

Full title:

Improving prediction of age at menopause using multiple Anti Mullerian Hormone measurements; Tehran Lipid-Glucose Study

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Abstract:

Context

Several statistical models were introduced for prediction of age at menopause using a single measurement of Anti Mullerian Hormone (AMH), however individual prediction is challenging and need to be improved.

Objective

Whether multiple AMH measurements can improve the prediction of age at menopause.

Design.

All eligible reproductive aged women (n=959) were selected from the Tehran Lipid and Glucose Study. The serum concentration of AMH was measured at the time of recruitment and twice after that with on average 6 years interval. An accelerated failure time model with Weibull distribution was used to predict age at menopause, using a single AMH value versus model included annual AMH decline rate. The adequacy of these models was assessed using C-statistics.

Results:

The median follow-up period was 14 years and 529 women reached menopause. Adding the annual decline rate to the model included single AMH, improved the model discrimination's adequacy from 70% (95% CI: 67% to 71%) to 78% (95% CI: 75% to 80%) in terms of c-statistic. The median of differences between actual and predicted age at menopause for the first model was -0.48 years and decreased to -0.21 in model including decline rate. The predicted age at menopause for women with the same amount of age-specific AMH, but annual AMH decline rate of 95 percentiles was about one decade lower than those with decline rate of 5 percentiles.

Conclusion

Prediction of age at menopause could be improved by multiple AMH measurements, it will be useful in identifying women at risk of early menopause.

Keywords:

Anti Mullerian Hormone (AMH), Menopause, Tehran Lipid and Glucose Study (TLGS), Reproductive Ageing.

Précis

This study revealed that multiple Anti Mullerian Hormone (AMH) measurements can improve the individual prediction of age at menopause.

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Introduction

Prediction of menopause is a critical need of today life, while individualized counseling and oocyte preservation can be options for women concerned by early menopause. Accurate estimation of time of menopause could also identify those at higher risk of cardiovascular disease, osteoporosis, breast and endometrial cancers due to early or late menopause^{1,2}. So far, much effort has been made for precise prediction of menopausal age³⁻⁶, despite lots of achievements, there is a long way ahead. Among predictor markers available, serum levels of Anti Mullerian Hormone (AMH) has emerged as a promising one⁷, considering its unique characteristics, including secretion exclusively in ovarian follicles, being mostly constant throughout the menstrual cycle or from one cycle to another, and gradually decrease with ageing⁸.

Although several studies show that the time of menopause may be predicted via a mathematical model on the basis of a single AMH measurement and the age of the woman^{3,9-11}, these predictions are less effective for women with extreme menopausal ages, for whom this prediction is more critical⁴. Repeated AMH measurement may help to improve the accuracy of prediction¹¹, as the rate of AMH declines may not be the same for all reproductive age women¹². This rate may be influenced by several life styles and environmental factors, e.g. AMH levels decrease at a faster rate in women who smoke¹³.

The present study is an extension of follow up time a previous study that this group published⁶. We also used information from two more AMH measurements in 6 yearly intervals (on average). We aim to assess whether repeated AMH measurements can improve our previous prediction of age at menopause.

Material and methods

We used cohort data from the Tehran Lipid and Glucose Study (TLGS), initiated in 1998 for assessment of risk factors of non-communicable diseases in an urban population. Study objective and design have been described in more detail elsewhere¹⁴. In the current study, we selected women aged 20- 50 years with regular and predictable menstrual cycles at the initiation of study, and had proven natural fertility

without history of hysterectomy, oophorectomy, or any other kind of ovarian surgery. The cohort participants were physically examined every 3 years; follow-up assessments include a general physical examination and an interview during which the date of the last menstrual cycle is recorded and their overnight fasting blood samples were collected for future use. At the time of the present study, follow ups at time points 1 through 5 had been completed, leading to an approximate follow-up time of 18 years. Menopause was defined using the World Health Organization classification as the 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. Details of included and excluded participants and menopausal status at the end of study are presented in figure 1. For the purpose of the current study, the stored plasma samples of baseline, 3rd and 6th follow ups were used for AMH measurements. The storage times were calculated based on the period between the date of sample collection and the date of AMH measurement. All AMH measurements were performed in the same laboratory in the Research Institute for Endocrine Sciences using the same assay method and kit (Gen II kit, Beckman Coulter, Inc, Fullerton, California, USA) and the Sunrise ELISA reader (Tecan Co, Salzburg, Austria) by a single experienced laboratory technician. AMH Gen II controls A79766 were used at two levels of concentration to monitor accuracy of assays. Intra- assay and inter assay coefficients of variation were 1.9% and 2.0%, respectively.

