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Antral Follicle Count Predicts Natural Menopause in a Population-Based Sample: The CARDIA Women's Study

Melissa F. Wellons, MD¹, Gordon Wright Bates, MD², Pamela J. Schreiner, PhD³, David S. Siscovick, MD⁴, Barbara Sternfeld, PhD⁵, and Cora E. Lewis, MD⁶

¹Department of Medicine, Vanderbilt University, 2525 West End Avenue, Suite 600, Nashville, TN 37203

²Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Alabama at Birmingham, 619 19th Street South, Room 10390 19th Street South, Birmingham, AL 35249

³Division of Epidemiology and Community Health, University of Minnesota, 1300 S 2nd St., Suite 300, Minneapolis, MN 55454

⁴Cardiovascular Health Research Unit, Departments of Medicine and Epidemiology, University of Washington, 1730 Minor Avenue, Suite 1360, Seattle, WA 98101

⁵Kaiser Permanente, Division of Research, Epidemiology and Prevention, 2000 Broadway Oakland, CA 94612

⁶Division of Preventive Medicine, Department of Medicine, University of Alabama Birmingham, 1717 11th Avenue South, Room 614, Birmingham, AL 35205

Abstract

Objective—The timing of menopause is associated with multiple chronic diseases. Tools to predict this milestone have relevance for clinical and research purposes. Among infertile women, a positive relationship exists between antral follicle count (AFC) and response to controlled ovarian hyperstimulation, a marker of ovarian reserve. However, a relationship between AFC and menopause that is age-independent has not been demonstrated. Thus, our objective was to evaluate the relationship between AFC measured in women at ages 34–49 and incident natural menopause over 7-years of follow-up.

Methods—The Coronary Artery Risk Development in Young Adults (CARDIA) study is a longitudinal community-based study (Chicago, Illinois; Birmingham, Alabama; Minneapolis, Minnesota; and Oakland, California) begun in 1985–1986. In 2002–03, the CARDIA Women's Study measured FSH levels and performed a transvaginal ultrasound protocol that included AFC (2mm–10mm follicles on both ovaries). Incident natural menopause was assessed by survey in 2005–06 and 2009–10.

Results—In our sample (n=456), median AFC and FSH were 5 (IQR 2–9) and 7.8 mIU/mL (IQR 5.6–11.0), respectively, at a mean age of 42 (range 34–49) in 2002–03. 101 women reported natural menopause by 2009–10. In Cox models, current smoking, stable menses, FSH>13, and AFC ≤ 4 were independently associated with incident natural menopause. Compared to AFC >4, those with AFC ≤ 4 were nearly twice as likely to have undergone menopause over 7-years of follow-up (HR 1.89, 95% CI 1.19–3.02) after adjustment for covariates.

Corresponding Author: Melissa Wellons, MD, MHS., Vanderbilt University Medical Center, 2525 West End Avenue, Suite 600, Nashville, TN 37203, 615.343.6756 voice, 615.936.8291 fax, Melissa.Wellons@Vanderbilt.edu.

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Conclusion—AFC is independently associated with natural menopause over 7-years of follow-up after controlling for other markers of ovarian aging.

Keywords

Antral Follicle Count; Menopause; Ovarian Aging; Ovarian Reserve; FSH

Introduction

Menopause is an inevitable life event for most women (and all women who live long enough) and is thought to represent the complete cessation of ovarian oocyte production. The timing of menopause is associated with multiple chronic diseases such as coronary heart disease, stroke, breast cancer, and osteoporosis^{1–6}. Thus, tools to predict this milestone have potential relevance to the assessment of chronic disease risk for epidemiologic and clinical purposes.

Antral follicle count (AFC) is a tool that accurately predicts the ovary's ability to produce oocytes when stimulated by gonadotropins⁷ but AFC's ability to predict menopause is relatively unstudied because of the length of follow-up needed to assess this outcome. Broer et al followed 185 Dutch women for 11 years with 48 experiencing menopause⁸. They did not find an independent association between baseline AFC and future menopause after controlling for age. Our aim was to examine AFC's association with incident menopause in a larger sample of black and white premenopausal women recruited from the community.

