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## A characterization of the relationship of ovarian reserve markers with age

Mitchell P. Rosen, M.D.<sup>a</sup>, Erica Johnstone, M.D.<sup>a</sup>, Charles E. McCulloch, Ph.D.<sup>b</sup>, Sonya M. Schuh-Huerta, Ph.D.<sup>c</sup>, Barbara Sternfeld, Ph.D.<sup>d</sup>, Renee A. Reijo-Pera, Ph.D.<sup>c</sup>, and Marcelle I. Cedars, M.D.<sup>a</sup>

<sup>a</sup>Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco

<sup>b</sup>Department of Epidemiology and Biostatistics, University of California, San Francisco

<sup>c</sup>Institute for Stem Cell Biology and Regenerative Medicine, Stanford University, Stanford

<sup>d</sup>Division of Research, Kaiser Permanente, Oakland, California

### Abstract

**Objective**—To identify markers of ovarian age that best match the pattern of oocyte loss seen in histology specimens.

**Design**—Cross-sectional study.

**Setting**—University.

**Patient(s)**—Caucasian women (n = 252) aged 25–45 years.

**Intervention(s)**—none.

**Main Outcome Measure(s)**—The relationship between antral follicle count (AFC), antimüllerian hormone (AMH), inhibin B, FSH, and E<sub>2</sub> with age was estimated using the power model, which previously has been shown to most accurately describe oocyte loss in histologic specimens. The power model was fit to each marker and used to compare the rates of change at ages 30 and 40 with the histologic pattern. Among those markers following the pattern, R<sup>2</sup> was used to compare the degree of relationship with age.

**Result(s)**—Both AMH levels and AFC exhibited significant progressive declines with age. The average rates of loss per year for AFC and AMH were, respectively, −0.57 and −1.09 at age 30, and −1.33 and −3.06 at age 40. FSH, inhibin B, and E<sub>2</sub> did not exhibit progressive rates of change. The R<sup>2</sup> for AFC was 27.3% and for AMH was 22.7%.

**Conclusion(s)**—Only AFC and AMH follow the pattern of oocyte loss observed histologically. Although AMH may be more cost-effective, AFC is a slightly more accurate noninvasive measure for ovarian aging.

### Keywords

AFC; AMH; ovarian reserve; fertility; FSH; oocyte; follicle

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Reprint requests: Mitchell P. Rosen, M.D., Department of Obstetrics, Gynecology and Reproductive Sciences, 2356 Sutter Street, 7th Floor, San Francisco, CA 94115 (rosenm@obgyn.ucsf.edu).

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Wide variability exists between women both in the age at which menopause occurs and in the onset of diminished reproductive capacity (1). As ovarian function has profound impacts on women's hormonal milieu and their subsequent risk for the development of disease, as well as reproductive potential, improving our understanding of reproductive aging is critical to improving quality of life for all women. The quantity and quality of oocytes (ovarian reserve) has been linked to ovarian function and so there is significant interest in developing noninvasive testing to characterize the rate and pattern of oocyte loss.

Several studies have directly assessed the rate of oocyte loss. Using cross-sectional data from multiple autopsy studies, Faddy et al. developed a mathematical model for rate of follicle count decline (2–4). Their original analysis suggested a sudden acceleration in the decline of oocytes at approximately 37 years of age (i.e., a biphasic relationship) (3). This pattern had been widely accepted because it mirrored the decline in fertility noted earlier and the increase in spontaneous abortion (largely from increasing aneuploidy). However, in a reanalysis of their data, a gradual acceleration in decline fit the data better than the biphasic relationship (5, 6). Recently, Hansen et al. studied the rate of nongrowing follicles within a single population and confirmed a gradual acceleration in the rate of loss over time and demonstrated the power model to better describe this decline (7). We therefore utilized the power model as a platform to determine whether markers of ovarian reserve mirror this pattern of loss.

During the past decade, research has sought to identify noninvasive (indirect) markers of ovarian age. Several studies have correlated noninvasive markers to follicle count in histologic specimens in both the human and animal models (8–10). We recently characterized the relationship of antral follicle count (AFC) with chronological age and found that the pattern corresponded to a gradual acceleration of loss seen by Hansen et al. (7, 11). No studies have determined whether the serum markers of ovarian age follow a similar pattern.

