Modeling Age at Menopause Using Serum Concentration of Anti-Mullerian Hormone

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Context: Anti-Mullerian hormone (AMH) has already been used for prediction of age at menopause with promising results.

Objective: We aimed to improve our previous prediction of age at menopause in a population-based cohort by including all eligible subjects and additional follow-up time.

Design and Setting: All reproductive-aged women who met our eligibility criteria were selected from the Tehran Lipid and Glucose Study. The serum concentration of AMH was measured at the time of recruitment, and participant's date of menopause was recorded over a 10-year follow-up.

Subjects: A total of 1015 women, aged 20 to 50 years, with regular and predictable menstrual cycles at the initiation of the study were recruited.

Main Outcome Measure: The actual ages at menopause were compared with the predicted ones obtained from accelerated failure time model.

Results: We observed 277 occurrences of menopause. Median menopausal age was 50 years (range 30.1–58.2 years). The median (SD) of differences between the actual menopausal age and those predicted by our model was 0.5 (2.5) years. Model adequacy (measured by C-statistics) for correct prediction of age at menopause was 92%. The estimated ages at menopause and their 95% confidence intervals for a range of values of AMH and age were calculated and summarized in a table.

Conclusions: Using a model built on age and AMH, we can predict age at menopause many years earlier. This could provide opportunities for interventions in those who are at risk of early or late menopause. **(*J Clin Endocrinol Metab* 98: 729–735, 2013)**

Accurate estimation of time of menopause could facilitate the preventive management of age-related female infertility, metabolic and cardiovascular disturbances, cognitive impairment, osteoporosis, and breast, uterine, and intestinal cancers (1–8).

Among the various endocrinological and sonographic markers that have been used to predict age at menopause and to assess ovarian reserve status, anti-Mullerian hormone (AMH) has recently attracted a lot of interest (9–12). First introduced in 2002 as a serum biomarker for assessment of ovarian aging (13), AMH has since been used as a tool for prediction of age at menopause. A few existing cohort studies have limitations such as small sample size (14), not including women from early reproductive

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2012-3176 Received August 25, 2012. Accepted December 3, 2012.
First Published Online January 11, 2013

Abbreviations: AMH, Anti-Mullerian hormone; CI, confidence interval; DSL, Diagnostic System Laboratories; S (t), survival function; TLGS, Tehran Lipid and Glucose Study.

age (14–16), and not having a long-enough follow-up duration (17). The results from these studies have failed to provide reliable and consistent estimations of age at menopause based on AMH and have had limited clinical utility. Our previous study was the initial report of the 6-year follow-up of a quarter of reproductive-aged female population (266 of 1265) of the Tehran Lipid and Glucose Study (TLGS) (17). We then built a statistical model to predict age at menopause based on 63 events of menopause. Three years on, we have now used all eligible women in TLGS (1015) and have considerably more people who have reached menopause (277 vs 63) within a wide age range and are in a position to re-examine the question and provide more reliable estimations of age at menopause.

Subjects and Methods

We selected our subjects from the TLGS cohort. This is an ongoing prospective population-based cohort study that began in 1998 to explore the prevalence and risk factors of noncommunicable diseases (18). After consenting to participate, 15 005 ethnic Iranian residents aged >3 years, of District 13 of the capital Tehran, were recruited and followed up at 3-year intervals. We examined all women aged 20 to 50 years in TLGS and selected those who met our eligibility criteria, which included having regular and predictable menstrual cycles at the initiation of the study, having proven natural fertility (at least 1 term pregnancy within 1 year after stopping contraception), and having no history of endocrine disorders, hysterectomy, oophorectomy, or any other kind of ovarian surgery. We also excluded those with incomplete data or those for whom blood samples were not available.

The study subjects were followed on average for 10 years. Follow-up assessments included a general physical examination and an interview during which the date of the last menstrual cycle was recorded. We defined menopause according to the World Health Organization classification as a condition of absence of spontaneous menstrual bleeding for more than 12 months, for which no other pathologic or physiologic cause could be determined. The time point of 1 year before the 12-month period of no menstrual bleeding was regarded as date of menopause. For the purpose of the current study, follow-up began at the time of the first interview and ended at their last follow-up visit or when women reached menopause.

