

Original Research Article

Age at Menarche and Parity are Independently Associated with Anti-Müllerian Hormone, a Marker of Ovarian Reserve, in Filipino Young Adult Women

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Objectives: Despite ample evidence of variation in timing of menopause, little is known about the extent or underlying causes of individual variation in ovarian reserve and age-related follicular decline. Anti-Müllerian hormone (AMH), a hormonal marker of ovarian reserve, may be a useful tool to clarify these questions. We describe AMH in a cohort of Filipino young adult women, and evaluate whether ovarian reserve in early adulthood relates to measures of life history scheduling (menarcheal age) and reproductive effort (parity).

Methods: Data and samples are obtained from 294 nonpregnant participants (21.5 years \pm 0.3) in the Cebu Longitudinal Health and Nutrition Survey. Plasma AMH was assayed using an enzyme immunoassay and relationships between AMH, menarcheal age, and parity were examined.

Results: Mean AMH was 4.3 ng/mL. In multiple regression models, women who experienced menarche earlier had significantly higher AMH as young adults ($P < 0.05$). Women with two ($P < 0.05$) and three or more ($P < 0.01$) children had significantly lower AMH than those with no children. These associations were independent of age, smoking, and body mass index.

Conclusions: These findings suggest that individual variation in life history scheduling and reproductive history could contribute to variation in ovarian reserve. Moreover, they demonstrate the utility of AMH as a tool for human reproductive ecology, and highlight the need for further research clarifying the extent of human population variation in ovarian reserve and the behavioral and ecological influences underlying this variation. *Am. J. Hum. Biol.* 00:000–000, 2012. © 2012 Wiley Periodicals, Inc.

Menopause, the event marking cessation of ovarian activity sufficient to support monthly menstrual cycling, is the outward signifier of the end a lifelong process of female reproductive senescence. As the timing of menopause precedes senescent decline in other organ systems by several decades (Hill and Hurtado, 1991), the decoupling of reproductive and somatic senescence is a defining feature of the derived human life history (Robson et al., 2006), and remains the source of extensive theoretical speculation among human evolutionary biologists (e.g., Ellison, 2001; Ellison, 2010; Hawkes et al., 1998; Kaplan et al., 2000; Kaplan et al., 2010; Peccei, 2001). Although the best estimates of menopausal timing in the United States suggest that it occurs at approximately 51 years (McKinlay et al., 1992), the timing of menopause is variable within and across populations (Castelo-Branco et al., 2006; Leidy Sievert, 2006; Morabia et al., 1998; Thomas et al., 2001), normally occurring between the ages of 45 and 55 years (WHO, 1996).

As menopause is caused by the depletion of the stock of primordial ovarian follicles (known as ovarian reserve), variability in the timing of menopause reflects interindividual differences in ovarian reserve. Ovarian follicles are initially formed *in utero*, and immediately after formation, the pool of follicles begins to decline in a process known as follicular atresia (Baker, 1963; Block, 1953; Forabosco and Sforza, 2007; Forabosco et al., 1991; Hansen et al., 2008), a blanket term for degenerative follicle death through apoptotic or other pathways (Kaipia and Hsueh, 1997; Tingen et al., 2009). At birth, women have between 500,000 and 1,000,000 follicles, of which approximately 40% are

lost by the time women reach puberty (Wallace and Kelsey, 2010). By comparison, over a woman's entire reproductive lifespan, at most 400 follicles will be lost to ovulation. Therefore, atresia, not ovulation, is responsible for the loss of the vast majority of follicles, and any variability in the timing of reproductive senescence is likely to stem from differences in initial follicular endowment or the rate at which follicles are lost through atresia (Leidy, 1994; Thomford et al., 1987). Although many mathematical models have been derived to describe the trajectory of follicle loss across the lifecycle (for a recent review, see Coxworth and Hawkes, 2010), such models are based on a relatively small and potentially unrepresentative database of histological follicle counts from cross-sectional samples; as such, these models cannot be generalized to describe the trajectories of reproductive senescence in individual women (Broekmans et al., 2009; Coxworth and Hawkes, 2010). As menopause is the only point at which an individual woman's ovarian reserve can be noninvasively and

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unambiguously determined (Broekmans et al., 2009), most studies of variation in ovarian reserve or the lifelong process of ovarian aging have, by necessity, primarily focused on the timing of the event of menopause (Leidy, 1994; Leidy Sievert, 2006), which is only informative of the end point of the trajectory of reproductive senescence.

