

Variations in serum müllerian inhibiting substance between white, black, and Hispanic women

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Objective: To compare serum müllerian inhibiting substance (MIS) levels between white, black, and Hispanic women to determine whether ovarian aging occurs at a different time course for women of different racial groups.

Design: Longitudinal study of serum MIS levels in women of different race and ethnicity over two different time points.

Setting: Women's Interagency HIV Study, a multicenter prospective cohort study.

Patient(s): Serum samples obtained from 809 participants (122 white, 462 black, and 225 Hispanic women).

Intervention(s): Comparison of serum MIS between women of different race and ethnicity at two time points (median age 37.5 years and 43.3 years).

Main Outcome Measure(s): Variation in MIS by race and ethnicity over time, controlling for age, body mass index, HIV status, and smoking.

Result(s): Compared with white women, average MIS values were lower among black (25.2% lower) and Hispanic (24.6% lower) women, adjusting for age, body mass index, smoking, and HIV status.

Conclusion(s): There is an independent effect of race and ethnicity on the age-related decline in MIS over time. (Fertil Steril® 2009;92:1674–8. ©2009 by American Society for Reproductive Medicine.)

Key Words: Müllerian inhibiting substance, antimüllerian hormone, ovarian reserve, race, ethnicity

There is a growing body of medical literature that indicates that female reproductive function may differ by race. Within the context of the treatment of infertility, race differences have been addressed by several studies examining IVF out-

comes. Initial small studies (1–4) on racial differences in outcomes from assisted reproductive technology produced conflicting results. More recently two large studies demonstrated differences in pregnancy rates and miscarriage rates by race (5, 6). Seifer et al. (5) examined the Society for Assisted Reproductive Technology (SART) database of >80,000 cycles for the years 1999 and 2000 and found lower pregnancy and higher miscarriage rates among black as compared with white women when controlled for age. Also using the SART database, Purcell et al. (6) demonstrated lower pregnancy rates in Asian-American women as compared with white women when examining the SART database of >25,000 cycles.

Furthermore, race also may influence the prevalence of premature menopause. Luborsky et al. (7) noted differences between white, black, and Hispanic women and concluded that the prevalence of premature ovarian failure appears to vary by race. Thus, the longevity of ovarian function may be influenced by race and ethnicity within the context of IVF, a common treatment of infertility, and the epidemiology of premature ovarian failure.

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These racial and ethnic differences in reproductive outcomes may result from racial differences in ovarian reserve. Müllerian inhibiting substance (MIS) or antimüllerian hormone (AMH) has been identified recently as the earliest, most sensitive serum marker of ovarian reserve (8–10). It is also a measure that is relatively stable throughout the menstrual cycle; therefore, MIS/AMH is an optimal analyte for exploring the question of whether ovarian aging may differ by race (10–15). Here we report the findings of a comparison of serum MIS/AMH levels between white, black, and Hispanic women enrolled in the Women’s Interagency HIV Study (WIHS) to explore whether ovarian aging occurs at a different time course for different racial groups.

MATERIALS AND METHODS

Study Population

This study was nested in the WIHS, the largest ongoing multicenter prospective cohort study of HIV infection and related health conditions among HIV-infected women and high-risk seronegative women in the United States. The WIHS protocols and procedures have been described previously (16). Participants in WIHS were eligible to contribute data to this analysis if they had completed a study visit at age 36 to 40 years and another between the ages of 41 and 46 years and had stored serum available from both visits. Samples were withdrawn from the repository accordingly, to investigate the effect of race and ethnicity on age-related decline in MIS/AMS. Of the 891 potentially eligible participants, we excluded from analysis 42 with incomplete body mass index (BMI) data, 14 with incomplete smoking data, 3 who had seroconversion between their two visits, and 23 whose self-identified race was not black, white, or Hispanic.