Methods

Study Population

Data were from the Coronary Artery Risk Development in Young Adults (CARDIA) study, a longitudinal, epidemiologic investigation of the evolution of cardiovascular risk among young adults^{9,10} and from the ancillary CARDIA Women's Study (CWS). For CARDIA, participants 18–30 years were recruited from the populations of Birmingham, Chicago, and Minneapolis and through the membership in a large healthcare plan (Oakland, California). Baseline examinations were performed in 5115 (51% of eligible persons contacted) in 1985–86, including 2788 women. The population was balanced according to age, sex, education, and race at each CARDIA site. A description of the methodology for recruiting subjects and performing data collection is detailed elsewhere^{9,10}.

The CWS was an ancillary study to CARDIA designed to examine the associations of androgens, polycystic ovaries, and clinical features of the polycystic ovary syndrome with subclinical atherosclerosis. Women eligible for CWS had to have attended the 2000–01 CARDIA examination, have at least one ovary, and not be pregnant. The CWS examination occurred in 2002–03 and the examination components are detailed elsewhere^{11–13}.

Sample Selection

A total of 1163 women participated in the CWS. The initial CWS TVUS protocol did not include antral follicle count. In 2003, however, the protocol was changed to include antral follicle count. This change was made secondary to the publication of the Rotterdam criteria for defining polycystic ovarian syndrome, criteria which included follicle count assessments. Thus, of the 1163 CWS participants, 705 women underwent a TVUS protocol that included an antral follicle count. With regard to demographic and clinical characteristics listed in Table 1, compared to the women enrolled in CWS who underwent TVUS protocol that included AFC (n=705) the 458 who did not and were not included were younger (41.7 vs.

42.4; $p=0.002$), more often black (58% vs. 50%; $p=0.005$), and less often from the Minneapolis, MN site (0% vs. 34%; $p<0.001$).

For the current analyses, participants were included only if they had undergone a TVUS protocol that included AFC measurement ($n=705$) (Figure 1). Participants were then excluded if they were missing one ovary, both ovaries, or a uterus on TVUS ($n=130$). Participants were excluded if missing covariates ($n=18$) or menopause status at both the 2005–06 and 2009–10 contacts ($n=15$). Participants were excluded if they reported ovarian surgery or menopause at TVUS ($n=29$) or reported ovarian surgery or surgical menopause at the 2005–06 or 2009–10 contacts ($n=57$).

After these exclusions, 456 women remained in the final sample (Figure 1). As compared with the final sample ($n=456$), excluded women with measured FSH ($n=243$ of 249 excluded) or measured BMI ($n=248$ of 249 excluded) had higher FSH (18.1 mIU/mL in excluded women vs. 11.3 mIU/mL in included women; $p<0.001$) and BMI (31.2 in excluded women vs. 29.7 in included women; $p=0.01$).

Variables

TVUS—TVUS was performed by ARDMS-certified sonographers and targeted to the follicular menstrual cycle phase in regularly cycling women. Thirteen sonographers total (a range of 2–5 sonographers per CARDIA field center site) performed transvaginal ultrasounds on participants in the current analyses. A 5–7.5 MHz vaginal probe was used to search for each ovary. If no ovary was found after 2 minutes, iliac vessels were photographed. When an ovary was found, antral follicles (follicles measuring 2–10 millimeters) were counted. AFC comprised the total number of follicles on both ovaries.

The CWS included a quality assurance (QA) protocol for ultrasonography. For our analyses, data from a repeat transvaginal ultrasound by a QA sonographer was available for a subset of 28 participants. For AFC ≤ 4 vs. >4 , the inter-rater reliability was high ($\kappa=0.85$) between the QA ultrasound and the original ultrasound.