Although many studies have reported associations between various socio-demographic, reproductive, or developmental factors and menopausal timing (for a general review, see Leidy Sievert, 2006), only a few are consistent predictors (reproductive characteristics, such as parity: Harlow and Signorello, 2000; marital status: Leidy Sievert et al., 2001; smoking: Parente et al., 2008). The inconsistency that characterizes many other associations may stem at least in part from methodological issues (Canavez et al., 2011; Harlow and Signorello, 2000), as accurate assessment of menopausal age can be difficult (Leidy Sievert, 2006; Leidy Sievert and Hautaniemi, 2003; Wood, 1994). For instance, many studies of menopausal timing from non-Western populations report mean recalled age at menopause (e.g., Goodman et al., 1985; Sarin et al., 1985; Wasti et al., 1993). This is problematic, because use of recall data and calculation of mean ages of menopause tends to bias downward estimates of menopausal age (Leidy Sievert and Hautaniemi, 2003), implying that some of the most interesting comparative data points, from the perspective of understanding population variation in reproductive senescence and its correlates, may be methodologically suspect (discussed in Reynolds and Obermeyer, 2001; Reynolds and Obermeyer, 2003). Thus, understanding of variation in menopausal timing, and by extension ovarian reserve, is relatively coarse-grained.

Anti-Müllerian hormone (AMH), a hormonal marker of ovarian reserve, holds promise to help overcome many of these methodological challenges (Bentley and Muttukrishna, 2007; La Marca and Volpe, 2006; La Marca et al., 2009; van Rooij et al., 2002; Visser et al., 2006). Also commonly referred to as Müllerian-inhibiting substance, AMH is secreted by granulosa cells in growing primary, secondary, and small antral ovarian follicles in females, with secretion highest in the secondary and small antral stages and ending abruptly with further follicle growth (Visser et al., 2006; Weenen et al., 2004). AMH levels in women are low to nondetectable at birth, rise in childhood, and peak during adolescence or early adulthood, and then decline gradually with age (Hagen et al., 2010; La Marca et al., 2010; Lee et al., 1996). AMH is useful as a marker of ovarian reserve because it is produced in proportion to the number of growing follicles, which is itself thought to reflect of the number of primordial follicles (Bentley and Muttukrishna, 2007; La Marca et al., 2009; Scheffer et al., 1999; Visser et al., 2006). The association between ovarian reserve and AMH first confirmed in mice (Kevenaar et al., 2006) has also been documented in macaques (Appt et al., 2009) and, using histologically determined primordial follicle counts, in humans (Hansen et al., 2010). The biomedical community has quickly recognized the practical implications of this relationship: as AMH levels decline predictably with age, the hormone can be used as a biomarker of ovarian aging (de Vet et al., 2002). As such, AMH is increasingly being regarded as an important complementary source of information for forecasting the menopausal transition alongside other markers of ovarian aging such as follicle-stimulating hormone (Broer et al., 2011; Sowers et al., 2008; Tehrani et al., 2009; Tehrani et al., 2011; van

Disseldorp et al., 2008; van Rooij et al., 2004; van Rooij et al., 2005).

Here, we evaluate hypotheses aimed at clarifying the contributions of important developmental and reproductive parameters to variation in AMH. The first is based on a recent report that suggested ovarian primordial follicle loss (to recruitment and/or atresia) increases until age 14 before declining (Wallace and Kelsey, 2010), which the authors speculate is owing to the altered hormonal milieu brought about by puberty. If loss of primordial follicles slows at puberty, as indicated by this model and other studies (Crisp, 1992; Faddy et al., 1983; Tingen et al., 2009), women who enter puberty earlier should have higher AMH as young adults. The second hypothesis, derived from the documented association between higher parity and later menopause (Cramer et al., 1995; Gold et al., 2001; Hardy and Kuh, 1999; Henderson et al., 2008; Whelan et al., 1990), is that women who have higher parity will have higher AMH. We use data from nonpregnant young adult women ($n = 294$, sample age = $21.5 \text{ years} \pm 0.3$), followed prospectively since birth, to ascertain the relationships between parity, menarcheal age, and ovarian reserve (as reflected by AMH levels), controlling for important potentially confounding influences.