Human immunodeficiency virus infection was detected previously with use of enzyme immunoassay–Western blot methods. Race was categorized as either white (women who self-identified as white non-Hispanic), black (women who self-identified as black non-Hispanic), or Hispanic (which included self-identified Hispanic, white Hispanic, and black Hispanic women). Written informed consent was obtained from all WIHS participants, and study procedures were approved by the human subjects protection committees at all participating institutions (Bronx, NY; Brooklyn, NY; Chicago, IL; Los Angeles, CA; San Francisco, CA; and Washington, DC). The laboratory protocol for this study was approved by the Institutional Review Board at Women and Infants Hospital, Providence, Rhode Island.

Assay

Serum levels of MIS/AMH were measured with use of an ELISA kit (DSL-10-14400; Diagnostic Systems Laboratories, Webster, TX) according to manufacturer recommendations. Samples were run in duplicate by a single operator without knowledge of group assignment. The lower limit of sensitivity was 0.10 ng/mL, and interassay coefficients of

variation were 6%, 7%, and 10% at doses of 1.5, 2.2, and 8.1 ng/mL, respectively.

Statistical Analysis

Univariate comparisons were made by race and ethnicity and MIS/AMH for the following potential confounders: age, BMI, HIV infection status, and smoking (current, former, or never). Medians and interquartile ranges (IQR) were reported for continuous variables. Statistical comparisons conducted include χ^2 tests for categorical variables and the Kruskal-Wallis test for continuous variables. Multivariate linear regression analysis was conducted to assess the effect of race and ethnicity on serum MIS/AMH, adjusting for potential confounders as already listed.

To assess the effect of race and ethnicity on serum MIS/AMH, we specified a repeated-measures model with a random intercept for log-transformed AMH that incorporated left-censoring for undetectable values and adjusted for potential confounders as already listed (17). Age, BMI, and smoking status were time dependent. Race, ethnicity, and HIV status were fixed. Because a log-transformed outcome was used, the exponentiated betas represent the ratio of MIS levels in the raw scale for one group compared with the reference group for categorical factors or a one-unit difference in continuous factors. Subtracting 1 from the ratio and multiplying the result by 100 yields the percent difference. All analyses were conducted in SAS version 9 (SAS Institute Inc., Cary, NC).

RESULTS

We investigated longitudinal serum MIS/AMH levels among 809 WIHS participants, of whom 122 (15.1%) were white, 462 (57.1%) were black, and 225 (27.8%) were Hispanic. By design, the age range at visit 1 was 36 to 40 years (median 37.5 years) and at visit 2 was 41 to 46 years (median 43.3 years). The median time between visits was 5.3 years (range 1.5–8.7 years). Of the 809 participants, 628 (77.6%) were HIV infected and 181 (22.4%) were HIV uninfected; all participants’ HIV status was the same at both study visits.

White women were more likely to have HIV infection, were significantly older at the second visit ($P=.04$), and had significantly lower BMI at both visits ($P<.001$), as compared with black and Hispanic women (Table 1). A greater proportion of white and Hispanic women had never smoked compared with black women ($P<.001$). Median MIS/AMH was lower at the second visit than the first for all three racial categories, because all subjects were older (Table 1; Fig. 1). Müllerian inhibiting substance/AMH did not differ significantly by race and ethnicity at either time point ($P>.05$ for both visits), and there were no significant differences in magnitude of change in MIS/AMH values between time points by race. The median decrease between visits in MIS/AMH was 0.7 ng/mL for white women and 0.6 ng/mL for black and Hispanic women. However, although all three racial groups had similar

TABLE 1

Demographics of 809 WIHS participants at each of two study visits.