Statistical analysis

We calculated the follow-up time for each individual woman. This was the period between the date of recruitment to the TLGS cohort and the end of follow-up date for current study defined as the date of last follow-up round or lost to follow up for all those not reached menopause (censored), or time of menopause for others reaching menopause. The average AMH decline rate over the entire duration of follow-up was calculated using the first and the last AMH measurements before the end of follow-up date, for which we divided the difference between the last AMH measurement and the baseline by the corresponding time interval in years to work out the average annual decline (ng/ml/year). The normal-

based methodology described by Altman and Chitty¹⁵, and Royston and Wright¹⁶, was used to estimate age-specific AMH percentiles, details reported previously¹⁷; this method was also used to provide age specific AMH annual decline rate percentiles.

To predict individual age at menopause, an accelerated failure time modeling was applied by considering a parametric Weibull distribution for the failure time¹⁸. Analysis was performed by assigning sampling weights of 20 to each case, who reach menopause before 45 or after 54 years to compensate for their low prevalence. Predictive performance of the baseline AMH measurement and the average AMH annual decline rate were assessed. The median predicted age at menopause and its 95% confidence interval (CI) were calculated using the following formula:

Age at Menopause = $\{[-\ln(S(t_{\text{Median}})]^{1/p}\} \exp(\beta X)$; \ln is logarithmic function, $S(t_{\text{Median}})$ is the median survival function, p is the parameter of Weibull distribution, \exp is exponential function, β is regression coefficient of survival model and X s are the exploratory variables including age, AMH and AMH decline rate.

Predictions exceeding maximum expected menopausal age in Iranian women (> 65 years) were excluded. Estimated coefficients derived from accelerated failure time modeling with annual decline rate effect were applied to calculate prediction of age at menopause as follows:

Age at Menopausal = $\{[-\ln(0.5)]^{0.042}\} \times \exp(3.32 + 0.093\text{AMH} + 0.015\text{Age} - 0.88 \text{ annual decline rate})$.

In this model, we calculated formula for median survival time (0.5), considering the estimated coefficients for different parameters resulted from model using Weibull distribution; they were 0.093, 0.015 and 0.88 for AMH, age and annual decline rate, respectively. The shape parameter for Weibull distribution was estimated to be 0.042. Statistical analysis was re-run by adding the sample storage times to the model. We also repeated analysis by considering age-specific AMH percentiles (instead of AMH) and AMH decline rates or its percentiles, as this approach eliminated the need of including age as a predictor variable.

Adequacy of the models was assessed using C-statistics; the 95% confidence interval (CI) of each C-statistic was derived through bootstrapping with 200 iterations; C-statistics were compared using the Lincom Stata function¹⁹. The agreement and disagreement graph were run to illustrate the models' performance by comparison of the predicted and observed age at menopause (in those who reached menopause), using the Bland-Altman method. The Kernel density plot by age-specific AMH level (Low-Median, High) and percentiles of AMH (5%, 25%, 50%, 75%, 95%) were depicted to show the relationship between the distribution of age at menopause, AMH levels and AMH decline rates. Estimated ages at menopause and their 95% CI for arbitrary values of AMH, age and percentiles of AMH decline rate (5%, 25%, 50%, 75%, 95%) were calculated. Statistical analyses were performed using STATA version 14 (STATA Corporation, College Station, TX) and SPSS software version 21 (SPSS Inc., Chicago, IL).