MATERIALS AND METHODS

Study population

Data and samples are from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a prospective, population-based study in Cebu City, the Philippines. The study is a 1-year birth cohort that originally invited all pregnant women in 33 randomly selected communities in Metro Cebu to participate in the study. Women in the current analysis were enrolled into the cohort as infants ($n = 1,447$) in 1983–1984 and have been followed prospectively since birth through young adulthood. Data are obtained from follow-up surveys conducted in 1994–1995, 1998–1999, 2002, and 2005 (for a recent overview of the study's history and design, see Adair et al., 2011). Blood samples for the analysis of AMH were taken from a random subsample of women ($n = 330$) from the larger pool of participants for whom blood from the 2005 follow-up was available. This research was conducted under conditions of informed consent with human subjects' clearance from the Institutional Review Boards of the University of North Carolina, Chapel Hill, and Northwestern University.

Data collection

Interview data were collected during interviews in respondents' homes during the 2005 surveys. Menarcheal status was assessed at each preceding survey starting in late childhood, during the 1994–1995, 1998–1999, and 2002 surveys, when participants were 11.5 ± 0.4 , 15.5 ± 0.6 , and 18.7 ± 0.3 years old, respectively. Girls were asked to report their menstrual status and the month and year of their first period (for details, see Adair, 2001). During the 2005 survey, venipuncture blood samples were collected in the morning into ethylenediaminetetraacetic acid-coated tubes in the participants' homes, and then kept in coolers on ice packs for ≤ 2 h. Samples were then centrifuged, frozen at -70°C , and shipped to Northwestern University on dry ice where they were stored at -80°C until analyzed.

TABLE 1. Sample characteristics, mean \pm SD unless otherwise noted

	Total sample (n = 294)	Nulliparous (n = 207)	1 Child (n = 53)	2 Children (n = 25)	3+ Children (n = 9)	P ^a
AMH (ng/mL)	4.3 \pm 2.2	4.5 \pm 2.2	4.1 \pm 2.3	3.5 \pm 2.1	2.8 \pm 1.2	^b
Menarcheal age (years)	12.8 \pm 1.3	12.9 \pm 1.4	12.6 \pm 1.0	12.6 \pm 1.0	13.0 \pm 1.4	
Age (years)	21.5 \pm 0.3	21.5 \pm 0.3	21.5 \pm 0.3	21.5 \pm 0.3	21.7 \pm 0.4	
BMI (kg/m ²)	20.5 \pm 3.5	20.2 \pm 3.7	21.3 \pm 2.7	21.0 \pm 2.8	22.1 \pm 3.7	
Smoker (%)	6.1	6.7	3.8	8.0	0	

^aP-value from ANOVA or χ^2 comparing women of different parities.

^bP < 0.05.

TABLE 2. Multivariate predictors of AMH, $\beta \pm SE$ (n = 294)^a

	Model 1	Model 2	Model 3
Menarcheal Age (years)	-0.24 \pm 0.10 ^b	-0.26 \pm 0.10 ^b	-0.28 \pm 0.11 ^b
1 Child ^c		-0.47 \pm 0.35	-0.44 \pm 0.36
2 Children		-1.06 \pm 0.4 ^b	-1.02 \pm 0.47 ^b
3+ Children		-1.63 \pm 0.43 ^d	-1.50 \pm 0.45 ^d
Age (years)			-0.04 \pm 0.32
BMI (kg/m ²)			-0.02 \pm 0.03
Current smoker (Yes)			-0.23 \pm 0.48
Model R ²	0.02	0.05	0.06

^aAll models reported with robust standard errors.

^bP < 0.05.

^cNulliparous = comparison group.

^dP < 0.01.

Laboratory analysis

Plasma AMH was measured with an ELISA using a commercially available enzyme-immunoassay protocol (DSL, Beckman Coulter, reference #DSL-10-14400). Three controls were included with each assay (low, medium, and high) with interassay coefficients of variation (standard deviation [SD]/mean) of 6.5, 2.7, and 9.7%, respectively.

