Title

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Journal

Menopause The Journal of The North American Menopause Society, 20(11)

ISSN

1072-3714

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Publication Date

2013-11-01

DOI

10.1097/gme.0b013e31828950fa

Peer reviewed

Published in final edited form as:
Menopause. 2013 November ; 20(11): 1139–1146. doi:10.1097/GME.0b013e31828950fa.

DOES ACCELERATED REPRODUCTIVE AGING UNDERLIE PRE-MENOPAUSAL RISK FOR CARDIOVASCULAR DISEASE?

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Abstract

Objective—The menopausal transition is associated with an increase in risk for cardiovascular disease; however, whether variability in reproductive aging relates to cardiovascular risk factors in the pre-menopausal period has not been studied.

Methods—In a multi-ethnic sample of 951 healthy, regularly-cycling women (ages 25–45, mean=35.2[5.5]), the current study examined Anti-Mullerian hormone (AMH), a validated marker of ovarian reserve, in relation to the overall number of cardio-metabolic risk factors calculated as the sum of the five components of metabolic syndrome (triglycerides ≥150 mg/dL; high-density lipoprotein <50 mg/dL; HOMA-IR ≥2.6; waist circumference ≥the race-specific cut-off, and hypertensive [versus normotensive] status) as well as in relation to each of these risk factors individually.

Results—In age-adjusted models, results showed that the number of cardio-metabolic risk factors was 52.1% higher among women with low compared to high AMH levels and 46.0% higher among women with mid compared to high AMH levels. In addition, results showed that low and mid levels of AMH (compared to high) were associated with an increase in risk with respect to HDL (OR=1.814, 95% CI: 1.211, 2.718; OR=1.568, 95% CI: 1.083, 2.269, respectively), waist circumference (OR=2.012, 95% CI: 1.380, 2.934; OR=1.881, 95% CI: 1.333, 2.654, respectively), and hypertensive status (OR=2.373, 95% CI: 1.095, 5.143; OR=2.052, 95% CI: 0.976, 4.314, respectively) outcomes. Associations, however, attenuated when BMI was covaried (*P*'s>.05).

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The authors have nothing to disclose.

Conclusion—Cross-sectional evidence suggests that having a greater ovarian reserve is associated with having a healthier cardio-metabolic risk factor profile. Future longitudinal studies are needed to determine whether this association may be mediated by BMI.

Key terms

Anti-Mullerian hormone (AMH); cardiovascular risk; cardio-metabolic risk; metabolic syndrome; ovarian aging; ovarian function; reproductive aging

The menopausal transition is associated with an increase in risk for cardiovascular disease (CVD),[1–12] the leading cause of death in women.[13] As the number of post-menopausal US women rises,[14] proportionate increases in CVD will have enormous public health implications. Despite this, there is a paucity of research examining the relation between variability in reproductive aging and CVD risk in the pre-menopausal period, a time when interventions to slow menopause onset and/or lessen the clinical impact of its sequelae may be possible. Recent methodological advances in the measurement of reproductive aging, including the assessment of Anti-Mullerian hormone (AMH), a biochemical marker of ovarian reserve, are now opening up new opportunities to address this gap in our knowledge.

AMH is a hormone secreted by the granulosa cells of the pre-antral and small antral follicles of the human ovary.[15] AMH plays a key role in inhibiting the early stages of follicle growth, thereby preserving the ovarian reserve by limiting initial recruitment of primordial follicles into the pool of growing follicles.[16–17] Because AMH levels are reflective of the number of small growing follicles, which are themselves proportional to the number of primordial follicles, AMH indexes the ovarian reserve.[18–19] Support for its use in this capacity stems from studies showing AMH correlates with the number of primordial follicles remaining in the ovary[20]; it relates inversely to chronological age in adult women[18, 21]; it predicts ovarian response in treatment protocols using assisted reproductive technologies[22–23] as well as fecundity in fertile women[24]; and it relates prospectively to the timing of menopause.[25–26] AMH also possesses several measurement advantages, making it particularly well-suited for use in epidemiological studies. That is, AMH shows excellent within-person cycle-to-cycle reproducibility[27–28]; it is stable across the menstrual cycle [29–31]; and it is not impacted by use of oral contraceptives.[31–32]. Moreover, AMH has recently been incorporated into the revised STRAW staging system for reproductive aging, albeit for supportive and not diagnostic purposes.[33]