Results

Of a total of 2412 women, aged 20 to 50 years from the TLGS cohort, 959 met our eligibility criteria. Characteristics of study participants are presented in table 1. The mean (SD) of age of participants at the initiation of the study, third and sixth follow ups were 36(7.1), 42(7.2) and 49(6.9) years and their corresponding serum AMH levels were 1.8(1.7), 0.89(1.17) and 0.53(0.90) ng/ml respectively. The median (range) follow-up time was 5110 days (range 150–6570), and 529 women reached menopause over this period. Age specific AMH annual decline rate percentiles for 5%, 25%, 50%, 75%, and 95% in our population were estimated to be 0.006, 0.032, 0.079, 0.14, and 0.29 ng/ml/year respectively. Analysis of annual decline rate by age groups (≤ 40 and > 40 years old) showed that the decline rate for women ≤ 40 years old is faster than those above 40 (-.80; 95%CI: -1.0 to -.59 versus -.03; 95%CI: -.11 to -.05).

The median predicted age at menopause based on model including age, AMH and annual AMH decline rate were 50.8 years. Corresponding median actual age was 51. Table 2 present the results from various models after taking into account different parameters for the prediction of time to menopause. Including annual decline rate in the model 2 (C statistics: 78%; 95%CI: 75% to 80%) improved the model

discrimination's adequacy in comparison with model 1 (C statistics: 70% 95% CI: 67% to 71%) that does not contain this parameter. Including Age-specific AMH (Model 3 did not provide substantially better results (C-statistics: 72%; 95% CI: 69% to 74%). Model 4 including age, AMH, annual decline rate and sample storage time; the effect of storage times as a potential confounding variable was not statistically significant (table 2).

Comparing the predictive capacities of the survival models with and without annual AMH decline rate revealed a statistically significant difference between c-statistics ($p=0.035$) (table 2). The median of differences between actual and predicted age at menopause (the Bland-Altman method) for model 1 and 2 were -0.48 years (range, -2.21 to 2.95 years) and -0.21(range: -2.24 to 3.75), respectively (Figure 1). We plotted the predicted versus the actual age at menopause which showed a reasonable fit, particularly within 34 to 59 age range (Figure2).

We observed a decreasing trend in age at menopause by increasing the percentiles of annual decline rate in all categories of age-specific AMH (see kernel density plots in figure 3); e.g. the predicted age at menopause for women with low baseline age-specific AMH and high annual AMH decline rate (95th percentile) was 34 years; however it was 43.5 years for those with the same age-specific AMH value but low annual AMH decline rate (5th percentile). For medium values of baseline age-specific AMH, the difference between 5th and 95th percentile of AMH annual decline rate for predicted age at menopause was 11.7 years (40.5 versus 52.2 years) (figure 3) Estimated ages at menopause and their 95% CI for arbitrary values of AMH, age and percentiles of AMH annual decline rate using model 2 are presented in table 3.

Discussion:

The present study revealed that addition of the AMH annual decline rate improves the prediction of menopause. We found that, on average for the same amount of age-specific AMH, the predicted age at menopause for those with the highest AMH decline rate (95th percentiles) was about one decade lower

than those with the lowest (5th percentiles). The difference between the actual and predicted age at menopause decreased by 0.27 years by including the AMH annual decline rate to the model. This model revealed a reasonable fit, particularly within 34 to 59 years age range.

The wide variation in age at menopause (40-60 years) may be the result of considerable differences between individuals in the number of follicles at birth and/or speed of follicle pool depletion; the size of the primordial follicle pool is an important determinant for the length of the individual ovarian life span²⁰. Studies reveal that a combination of both genetic and environmental factors are responsible for this inter-individual variation in age at menopause²¹⁻²³. Data shows contradictory findings in terms of environmental factors including lifestyles and hormonal contraception on the reproductive lifespan and age of natural menopause except for smoking, in particular for current smoking, which accelerates the age of spontaneous menopause²⁴.

Due to the inherent necessity to remove an ovary to quantify the primordial follicle pool, it is not feasible to assess, *in vivo*, the relationship between the true ovarian reserve and natural age at menopause. Several efforts have been made to predict age at natural menopause using proxy variables^{25,26}; of all the hormonal and sonographic factors investigated, AMH is considered an optimum and reliable parameter in the assessment of ovarian reserve, providing a precise estimation of follicle pool²⁷.

