Obesity adversely affects serum anti-müllerian hormone (AMH) levels in Caucasian women

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Abstract

Objective Previous studies regarding the effect of obesity on serum anti-müllerian hormone (AMH) levels have been conflicting. Our aim was to determine the effect of obesity on serum AMH levels among women from different racial backgrounds. **Methods** The medical records of 350 women (159 Caucasian, 99 African-American, 58 Hispanic, 34 Asian with ages 16–46) evaluated for infertility at an academic-affiliated center and who had AMH levels measured as part of their evaluation were reviewed. Age, AMH, body mass index (BMI), self-reported race, etiology of infertility, smoking history, maximum serum early follicular follicle-stimulating hormone (FSH) levels, antral follicle count (AFC), and history of ovarian surgery, chemotherapy, or radiotherapy were recorded. **Results** Age correlated negatively with AMH and antral follicle count across all races ($p < 0.05$). After adjusting for age, polycystic ovary syndrome diagnosis, and smoking, elevated BMI had a negative correlation with AMH in Caucasian women ($\beta = 0.17$, $p = 0.01$) but not in African-American, Hispanic, or Asian women. **Conclusion** Elevated BMI correlates negatively with AMH in Caucasian women but not in African-American, Hispanic, or Asian women. Additional studies are needed to elucidate

further the effect of race on the interaction between obesity and ovarian reserve.

Keywords Anti-müllerian hormone (AMH) · Body mass index · Obesity · Race/ethnicity

Introduction

With approximately 68.8 % of the population being either overweight (body mass index (BMI) ≥ 25) or obese (BMI ≥ 30), obesity continues to be an epidemic in the USA [1]. Obesity has been associated with negative reproductive outcomes. Obese women are more prone to anovulation and abnormal uterine bleeding, endometrial hyperplasia/cancer, infertility, miscarriage, and pregnancy complications, compared to normal-weight women [2–6]. Although infertility associated with obesity has been related to anovulation, it has been shown that the time to spontaneous pregnancy is much longer in obese women, even in those with regular menstrual cycles [4, 7, 8]. Moreover, obese women undergoing controlled ovarian hyperstimulation (COH) with oocyte retrieval for in vitro fertilization (IVF), in which spontaneous ovulation is not a factor, also have worse outcomes than normal-weight women. They have poorer responses to assisted reproduction treatment with increased amounts of gonadotropin used, increased cancellation rates, decreased number of oocytes retrieved, decreased implantation, clinical pregnancy and live birth rates, and increased miscarriage rates [9–13]. Although the effect of obesity on fertility is likely multi-faceted, it has been demonstrated that obese patients exhibit an altered ovarian follicular environment in multiple systems, including steroidogenic action, metabolism, and inflammation, which may contribute to these poorer outcomes [14].

Diminished ovarian reserve refers to decreased oocyte quantity and quality or reproductive potential [15]. Anti-müllerian

Capsule Elevated BMI correlates negatively with AMH in Caucasian women but not in African-American, Hispanic, or Asian women.

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hormone (AMH) has become an increasingly useful marker for assessing ovarian reserve [16, 17]. AMH is expressed by small preantral and early antral follicles, and thus, its serum level indirectly reflects the size of the primordial follicle pool. Because AMH can be measured anytime during the menstrual cycle and typically demonstrates minimal inter-cycle and intra-cycle variability, it appears to be an early, reliable, and direct indicator of declining ovarian function [18].

Studies examining the relationship between BMI and AMH have had conflicting results. When examining the effect of obesity on AMH levels, studies focusing on premenopausal females did not yield any significant findings [19–21]. There was, however, a significant correlation between obesity and AMH levels among late reproductive aged women as well as those demonstrating diminished ovarian reserve, where increased BMI was associated with lower serum AMH levels [22, 23].

Racial and ethnic disparities have also been demonstrated in reproductive medicine, such as earlier puberty in African-American and Hispanic women compared with Caucasian women, significantly lower live birth rates after assisted reproductive technology (ART) in all racial and ethnic groups compared with Caucasians, and differences in perimenopausal symptomatology and possibly timing in various racial/ethnic groups compared with Caucasians [24]. Compared with Caucasian women, average AMH values were found to be decreased among African-American (25.2 %) and Hispanic (24.6 %) women after adjusting for age [25]. However, in another study, compared to Caucasian women, African-American women were shown to have lower AMH levels at younger ages (ages 25–30) but experience less of a reduction in AMH with advancing age, whereas Hispanic and Asian women between the ages of 25 and 45 have lower AMH levels [26].