In the current study, we evaluated the association between reproductive aging, indexed by AMH levels, and cardiovascular risk among 951 regularly-cycling, pre-menopausal women. The primary study objective was to examine AMH levels in relation to *overall* cardiovascular risk marked by the total number of cardio-metabolic risk factors calculated as the sum (ranging between 0–5) of the five components of metabolic syndrome: 1) triglycerides ≥150 mg/dL; 2) high-density lipoprotein [HDL] <50 mg/dL; 3) homeostasis model assessment of insulin resistance [HOMA-IR] ≥2.6; 4) waist circumference ≥88 cm for white, African-American, and Latina women and ≥80 cm for Chinese women; and 5) hypertensive (versus normotensive) status. Secondarily, AMH levels were examined in relation to each of these risk factors individually. We hypothesized that having a greater

ovarian reserve indexed by higher AMH levels would be related to having a healthier cardio-metabolic risk factor profile.

MATERIALS AND METHODS

Participants

The current sample included participants in the Ovarian Aging (OVA) Study, an investigation of the correlates of reproductive aging. Participants were recruited through Kaiser Permanente (KP) of Northern California, a large, integrated health care delivery system that provides medical care to approximately one-third of the population of Northern California. The KP membership compared to the population of Northern California is generally representative in its socio-demographic and health-related characteristics, especially when the comparison is limited to those with health insurance.[34] Women were included in the OVA Study if they were between 25–45 years of age, had regular menses, had their uterus and both ovaries intact, self-identified as white, African-American, Latina, Chinese, or Filipina, and were able to speak/read English, Spanish, or Cantonese. Exclusions included the self-report of major medical illnesses, use of medications affecting the menstrual cycle in the 3 months prior to study participation, and current pregnancy or breastfeeding.

The OVA Study protocol included an in-person medical history interview, trans-vaginal ultrasound, anthropometric assessment, blood draw, and self-report questionnaires. Of 1019 total participants, 951 women were included in the current analysis. Of the 68 women who were excluded, 41 Filipina women were excluded due to their small numbers and 27 women were excluded due to missing data on a variable of primary interest. The study protocol was approved by the University of California San Francisco Committee on Human Research as well as the KP of Northern California Institutional Review Board. Informed, written consent was obtained from all study participants.

Measures

Anti-Mullerian hormone (AMH)—AMH (ng/mL) was assayed using two commercially available ELISAs from Beckman Coulter (Marseille, France) both of which use a two-site sandwich immunoassay. The Immunotech assay was used for the majority of the sample (84%) until this assay was retired and the second generation assay (Gen II) was used for the remainder of the samples. Among 44 women on whom both assays were performed, regression analyses showed excellent correspondence between the assays (R^2=0.94) which has also been demonstrated in prior studies.[35–36] AMH values based on the Immunotech assay were adjusted using the equation of the line with Immunotech predicting Gen II. The Gen II assay sensitivity was 0.16 ng/mL, the intra-assay coefficient of variation (CV) was 1.4%, and the inter-assay CV was 12.5%.

Cardio-metabolic risk factors—Parameters of cardio-metabolic health were selected to represent the individual components of metabolic syndrome (triglycerides, HDL, HOMA-IR, waist circumference, and hypertension). Assays for triglycerides, HDL, fasting glucose, and insulin were performed by Quest Diagnostics (San Jose, CA). Lipids were assayed using

enzymatic methods (triglycerides: intraassay coefficient of variation [CV] was 1.99–3.45%; HDL: intraassay CV was 1.15–2.02%). Fasting glucose was assayed by the glucose oxidase method (intraassay CV: 1.25–2.00%) and insulin was assayed using the Siemens Immulite (Tarrytown, NY) immunochemiluminometric assay (intraassay CV: 3.64–6.64%). HOMA-IR was calculated as insulin (uIU/mL) X glucose (mg/dL)/405.[37] Waist circumference was derived from a standardized anthropometric assessment performed by a study nurse; two measurements were taken to the nearest 0.1 cm at the narrowest part of the torso and averaged. Lastly, previously diagnosed hypertension (yes/no) and use of anti-hypertensive medications (yes/no) was derived from an in-person medical history interview; endorsement of one or both items was used as a surrogate for elevated systolic/diastolic blood pressure which was not assessed in the study protocol. Risk factors were coded dichotomously according to commonly used clinical cut-offs as follows: 1) triglycerides (1=≥150 mg/dL vs. 0=<150 mg/dL); 2) HDL (1=<50 mg/dL vs. 0=≥50 mg/dL); 3) HOMA-IR (1=≥2.6 vs. 0=<2.6)[38]; 4) waist circumference (1=≥88 cm vs. 0=<88 cm for White, African-American, and Latina women and 1=≥80 cm vs. 0=<80 cm for Chinese women); and 5) hypertension (1=hypertension diagnosis/use of anti-hypertensive medication vs. 0=no hypertension diagnosis/use of anti-hypertension medication). In addition, a summary score was computed reflecting the total number of cardio-metabolic risk factors possessed by each participant (range 0–5).