Single AMH measurement have been used for prediction of age at menopause in several studies using various statistical models because of the complexity of the pattern of decline of AMH by age. In some studies a quadratic decline function of AMH with age best fit the data^{28,29}, while others introduced models with polynomials or flexible splines^{3,30,31}. Nevertheless the pattern of declining age-specific AMH with age remains a matter of controversy; with some reporting parallel decline^{29,32} and others observing converging AMH levels with higher age^{17,28,33}. The individual decline of AMH levels depended on both the initial follicle pool (indirectly estimated by AMH level) and factors that may facilitate or delay dynamic decline in the primordial follicle pool^{34,35}. Hence addition of the individual AMH decline rate to

the model built based on a single AMH measurement may improve prediction of age or time to menopause.

In our previous preliminary study of 266 women followed for an average duration of 6.5 years, we found that each woman had her own specific AMH trajectory; consequently the shared random-effects joint model (including the specific AMH trajectory of each woman) was better fitted for individual prediction of menopause³⁶. Having a larger sample size (959 vs 266) and an 8-fold menopausal event rate (522 vs 63) and longer follow-up time (14.0 vs 6.5) makes our present study much more powerful and enables us to predict age at menopause more precisely.

In agreement with the results of our study, The Penn Ovarian Aging Study of 293 women with 2 measures of AMH over a 14-year follow-up, revealed that rate of AMH change was a strong independent predictor of time to menopause even after adjustment for baseline AMH, age and smoking habits, especially for the 35–39 year age group¹²; they reported that menopause occurred approximately 2 years later in women with similar baseline AMH levels but slow rate of AMH change, compared to those with faster change rates. Kat et al also reported that the fall in AMH levels over time does not follow a fixed pattern for individual women and models including both age-specific AMH levels and decline rates were the best fit ones for their data set³⁷.

The trend of declining of AMH by age differed in those with low and high age-specific AMH levels, but this difference decreased with increasing chronological age^{12,38}; as a result the added value of AMH decline rate, for improving the prediction of age at menopause for aged women is doubtful³⁷. In present study, in agreement to the Freeman et al study¹², we found that while the impact of AMH decline rate, for improving the prediction of age at menopause, was decreased in women aged >40 (Table 2), it remained statistically significant predictor. In contrast, Kat et al reported that the overall decline rate after age 40 accelerated, and observed no added value for including this decline rate to improve prediction of age at menopause in women aged >40³⁷. These contradictory results may partly be explained by their random effect modeling and lack of essential assumption for preventing bias in estimates of regression

coefficients in their model. Additionally the declining predictive capacity of AMH with age increase in women may be due to the lack of non-proportional effects and heterogeneity present within the population, e.g. older women or those with lower AMH percentiles have more hazards of menopause and they reach menopause earlier, as a consequence, the average hazard of menopause in those with low age-specific AMH or older women is relatively more reduced than in the higher age-specific AMH or younger women. The same data set was used in another study to compare the prediction value of model after the addition of AMH decline rate applying the Cox proportional hazards models with time-varying covariates³⁸; they found that except for women aged 20-25 y, this addition, did not improve their predictions of menopause. This observation may be partly explained by time variation of hazard of menopause in various age and age-specific AMH women that may limit the feasibility of the cox model of prediction. While there is some doubt about the capability of AMH to precisely predict of early menopause, in a recent nested case control study conducted within the Nurses' Health Study II cohort, after adjustment for confounders, lower AMH levels were significantly associated with higher risk of natural menopause, prior to age 45³⁹.

The median actual and predicted ages of menopause of our study (51 and 50.8, respectively) were slightly higher than the national Iranian median age at menopause of 50 years⁴⁰, which it might be explained by inclusion of women between 20 -50 years, who still have regular menstrual cycles at initiation of the study, this criterion has filtered out women experiencing an irregular cycle due to imminent ovarian failure at a young age. On average, there was only -0.21(range: -2.24 to 3.75) years difference between the actual and predicted age at menopause when the comparison was limited to those who had already reached menopause in the TLGS cohort (n=437); which is considered as a precise prediction, while it may be criticized by using the same group of women for estimation of the model coefficients.