Follicle Stimulating Hormone (FSH)

Blood samples were drawn on the day of TVUS. Within one hour of blood draw, samples were processed into aliquots and frozen. FSH was measured in serum using a sequential two-step immunoassay (“sandwich”) assay (Beckman Coulter, Brea, CA) by the University of Alabama, Birmingham (UAB) OB/GYN Research and Diagnostic Laboratory. For FSH, the intra-assay CVs ranged from 3.8–5.4% and the inter-assay CVs ranged from 3.9–4.2% in the UAB OB/GYN Research and Diagnostic Laboratory.

Menopause

The primary outcome was incident natural menopause assessed by self-report. Participants completed a self-administered questionnaire (2005–06) or were surveyed by phone (2009–10) with the question “Have you gone through menopause or the change of life?” followed by “If yes, how did your periods stop?” with the options of “naturally” “surgically” or “other”. Participants were asked “How old were you when this occurred?”.

Validation of the Natural Menopause Definition—The definition of menopause was based on self-reported questionnaire data from the 2000–01 CARDIA examination and was validated against FSH levels available in the subset of women who also participated in CWS in 2002–03. The two questions used in the definition were “Have you gone through menopause or the change of life?” and “If yes, how did your periods stop?”. An FSH level

>40 mIU/mL at the CWS exam was used as a validation of hypogonadotropic ammenorhea/menopause¹⁴.

At the 2000–01 exam (ages 33–45), 18 women reported “yes” to “Have you gone through menopause or the change of life?” and “naturally” to “If yes, how did your periods stop?” Of these women, 14/18 (78%) had menopausal FSH levels >40 mIU/mL (FSH range 16–137 mIU/mL) at the 2002–03 CWS exam. The 18 women who met the definition of menopause at the 2000–01 CARDIA examination were excluded from the current analytic sample because these women met the definition for prevalent natural menopause.

Other Gynecologic Characteristics

In the CWS, participants who affirmed that they had experienced menses in the previous 12 months and denied that they were always pregnant, breastfeeding, or using hormonal contraception during the previous 12 months were also asked the following question: “In the past 12 months, have your periods: 1) become farther apart, 2) become closer together, 3) occurred at more variable intervals, 4) stayed the same, 5) stopped completely, or 6) not sure”. The responses were dichotomized to stable menses (“stayed the same”) vs. all other answers. Participants were also asked “Are you currently using birth control pills, implants or injections?”

Sociodemographic, Lifestyle, and Anthropometric Data

Race and birthdate were obtained at baseline (1985–86). Smoking history was collected in 2000–01 and categorized as current, past, or never. Weight (at TVUS) and height (2000–01) were measured according to standardized protocols¹⁵. Body mass index (BMI) was computed in kg/m².

Statistical Methods

Goodness of fit analyses was used to determine the optimal dichotomous cutpoint for AFC (range 0–25) and FSH (range 1–60 mIU/mL). Goodness of fit, as reflected by the c-statistic, was maximized for the prediction of incident menopause at AFC of 4 vs. >4 (c-statistic 0.66) and FSH >13 vs. 13 mIU/mL (c-statistic 0.67). Sociodemographic and clinical characteristics were compared in women with AFC 4 vs. >4 using t-tests, Chi-square tests of proportions, and Kaplan Meier survival analyses.

The difference between year of the TVUS exam and year of incident menopause, calculated from age at baseline and self-reported age at natural menopause, was used as the time to incident menopause for survival analysis. Cox proportional hazards regression was performed with AFC 4 vs. >4 as the main exposure variable and incident natural menopause as the outcome. Adjustment for age, current smoking, race, FSH (>13 vs. 13 mIU/mL), stable vs. not stable menses, hormonal contraceptive use, and CARDIA center was performed. Adjustment for BMI was performed in the subsample with complete data (n=452). The proportional hazards assumption was tested as the multiplicative interaction of AFC and time-to-event. Analyses were performed using SAS statistical software (version 9.1, SAS Institute Inc, Cary, NC).