Analytical Plan—First, to address the primary study objective, negative binomial regression analyses were performed to model the relation between AMH levels and number of cardio-metabolic risk factors. AMH levels (categories: low, mid, and high) were derived by dividing the AMH distribution into tertiles. Number of cardio-metabolic risk factors was derived by taking the simple sum (possible range 0–5) of the five components of metabolic syndrome coded: 1) triglycerides (1=≥150 mg/dL, 0=<150 mg/dL); 2) HDL (1=<50 mg/dL, 0=≥50 mg/dL); 3) HOMA-IR (1=≥2.6, 0=<2.6); 4) waist circumference (1=≥88 cm vs. 0=<88 cm for White, African-American, and Latina women and 1=≥80 cm vs. 0=<80 cm for Chinese women); and 5) hypertension (1=hypertension diagnosis/use of anti-hypertensive medication, 0=no hypertension diagnosis/use of anti-hypertension medication). Results for models adjusted for age and adjusted for covariates (age, cigarette smoking, race/ethnicity, menarcheal age, past use of hormonal contraception, and parity) are reported. Cigarette smoking was coded: 1=current/past smoking, 0=never smoked; race/ethnicity was dummy coded using White as the reference group; past use of a hormonal method of contraception was coded: 1=past use, 0=no use; and parity was coded: 1=1+ live births, 0=no live births. Next, in secondary analyses, logistic regression analyses were performed to examine the relation between AMH levels and individual cardio-metabolic risk factors using the same dichotomous coding as described above. Results for models adjusted for age and adjusted for covariates (age, cigarette smoking, race/ethnicity, menarcheal age, past use of hormonal contraception, and parity) are reported. Lastly, to characterize the role of obesity in explaining associations between AMH levels and cardio-metabolic risk, all analyses were repeated additionally including BMI as a covariate. Analyses were performed using SAS statistical software version 9.3.

RESULTS

Sample Characteristics

The mean age in the sample (*N*=951) was 35.2 (SD=5.5) and the racial/ethnic composition included 29.3% White, 24.9% African-American, 23.4% Latina, and 22.4% Chinese women. The AMH distribution was divided into tertiles representing low (*n*=317), mid (*n*=317), and high (*n*=317) AMH levels. In the low AMH tertile, mean AMH was 0.77 (SD=0.4), range=0.16–1.47; in the mid AMH tertile, mean AMH was 2.40 (SD=0.6), range=1.48–3.41; and in the high AMH tertile, mean AMH was 6.34 (SD=2.7), range=3.42–19.28. Descriptive information for the full sample as well as for women in each AMH tertile is reported in Table 1. As expected, age varied significantly across AMH tertiles with the mean age progressively decreasing across low, mid, and high AMH levels (*P*<.001). With respect to race/ethnicity, there was a significant difference in the proportion of White women in the low (22.7%) vs. high (36.0%) AMH tertile (*P*<.05). There were also significant differences in the proportion of Latina women in the low (29.3%) vs. mid (21.8%) and low (29.3%) vs. high (19.2%) AMH tertiles (*P*'s<.05). With respect to the cardio-metabolic risk factors, the proportion of women with low HDL (<50 mg/dL), high glucose (≥100 mg/dL), high waist circumference (≥ the race-specific cut-off), and hypertension (yes/no) was significantly higher in the low vs. high AMH tertile (*P*'s<.05). The proportion of women with low HDL (<50 mg/dL), high waist circumference (≥ the race-specific cut-off), and hypertension (yes/no) was also significantly higher in the mid vs. high AMH tertile (*P*'s<.05). Lastly, the proportion of obese women (BMI ≥ 30 kg/m^2) varied significantly between all AMH tertiles (*P*'s<.05) with the proportion of obese women decreasing across low, mid, and high AMH levels.

