Maturitas 81 (2015) 493–498

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Anti-mullerian hormone (AMH) is associated with natural menopause in a population-based sample: The CARDIA Women's Study

Sangeeta Nair[a], James C. Slaughter[b], James G. Terry[a], Duke Appiah[c], Imo Ebong[d], Erica Wang[e], David S. Siscovick[f], Barbara Sternfeld[g], Pamela J. Schreiner[c], Cora E. Lewis[h], Edmond K. Kabagambe[i], Melissa F. Wellons[i,*]

[a] Department of Radiology and Vanderbilt Translational and Clinical Cardiovascular Research Center (VTRACC), Vanderbilt University, 2525 West End Avenue, Suite 600, Nashville, TN 37203, United States
[b] Department of Biostatistics, Vanderbilt University School of Medicine, 2525 West End Avenue, Suite 1100, Nashville, TN 37203, United States
[c] Division of Epidemiology and Community Health, University of Minnesota, 1300 S 2nd St., Suite 300, Minneapolis, MN 55454, United States
[d] Loma Linda University Medical Center Transplantation Institute, 25865 Barton Road, Suite 101, Loma Linda, CA 92354, United States
[e] Department of Obstetrics and Gynecology, Cedars Sinai Medical Center, San Diego, CA 90048, United States
[f] New York Academy of Medicine, New York, NY 10029, United States
[g] Kaiser Permanente, Division of Research, Epidemiology and Prevention, 2000 Broadway, Oakland, CA 94612, United States
[h] Division of Preventive Medicine, Department of Medicine, University of Alabama Birmingham, 1717 11th Avenue South, Room 614, Birmingham, AL 35205, United States
[i] Department of Medicine and Vanderbilt Translational and Clinical Cardiovascular Research Center (VTRACC), Vanderbilt University, 2525 West End Avenue, Suite 600, Nashville, TN 37203, United States

ARTICLE INFO

Article history:
Received 28 May 2015
Received in revised form 5 June 2015
Accepted 5 June 2015

Keywords:
Anti-mullerian hormone
Menopause
Ovarian aging
Ovarian reserve
FSH
CARDIA

ABSTRACT

Objective: AMH is associated with menopausal timing in several studies. In contrast to prior studies that were restricted to women with regular cycles, our objective was to examine this association in women with either regular or irregular menstrual cycles.
Methods: CARDIA is a longitudinal, population-based study that recruited adults ages 18–30 when it began in 1985–1986. AMH was measured in serum stored in 2002–2003. Natural menopause was assessed by survey in 2005–2006 and 2010–2011.
Results: Among 716 premenopausal women, median [25th, 75th] AMH was 0.77 [0.22–2.02] ng/dL at a median age of 42 [39–45] years. Twenty-nine percent of the women ($n = 207$) reported natural menopause during 9 years of follow up. In fully adjusted discrete-time hazard models, a 0.5 ng/dL AMH decrement was associated with higher risk of menopause ($p < 0.001$). Hazard ratios varied with time since AMH measurement. The HR (95% CI) for menopause was 8.1 (2.5–26.1) within 0–3 years and 2.3 (1.7–3.3) and 1.6 (1.3–2.1) for 3–6 and 6–9 years, respectively. When restricted to women with regular menses, results were similar (e.g., HR = 6.1; 95% CI: 1.9–20.0 for 0–3 years).
Conclusion: AMH is independently associated with natural menopause. AMH appears most useful in identifying women at risk of menopause in the near future (within 3 years of AMH measurement).

1. Introduction

Follicles are the functional units of the ovary that each contains an oocyte and its surrounding granulosa cells. These follicles are necessary for fertility and menstrual cycling and constitute a woman's "ovarian reserve" [1]. Menopause represents the loss of ovarian reserve and is an inevitable life event for all women who live long enough [2,3]. The timing of this life event is associated with multiple chronic diseases such as breast cancer (late menopause) and coronary heart disease, stroke, and osteoporosis (early menopause) [4–9]. Thus, biomarkers that can estimate ovarian reserve and the onset of menopause may also have utility in identifying women at low or high risk of common chronic diseases.

Anti-mullerian hormone (AMH), a dimeric TGF-beta superfamily glycoprotein is produced by the granulosa cells of ovarian

* Corresponding author at: Vanderbilt University Medical Center, 2525 West End Avenue, Suite 600, Nashville, TN 37203, United States. Tel.: +1 615 343 6756; fax: +1 615 936 8291.
E-mail address: Melissa.Wellons@Vanderbilt.edu (M.F. Wellons).

http://dx.doi.org/10.1016/j.maturitas.2015.06.026
0378-5122/

follicles in women [3]. AMH has recently emerged as a potentially useful biomarker of ovarian reserve and of the timing of future menopause. Its utility in estimating the onset of menopause has been demonstrated in regularly cycling women from Dutch, Iranian, and US cohorts [10–12]. A particular strength of AMH as a biomarker of ovarian reserve is its relative stability across the menstrual cycle as compared with other ovarian reserve hormones [13,14]. This makes it especially useful for epidemiologic studies with stored biospecimens from women in various reproductive stages or that that are drawn at a time when the menstrual cycle phase is unclear or unknown.