Regarding strengths of the study, ours has the advantage of development of an accelerated failure time using Weibull distribution in a population-based cohort of women at their various time points of reproductive life span, using three time measurements of AMH; this model has an intuitive physical

interpretation and would be a useful alternative to the Cox model in survival analysis^{41,42}. It provides robust inference procedures which are valid in situations when the essential assumptions for Cox model (independency and lack of distributed error) are not met. Using the model predictions, we estimated ages at menopause and their 95% CI for arbitrary values of AMH and age considering various percentiles of the annual AMH decline rate. The size of the sample in our study (~1000) and its follow up time (~ 14 years) are one of the largest and longest among the studies available. More than half of participants approached menopause while in the study, which enables us to assess the reliability of prediction. The intra-assay and inter assay variability in AMH measurement is likely to be minimal as all AMH assays were performed in the same laboratory by an expert person.

Our study of course has its limitations as well. We did not measure other ovarian aging markers, including antral follicle counts. We have not used the most sensitive assay for AMH measurement (pico AMH assay), a method which is capable of detecting women with very low ovarian reserves⁴³. Nevertheless the results from the Gen II and pico AMH assays are highly correlated; moreover the results of Gen II assay may be translated to pico one using the following equation: (pico AMH = 0.01 + 1.69 * GenII)⁴⁴. We used stored samples that had not been collected on any specific days of the menstrual cycles; however, this may have minimal impact on our results, because serum AMH levels are considered to be unaffected by long-term storage and are independent of menstrual cycle in particular after the age of 30, this level differs up to 0.5 ng/mL throughout the menstrual cycle^{45,46}. Regarding the stability of AMH in frozen sample, it has been shown that 4 years storage at -80°C and episodes of thawing have little impact on AMH levels analyzed by AMH Gen II assay⁴⁷ and there was no significant trend in the long term stability of those samples stored at -70 °C over 15 months⁴⁸. While the mean storage time for baseline samples of our study is 8.7 years, re-running the analysis with adjusting for sample storage time did not change our results, findings that support minimal impact of sample storage time on our interpretation. We selected women with previously normal fertility; therefore, this model is not applicable

to infertile women, whose ovarian aging process is influenced by their underlying reproductive abnormality^{49,50}.

In conclusion we found that including AMH decline rate improves the prediction of individual age at menopause in women without infertility. However there is a long way to go before using multiple AMH measurements for prediction of age at menopause in daily practice, AMH decline rate may be one step forward for accurate identification of women at risk of early menopause, information could lead them to make important life decisions such as attempting conception earlier or preserving fertility by storing oocytes.

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Legends for Figures and Tables

Table 1: Characteristics of the study participants at baseline and follow-ups

Table2: Models for prediction of age at menopause according to various parameters including baseline AMH, age, age-specific AMH and annual AMH decline rate

Table3: Predicted median of age at menopause according to the arbitrary amounts of AMH and percentiles of annual AMH decline rate

Figure 1: Agreement between actual and predicted ages at menopause using the Bland-Altman method.

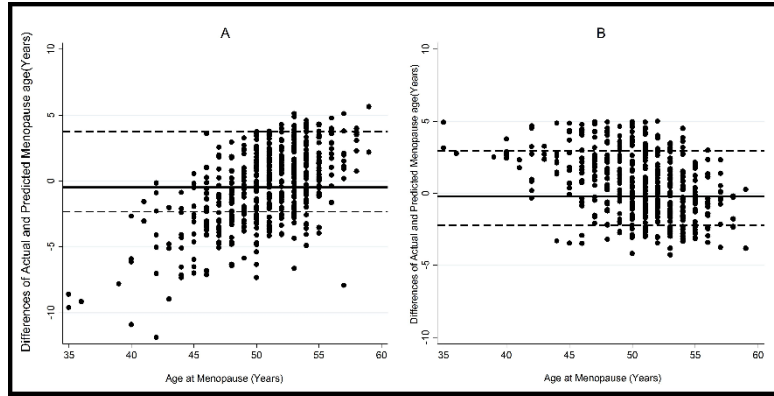
The thick black line represents the median of differences between actual and predicted age at menopause; dash lines represent the interquartile range, A: Model 1 for prediction of age at menopause including: age, AMH, B: Model 2 for prediction of age at menopause including: Age, AMH, annual AMH decline rate.