Association of AMH and the overall number of cardio-metabolic risk factors— Negative binomial regression analyses were performed to model the number of cardio-metabolic risk factors (possible range 0–5) as predicted by AMH levels (categories: low, mid, and high). Results of age-adjusted (Model 1), and covariate-adjusted (Model 2) models are reported in Table 2. Results showed that independently of age the number of cardio-metabolic risk factors was 52.1% higher (95% CI: 1.215, 1.905) among women with low vs. high AMH levels and 46.0% higher (95% CI: 1.181, 1.806) among women with mid vs. high AMH levels. In addition, results of analyses examining the predicted number of cardio-metabolic risk factors across AMH levels at five pre-specified ages (i.e., 25, 30, 35, 40, 45) are described in the following. Estimated at age 25, the predicted number of cardio-metabolic risk factors was 0.95, 0.91, and 0.62 for low, mid, and high AMH levels, respectively. In parallel, values were 1.00, 0.96, and 0.66 (at age 30); 1.06, 1.02, and 0.70 (at age 35); 1.13, 1.08, and 0.74 (at age 40); and 1.19, 1.15, and 0.78 (at age 45) for low, mid, and high AMH levels, respectively. Figure 1 depicts these results, showing the number of cardio-metabolic risk factors was related positively to age and that at every age a greater number of cardio-metabolic risk factors was predicted by low AMH levels relative to high AMH levels as well as mid AMH levels relative to high AMH levels. When analyses were repeated additionally controlling for covariates (cigarette smoking, race/ethnicity, menarcheal age, past use of hormonal contraception, and parity) (Model 2), a similar pattern of results was found. That is, the number of cardio-metabolic risk factors was 27.2% higher

(95% CI: 1.037, 1.561) among women with low vs. high AMH levels and 31.1% higher (95% CI: 1.079, 1.592) among women with mid vs. high AMH levels.

Association of AMH and individual cardio-metabolic risk factors—Logistic regression analyses were performed to examine AMH levels (comparing low and mid levels to high levels) in relation to individual cardio-metabolic risk factors. Results of age-adjusted (Model 1) and covariate-adjusted (Model 2) models are reported in Table 3. In age-adjusted models, AMH levels were related significantly to HDL, waist circumference, and hypertensive status (but not to triglycerides or HOMA-IR). Specifically, with respect to HDL, low vs. high AMH levels were associated with a 81% (OR=1.814, 95% CI: 1.211, 2.718) increased odds of having HDL <50 mg/dL vs. ≥50 mg/dL; and mid vs. high AMH levels were associated with a 57% (OR=1.568, 95% CI: 1.083, 2.269) increased odds of having HDL <50 mg/dL vs. ≥ 50 mg/dL. With respect to waist circumference, low vs. high AMH levels were associated with a 101% (OR=2.012, 95% CI: 1.380, 2.934) increased odds of having a waist circumference ≥ vs. < the race-specific cut-off; and mid vs. high AMH levels were associated with an 88% (OR=1.881, 95% CI: 1.333, 2.654) increased odds of having a waist circumference of ≥ vs. < the race-specific cut-off. With respect to hypertensive status, low vs. high AMH levels were associated with a 137% (OR=2.373, 95% CI: 1.095, 5.143) increased odds of being hypertensive vs. normotensive; and mid vs. high AMH levels were associated with a 105% (OR=2.052, 95% CI: 0.976, 4.314) increased odds of being hypertensive vs. normotensive. In models additionally adjusted for covariates (cigarette smoking, race/ethnicity, menarcheal age, past use of hormonal contraception, and parity) associations between AMH levels and HDL, waist circumference, and hypertensive status outcomes persisted albeit at the level of a statistical trend for HDL and hypertensive status (*P*'s<.10).

Role of BMI in explaining associations between AMH and cardio-metabolic risk factors—Follow-up analyses were performed to characterize the potential role of BMI in explaining associations between AMH levels and the overall number of cardio-metabolic risk factors as well as AMH levels and individual cardio-metabolic risk factors. First, negative binomial regression analyses were again performed to model the number of cardio-metabolic risk factors as predicted by AMH levels (categories: low, mid, and high) but this time excluding waist circumference from the summary score (possible range 0–4). Results showed that independently of age the number of cardio-metabolic risk factors was 48.1% higher (95% CI: 1.126, 1.948) among women with low vs. high AMH levels and 41.8% higher (95% CI: 1.096, 1.835) among women with mid vs. high AMH levels. In models additionally adjusted for covariates (cigarette smoking, race/ethnicity, menarcheal age, past use of hormonal contraception, and parity) associations attenuated partially showing the number of cardio-metabolic risk factors was 24.5% higher (95% CI: 0.960, 1.615) among women with low vs. high AMH levels and 28.0% higher (95% CI: 1.003, 1.633) among women with mid vs. high AMH levels. Finally, in models additionally adjusted for BMI associations between AMH levels and the overall number of cardio-metabolic risk factors attenuated completely (*P*'s >.10).