Statistical analysis

Analyses were performed with Stata 11.0 (Stata, College Station, TX). Parity was coded on a four-level scale from 0 to 3+ children. As pregnancy is associated with diminished AMH levels (Nelson et al., 2010), women who were pregnant at the time of blood collection were excluded from these analyses. To account for women who may have been early in pregnancy during the 2005 blood draw, but not yet aware they were pregnant, pregnancy status during sample collection was verified retrospectively using reproductive histories collected in 2007 and 2009. As smoking was infrequent (<10% of women in the sample reported smoking) and at low dosage (4% of women smoked but not daily, only 3% of women smoked any amount of cigarettes daily), smoking status was coded as a dummy variable, denoting women who reported smoking any number of cigarettes at the time of interview. AMH was analyzed as a continuous variable. A series of regression models was run, beginning with age at menarche alone as predictor, then adding dummy variables for each level of parity, followed by variables that might confound associations, namely smoking status, age at sample collection, and body mass index (BMI, kg/m²) (Freeman et al., 2007; Steiner et al., 2010; Su et al., 2008). Models were restricted to a subsample of nonpregnant women for whom all variables were available (n = 294). Women not included in this analysis did not differ in AMH level, par-

ity, menarcheal age, or age at blood draw (among those nonpregnant women for whom we had AMH data were not included owing to missing data, all P > 0.05). Regression models were tested for heteroskedasticity with Stata's "hettest" command, and robust standard errors were estimated when needed.

RESULTS

Characteristics of the women included in the study are summarized in Table 1. The sample was relatively young, ranging from 20.8 and 22.4 years. Age at menarche occurred on average at 12.8 years, and while 29.6% of women had given birth to at least one child, the majority of women in the sample were nulliparous. Based on their BMI, this sample is relatively lean, with 85 women classifiable as underweight (BMI \leq 18.5) and only 31 women who were overweight (BMI \geq 25).

Consistent with our predictions, women who reached menarche earlier had higher AMH (P < 0.05) measured at a mean of 21.5 years (Table 2, Model 1). Adding terms for number of prior pregnancies (Model 2) revealed a statistically significant inverse relationship between parity and AMH: contrary to our hypothesis, women with 2 (P < 0.05) or 3+ (P < 0.01) children had lower AMH levels than nulliparous women. The association with menarcheal age slightly strengthened after adjustment for parity. In the final model (Model 3), women's current smoking status, age at sample collection, and BMI were added to the model, and were not significant predictors of AMH in this population. The coefficient for menarcheal age strengthened, and those for 2 or 3+ children attenuated slightly, but all remained significant (P < 0.05).

In the fully adjusted model, each year later menarche predicted about 12% of a SD reduction in adult AMH, and having 2 or 3+ children each predicted roughly 50% of a SD decrease in AMH although women who had only given birth to one child did not vary from non-mothers in AMH. The overall association with parity was significant (F(3, 286) = 4.25, P < 0.01).

Mean levels of AMH predicted for each parity level, adjusting for all other model covariates, are shown in Figure 1. The effects of menarcheal age and parity on AMH in early adulthood are statistically independent as shown in Figure 2.

DISCUSSION

In this sample of Filipino young adult females, we found significant associations between both maturational tempo and parity and AMH measured in young adulthood. Consistent with our predictions and previous research, women who experienced menarche earlier had higher AMH as young adults than women who matured later.

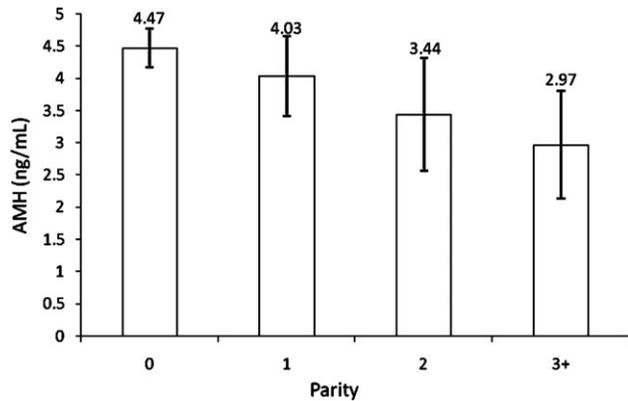


Fig. 1. Relationship between AMH and Parity. Bars are 95% confidence intervals, and predicted means for each level of parity from the fully adjusted model are displayed above each bar.