Blood samples were collected at baseline and each follow-up visit and stored at −80°C for future use. We measured serum AMH at the time of recruitment, using stored samples by the two-site enzyme immunoassay method using Gen II kit (Beckman Coulter, Inc, Fullerton, California) and the Sunrise ELISA reader (Tecan Co, Salzburg, Austria). All AMH measurements were performed simultaneously at the same laboratory. AMH Gen II controls A79766 were used at two levels of concentration to monitor accuracy of assay. The intra- and interassay coefficients of variation were 1.9% and 2.0%, respectively.

Statistical analysis

To predict individual age at menopause, we used accelerated failure time modeling (19). Using Cox-Snell residuals, Weibull distribution was found to be the best fit and was used for the modeling (20). We considered our subjects to be at risk since they were born. Analysis was repeated after assigning sampling weights of 10 to those who reached menopause before 45 or after 54 years to compensate for their low numbers (21). The model coefficients were calculated, and the formula obtained was used to estimate average menopausal age for a range of age and AMH values (AMH = 0.1–4.5 ng/dl and age = 20–49 y). The median predicted age at menopause [S (t) (survival function) = 0.5] and its 95% confidence interval (CI) [S (t) = 0.025 and 0.975] were calculated.

We assessed our model predictions by comparing the predicted and observed age at menopause in those who had reached menopause using the Bland-Altman method (22). The Kaplan-Meier curves were plotted to compare event-free cumulative survival in women who had reached menopause and our model predictions for all women in the cohort (23). Excluded were those for whom our model predictions exceeded maximum expected menopausal age in Iranian women, which was 65 years old (24). The C-statistic was calculated to evaluate the adequacy of menopause prediction (25).

Data were analyzed using SPSS version 17 statistical software (SPSS Inc, Chicago, Illinois) and Stata version 11.2 (Statacorp, College Station, Texas).

The study protocol was approved by the Medical Ethics Committee of the Research Institute for Endocrine Sciences, and written informed consent was obtained from all participants.

Results

Of a total of 2412 women aged between 20 and 50 years in the TLGS cohort, 1015 met our eligibility criteria. The mean (SD) age and AMH serum concentration of the participants were 36.7 (7.5) years and 1.65 (1.81) ng/dl, respectively. Mean follow-up period was 3594 days (range, 1942–4481 d), and 277 women reached menopause while in the study. The median age at menopause was 50 years (range 30.1–58.2 y). Characteristics of the study participants have been summarized in Table 1.

Table 1. Characteristics of Study Participants

Characteristics	Mean (SD)
Age, y	36.7 (7.5)
Parity	2.5 (1.4)
Systolic blood pressure, mm Hg	111.2 (13.4)
Diastolic blood pressure, mm Hg	75.2 (9.3)
Body mass index, kg/m^2	27.1 (4.7)
Waist circumference, cm	86.5 (10.7)
Wrist circumference, cm	15.9 (0.97)
Hip circumference, cm	104.2 (8.7)
AMH, ng/dL	
<30 y (n = 197)	3.96 (2.34)
30–40 y (n = 435)	1.73 (1.45)
>40 y (n = 383)	0.61 (0.81)

Coefficients derived from accelerated failure time modeling were calculated as follows: menopausal age = $\{[-\ln(0.5)]^{0.060388}\} \times \exp(3.18019 + 0.1608897\text{AMH} + 0.016068\text{age})$ (equation 1).

The median predicted age at menopause was 52 years. In the Bland-Altman method, the median of differences between actual and predicted age at menopause was equal to 0.51 years (SD = 2.45; range, −5.4 to 9.2 y) showing a good agreement between the two (Figure 1). Estimated ages at menopause and their 95% CI for arbitrary values of AMH and age are summarized in Table 2. C-statistics showed that age alone has an adequacy of 84% to predict age at menopause correctly; this figure rose to 92% when AMH was added to the model.