Next, logistic regression analyses were again performed to examine AMH levels in relation to individual cardio-metabolic risk factors (excluding waist circumference). In models additionally adjusted for BMI all associations between AMH levels and cardio-metabolic risk factor outcomes including triglycerides (low vs. high AMH levels: OR=0.734, 95% CI: 0.374, 1.438; mid vs. high AMH levels: OR=0.671, 95% CI: 0.354, 1.272), HDL (low vs. high AMH levels: OR=1.095, 95% CI: 0.690, 1.735; mid vs. high AMH levels: OR=1.090, 95% CI: 0.716, 1.658), HOMA-IR (low vs. high AMH levels: OR=0.610, 95% CI: 0.316, 1.175; mid vs. high AMH levels: OR=0.838, 95% CI: 0.461, 1.522), and hypertensive status (low vs. high AMH levels: OR=1.503, 95% CI: 0.672, 3.361; mid vs. high AMH levels: OR=1.346, 95% CI: 0.613, 2.954) were non-significant.

DISCUSSION

Based on previous studies showing the menopausal transition is associated with an increase in risk for CVD,[1–12] we sought to determine whether variability in reproductive aging may similarly relate to cardio-metabolic risk factors in the pre-menopausal period, an optimal time to prevent or delay potential reproductive aging-related sequelae. In the current sample of 951 healthy, regularly-cycling women, AMH, a biochemical marker of ovarian reserve, was examined in relation to a summary score (range 0–5) reflecting the total number of cardio-metabolic risk factors possessed by each woman. In age-adjusted analyses, results showed that low and mid levels of AMH (compared to high) were associated with a 52.1% and a 46.0% increase, respectively, in the number of cardio-metabolic risk factors. In analyses additionally adjusted for cigarette smoking, race/ethnicity, menarcheal age, past use of a hormonal method of contraception, and parity, associations remained statistically significant showing low and mid levels of AMH (compared to high) were associated with a 27.2% and a 31.1% increase, respectively, in the number of cardio-metabolic risk factors. Taken together, results suggest that independently of confounding factors, having a greater ovarian reserve, marked by high AMH, was associated with having a healthier cardio-metabolic risk factor profile.

In secondary analyses, AMH was also examined in relation to individual cardio-metabolic risk factors, coded dichotomously according to common clinical cut-offs. In age-adjusted analyses, results showed that low and mid levels of AMH (compared to high) were associated with an increase in risk with respect to HDL, waist circumference, and hypertensive status. However, when models were additionally adjusted for cigarette smoking, race/ethnicity, menarcheal age, past use of a hormonal method of contraception, and parity, associations with HDL and hypertensive status attenuated to the level of a statistical trend. Moreover, when all analyses were repeated with additional adjustment for BMI, associations between AMH and the total number of cardio-metabolic risk factors as well as associations between AMH and HDL/hypertensive status all fully attenuated. This pattern of results in which effects of AMH on cardio-metabolic outcomes fully attenuated when BMI was covaried suggests obesity may play a mechanistic role in explaining links between reproductive aging and cardio-metabolic risk. Although the potential meditational role of BMI could not be directly tested in this cross-sectional dataset, interestingly, evidence drawn from the menopause literature is consistent with this idea. That is, the menopausal transition has been associated with an increase in weight gain[39] which has been

thought to at least partially explain subsequent decrements in cardio-metabolic risk factor profiles observed post-menopausally.[40–42]