Given these studies that suggest the existence of racial disparities in reproductive health, there has been surprisingly little research on the impact of race/ethnicity on obesity in the context of fertility. In this study, we sought to determine whether the association between obesity and AMH would be dependent on race. We hypothesized that patients with increased BMI would have lower ovarian reserve as determined by serum AMH levels. We further hypothesized that this negative correlation between BMI and AMH would be stronger in non-Caucasian women.

Materials and methods

Patient population

The medical records of 472 reproductive age women (age 16–46) undergoing fertility workup from January 2012 to March 2014 and who had AMH levels measured as part of their evaluation were reviewed. Age, AMH, BMI, self-reported race, etiology of infertility, smoking history, maximum serum early follicular follicle-stimulating hormone (FSH) levels, antral

follicle count (AFC), and history of ovarian surgery, chemotherapy, or radiotherapy were recorded. Body mass index for each subject was calculated using the following formula: weight (kg)/height (cm²). Smoking history was defined as those who had never smoked and those who had ever smoked, which included those who currently smoked or who had formerly smoked. Diminished ovarian reserve (DOR) was defined as a baseline serum FSH >10 IU/l. Polycystic ovarian syndrome (PCOS) was diagnosed according to Rotterdam criteria [27]. Women with identified medical conditions or iatrogenic interventions that could diminish their ovarian reserve or those whose race was not reported or available were excluded from the study. Of the 472 women whose medical records were reviewed, 350 women who met inclusion criteria were included in the study, which was approved by the Institutional Review Board of Albert Einstein College of Medicine, Montefiore Medical Center.

AMH and FSH measurements

Random serum AMH levels, unrelated to cycle day, were measured in a commercial laboratory (ReproSource, Woburn, MA, USA), based on research-use-only materials and reagents from Beckman Coulter DSL (Chaska, MN, USA), and applied uniformly for all patient samples. Intra- and inter-assay coefficients of variation (CV) with serum control samples were 5–9 % and 7–12 %, respectively. FSH was measured on day 2 or 3 of the menstrual cycle by a solid-phase two-site chemiluminescent immunometric assay (Immulite 2000, Siemens) with an assay sensitivity 0.1 mIU/ml, intra-assay CV 4.2 %, and inter-assay CV 7.9 %. A maximum serum early follicular FSH was defined as the greatest historical baseline serum FSH level recorded for each subject (i.e., any time prior to or within 3 months of the collection of the patient's random serum AMH level).

AFC measurements

Antral follicle count measurements for each subject were determined by transvaginal ultrasonography on day 2 or 3 of the menstrual cycle.

Statistical analysis

Data are presented as mean±SD. Kruskal-Wallis and chi-square tests were used to test the differences in demographics between racial groups for continuous and binary data, respectively. Student's *t* test or Mann-Whitney *U* tests were used to compare groups, and Pearson or Spearman rank correlations were used to analyze associations between groups. Linear regression analysis was performed to investigate the effect of age, BMI, smoking (where indicated), and the presence of PCOS on AMH and AFC for each race category. Log, square, or one over square transformations were performed for non-

normally distributed data. Statistical analyses were performed using the Stata/IC 12.0 program, and a p value of <0.05 was considered to be statistically significant.

Results

Demographics of the study population are presented in Table 1. Of the 350 subjects, 99 were African-American (AA), 159 Caucasian (C), 58 Hispanic (H), and 34 Asian (A). All four groups (AA, C, H, A) showed no differences in mean age, AMH, maximum FSH, or etiology of infertility. There was a difference in mean BMI among all groups ($p<0.0001$) (Table 1). AA women had greater mean BMI compared to C women (30.7 ± 6.8 vs. 25.9 ± 6.0 , respectively; $p<0.0001$). AA, C, and H women had greater mean BMI compared to A women ($p<0.001$, $p=0.027$, $p<0.001$, respectively). Forty-seven percent of AA, 19 % of C, 29 % of H, and finally 6 % of A women were obese. C and A women had greater mean AFC compared to H women ($p=0.003$ and $p=0.054$, respectively). AA women smoked less compared to C women ($p=0.015$).