Figure 2: Nomogram of actual vs. predicted Age at Menopause, Line: Actual Age at Menopause, Dash: Predicted Age at Menopause

Figure 3: Kernel Density Plot for the Relation between Age-specific AMH Concentrations, annual AHM decline rate and the distribution of age at menopause according to the percentiles of annual AMH decline rate, Line: Low age-specific AMH, Dash: Medium age-specific AMH, Dash-dot: High age-specific AMH

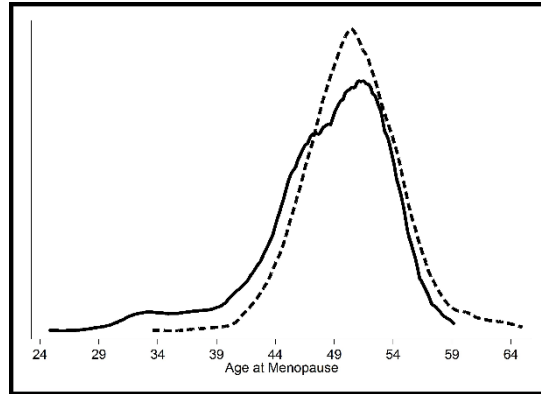
A: Percentile 5% of AMH Decline Rate, B: Percentile 25% of AMH Decline Rate, C: Percentile 50% of AMH Decline Rate, D: Percentile 75% of AMH Decline Rate, E: Percentile 95% of AMH Decline Rate

Figure 1



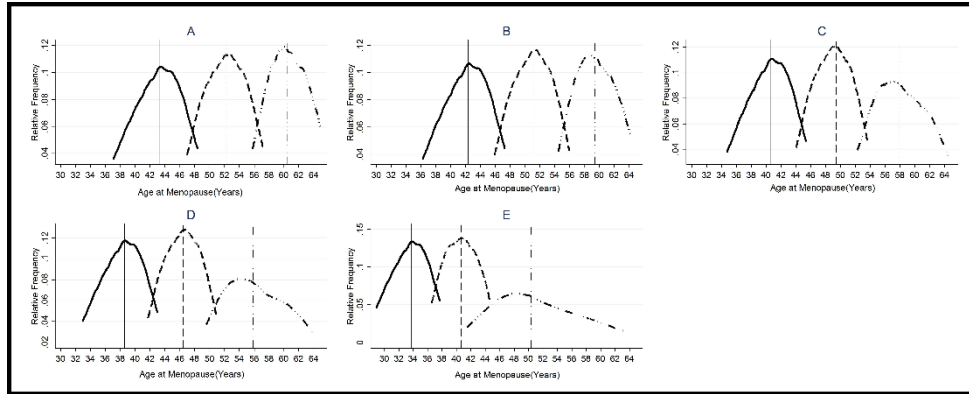
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Figure 2



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Figure 3



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Table 1

characteristics	Baseline n=959	3 rd follow-up n=959	6 th follow-up n=734
Age, (years), Mean (SD)	36(7.1)	42(7.2)	49(6.9)
Parity, (n), Mean (SD)	2.8(1.3)	2.7(1.6)	2.8(1.5)
Systolic Blood Pressure, (mmHg), Mean (SD)	111(13.3)	108(14.9)	110(15.1)
Diastolic Blood Pressure, (mmHg), Mean (SD)	75(9.3)	72(9.5)	76(9.8)
Body Mass Index, (kg/m ²), Mean (SD)	27(4.7)	28(4.6)	29(4.5)
Waist Circumference, (cm)Mean (SD)	85(11)	88(12)	89(12)
Hip Circumference, (cm), Mean (SD)	104(8.9)	104(8.9)	105(9.1)
Wrist Circumference, (cm), Mean (SD)	16(0.97)	16(1.0)	17(1.2)
^ε Anti Mullerian Hormone, (ng/ml), Mean (SD)	1.8(1.7)	0.89(1.17)	0.53(0.90)
^ε Storage time for serum samples,(years),	8.7(0.5)	4.2(0.9)	1.0(0.8)
Menopause, n (%)	0(0%)	211(22%)	522(71%)