The current finding that low and mid levels of AMH (compared to high) are related to having a greater waist circumference is consistent with several previous studies showing AMH is lower among obese women[43–45] although not all studies have found an association between AMH and BMI.[46–48] Also, the current finding that high AMH is associated with having fewer cardio-metabolic risk factors which were selected to represent the components of metabolic syndrome is consistent with one recent study in which AMH and HOMA-IR were shown to be inversely related[47] although AMH and HOMA-IR were unrelated in the current study. Otherwise, because the current study is the first (to our knowledge) to systematically examine AMH in relation to conventional cardio-metabolic risk factors in a large and ethnically diverse sample of healthy, regularly-cycling women its comparison to the existing literature is limited. Other previous studies examining CVD in pre-menopausal women suggest collectively that disruptions in ovarian function are related to an increase in cardiovascular risk; however, such disruptions have been marked by indicators such as anovulation, lower estradiol, and menstrual cycle irregularity and have not included assessments of ovarian reserve in particular.[49–55]

In the current study, the proportion of White women was significantly lower in the low (23%) compared to high (36%) AMH tertile and the proportion of Latina women was significantly greater in the low (29%) compared to mid (22%) and high (19%) AMH tertiles, suggesting there may be a relation between race/ethnicity and AMH. Although most previous studies have included samples comprised of predominately White women, one study comparing AMH declines across race/ethnic groups reported that the average decline in AMH was greater among African-American and Latina women than in White women.[48] More generally, evidence also suggests that racial/ethnic differences are present across a variety of reproductive health outcomes, including pubertal timing, outcomes of assisted reproductive technologies, and age at menopause (for review see[56]). In addition, consistent with a large literature documenting racial/ethnic disparities in CVD risk,[57–58] the current study showed strong associations between race/ethnicity and cardio-metabolic risk with the African-American and Latina (compared to White) women showing 2 to 9-fold increases in the odds of having poorer cardio-metabolic outcomes for HDL, waist circumference, and hypertension (results not shown). Such strong associations between race/ethnicity and the cardio-metabolic outcomes, likely account for the partial attenuation in effects of AMH on HDL and hypertension when race/ethnicity was statistically controlled.

The current study had several weaknesses, most notably including that the study design was cross-sectional, limiting conclusions regarding the direction of association between AMH and cardio-metabolic risk factor profiles. Although we conceptualized that accelerated reproductive aging, indexed by AMH, may be a risk factor for the promotion of cardiovascular risk in the pre-menopausal period, it is possible that cardio-metabolic risk factors may also influence the ovarian reserve and/or processes related to the regulation of folliculogenesis. In fact, it has been suggested in a previous study that cardiovascular disease may play a causal role in the onset of earlier menopause rather than the reverse.[59] Other weaknesses of the current study included the use of having received a previous hypertension

diagnosis and/or used anti-hypertensive medications as a surrogate for measured blood pressure and the absence of more definitive pre-clinical markers of atherosclerotic disease such as endothelial dysfunction or carotid artery intima-medial thickness. Primary strengths of the current study were its novel emphasis on examining reproductive aging in relation to cardiovascular risk in the pre-menopausal period among healthy, regularly cycling women as well as its relatively large size and representation of women of racial/ethnic minorities.

In conclusion, results of the current study provide preliminary support for the hypothesis that greater reproductive aging may relate to an increase in cardio-metabolic risk in the pre-menopausal period as evidenced by cross-sectional associations between having a greater ovarian reserve, marked by high AMH, and having fewer cardio-metabolic risk factors. Improved understanding of links between ovarian function and cardiovascular risk may aid in identifying risk factors for atherosclerotic disease development pre-menopausally that are associated with variability in CVD post-menopausally. The examination of such associations in the pre-menopausal period may point to earlier opportunities for intervention among women at greatest risk for CVD by virtue of having an accelerated trajectory of ovarian follicle loss and, therefore, anticipated earlier entry into menopause. In order to flesh out these potential implications, future research should employ longitudinal study designs to evaluate whether declines in ovarian reserve *over time* are related to cardio-metabolic risk, whether associations may be bi-directional, what mechanisms in particular (such as obesity) may drive such links, as well as whether such processes may operate similarly across women of different racial/ethnic backgrounds who appear to vary in terms of risk both across cardiovascular and reproductive outcomes.

Acknowledgments

Preparation of this manuscript and the research described here were supported by NIH/NICHD and NIH/NIA (R01 HD044876); NIH/NIA (K08 AG03575); and NIH/UCSF-CTSI (UL1 RR024131).