Results

In our final sample (n=456), median AFC and FSH were 5 (IQR, 2–9) and 7.8 mIU/mL (IQR 5.6–11.0), respectively, at a mean age of 42 (range 34–49) in 2002–03. Over seven years of follow-up, 101 women reported natural menopause. In 2002–03, women with AFC 4 versus >4 were older and had higher FSH (Table 1). Women with AFC 4 versus >4 had a significantly higher incidence of menopause over 7 years of follow-up (HR 3.20, 95% CI

2.11–4.83) (Figure 2). Adjustment for age, smoking, race, FSH (>13 vs. ≤13 mIU/mL), stable vs. not stable menses, current hormonal contraceptive use, and examination center attenuated the HR, but AFC remained a significant independent predictor of incident natural menopause (HR 1.89, 95% CI 1.19, 3.02) (Table 2). Additional adjustment for BMI did not significantly alter the results. In the subsample of women with stable menses and not taking hormonal contraception (n=219), the hazard of incident menopause for AFC ≤4 versus >4 was 3.24 (95% CI 1.51, 6.96) after adjustment for age, smoking, race, FSH (>13 vs. ≤13 mIU/mL) and examination center.

Conclusions

Among women initially ages 34–49, 7-year hazard of natural menopause was almost 2-fold higher for women with a low AFC (≤4), even after controlling for other known factors associated with menopause. Multiple prospective studies have shown a relationship between lower AFC and a low production of oocytes during controlled ovarian stimulation for infertility¹⁶, but a relationship between AFC and menopause that is independent of age has not been demonstrated previously. One population-based prospective study of AFC and fertility decline is currently ongoing¹⁷, but to our knowledge, ours is the first study that is large enough to describe the prospective relationship between AFC and natural menopause.

Markers of ovarian aging included in 2001 NIH-sponsored Stages of Reproductive Aging Workshop (STRAW) algorithms were menstrual cycle characteristics and FSH levels¹⁸. Several longitudinal cohort studies of US women such as the Study of Women Across the Nation (SWAN)¹⁹ and the Michigan Bone Health and Metabolism Study²⁰ have followed FSH levels for up to 14 years in initially premenopausal women. These studies have shown that FSH levels increase as women approach menopause. However, FSH's utility in predicting the timing of an individual woman's menopause is limited given its variability over the menstrual cycle²¹ and suppression by exogenous estrogen and obesity¹⁹.

AFC's strength as compared with FSH is its stability over the menstrual cycle. A limitation of our study is that anti-Müllerian Hormone (AMH) was not measured, as AMH has emerged as a significant biomarker of future menopause in Dutch and Iranian cohorts^{8,22,23}, with some suggestion that it may be a superior marker of menopause as compared with AFC⁸. Like AFC, AMH is stable across the menstrual cycle, although it may be altered by BMI²⁴.

There is considerable debate regarding the gold standard for defining reproductive failure and ovarian oocyte depletion (i.e. menopause). Markers of ovarian aging included in the recently published 2012 NIH-sponsored Stages of Reproductive Aging Workshop (STRAW +10) algorithms are menstrual cycle characteristics as well as an expanded repertoire of biomarkers including FSH levels, AFC and anti-Müllerian Hormone (AMH)²⁵. The STRAW+10 executive summary states that self-reported menstrual characteristics (i.e. the self-report of 12 months of amenorrhea that hinges on the self-report of a final menstrual period) are the most practical criteria for defining menopause. This consensus definition was in part based on the lack of standardization and cost of biomarker assays. Use of the expanded repertoire of biomarkers included in the STRAW + 10 algorithm carried the caveat that “although additional biomarkers, especially AMH and AFC, have considerable promise, the lack of standardized assays and data from non-infertility populations remain important limitations to their incorporation into the STRAW staging system and their utility as clinical tools for staging reproductive aging.”

The strength of our study is that potential biomarkers of menopause were assessed in a community-based, non-infertility population. A potential limitation is our definition of

natural menopause. Our definition was derived from self-reported questions available in CARDIA at multiple time points (2000–01, 2005–06, and 2009–10). The definition was thus a practical definition based on the questions regarding menopause that were asked as the most CARDIA contact points (examinations or phone surveys). The menopause definition used was validated by FSH levels (see *Validation of Menopause Definition*).