A graphical representation of menopause-free survival, using the Kaplan-Meier plot showed similarity of survival experiences when actual and predicted ages at menopause were compared (Figure 2). The similarity was more prominent when the subset of women who had reached menopause was used (Figure 2A) instead of the whole study population (Figure 2B).

Discussion

We introduced a model to predict age at menopause using current age and AMH levels and improved our previous estimates of the coefficient of this model (equation 1 and Table 2). We identified the median ages at menopause and their 95% CI for women with varying levels of serum AMH concentrations. Median age at menopause for the model predictions in the TLGS cohort was 52 years. We found acceptable agreement between actual age at menopause and model predictions using the Bland-Altman method. The Kaplan-Meier plot showed similarity of menopause-free survival when actual and predicted menopausal ages were compared.

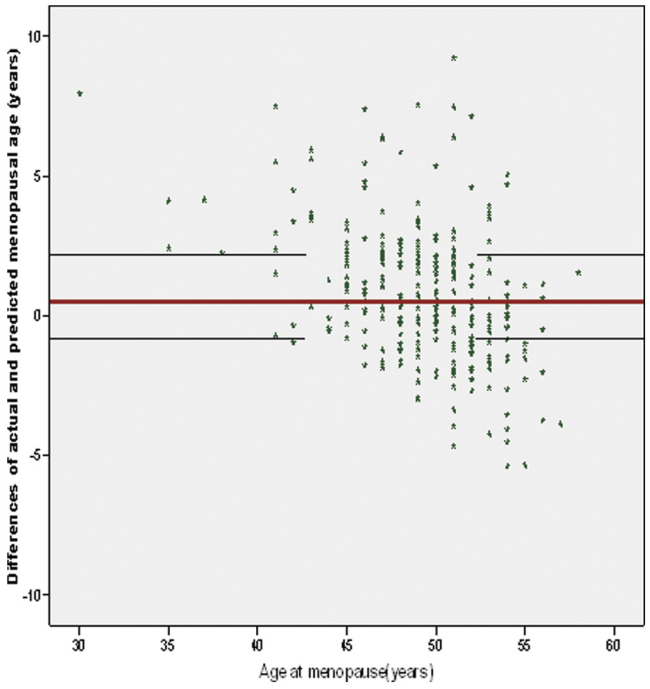

Figure 1. Agreement between actual and predicted ages at menopause using the Bland-Altman method. The red line represents median of differences between actual and predicted age at menopause; dotted lines represent the interquartile range.

AMH has several characteristics that make it a suitable biologic marker for ovarian aging. Secreted exclusively in ovarian follicles, it gradually decreases with increasing age (26); it is independent of the menstrual cycle, and only minor fluctuations in serum concentrations have been observed during the normal menstrual cycle, which is consistent with continuous noncyclic growth of small follicles (27, 28). The AMH level remains almost constant from one cycle to another and has a high intraclass correlation coefficient as a result of which only one measurement provides a reliable estimate of its mean in each woman (16, 29, 30).

Current predictions of age at menopause using serum AMH levels are still limited in number and quality; those available generally suffer from a small number of menopausal events within their relevant cohorts (17, 31). Other limitations are lack of women from early reproductive age in their samples (14, 15), not having access to the actual age at menopause in cohort members, and using available estimates from other populations (32). Van Disseldorp et al (32) used statistical modeling in cross-sectional data to provide estimates of age at menopause for 144 women aged 25 to 44 years based on their present AMH levels; they were, however, unable to validate their prediction against actual age at menopause. Sowers et al (14) also used statistical modeling for AMH serum concentration in a longitudinal study of 50 premenopausal and perimenopausal women, all of whom reached menopause while in the study; they found that the value of AMH could precisely predict the time to menopause, although they were unable to check their model in younger women. Broer et al (31) calculated the age range in which menopause will subsequently occur based on a study of 257 women (age 21–46 y) selected from three cohorts. However, their results may be partly influenced by the difference in the age distribution between the cohorts and two different AMH assays. In a 14-year follow-up in the Penn Ovarian Aging Study, conducted on 401 late reproductive-age women to predict time to menopause (15), quartiles of AMH were calculated for all of the study subjects, regardless of the fact that AMH varies with age and therefore its quartiles should be calculated separately for each age range; the generalizability of the study was also limited by using a sample of late reproductive-age women. Our previous pa-