Correlation of age, smoking, PCOS, and BMI with AMH

We analyzed the correlation of age, smoking, PCOS, and BMI with AMH within each race (Table 2). On univariate analysis, age correlated negatively with AMH (AA: $r=-0.46$, $p<0.0001$; C: $r=-0.57$, $p<0.0001$; H: $r=-0.51$, $p<0.0001$; and A: $r=-0.64$, $p<0.0001$) and AFC (AA: $r=-0.42$, $p=0.0005$; C: $r=-0.43$, $p<0.0001$; H: $r=-0.54$, $p=0.0002$; and A: $r=-0.61$, $p=0.001$) among all races. We did not find any difference in serum AMH levels between current or former smokers versus never smokers among each race (AA: 1.7 ± 0.6 vs. 1.9 ± 0.3 ng/ml, $p=0.9$; C: 2.5 ± 0.9 vs. 2.4 ± 0.3 ng/ml, $p=$

Table 2 Effect of age, smoking, PCOS, and BMI on AMH across different racial groups

	AA		C		H		A	
	β	p	β	p	β	p	β	p
Age	-0.3	0.001	-0.4	<0.001	-0.45	<0.001	-0.37	0.04
PCOS ^a	0.43	<0.001	0.26	<0.001	0.3	0.01	–	–
BMI ^b	0.1	0.3	0.17	0.013	-0.14	0.2	0.04	0.8
Smoking ^c	–	–	0.04	0.6	0.22	0.05	–	–

^a There were no women with PCOS diagnosis among Asians

^b BMI was transformed to fit into model (one over squared)

^c Smoking was not included in the model for AA and A women

0.07; H: 2.7 ± 1.1 vs. 1.4 ± 0.2 ng/ml, $p=0.08$, respectively). There was only one smoker among Asian patients, insufficient for statistical analysis. As expected, women with PCOS had higher serum AMH levels compared to women without PCOS (AA: 6.9 ± 2.7 vs. 1.5 ± 0.2 ng/ml, $p=0.002$; C: 6.4 ± 1.5 vs. 1.9 ± 0.2 ng/ml, $p<0.0001$; and H: 4.1 ± 1.2 vs. 1.3 ± 0.2 ng/ml, $p=0.02$, respectively). There was not any woman with PCOS diagnosis among Asians. BMI correlated negatively with AMH among C women ($r=-0.24$, $p=0.002$) (Fig. 1), but not among AA, H, or A women. In a model incorporating age, BMI, smoking, and presence or absence of PCOS, BMI still correlated negatively with AMH among C women ($\beta=0.17$, $p=0.01$) but not among women from other races (Table 2). The results were similar when we excluded women with PCOS; BMI still correlated negatively with AMH among C women ($\beta=0.16$, $p=0.037$) but not among women from other races. On multivariate analysis, age correlated negatively with AMH among all races (AA: $\beta=-0.3$, $p=0.001$; C: $\beta=-0.4$, $p<0.001$; H: $\beta=-0.45$, $p<0.001$; and A: $\beta=-0.37$, $p=0.04$, respectively) after controlling for PCOS diagnosis, BMI,

Table 1 Demographics of women studied

	African-American ($n=99$)	Caucasian ($n=159$)	Hispanic ($n=58$)	Asian ($n=34$)	p
Age (year)	37.6 ± 5.2	36.3 ± 6.0	38.1 ± 4.8	35.8 ± 5.2	0.12
BMI (kg/m^2)	$30.7\pm6.8^{\text{a,b}}$	$25.9\pm6.0^{\text{a,c}}$	$28.1\pm5.9^{\text{d}}$	$22.9\pm4.4^{\text{b,c,d}}$	<0.0001
Max FSH (IU/l)	8.2 ± 3.7	9.0 ± 5.0	9.8 ± 5.2	9.3 ± 6.5	0.5
AFC (#)	10.3 ± 6.0	$13.3\pm8.7^{\text{e}}$	$9.3\pm7.1^{\text{e,f}}$	$13.3\pm9.0^{\text{f}}$	0.0026
AMH (ng/ml)	1.9 (1.3–2.4)	2.4 (1.8–3.0)	1.5 (1.1–2.0)	3.2 (0.9–5.4)	0.14
Smoking, n (%)					
Never smoked	90 (90.9) ^g	126 (79.2) ^g	51 (89.5)	33 (97.1)	0.008
Ever smoked	9 (9.1)	33 (20.8)	6 (10.5)	1 (2.9)	
Diagnosis					
DOR	21 (21.2)	47 (29.6)	20 (34.5)	13 (38.2)	0.21
PCOS	6 (6.1)	17 (10.7)	5 (8.6)	0 (0.0)	0.4
Other	72 (72.2)	95 (59.7)	33 (56.9)	21 (61.8)	

Data are mean $\pm$ standard deviation, n (%), or mean (95 % confidence interval)

p values: $a=<0.0001$, $b=<0.0001$, $c=0.027$, $d=<0.0001$, $e=0.003$, $f=0.054$, $g=0.015$ (comparisons are made between groups that have the same letter)

Fig. 1 Increased body mass index (BMI) is associated with decreased anti-müllerian hormone levels in Caucasian women ($r=-0.24$, $p=0.002$)

and smoking. Finally, PCOS diagnosis was positively correlated with AMH among AA, C, and H women (AA: $\beta=0.43$, $p<0.001$; C: $\beta=0.26$, $p<0.001$; and H: $\beta=0.3$, $p=0.01$, respectively), after controlling for age, BMI, and smoking. Among Asian race, there were not enough women with PCOS for statistical analysis.