Our definition of natural menopause was also validated by one question regarding menstrual periods (data not shown previously). At the 2009–10 phone survey, a question regarding menstrual periods was asked of all CARDIA women. Of the 101 women meeting the research definition of natural menopause in the current study and who also answered this menstrual period question, 92/98(94%) women reported that in the past 12 months their menstrual periods has stopped completely or that they had not had a period in over 12 months. Only 6/98 (6%) women gave answers suggesting that they were still having menstrual periods and it is unknown as to whether these women were currently taking exogenous hormones that could have caused menstrual bleeding.

In conclusion, we found that AFC is independently associated with incident natural menopause over seven years of follow-up after accounting for more established markers of the timing of menopause. Although our findings suggest that AFC has potential to help in the prediction of the timing of natural menopause, more research is needed to determine whether AFC and other biomarkers of ovarian aging can provide meaningful information for individual women and the clinicians who care for them. However, from a research and epidemiologic perspective, AFC holds promise as a tool for assessing the relationship between ovarian functional decline and later health outcomes.

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Figure 1.
Study Inclusion and Exclusion

Figure 2.
Kaplan-Meier Cumulative Survival Curve for Incident Menopause by Antral Follicle Count ≤ 4 vs. > 4 for 456 Women Aged 34–49 at Transvaginal Ultrasound (2002–03), followed through 2009–10

Table 1

Characteristics at Transvaginal Ultrasound (TVUS) of 456 Women Ages 34–49 with Antral Follicle Count (AFC) 4 versus >4, The CARDIA Women's Study^{*}

	AFC category at TVUS		p-value
	AFC 4 (n=193)	AFC >4 (n=263)	
Age, y	43.2 (3.5)	41.4 (3.5)	<0.001
Black Race, %	87 (45%)	111 (42%)	0.50
CARDIA Examination Center, %			<0.001
• Birmingham, AL	48 (25%)	32 (12%)	
• Chicago, IL	31 (16%)	59 (22%)	
• Minneapolis, MN	78 (40%)	91 (35%)	
• Oakland, CA	36 (19%)	81 (39%)	
Current Hormonal Contraceptive User, %	37 (19%)	34 (13%)	0.07
Smoking History, %			0.54
• Current Smoker	37 (19%)	56 (21%)	
• Past Smoker	43 (22%)	48 (53%)	
• Never Smoker	113 (59%)	159 (60%)	
FSH, mIU/mL	16.2 (20.8)	7.8 (4.5)	<0.001
Stable Menses, %	88 (46%)	142 (54%)	0.08

Abbreviations: FSH, follicle stimulating hormone; CI, confidence interval

^{*} Data are presented as mean (SD) or n (%).

Table 2

Multivariable-Adjusted Hazards Ratios of Risk Factors for Incident Menopause from 2002–2010 in 456 CARDIA Women's Study Participants.

	Hazard ratio (95% CI)	p-value
Antral Follicle Count 4 (vs. >4)	1.89 (1.19, 3.02)	0.008
Age (per year)	1.37 (1.25, 1.50)	<0.001
Black Race (vs. White)	0.66 (0.41, 1.04)	0.07
CARDIA Examination Center		
• Chicago, IL *	1.37 (0.65, 2.87)	0.26
• Minneapolis, MN	1.18 (0.59, 2.35)	0.65
• Oakland, CA	1.49 (0.71, 3.15)	0.29
Smoking History		
• Current (vs. Never)	1.75 (1.07, 2.87)	0.03
• Past (vs. Never)	1.27 (0.78, 2.09)	0.34
FSH >13 mIU/mL (vs. ≤13)	1.98 (1.26, 3.12)	0.003
Current Hormonal Contraceptive Use (vs. none)	0.51 (0.24–1.10)	0.09
Stable Menses (vs. Not Stable)	0.63 (0.42, 0.96)	0.03

Abbreviations: FSH, follicle stimulating hormone; CI, confidence interval

* Compared to Birmingham, AL Center