However, contrary to our expectations, women with higher parity had lower AMH than nulliparous women, independent of the effect of maturational tempo. These effects were robust to inclusion of controls for age at sample collection, BMI, and smoking. These results suggest that AMH, a proxy for ovarian reserve, is related to indices of life history scheduling (menarcheal age) and reproductive effort (parity) (Ellison, 2003) in young adult women.

AMH levels in this population were similar to those from 24-year-old women in the United States (mean = 4.1 ng/mL, Seifer et al., 2011), but they were considerably lower than the levels reported among 18- to 22-year-old women in the Netherlands (median = 7.6 ng/mL, Kerkhof et al., 2010). The limited comparative data from women matched by age, and differences in laboratory protocol across studies, preclude drawing strong conclusions from these crosspopulation differences. Future work conducted using a common protocol with samples from multiple populations, ideally analyzed in the same laboratory setting, would help establish the extent of population variation in AMH levels.

Our finding that AMH levels are higher among women who matured earlier is consistent with a study by Kerkhof et al. (2010), who similarly reported an inverse association between AMH levels in young adulthood and menarcheal age. The authors proposed that this might be owing to girls who have larger follicle pools having higher estrogen levels, which could lower the age of first menses, a possibility supported by findings suggesting that AMH might be involved in the regulation of estrogen synthesis (Kevenaar et al., 2007). Our hypothesis that women who matured earlier would have higher AMH as adults was based on the suggestion that primordial follicle loss is greatest before puberty (Crisp, 1992; Faddy et al., 1983; Finch and Kirkwood, 2000; Leidy, 1994; Tingen et al., 2009; Wallace and Kelsey, 2010). Although our results confirmed this hypothesis, it is unclear whether AMH and menarcheal age are associated because of an effect of the size of the follicle pool on the timing of puberty, as Kerkhof et al. posit, or vice versa. As AMH secretion begins in childhood (Hagen et al., 2010; Lee et al., 1996), repeat measurements of AMH as individuals progress through

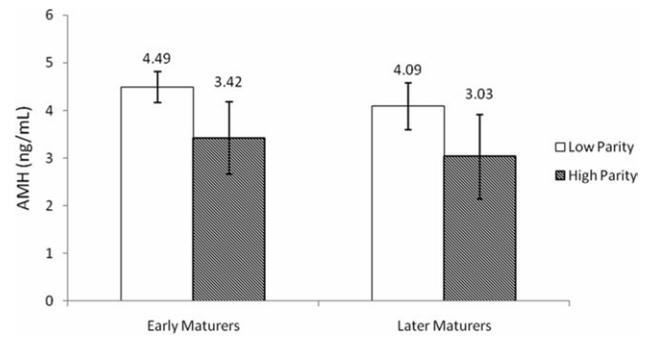


Fig. 2. Independent effects of parity and menarcheal age on ovarian reserve. This graph shows the independent relationships between maturational timing and AMH and parity and AMH, means and 95% confidence intervals are calculated predicted values adjusted for all other model covariates. Here, maturational timing was modeled as a median split dummy variable (early maturers' age at menarche ≤ 13 years and late maturers' menarcheal > 13 years), as was parity (low = 0 or 1 child, high = 2 or 3+ children).

puberty could help clarify this issue. Although earlier studies have shown lower AMH among obese women (Freeman et al., 2007; Steiner et al., 2010; Su et al., 2008), we found no relationship between BMI and AMH levels. This likely reflects the fact that women in our sample are relatively lean, with only around 10% of women meeting the definition of overweight or obese based on BMI.