Table 2. Average Age at Menopause for Individual Women Aged 20 to 49 Years, When Different Serum Concentrations of AMH Are Assumed

AMH, ng/dL	Age, y							
	20	22	24	26	28	30	32	34
0.1	33 (27–36)	34 (28–38)	35 (29–39)	36 (30–40)	37 (31–41)	39 (32–43)	40 (33–44)	41 (34–46)
0.3	34 (28–38)	35 (29–39)	36 (30–40)	37 (31–41)	39 (32–43)	40 (33–44)	41 (34–46)	43 (35–47)
0.5	35 (29–39)	36 (30–40)	37 (31–41)	39 (32–43)	40 (33–44)	41 (34–46)	43 (35–47)	44 (36–49)
0.7	36 (30–40)	37 (31–41)	39 (32–43)	40 (33–44)	41 (34–46)	43 (35–47)	44 (36–49)	45 (37–50)
0.9	37 (31–41)	39 (32–43)	40 (33–44)	41 (34–46)	43 (35–47)	44 (36–49)	45 (37–50)	47 (38–52)
1.1	39 (32–43)	40 (33–44)	41 (34–46)	43 (35–47)	44 (36–49)	45 (37–50)	47 (38–52)	48 (40–54)
1.3	40 (33–44)	41 (34–46)	43 (35–47)	44 (36–49)	45 (37–50)	47 (38–52)	48 (40–54)	50 (41–55)
1.5	41 (34–46)	43 (35–47)	44 (36–49)	45 (37–50)	47 (38–52)	48 (40–54)	50 (41–55)	52 (42–57)
1.7	43 (35–47)	44 (36–49)	45 (37–50)	47 (38–52)	48 (40–54)	50 (41–55)	52 (42–57)	53 (44–59)
1.9	44 (36–49)	45 (37–50)	47 (38–52)	48 (40–54)	50 (41–55)	52 (42–57)	53 (44–59)	55 (45–61)
2.1	45 (37–50)	47 (38–52)	48 (40–54)	50 (41–55)	52 (42–57)	53 (44–59)	55 (45–61)	57 (47–63)
2.3	47 (38–52)	49 (40–54)	50 (41–55)	52 (42–57)	53 (44–59)	55 (45–61)	57 (47–63)	59 (48–65)
2.5	49 (40–54)	50 (41–55)	52 (42–57)	53 (44–59)	55 (45–61)	57 (47–63)	59 (48–65)	61 (50–>65)
2.7	50 (41–55)	52 (42–57)	53 (44–59)	55 (45–61)	57 (47–63)	59 (48–65)	61 (50–>65)	63 (51–>65)
2.9	52 (42–57)	53 (44–59)	55 (45–61)	57 (47–63)	59 (48–65)	61 (50–>65)	63 (51–>65)	65 (53–>65)
3.1	53 (44–59)	55 (45–61)	57 (47–63)	59 (48–65)	61 (50–>65)	63 (51–>65)	65 (53–>65)	>65 (55–>65)
3.3	55 (45–61)	57 (47–63)	59 (48–65)	61 (50–>65)	63 (51–>65)	65 (53–>65)	>65 (55–>65)	
3.5	57 (47–63)	59 (48–65)	61 (50–>65)	63 (51–>65)	65 (53–>65)	>65 (55–>65)		
3.7	59 (48–65)	61 (50–>65)	63 (53–>65)	65 (53–>65)	>65 (55–>65)			
3.9	61 (50–>65)	63 (51–>65)	65 (53–>65)	>65 (55–>65)				
4.1	63 (51–>65)	65 (53–>65)	>65 (55–>65)					
4.3	65 (53–>65)	>65 (55–>65)						
4.5	>65 (55–>65)							

per was a 6-year follow-up of 266 reproductive-aged women participants of the TLGS that documented 63 menopausal events of which very few were early ones (17).