Our aim in this study was to examine AMH's association with incident menopause in premenopausal women from CARDIA Women's Study (CWS). These women were recruited from the general population and inclusion in CWS was not contingent on proven fertility or status in a certain menstrual cycle phase or reproductive aging stage.

2. Materials and methods

2.1. Study population

We utilized data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, a longitudinal, epidemiologic investigation of the evolution of cardiovascular risk among young adults [15,16] and the CARDIA Women's Study (CWS), an ancillary study to CARDIA. Participants 18–30 years old were recruited from the populations of Birmingham, Chicago, and Minneapolis and through a Kaiser Permanente membership plan (Oakland, California). Baseline examinations were performed in 5115 participants (51% of eligible persons contacted) in 1985–1986, a sample that included 2788 women. The population was balanced according to age (18–24 or 25–30 years), sex, education (less than high school vs. high school or more), and race (black and white) at each CARDIA site. A description of the methodology for recruiting subjects and performing data collection is detailed elsewhere [15,16]. An institutional review board at each site approved all study procedures; written informed consent was obtained from study participants prior to assessments.

The CWS was 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 2000–2001 CARDIA (year 15) examination, have at least one ovary, and not be pregnant. Women with a history of hysterectomy or menstrual cycle irregularity were eligible for participation. The CWS examination occurred in 2002–2003 and the examination components that included a blood draw and a trans-vaginal ultrasound are detailed elsewhere [17–19]. Blood draws for CWS were targeted to the follicular phase of the menstrual cycle.

2.2. Sample selection

A total of 1163 women participated in the CWS and 1123 of these had serum available for AMH measurement. For the current analyses, participants were excluded if they reported a history of prevalent natural menopause or hysterectomy at baseline or were missing covariates from the CWS baseline examination which occurred between 2002 and 2003. They were also excluded if data on menopause status were missing from both the 2005–2006 and 2010–2011 examination or if they reported a history of hysterectomy at either examination. After these exclusions, 716 women remained in the final sample.

2.3. Data collection

2.3.1. Assays

Blood samples were drawn in 2002–2003 from the antecubital vein using a protocol that ensured minimal stasis and immediate refrigeration at 4 °C. Within 1 h of blood draw, serum samples were processed into aliquots and frozen at −70 °C until shipped to the ReproSource Laboratory (Boston, MA) in 2014 for analyses.

2.3.1.1. AMH. AMH was measured in stored serum samples using Ansh Laboratories (Webster, TX) Ultra-Sensitive AMH ELISA. For this assay, the lower limit of detection (LLOD) is 0.02; the lower limit of quantification (LLOQ) is 0.09. The intra-assay CVs ranged from 3 to 7% and the inter-assay CVs ranged from 5 to 10% in the ReproSource Laboratory. For the purposes of this analysis, 0.089 was applied to all AMH values ≤0.09. In a pilot project of a random sample of CWS participants ($n = 129$) the Beckman Generation II assay was run in parallel with the Ansh Ultra-Sensitive assay. The results of these assays correlated highly ($r = 0.99$).

2.3.1.2. Estradiol, progesterone and follicle stimulating hormone (FSH). Estradiol, progesterone, and FSH were measured in serum with chemiluminescent immunoassays by the ReproSource Laboratory using either the Immulite 2000 or Cobas 411e systems.

2.4. Menopause definition

The primary outcome was self-reported incident natural menopause. Participants completed a self-administered questionnaire during the CARDIA year 20 (2005–2006) and/or year 25 examination (2010–2011) 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?", which was used in analysis as age at menopause. Our definition of natural menopause was also validated against a question regarding the date of last menstrual period. Of the 207 women who reported an incident natural menopause, 202 reported both age and calendar year at which menopause occurred. Ninety-four percent (191/202) reported a date within ± 1 year of their reported age at menopause.

2.5. Covariates

2.5.1. Reproductive characteristics

Participants in CWS (2002–2003) completed a self-administered questionnaire with the question "Are your menstrual periods regular or irregular. By irregular we mean that you could predict when you period would start at least half the time". Participants were also queried regarding their current use of hormonal contraceptives.

2.5.2. Sociodemographic, lifestyle, and anthropometric data

Race and birth date were obtained at the year 0 examination (1985–1986). Smoking history was collected at the year 15 examination (2000–2001) and women were categorized as current, past, or never smokers. Weight (at the CWS baseline examination) and height (2000–2001) were measured according to standardized protocols [20]. Body mass index (BMI) was computed in units of kg/m^2. Total physical activity score was calculated using a previously validated algorithm in CARDIA [21].

2.6. Statistical methods

To summarize characteristics of women in CWS, we distributed them into two groups depending on whether their baseline AMH