^ε Only reported for those not reached menopause

Table 2

All participants (n=959)				
Parametric Survival Models	Parameters	Regression coef. (95%CI)	P-value	C-statistics (95%CI)
Model 1: Age, AMH	AMH (ng/ml)	.04 (.03 to .05)	<0.001*	.70 (.67 to .71)
Model 2: Age, AMH, annual AMH decline rate	AMH (ng/ml)	.09 (.08 to .11)	<0.001*	.78 (.75 to .80)
	Annual AMH decline rate(ng/ml/year)	-.88 (-.99 to -.76)	<0.001*	
Model 3: Age, Age-specific-AMH, annual AMH decline rate	Age-specific-AMH	.17 (.11 to .22)	<0.001*	.72 (.70 to .74)
	Annual AMH decline rate(ng/ml/year)	-.20 (-.37 to -.02)	0.028*	
Model 4: Age, AMH, annual AMH decline rate, storage times	AMH(ng/ml)	.09 (.08 to .096)	<0.001*	.81 (.79 to .83)
	annual AMH decline rate (ng/ml/year)	-.78 (-.85 to -.71)	<0.001*	
	Storage time 1(years)	.007 (-.0007 to .015)	0.073	
	Storage time 2(years)	.001 (-.0033 to .006)	0.494	
	Storage time 3(years)	-.003(-.0080 to .002)	0.316	
Participants aged <40 years(n=661)				
Parametric Survival Models	Effects	Regression coef. (95%CI)	P-value	C-statistics (95%CI)
Model 1: Age, AMH	AMH (ng/ml)	.05 (.03 to .08)	<0.001*	.71 (.69 to .74)
Model 2: Age, AMH, annual AMH decline rate	AMH (ng/ml)	.11 (.08 to .13)	<0.001*	.78 (.76 to .81)
	Annual AMH decline rate (ng/ml/year)	-1.01(-1.19 to -.83)	<0.001*	
Model 3: Age, Age-specific-AMH, annual AMH decline rate	Age-specific-log AMH	.40 (.32 to .47)	<0.001*	.77 (.74 to .79)
	Annual AMH decline rate (ng/ml/year)	-.80(-1.0 to -.59)	<0.001*	

Participants aged ≥ 40 years (n=353)				
Parametric Survival Models	Effects	Regression coef. (95%CI)	P-value	C-statistics (95%CI)
Model 1: Age, AMH	AMH (ng/ml)	.02 (.01 to .03)	<0.001*	.72 (.69 to .74)
Model 2: Age, AMH, annual AMH decline rate	AMH (ng/ml)	.07 (.06 to .08)	<0.001*	.82 (.80 to .84)
	Annual AMH decline rate (ng/ml/year)	-.72 (-.82 to -.61)	<0.001*	
Model 3: Age, Age-specific-AMH, annual AMH decline rate	Age-specific-AMH	.08(.04 to .11)	<0.001*	.74 (.71 to .76)
	Annual AMH decline rate (ng/ml/year)	-.03(-.11 to -.05)	0.049*	

AMH; Anti-Müllerian hormone; Annual AMH decline rate was calculated according (last AMH-baseline AMH) / time intervals (years), reported as AMH (ng/ml/year); Age-specific-AMH was calculated based on the normal- based methodology.