	Race			P value*
	White (n = 122)	Black (n = 462)	Hispanic (n = 225)	
HIV status				.09
Negative	18 (15)	111 (24)	52 (23)	
Positive	104 (85)	351 (76)	173 (77)	
Median age (y) (IQR)				
Visit 1	37.5 (37.3, 38.2)	37.5 (37.3, 38.5)	37.4 (37.2, 38.2)	.38
Visit 2	43.3 (43.0, 43.4)	43.2 (42.5, 43.4)	43.2 (42.6, 43.4)	.04
Change	5.6 (4.6, 6.0)	5.1 (4.1, 5.9)	5.4 (4.2, 6.0)	.007
Median BMI (IQR)				
Visit 1	24.8 (21.6, 28.4)	27.4 (23.9, 32.9)	27.9 (24.5, 32.1)	<.001
Visit 2	24.4 (21.6, 29.0)	28.0 (23.9, 33.2)	28.0 (24.7, 32.3)	<.001
Change	-0.4 (-1.7, 1.4)	0.2 (-2.3, 2.7)	0.2 (-1.6, 2.6)	.22
Smoking				
Visit 1				<.001
Never	37 (30)	90 (19)	69 (31)	
Former	33 (27)	78 (17)	51 (23)	
Current	52 (43)	294 (64)	105 (47)	
Visit 2				<.001
Never	36 (30)	80 (17)	59 (26)	
Former	38 (31)	103 (22)	58 (26)	
Current	48 (39)	279 (60)	108 (48)	
MIS/AMH				
Visit 1				
Median (IQR)	1.2 (0.6, 2.1)	1.0 (0.4, 1.8)	1.0 (0.4, 1.7)	.13
Undetectable (<0.1)	12 (10)	64 (14)	29 (13)	.50
Visit 2				
Median (IQR)	0.4 (0.1, 0.9)	0.2 (0.1, 0.7)	0.3 (0.1, 0.7)	.21
Undetectable (<0.1)	40 (33)	202 (44)	91 (40)	.09
Change	-0.7 (-1.2, -0.3)	-0.6 (-1.1, -0.2)	-0.6 (-1.1, -0.2)	.29

Note: Values represent No. (%) unless otherwise indicated.

* P values indicate overall differences by race/ethnicity.

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proportions of undetectables at the first visit, black and Hispanic women had a higher proportion at the second visit.

We first conducted univariate linear regression analysis to assess the effect of age on MIS/AMH, stratified by race. For a 1-year difference in age, MIS/AMH for the older women was 20.9% lower for white women, 22.8% lower for black women, and 22.1% lower for Hispanic women ($P<.001$ for all three models; data not shown). Multivariate linear regression analysis (Table 2) suggested a difference in the level of MIS/AMH by race. When we controlled for age, BMI, HIV status, and smoking, black women had an average MIS/AMH value that was 25.2% lower than the average MIS/AMH value for white women ($P=.037$). The average MIS/AMH value for Hispanic women was 24.6% lower than for white women; however, this difference was only marginally significant ($P=.063$). In addition to black race, another significant predictor of lower MIS/AMH was age

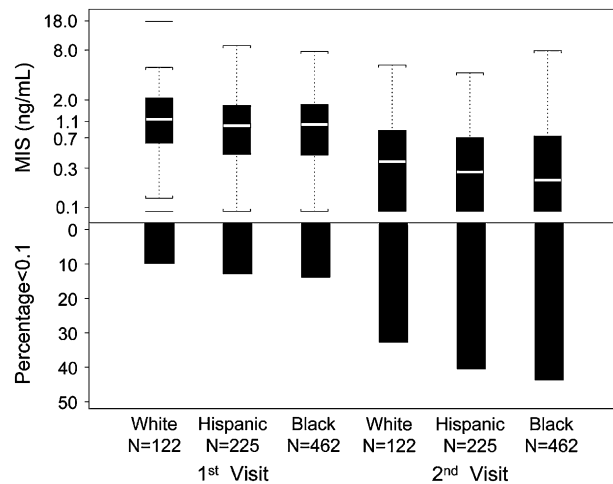
(22.3% lower per 1-year increase in age, $P<.001$). Body mass index, smoking, and HIV infection were not significantly associated with MIS/AMH in this analysis.