Correlation of age, smoking, BMI, and PCOS with AFC

On univariate analysis, age correlated negatively with AFC (AA: $r=-0.42$, $p=0.0005$; C: $r=-0.43$, $p<0.0001$; H: $r=-0.54$, $p=0.0002$; and A: $r=-0.62$, $p=0.001$) among all races. As expected, women with PCOS had higher AFC compared to women without PCOS among AA (19 ± 2.3 vs. 9.7 ± 0.7 , $p=0.005$) and C women (24.5 ± 3.2 vs. 12 ± 0.7 , $p=0.0001$), respectively. There were too few Hispanic women with PCOS whose AFC were recorded for statistical analysis. We did not find any difference in AFC between current or former smokers versus never smokers among each race. Finally, there was no correlation between BMI and AFC in any group.

Discussion

In this study, we demonstrated a negative correlation between BMI and AMH levels in Caucasian women but not in African-American, Hispanic, or Asian women. We also found that age was significantly and negatively correlated with AMH levels and AFC across all racial groups, and a diagnosis of PCOS positively correlated with AMH among AA, C, and H women.

With over one-third of reproductive age females in the USA having a body mass index of 30 or greater, the impact of obesity on reproductive health and fertility continues to be a relevant and imperative area of research [1]. In particular, there has been numerous studies examining the effect of body

mass index on ovarian reserve via AMH levels; however, the results have been conflicting.

Shaw et al. examined 135 Caucasian premenopausal women, 16 % of which were obese ($\text{BMI} \geq 30$), who were younger than age 45 with a mean age of 41 ± 2.48 years in a prospective case-control study for the association of AMH levels and breast cancer risk and found no correlation between AMH levels and BMI [19]. Sahmay et al. also demonstrated no correlation between AMH levels and BMI during a cross-sectional study of 259 premenopausal women, 14 % of which were obese, who were under the age of 45 [20]. Lastly, Halawaty et al. reported no correlation between AMH levels and BMI in a cross-sectional comparative study involving 50 non-obese women whose mean age was 46.1 years versus 50 obese women whose mean age was 46.2 years [21].

On the other hand, Freeman et al. reported a negative correlation between BMI and AMH in later reproductive age women. In a cross-sectional study of 122 Caucasian and African-American women with a mean age of 45.8 ± 5.2 years, Freeman et al. demonstrated that obese women had a mean AMH level that was 65 % lower than AMH levels of non-obese women; however, they found no difference between the two racial groups [22]. Furthermore, a cross-sectional study performed previously by Buyuk et al. explored the association between BMI and AMH and total number of oocytes retrieved during an IVF cycle. Buyuk et al. reported that increasing BMI was associated with lower random serum AMH levels in infertile women with DOR (day 3 FSH >10 IU/l) but not in women with normal ovarian reserve (NOR). Among women with DOR, mean random serum AMH levels were 33 % lower in overweight and obese women compared with women with normal weight; the same association was not true for women with NOR [23]. However, the interaction of race with BMI and AMH was not studied.

The conflicting nature of results from studies demonstrating no relationship between BMI and AMH levels may partly be explained by the discrepancies among the sample populations from each study. In studies performed by Shaw et al. and Sahmay et al., only 16 and 14 %, respectively, were obese ($\text{BMI} > 30$). Furthermore, while the study by Shaw et al. only utilized Caucasian females, studies by Sahmay et al. and Halawaty et al. did not examine the impact of race on AMH levels on their subjects. The mean ages of the subjects for these studies also showed a large discrepancy. The sample population in studies by Shaw et al. and Halawaty et al. are largely comprised of later reproductive age women, while in the study by Sahmay et al., the mean age of female participants was 32.05 ± 4.9 years in the non-obese ($\text{BMI} < 30$) and 32.89 ± 5.78 years in the obese group ($\text{BMI} \geq 30$) [19–21].

The mechanisms by which obesity affect ovarian function and in particular AMH levels remain largely unclear. Obesity may indirectly affect AMH levels through its potential disruption of the ovarian follicular environment. Studies have shown

that various biochemical markers involved in both inflammatory and oxidative stress responses have been elevated in the follicular fluid of obese women compared to their non-obese counterparts [14, 28].