Our current study included all eligible reproductive-aged women of the TLGS plus data obtained from an additional 4 years of follow-up. Having a bigger sample size (1015 vs 266) and a 5-fold menopausal event rate (277 vs 63) makes our present study much more powerful and enables us to predict age at menopause more precisely compared with our previous estimation. On average, there was a half-year difference between the actual and predicted age at menopause (SD = 2.45; range, −5.4 to 9.2 y). We had 40 women in our cohort who reached menopause before the age of 46, allowing validation of the model predictions for early menopause. Furthermore, in addition to age, AMH showed a higher independent predictive capacity and the model containing both age and AMH had a C-statistic value of 92% for proportion of correct predictions.

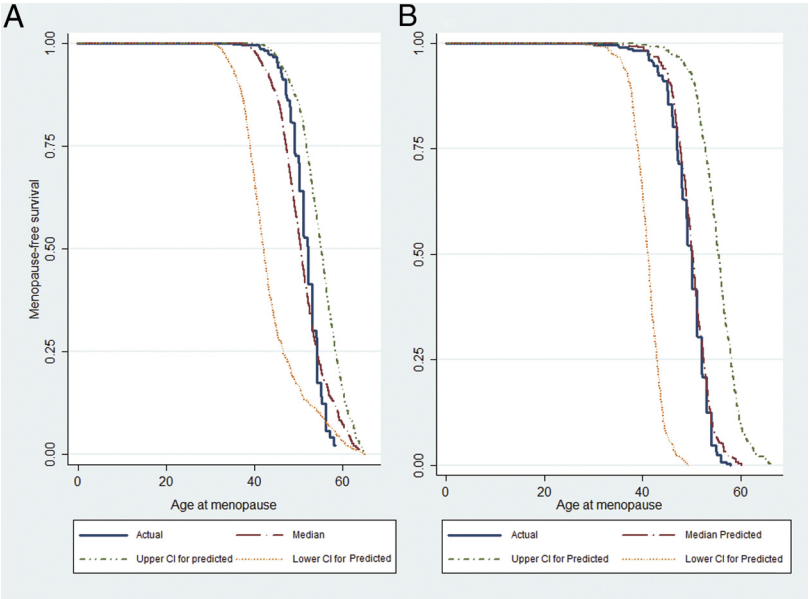

Figure 2. Kaplan-Meier menopause-free survival curves for actual and predicted ages at menopause and the 95% CI for predicted. A, Total population. B, The population of women who reached menopause.

The actual and predicted menopause-free survival plots were very similar when the comparison was limited to those who had already reached menopause in the TLGS cohort (n = 277). This could reflect the fact that the same group of women were used to estimate the model coefficients (Figure 2A). However, using the model for a larger population of all reproductive-aged women in TLGS and making the comparison with those who have actually experienced menopause does not show the same degree of similarity (Figure 2B). Women for whom our model predictions of age at menopause exceeded 65 years old (n = 89) were excluded from the survival plot. Their serum concentrations of AMH were at the fourth quartile of AMH for their age group. Our model may not provide accu-

Table 2. Continued

36	38	40	42	44	46	48	50
43 (35–47)	44 (36–49)	45 (37–50)	47 (38–52)	48 (40–54)	50 (41–55)	52 (42–57)	53 (44–59)
44 (36–49)	45 (37–50)	47 (38–52)	48 (40–54)	50 (41–55)	52 (42–57)	53 (44–59)	55 (45–61)
45 (37–50)	47 (38–52)	48 (40–54)	50 (41–55)	52 (42–57)	53 (44–59)	55 (45–61)	57 (47–63)
47 (38–52)	48 (40–54)	50 (41–55)	52 (42–57)	53 (44–59)	55 (45–61)	57 (47–63)	59 (48–65)
48 (40–54)	50 (41–55)	52 (42–57)	53 (44–59)	55 (45–61)	57 (47–63)	59 (48–65)	61 (50–67)
50 (41–55)	52 (42–57)	53 (44–59)	55 (45–61)	57 (47–63)	59 (48–65)	61 (50–67)	63 (51–69)
52 (42–57)	53 (44–59)	55 (45–61)	57 (47–63)	59 (48–65)	61 (50–>65)	63 (51–>65)	65 (53–>65)
53 (44–59)	55 (45–61)	57 (47–63)	59 (48–65)	61 (50–>65)	63 (51–>65)	65 (53–>65)	>65 (55–>65)
55 (45–61)	57 (47–63)	59 (48–65)	61 (50–>65)	63 (51–>65)	65 (53–>65)	>65 (55–>65)	
57 (47–63)	59 (48–65)	61 (50–>65)	63 (51–>65)	65 (53–>65)	>65 (55–>65)		
59 (48–65)	61 (50–>65)	63 (51–>65)	65 (53–>65)	>65 (55–>65)			
61 (50–>65)	63 (51–>65)	65 (53–>65)	>65 (55–>65)				
63 (51–>65)	65 (53–>65)	>65 (55–>65)					
65 (53–>65)	>65 (55–>65)						
>65 (55–>65)							