DISCUSSION

Almost all clinical studies to date have shown an inverse correlation between MIS/AMH and age, but none have controlled for race or ethnicity. One reason for this is that many of the original longitudinal clinical studies of MIS/AMH were conducted in the Netherlands, which has a homogeneous population. Van Rooij et al. (8) reported on 81 female volunteers with a mean age of 39.5 years who were followed for a mean duration of 4 years and were noted to have a 58% decline in MIS/AMH serum levels over that time interval. However, that cohort of women was not stratified by race or ethnicity. Most recently, van Disseldorp et al.

FIGURE 1

Standard box plots of MIS (*top panel*) showing the median (*white center line*), IQR (*black box*), 1.5 times the IQR (*whiskers*), and values >1.5 times the IQR (*solid detached lines*) and percentage of undetectable values (MIS <0.1 ng/mL; *bottom panel*) by racial category and visit.



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(18) demonstrated good conformity between observed distribution of age at menopause and that predicted from declining MIS/AMH levels. However, they also did not adjust for race or ethnicity.

The data from the current study demonstrate, for the first time, a significant difference in the mean level over time of MIS/AMH, a surrogate marker of ovarian aging, as a function

of race or ethnicity. Our study presents biochemical evidence of a difference in ovarian aging as assessed by serum MIS/AMH between black and white women and suggests a possible difference between white and Hispanic women, when controlling for age, BMI, smoking, and HIV status. Ovarian function of white women appears to be sustained longer over time than in black or Hispanic women. Specifically, on average minority women have 25% lower serum MIS/AMH values than white women when adjusting for age, BMI, smoking history, and HIV status. Implications of these findings may have potential broad applications for the life planning of minority women. As such, this information may influence minority women to seek medical assistance earlier if pregnancy is not accomplished easily. This information could influence physicians in their initial choice of fertility treatment options for minority women who may show earlier evidence of diminished ovarian reserve than their white counterparts. Finally, these data, if confirmed in follow-up studies, could have important implications for minority women who may experience an earlier onset of menopause compared with white women (19–21).

Our data further suggest that MIS/AMH levels also are unaffected by BMI, smoking, and HIV status. Our findings of BMI and HIV status having no influence on MIS/AMH serum levels are consistent with those of others (10, 22). However, our findings of smoking not affecting MIS/AMH are not consistent with a recent report by Freour et al. (23) demonstrating that MIS/AMH is diminished in current cigarette smokers. Further studies are needed to clarify this issue.

In conclusion, there is an independent effect of race and ethnicity on the age-related decline in MIS/AMH over time. It may be that the racial differences in pregnancy and miscarriage rates noted in large sample size IVF studies (5, 6) and in the onset of premature ovarian failure (7) may be

TABLE 2

Independent predictors of MIS/AMH among participants in the WIHS.

	Percent difference ^a	95% Confidence interval	P value
Race (vs. white)			
Black	–25.2	–43.0, –1.9	.037
Hispanic	–24.6	–43.9, 1.5	.063
Age ^b (y)	–22.3	–23.3, –21.2	<.001
BMI ^b	0.5	–0.6, 1.7	.347
(per unit increase)			
Smoking (vs. never) ^b			
Former	–6.1	–25.2, 17.7	.583
Current	–4.7	–22.7, 17.6	.655
HIV infected	–17.3	–33.9, 3.4	.097

^a From a repeated-measures model with a random intercept for log-transformed MIS incorporating left censoring for undetectable values and adjusted for all factors listed. Percent difference = $[\exp(\beta_X) - 1] \times 100$ where β_X is the regression coefficient for factor X.

^b Time-varying.

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attributable in part to inherent differences in ovarian reserve. Furthermore, the influence race and ethnicity may have on the measurement of serum MIS/AMH should be noted by both clinicians and investigators working with women of reproductive age.

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