Most data evaluating surrogate markers were derived from small observational studies, or from infertile populations who may or may not have received infertility medications. The values of these surrogate markers may differ between infertile women and the general population (12). In the current study, we quantify the relationship of each with age and compare it to the documented pattern of histologic decline in ovarian reserve. We propose that good surrogate markers of ovarian reserve would follow a pattern of loss with age similar to that of follicle loss observed histologically. Among those markers following the correct pattern, we hypothesized we could further distinguish them according to the quality of their fit with age. Improving our understanding of reproductive aging will have profound economic and social implications given the complex choices women face regarding the timing of childbearing and the growing burden of infertility.

## MATERIALS AND METHODS

The study population includes 252 Caucasian women aged 25–45, enrolled in a community-based cohort consisting of women not seeking treatment for fertility or other medical problems. This population is derived from the *Ovarian Aging (OVA)* study, which is a population-based multiethnic cohort designed to study the natural process of ovarian aging; it so far consists of measurements at a single time point, and our sample comprises the subset of non-Hispanic Caucasians.

Subjects were recruited from a sampling frame consisting of all age-eligible women members of the Kaiser Permanente Northern California Health Plan in geographical areas within reasonable distance to the research clinic. Institutional review board approval was

obtained both from Kaiser Permanente and the University of California, San Francisco. Inclusion required subjects to have intact ovaries and regular menses at 22- to 35-day intervals. Exclusion criteria included estrogen- or progestin-containing medications in the 3 months before enrollment, history of endometriosis, or any uterine or ovarian surgery.

All subjects underwent transvaginal ultrasound assessment of antral follicle count and ovarian volumes, performed on the second or fourth day of the menstrual cycle. Using a Shimadzu SDU-450XL machine, with a variable 4–8 MHz vaginal transducer, measurements of the transverse, longitudinal, and anteroposterior diameters of each ovary were made using electronic calipers. All echo-free structures in the ovaries with a mean diameter (of two dimensions) between 2 and 10 mm were counted as antral follicles. Antral follicle count for each subject was determined by summing total AFC for both ovaries. All examinations were performed by one of two examiners (M.I.C., M.P.R.). Our internal data have shown excellent correlations between repeated measurements ( $r^2 = 0.92$ ).

Serum hormonal assays were obtained on the second or fourth day of the menstrual cycle and performed in the CLASS Laboratory at University of Michigan. Follicle-stimulating hormone was measured with standardized two-site chemiluminescence immunoassays; intra-assay coefficients of variation (CVs) were 1.9%–2.1% and interassay, 5.2%–6.8%. Inhibin B was assayed using commercially an available ELISA kit from Diagnostic Systems Laboratories (Webster City, TX); intra-assay CV 3.3%–7.2%; interassay CV 7.8%–17%. Estradiol was assayed with an automated chemiluminescent assay using Bayer Diagnostics ACS:180 (Tarrytown, NY). Estradiol intra- and interassay CVs were 6.5%–6.9% and 13.6%–16.1%, respectively. Antimüllerian hormone was assayed using ELISA from Beckman Coulter (Marseille, France), using two-site sandwich-type immunoassay; intra-assay CV was 5.6% and interassay CV was 15.3%.

Descriptive statistics were calculated for demographic variables. The relationship between the serum markers with age was assessed using a power model regression (7):  $\text{marker} = A + B \times (\text{Age})^C$ . The shape of the relationship with age was used to help assess accuracy of the markers. We believe that the original scale probably may be related more to biological processes than log-transformed data, and therefore our analysis was performed using original data. We used the power model because previous data have suggested that oocyte loss based on histologic specimens and AFC follows a gradual accelerated loss with age (7, 11). In its original form, the parameters of the power model are not readily interpretable. We therefore rewrote the model using the following three parameters: value at age 30 and yearly rates of change at ages 30 and 40. Confidence intervals were derived for each of these parameters to compare to the trends observed in histologic data. Coefficients of determination ( $R^2$ ) were calculated for each marker of ovarian reserve and were used to compare model fits for each of the markers. A sensitivity analysis was performed by removing outliers (<5th and >95th percentile) and reanalyzing the data. All analyses were performed using SAS, version 9.12 (Cary, NC).

## RESULTS

Subject characteristics are given in Table 1. The mean age was 35.4 (range 25–45 years). Notably, the percentage of subjects who reported never smoking was 54.8% and those who had ever given birth was 14.7%.