To our knowledge, this is the first study to report a relationship between parity and AMH. As past studies have shown that menopause tends to occur at later ages among women with higher parity (e.g., Cramer et al., 1995; Gold et al., 2001; Hardy and Kuh, 1999; Henderson et al., 2008; Whelan et al., 1990), we hypothesized that higher parity would be associated with higher AMH in young adulthood. Our finding that higher parity is associated with *lower* ovarian reserve (as reflected by AMH) runs counter to these expectations. Importantly, all of the women in our sample are within a relatively narrow age range, adding confidence that our models are capturing an effect of parity rather than age or some correlate of age. It is difficult to interpret these results in light of the potential relationship between high-pregnancy progesterone levels and reduced follicle recruitment revealed by animal models (LaPolt et al., 1988; LaPolt et al., 1998; Pedersen and Peters, 1971), as reduced follicle recruitment would be expected to lead to a slower rate of depletion of the follicular pool and therefore a positive relationship between number of pregnancies and AMH. It is notable, however, that women lose a greater number of primordial follicles to atresia than to recruitment to the growing pool until they are roughly 30 years old (Gougeon et al., 1994). Although speculative, it may be that parity has a protective effect on ovarian reserve by reducing follicular recruitment only after this age when the majority of follicles are lost to recruitment rather than to atresia. Future follow-up of this sample will be necessary to clarify whether the relationship between parity and AMH will change at later ages, or continues to exhibit the inverse association between parity and AMH that we found in young adulthood.

There are a number of limitations to this study that warrant mention. Despite the strength and consistency of the association between parity and ovarian reserve, it

should be noted that the majority of the women in this study were nulliparous, and parous women generally only had one or two offspring. Although nongrowing follicle recruitment peaks at 18–20 years and declines thereafter (Wallace and Kelsey, 2010), a recent model of AMH levels over the lifecourse suggests that peak AMH levels may not occur until 24.5 years (Kelsey et al., 2011). However, longitudinal data are needed to know whether or not the women in this population experience an increase in AMH after 21.5 years and it is unclear whether the documented associations would change meaningfully with such an increase. Many initial studies report that AMH levels do not vary over the menstrual cycle (Hehenkamp et al., 2006; La Marca et al., 2006; Streuli et al., 2008), these previous findings have been called into question by more recent study (Sowers et al., 2010; Wunder et al., 2008). Data to control for day of menstrual cycle are not available for this study. Although it has been suggested that these fluctuations are so minor that they are not clinically relevant (La Marca et al., 2011), future studies should collect this information nonetheless. Finally, we are unable to identify and exclude women with polycystic ovarian syndrome (PCOS), important because women with PCOS have much higher levels of AMH (Cook et al., 2002; Fallat et al., 1997). This is particularly relevant, given that PCOS can lead to subfertility, and it could be the case that women in the nulliparous group have higher mean levels of AMH because of higher rates of PCOS, which could explain our finding of an inverse association between parity and AMH. Although we cannot confidently identify women with PCOS, participants were asked in 2005 whether or not they experienced “irregularity” in menstrual cycles from 2002 to 2005, and nulliparous women were not significantly more likely to report this than women with any number of children. PCOS has been found to have a prevalence rate of 6–10% (Goodarzi et al., 2011), and excluding the women with the top 6% of AMH values from the analysis does not change the statistical significance of the effect of having two or three or more prior pregnancies on young adult AMH levels, suggesting against our results being spurious. Future crosspopulation studies will need to carefully consider the potential confound of PCOS, especially in any work designed to test the association between parity and AMH.

In sum, we found that women who matured later or had higher parity had lower AMH as young adults. As AMH is a measure of ovarian reserve, these results suggest that developmental timing and reproductive behavior could contribute to heterogeneity in female reproductive senescence through an effect on the size of the follicular pool. This study highlights the utility of AMH as a tool to explore variation in ovarian reserve and as a complement to assessment of menopausal timing in efforts to clarify associations between environmental, developmental, and reproductive factors and the duration of the female reproductive lifespan. New methods that allow the quantification of AMH in finger stick dried blood spot samples may be useful in facilitating future work in these domains (McDade et al., submitted). The decoupling of female reproductive and somatic senescence is a defining consequence of the human life history strategy, and data such as these may be useful in establishing the extent of plasticity exhibited by the life history parameter of the female reproductive lifespan. For instance, it is tempting to cast the association between reduced ovarian reserve and parity as revealing a “cost of

reproduction” (Williams, 1966) wherein future reproductive potential is reduced as an expense of current energetic investment on reproduction. This is a question that will only be answerable with longitudinal data, but nevertheless illustrates the potential of utilizing AMH to clarify issues related to life history tradeoffs, reproductive ecology, and female reproductive senescence.

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