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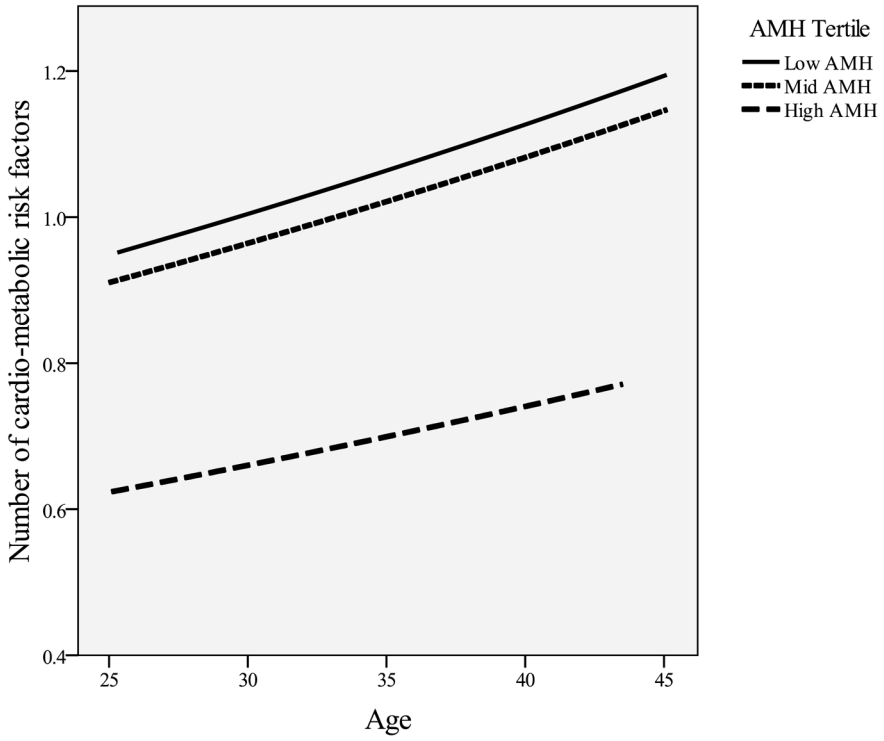

Figure 1.
The predicted number of cardio-metabolic risk factors in AMH tertiles across age in a sample of 951 pre-menopausal women.

Table 1

Descriptive statistics examining sociodemographic and cardio-metabolic risk factors in the full sample of 951 pre-menopausal women and among women in low, mid, and high AMH tertiles.

	Total (*N* = 951) **M = 3.17 (2.8) ng/mL Range = 0.16 – 19.28**	**Low AMH (*n* = 317)** **M = 0.77 (0.4) ng/mL Range = 0.16–1.47**	**Mid AMH (*n* = 317)** **M=2.40 (0.6) ng/mL Range = 1.48 – 3.41**	**High AMH (*n* = 317)** **M = 6.34 (2.7) ng/mL Range = 3.42 – 19.28**	**Test Statistic**	***P***
Sociodemographics:						
Age (in years)	35.2 (5.5), 25–45 y	38.6 (4.9), 25–45 y	34.9 (5.1), 25–45 y	32.2 (4.5), 25–44 y	$F = 137.5$	$< .001^{a,b,c}$
White (%)	29.3%	22.7%	29.0%	36.0%	$\chi^2 = 13.5$	$.001^{b}$
African-American (%)	24.9%	26.5%	26.5%	21.8%	$\chi^2 = 2.5$	.282
Latina (%)	23.4%	29.3%	21.8%	19.2%	$\chi^2 = 9.7$	$.008^{a,b}$
Chinese (%)	22.4%	21.5%	22.7%	23.0%	$\chi^2 = 0.3$	.881
Cardio-metabolic Risk:						
Triglycerides (% ≥ 150 mg/dL)	9.9%	12.3%	9.5%	7.9%	$\chi^2 = 3.6$	.168
HDL (% < 50 mg/dL)	27.4%	31.5%	29.3%	21.5%	$\chi^2 = 9.0$	$.011^{b,c}$
LDL (% ≥ 130 mg/dL)	12.9%	13.6%	12.3%	12.7%	$\chi^2 = 0.6$	.881
Glucose (%≥ 100 mg/dL)	6.9%	9.5%	6.9%	4.4%	$\chi^2 = 6.3$	$.044^{b}$
Insulin (%≥ 15 uIU/mL)	6.8%	6.4%	9.3%	4.8%	$\chi^2 = 5.0$	.081
HOMA-IR (%≥ 2.6)	12.2%	12.6%	14.8%	9.1%	$\chi^2 = 4.9$	.088
Waist Circum (%≥ cut-off*)	36.8%	43.8%	40.7%	25.9%	$\chi^2 = 25.1$	$< .001^{b,c}$
Hypertension (% rec'd dx)	7.4%	10.7%	7.9%	3.5%	$\chi^2 = 12.4$	$.002^{b,c}$
BMI (%≥ 30 kg/m^2)	28.9%	37.9%	30.0%	18.9%	$\chi^2 = 17.9$	$<.001^{a,b,c}$

AMH = Anti-Mullerian hormone

HDL = high-density lipoprotein

HOMA-IR = homeostasis model assessment of insulin resistance

*Waist circumference cut-offs were ≥ 88 cm for white, African-American, and Latina women and ≥ 80 cm for Chinese women.