Figure 1 displays the fits of the power model relationships between each ovarian reserve marker and age, with the relationship of follicle counts of histologic ovarian specimens and age. Coefficients of determination are noted. All but one of the markers has a relationship with age that mirrors the histologic relationship (panel F). Antimüllerian hormone levels

and AFCs exhibit gradual acceleration of oocyte loss with age, and FSH and E<sub>2</sub> levels exhibit an upturn with age. However, the upturn in FSH and E<sub>2</sub> levels occurs later than the downturn in follicle number in histologic specimens. Inhibin B does not match the histologic relationship.

Table 2 lists the estimates for the average values for the ovarian reserve markers at age 30 and rate of change per year at ages 30 and 40 that were derived from the fitted model. The average rates of loss are significant for AFC and AMH and are, respectively,  $-0.57$  and  $-1.09$  at age 30, and  $-1.33$  and  $-3.06$  at age 40. Estradiol, FSH, and inhibin B do not have a significant change at age 30 but do exhibit a significant change at age 40.

The quality of fit for the power model for each marker exhibiting the correct relationship is the following: AFC had the highest  $R^2$  (27.3%), followed by AMH (22.7%), FSH (18.4%), and E<sub>2</sub> (5.4%). The sensitivity analyses showed no alterations in the relationships between any of the noninvasive markers and age.

## DISCUSSION

In this study, we evaluated how serum markers of ovarian reserve decline with age in a community-based, regularly cycling Caucasian population and compared these patterns to those identified from histologic data (7). Of the markers considered, only AMH and AFC exhibited significant progressive declines with age, with AFC having a slightly better fit to the basic pattern observed histologically (Table 2); E<sub>2</sub> and inhibin B did not and therefore the data do not provide support for them as markers of ovarian reserve.

Antimüllerian hormone levels therefore appear to be the best *serum* marker of ovarian reserve (13–15). Simple correlation coefficients between age and AMH have been reported previously. A recent study evaluating the relationship between AMH and age at menopause in 144 participants reported an accelerated rate of decline with age (16). Reported correlations between age and AMH are dependent on the population studied ( $r = -0.30$  to  $-0.66$ ) (17–19). Perhaps the most similar patient group to ours is a subset analysis of 81 participants of the 162 subjects in their overall cohort; for that study, the reported correlation ( $r$ ) was  $-0.66$ , whereas we found an  $r$  of  $-0.46$ . Unlike our results, they do not report quantitative loss across ages and judge whether that marker fit the histologic pattern of oocyte loss.

Among those markers following the pattern,  $R^2$  was used to compare the degree of relationship with age. Antral follicle count had a slightly better fit with the power model compared with AMH ( $R^2 = 27.3\%$  vs  $22.7\%$ , respectively). However, the  $R^2$  for nongrowing follicles with age using the power model was reported by Hansen et al. to be 0.83 (7), much higher than ours. However, the population studied was from ages  $<1$  month to 51 years. For comparison, we reanalyzed their data and restricted the ages to that of our study sample (25–45 years) and found a reduced  $R^2$  of approximately 0.30 using either the raw or log-transformed values of AMH, much more similar to our results. The  $R^2$  for our data for the log-transformed AMH levels was 0.38, and for AFC it was 0.37.

Inhibin B is a biologically plausible biomarker of ovarian reserve because its decline leads to a rise in FSH levels, and it is produced by small preantral and antral follicles (20–22). Danforth et al. showed a statistically significant correlation of  $-0.54$  between inhibin B and age (20). Although their study included healthy volunteers and not infertile patients, it was small ( $n = 25$ ), and only included women between the ages of 39 and 52, not addressing correlation across the full reproductive age span. A larger study by Scheffer et al. composed of 162 participants from the general population, aged 25–46 years, showed that inhibin B was not significantly correlated with age ( $r = -0.12$  and NS) (23). In our study, inhibin B

levels did not show the expected gradual accelerated decline with age the other markers exhibited and thus was consistent with the work of Scheffer et al., suggesting poor correlation with age overall ( $r = 0.11$ ,  $P < .07$ ).

