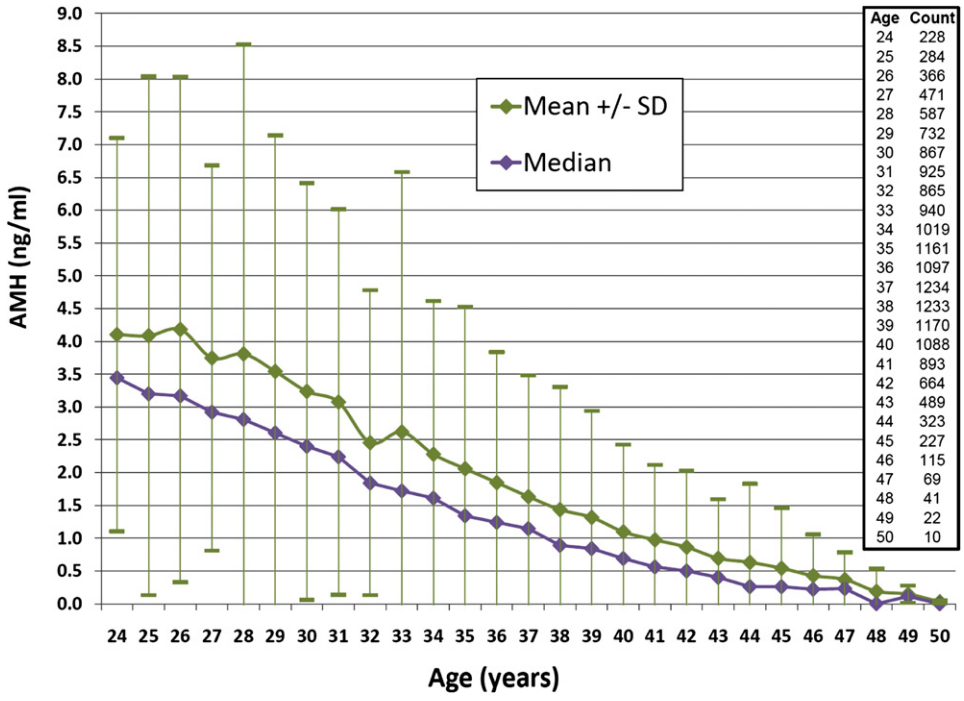
DISCUSSION

This is the largest study to date that examines age-specific medians, means, and SDs for serum AMH in women being evaluated at U.S. fertility centers. AMH measurements were performed using the same methodology in a single clinical reference laboratory using sera from women whose ages spanned most of the reproductive life cycle. Given the increasing utility and frequency of use of AMH in clinical evaluations of fertility, trends in age-specific reference values for AMH may provide added perspective for clinicians and couples who are considering fertility treatment options. Other U.S. investigators have examined age-specific reference values for AMH in much smaller sample sizes (702 women) over a narrower age range with no mention of where the assays were performed; these were published in abstract form (18). A smaller subset, 262 of the initial 702, had oocyte numbers that correlated with AMH means. However, performance characteristics of the assay were not mentioned, and the age ranges included in the study were limited and grouped by 5-year intervals. Furthermore, the study may not have been as inclusive of women of reproductive age (lower and upper ranges of stratified groups were stated as <30 to >41 of age) as the current study. That being said, the trend of the values reported in both studies are in concordance with one another.

Most recently, two European studies examined declines in serum AMH with age. Nelson et al. (19), with AMH values compiled from 3 different laboratories, derived an AMH nomogram from 4,590 women and validated it with an additional 4,588 women, producing similar results to our study. La Marca et al. (20) examined a smaller

FIGURE 1

Graph of AMH age-specific median values with mean ± SD AMH values for women ages 24–50 at 1-year intervals. The median was substantially lower than the average, suggesting non-normally distributed AMH values by age. Note that AMH values were generated using a laboratory-developed test from a single laboratory using materials and reagents from the Beckman/DSL Generation I AMH system. Values from different laboratories may vary.