In another recent study, Merhi et al. demonstrated a potential link between obesity and AMH by examining the interaction between leptin and AMH levels in primary cultures of luteinized human ovarian granulosa cells (GC) of women undergoing in vitro fertilization. Leptin treatment was shown to significantly suppress AMH and AMHR-II messenger RNA (mRNA) levels in both cumulus and mural granulosa cells. Furthermore, in the presence of pre-treatment with a JAK2/STAT3 inhibitor, leptin treatment did not alter AMH mRNA but continued to suppress AMHR-II mRNA in cumulus cells, possibly suggesting that leptin downregulates AMH gene expression in a JAK2/STAT3-independent manner [29]. The negative effect of adiposity and consequently obesity on physiologic processes such as this may also explain why obesity has been demonstrated to negatively impact serum AMH levels and not antral follicle count.

In this study, we sought to investigate not only the correlation between BMI and AMH levels but also whether race affected this relationship. To our knowledge, this is the first study to examine the association between BMI and AMH levels with direct correlations across different racial groups. First, we found no significant difference among AMH levels across all four racial groups, which is similar to findings reported by Freeman et al. when examining comparing AMH levels between African-American and Caucasian women but conflicts with the findings of both Seifer et al. and Bleil et al., which were expanded to also include Hispanic and Hispanic versus Asian women, respectively [22, 25, 26]. In addition, we found that age did have a significant negative correlation with both AMH levels and AFC across all races ($p < 0.05$), which is consistent with previous findings [30–33].

Interestingly, we demonstrated a negative correlation between BMI and AMH in Caucasian women but not in African-American, Hispanic, or Asian women. Given the previous mentioned finding by Merhi et al. that leptin may suppress AMH mRNA levels in human luteinized GC as well as additional studies demonstrating elevated levels of leptin in African-American versus Caucasian women even after controlling for adiposity, including body composition and fat distribution, a negative correlation between BMI and AMH levels in non-Caucasian, particularly African-American women, would be anticipated [34, 35]. However, given the findings from our study, the mechanism by which race affects the interaction of BMI on AMH levels remains unclear.

Strengths of this study include an increased sample size compared to the majority of prior studies examining the effect of BMI on AMH levels as well as the inclusion of patients from multiple racial groups. Furthermore, there was no significant difference in mean age across all racial groups. A potential limitation of the

study was that the sample population was composed primarily of women who were being evaluated for infertility. Furthermore, although we had a relatively larger sample size compared to that of prior studies, it still may be small for a subgroup analysis. For example, we found that BMI was negatively correlated with AMH among C women ($r = -0.24$, $p = 0.002$), which is a weak correlation, nonetheless significant, but not among AA, H, or A women. Increasing the sample size of the study to include a greater as well as an equal number of patients from each racial group, particularly Hispanic and Asian women, might have strengthened the significance of our findings. Furthermore, given the smaller sample size of Asian subjects, there were also only one smoker and no subjects with PCOS, and therefore, analysis of confounding factors was limited.

Another potential confounding factor in our study was the inclusion of patients with PCOS into the sample size. However, data examining the effect on BMI on AMH levels among women with PCOS have been conflicting. Woo et al. and Cassar et al. did not find any association between AMH and BMI or obesity, respectively, among women with or without PCOS [36, 37]. On the other hand, Piouka et al. showed that both overweight and obese women with PCOS had lower serum AMH levels when compared to lean women with PCOS [38]. Despite similar age and diagnosis, the discrepancy between these two studies is intriguing. However, the participants in the study by Woo et al. were Asians, and hence, overweight and obesity were defined differently ($\text{BMI} > 23 \text{ kg/m}^2$), and the race of the participants in Cassar et al. (a study from Australia) and Piouka et al. (a study from Greece with potentially Mediterranean participants) studies were not stated [36–38]. Furthermore, our data analysis utilized a model incorporating age, BMI, smoking, and the presence or absence of PCOS, in which BMI still correlated negatively with AMH among C women ($\beta = 0.17$, $p = 0.01$) but not among women from other races.

In summary, we found no significant correlation between AMH level and race. We did find that age was significantly correlated with AMH levels as well as AFC in an inverse manner across all racial groups. We also demonstrated a negative correlation between BMI and AMH levels in Caucasian women but not in African-American, Hispanic, or Asian women. Given this is the first study to our knowledge that directly examines the relationship between BMI and serum AMH levels across different racial groups, future clinical and basic studies are needed to elucidate further the complex interactions of race on the interaction between obesity and ovarian function.

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