Day 3 FSH and  $E_2$  levels have been utilized as a marker of ovarian reserve since the 1980s and was the first such marker (24–26). Elevated day 3 FSH and  $E_2$  levels correlate well with those in late perimenopause and menopause, and milder elevations have been considered the hallmark for ovarian aging (27). Earlier studies showed FSH levels to be significantly higher starting in the fifth decade of life (28, 29). Scheffer et al. showed that FSH ( $r = 0.25$ ,  $P < .05$ ) and day 3  $E_2$  ( $r = 0.29$ ,  $P < .05$ ) levels were significantly correlated with age (23). We similarly found that FSH ( $r = 0.37$ ,  $P < .001$ ) and day 3  $E_2$  ( $r = 0.22$ ,  $P < .001$ ) levels were correlated with age, and found that the yearly rate of change was significant only at older ages (Fig. 1, Table 2). Furthermore, the power model fit for day 3  $E_2$  shows a relatively poor association with age (Fig. 1). This suggests that  $E_2$  alone is not an accurate marker of ovarian aging.

The panels in Figure 1 show that there is a considerable amount of variation with any surrogate marker of ovarian reserve that cannot be explained by age alone. Even with the best surrogate markers, AFC and AMH, more than 70% of the variation in women of reproductive age is left unexplained by age. This finding further illustrates that age is not the sole determinant of ovarian reserve. Several studies have shown that there is considerable variation in the natural age of onset of menopause (30–33). Although the coefficients of variation for the surrogate markers are relatively low, they are similar to what has been observed histologically and therefore we consider them valid markers of ovarian reserve.

A major limitation of this study is that it used cross-sectional data, and so nonlinear longitudinal relationships are not recoverable. Another limitation is that the data set is limited to Caucasians. However, we made this decision to decrease potential ethnic variation. Currently, we are enrolling subjects of different ethnicities to address this shortcoming. Prospective longitudinal studies in the same women over time are planned to more accurately characterize the relationship of these noninvasive markers of ovarian reserve and aging. A strength of this study is the closer approximation to normative as the population was derived from the community and not an infertility clinic. However, determination of which ovarian reserve marker is more reliable is limited because of the absence of direct histologic specimens as an outcome for comparison. More studies are needed to compare these noninvasive tests with histologic assessments.

One must use caution when suggesting these markers are “true markers” of the number of follicles remaining in the ovary. It is noted that the number of growing antral follicles is correlated to the number of primordial follicles (34). Most of these markers of ovarian reserve, other than FSH, are the direct product of growing antral follicles. If there is a disturbance in the number of growing follicles, measures of ovarian reserve may not be reliable (10). For example, there is evidence that AMH levels may be temporally influenced by iatrogenic causes (35). One study showed that AMH levels decrease for a short time after ovarian cystectomy (11). Other studies suggest AMH levels decrease after uterine artery embolization or hysterectomy (36).

This is the first study to characterize the relationship of the noninvasive serum markers of ovarian reserve with age in a large general (noninfertility) population. We found that the only markers that follow the pattern of oocyte loss observed histologically were AFC and AMH. Although AMH may be more cost-effective, AFC was a slightly more accurate noninvasive measure for ovarian aging.