rate predictions at both extremes of the menopausal age range. This could be because the number of women who had reached menopause was low in that age range; this could be partly overcome when a greater number of women with very early or late menopause become available for study.

The median time of menopause of 52 years that has been derived from our models was higher than the national Iranian median age at menopause of 50 years (24), which might be explained by including women between the ages of 20 and 50 years who still have regular menstrual cycles at initiation of the cohort and excluding those who are in transition to menopause status.

Our study has the advantage of development of an accelerated time model in a population-based cohort of women at their various time points of reproductive life span. The follow-up time was 10 years on average, which is one of the longest among the existing studies (15, 31). About one-fourth of participants reached menopause while in the study, which enables us to validate our model. Furthermore, the intra-assay and interassay variability in our data is likely to be minimal because all AMH assays were performed in the same laboratory by an expert person.

Our study has some limitations as well. We did not measure other ovarian aging markers, including antral follicle counts. The study did not have a long enough follow-up for all participants to reach menopause. However, TLGS is an ongoing cohort and will have the opportunity to re-examine the question again in the future. We selected women with previously normal fertility; therefore, our model is not applicable to infertile women because their ovarian aging process is influenced by their underlying reproductive abnormality (33, 34). We used stored samples that had not been collected on any specific days of the menstrual cycles; however, this will have minimal impact on our results, because serum AMH levels are considered to be independent of menstrual cycle and are unaffected by long-term storage (35, 36). In our current study, we used the Gen II kit for AMH measurement, whereas we had used Diagnostic System Laboratories (DSL) assay kits in our previous study. Unfortunately, we were unable to create a valid agreement factor for converting the DSL assay to the Gen II assay because we did not have enough blood samples to repeat the assay in subjects for whom the measurement had been done using the DSL method except in 16 cases. Furthermore, there are not enough published data for precise translations of one assay to another (37–39). Therefore, we were unable to include most of women from the previous study in the current data modeling (n = 250).

In conclusion, we can predict average age at menopause in women of a particular age and a specific AMH level. For those predicted as being at risk of early menopause, this could lead to important life decisions such as attempting conception earlier or preserving fertility by storing oocytes. In addition, these women are at greater risk of osteoporosis, cognitive impairment, and cardiovascular diseases later in life, and preventive management should be considered for them. Similarly, reaching menopause at later ages is associated with an increase in risk of breast,

endometrial, and intestinal cancers, necessitating more intensive screening protocols to be considered.

Larger longitudinal population-based studies, in various ethnicities, starting with women in their early reproductive years and including a comprehensive basic assessment of their endocrine, ultrasound, and genetic profiles and following them until menopause are needed for more precise individual predictions of age at menopause usable in clinical settings.

Acknowledgments

We appreciate the substantial time and effort study participants contributed to this study. Acknowledgments are also due to research staff at the Tehran Lipid and Glucose Study Unit and staff of the Research Endocrine Laboratory. My special thanks go to Mrs. N. Shiva for language editing of the manuscript.

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This work was funded by the National Council of Scientific Research of the Islamic Republic of Iran, as a national research project.

Disclosure Summary: There are no conflicts of interest.

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