*a*Significant differences were between low AMH and mid AMH levels.

*b*Significant differences were between low AMH and high AMH levels.

[c] Significant differences were between mid AMH and high AMH levels.

Table 2

Results of negative binomial regression analyses examining AMH levels in relation to the number of cardio-metabolic risk factors in a sample of 951 pre-menopausal women.

	Model 1 (age-adjusted)		Model 2 (covariate-adjusted[a])	
	Factor change	**95% CI**	**Factor change**	**95% CI**
DV: Number of cardio-metabolic risk factors (range 0–5)				
Parity (1=1+ live births vs. 0=no births)	-	-	1.508***	1.270, 1.789
Birth control (1=past use vs. 0=never)	-	-	0.923	0.783, 1.089
Menarcheal age	-	-	0.920	0.878, 0.965
African-American	-	-	2.216***	1.670, 2.941
Latina	-	-	2.453***	1.835, 3.279
Chinese	-	-	1.156	0.825, 1.621
Smoking (1=current/past vs. 0=never)	-	-	0.873	0.720, 1.059
Age	1.012	0.996, 1.028	1.011	0.995, 1.026
AMH Low (vs. High)	1.521***	1.215, 1.905	1.272*	1.037, 1.561
AMH Mid (vs. High)	1.460***	1.181, 1.806	1.311**	1.079, 1.592

AMH = Anti-Mullerian hormone

†$P<.10$,

*$P<.05$,

**$P<.01$,

***$P<.001$

[a]covariates included age, cigarette smoking, race/ethnicity (with White as the reference group), menarcheal age, past use of hormonal birth control, and parity

Table 3

Results of logistic regression analyses examining AMH levels in relation to individual cardio-metabolic risk factors in a sample of 951 pre-menopausal women.

	Model 1 (age-adj.)		Model 2 (covariate-adj.[a])	
	OR	**95% CI**	**OR**	**95% CI**
DV: Triglycerides (0 = <150; 1 = ≥ 150 mg/dL)				
AMH Low (vs. High)	1.242	0.680, 2.269	0.995	0.528, 1.874
AMH Mid (vs. High)	1.082	0.612, 1.916	0.950	0.523, 1.726
DV: HDL (0 = ≥ 50; 1 = <50 mg/dL)				
AMH Low (vs. High)	1.814**	1.211, 2.718	1.440†	0.939, 2.209
AMH Mid (vs. High)	1.568*	1.083, 2.269	1.430†	0.969, 2.112
DV: HOMA-IR (0 = <2.6; 1 = ≥ 2.6)				
AMH Low (vs. High)	1.278	0.724, 2.253	1.085	0.608, 1.934
AMH Mid (vs. High)	1.646†	0.994, 2.724	1.474	0.877, 2.479
DV: Waist Circumference (0 = <cut-off; 1 = ≥ cut-off[b])				
AMH Low (vs. High)	2.012***	1.380, 2.934	1.594*	1.051, 2.418
AMH Mid (vs. High)	1.881***	1.333, 2.654	1.731**	1.182, 2.534
DV: Hypertension (0 = normotensive; 1 = hypertensive)				
AMH Low (vs. High)	2.373*	1.095, 5.143	1.966†	0.901, 4.291
AMH Mid (vs. High)	2.052†	0.976, 4.314	1.822	0.855, 3.883

AMH = Anti-Mullerian hormone

HDL = high-density lipoprotein

HOMA-IR = homeostasis model assessment of insulin resistance

† $P<.10$,

* $P<.05$,

** $P<.01$,

*** $P<.001$

[a] covariates included age, cigarette smoking, race/ethnicity (with White as the reference group), menarcheal age, past use of hormonal birth control, and parity

[b] waist circumference cut-offs were ≥ 88 cm for white, African-American, and Latina women and ≥ 80 cm for Chinese women.