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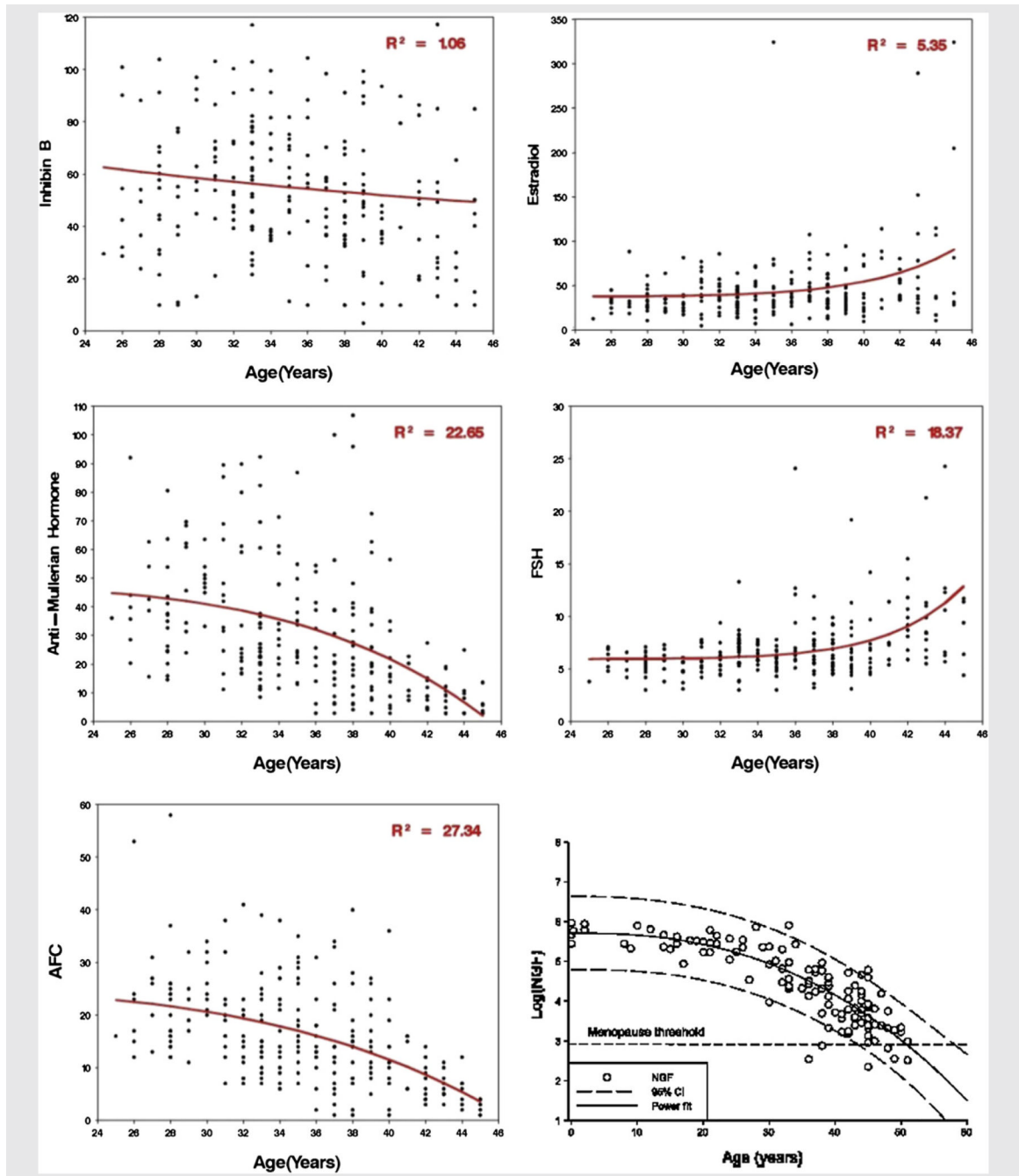
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**FIGURE 1.**  
Serum markers of ovarian reserve with age.

**TABLE 1**

Baseline characteristics of study participants (n = 252).

Variable	Mean $\pm$ SD	Minimum	Maximum
Age	35.38 $\pm$ 4.97	25	45
AFC	15.70 $\pm$ 9.37	1	58
Height (cm)	166.35 $\pm$ 6.13	148.20	182.40
Weight (kg)	67.74 $\pm$ 16.36	48.70	146.60
BMI	24.46 $\pm$ 5.63	17.41	58.35
Waist hip ratio	0.75 $\pm$ 0.05	0.42	0.96
Smoker			
Never	54.76%		
Current	13.49%		
Past	31.75%		
Parity			
None	64.1%		
1	15.4%		
>1	20.5%		

Estimates for the average values for the ovarian reserve markers at age 30 and rate of change per year at ages 30 and 40 that were derived from the fitted model.

**TABLE 2**

	Estimate values at age 30		Estimate rate of change/y at age 30		Estimate values at age 40		Estimate rate of change/y at age 40		$R^2$
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	
AFC	20.63	19.10 22.16	-0.57	-0.95 -0.19	11.50	10.06 12.93	-1.33	-1.72 -0.93	27.34
AMH (pmol/L)	41.29	37.37 45.22	-1.09	-1.99 -0.20	21.75	18.10 25.40	-3.06	-4.03 -2.08	22.65
E <sub>2</sub> (pg/mL)	37.25	26.91 47.59	0.80	-1.05 2.65	57.22	47.09 67.35	3.81	1.46 6.16	5.35
FSH (IU/L)	5.99	5.41 6.57	0.02	-0.02 0.06	7.49	6.80 8.17	0.47	0.33 0.60	18.37
Inhibin B (pg/mL)	58.19	52.48 63.89	-0.16	-0.90 0.58	52.24	46.25 58.22	-1.38	-2.57 -0.20	2.19