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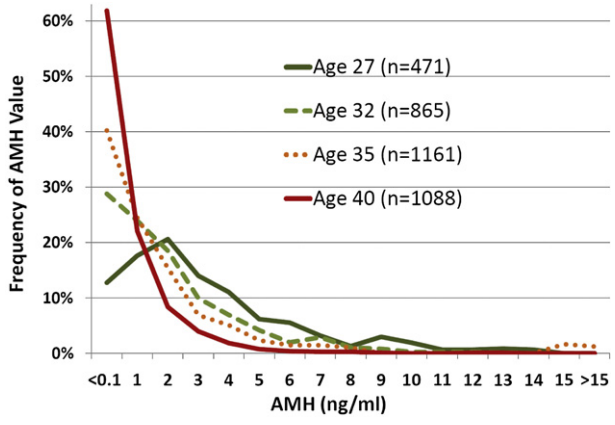
cohort of 277 women using a polynomial function and noted generally higher age-specific median values. However, La Marca et al. used the Immunotech assay (Beckman Coulter), which may have contributed to the differences in age-specific median values between our study and theirs.

The age-specific AMH reference values provided by the present study are informative for the population of women presenting to fertility clinics, as the values are derived from a large number of unselected women who presented for fertility evaluation at a wide variety of US fertility clinics. However, recognition that the provided age-specific reference values were not stratified for phenotypic parameters is of importance. Most recently it has been noted that AMH may be influenced by race/ethnicity (21), body mass index (BMI) (22), and/or the presence of polycystic ovaries (PCO) (23), which were uncharacterized parameters in the studied population. The relevance of this point is best evidenced by the examination of data in this study by year in which the measurements were obtained (i.e., 2007, 2008, 2009, and 2010). This showed a small increase each year in the age-specific median and mean values but not in reference control sera, coinciding with an increased frequency of test use in PCO patients and egg donors (data not shown) who are known to have higher AMH values. The data in women older than 32, however, are unlikely to be biased by inclusion of significant numbers of egg donors as they are generally not older than 32 years of age. Age-specific nomograms further controlling for variation in race/ethnicity, BMI, PCO, and fertility status await future study.

Median reference values were provided in addition to mean values because the combination is more informative when data are non-normally distributed, as was true for AMH in this study. The distribution of AMH values within a given year were skewed toward

FIGURE 2

Distribution of AMH values within single-year age groups (27, 32, 35, and 40 year olds) demonstrates with advancing age increasingly skewed distributions of AMH values.



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values lower than the mean (Fig. 2). Therefore, caution is advised when estimating the percent of the population contained within an SD from the mean, as most often this is estimated with rules applicable only to bell-shaped or normally distributed data. Thus, identifying the AMH value below which lies exactly half the population (the median) is a helpful reference point.

This study provides further benefit because the same laboratory and laboratory-developed test methodology were used for all AMH measurements so that all values can be compared uniformly. It is important to note that, historically, several different reagents/kits and methods have been used by laboratories to measure AMH, which has led to inconsistencies in the literature and misuse of value ranges. Most recently, there has been yet another introduction of different reagents for AMH measurement (AMH GenII by Beckman Coulter, Webster, TX), which has begun replacing the prior systems and has different performance characteristics. Caution is therefore advised when extrapolating ranges from one laboratory to another.

It was of interest to note that the decline in AMH reference values was more linear than biphasic (Fig. 1). This implies that the decline in follicular supply may not be biphasic as previously believed (24). In addition, although median and mean AMH values demonstrated a tight correlation between the rate of AMH decline and age, there was a large variation in AMH values observed within each year of age. This continues to support the concept that AMH values reflect follicular supply relatively independent of age.

AMH measurement continues to play an increasingly important role in the evaluation of a woman's follicular supply and fertility treatment options. This study provides an analysis of the trends in AMH reference values determined uniformly at one laboratory based on a large number of unselected women being evaluated in multiple U.S. fertility centers. It is important to note that in our study, without clinical outcome analysis, the provided reference values for AMH cannot be used in isolation to provide counseling about a woman's chance for a successful ovulation induction or ability to have a child. However, this information may serve as one component among others that improves the evaluation of a woman's reproductive potential and treatment options that she may consider to conceive.

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