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Table3: Predicted median of age at menopause according to the arbitrary amounts of AMH and percentiles of annual AMH decline rate

Percentiles of annual AMH decline rate AMH (ng/dl)	Age(year)						
	20	25	30	35	40	45	50
0.1							
P5%	37.08(32.25-39.78)	40.01(34.81-42.93)	43.18(37.56-46.33)	46.59(40.53-49.99)	50.28(43.74-53.95)	54.26(47.20-58.22)	58.55(50.94-62.82)
P25%	36.24(31.52-38.88)	39.11(34.02-41.96)	42.20(36.71-45.28)	45.54(39.62-48.86)	49.14(42.75-52.73)	53.03(46.13-56.90)	57.23(49.78-61.40)
P50%	34.77(30.25-37.31)	37.52(32.64-40.26)	40.49(35.22-43.44)	43.69(38.01-46.88)	47.15(41.02-50.59)	50.88(44.26-54.59)	54.91(47.77-58.91)
P75%	32.95(28.67-35.36)	35.56(30.93-38.15)	38.37(33.38-41.17)	41.41(36.02-44.43)	44.69(38.87-47.95)	48.22(41.95-51.74)	52.04(45.27-55.84)
P95%	28.88(25.12-30.99)	31.16(27.11-33.44)	33.63(29.25-36.08)	36.29(31.57-38.94)	<40	<45	<50
0.5							
P5%	38.48(33.47-41.29)	41.52(36.12-44.55)	44.81(38.98-48.08)	48.35(42.06-51.88)	52.18(45.39-55.99)	56.31(48.98-60.42)	60.76(52.86-65.20)
P25%	37.61(32.72-40.35)	40.58(35.30-43.54)	43.79(38.10-46.99)	47.26(41.11-50.71)	51.00(44.37-54.72)	55.03(47.88-59.05)	59.39(51.66-63.72)
P50%	36.08(31.39-38.72)	38.94(33.87-41.78)	42.02(36.55-45.09)	45.34(39.45-48.65)	48.93(42.57-52.50)	52.80(45.94-56.66)	56.98(49.57-61.14)
P75%	34.20(29.75-36.69)	36.90(32.10-39.60)	39.82(34.64-42.73)	42.97(37.38-46.11)	46.38(40.34-49.76)	50.04(43.54-53.70)	54.00(46.98-57.94)
P95%	29.97(26.07-32.16)	32.34(28.13-34.70)	34.90(30.36-37.45)	37.66(32.76-40.41)	40.64(35.35-43.61)	<45	<50
1.0							
P5%	40.30(35.06-43.24)	43.49(37.84-46.67)	46.93(40.83-50.36)	50.65(44.06-54.34)	54.65(47.55-58.64)	58.98(51.31-63.28)	63.65(55.37-68.29)
P25%	39.39(34.27-42.27)	42.51(36.98-45.61)	45.87(39.91-49.22)	49.50(43.06-53.11)	53.42(46.47-57.32)	57.65(50.15-61.85)	62.21(54.11-66.74)
P50%	37.80(32.88-40.55)	40.79(35.48-43.76)	44.01(38.29-47.22)	47.50(41.32-50.96)	51.25(44.59-54.99)	55.31(48.12-59.34)	59.69(51.92-64.04)
P75%	35.82(31.16-38.43)	38.65(33.63-41.47)	41.71(36.29-44.76)	45.01(39.16-48.30)	48.58(42.26-52.12)	52.42(45.60-56.24)	56.57(49.21-60.69)
P95%	31.39(27.31-33.68)	33.87(29.47-36.35)	36.55(31.80-39.22)	39.45(34.32-42.33)	42.57(37.03-45.67)	45.94(39.96-49.29)	<50
1.5							
P5%	42.22(36.72-45.30)	45.56(39.63-48.88)	49.16(42.77-52.75)	53.05(46.15-56.92)	57.25(49.80-61.42)	61.78(53.74-66.28)	66.67(57.99-71.53)
P25%	41.26(35.89-44.27)	44.53(38.73-47.77)	48.05(41.80-51.55)	51.85(45.11-55.63)	55.95(48.67-60.03)	60.38(52.53-64.79)	65.16(56.68-69.91)
P50%	39.59(34.44-42.48)	42.72(37.16-45.84)	46.10(40.10-49.47)	49.75(43.28-53.38)	53.69(46.70-57.60)	57.93(50.40-62.16)	62.52(54.39-67.08)
P75%	37.52(32.64-40.26)	40.49(35.22-43.44)	43.69(38.01-46.88)	47.15(41.02-50.59)	50.88(44.26-54.59)	54.91(47.76-58.91)	59.25(51.54-63.57)
P95%	32.88(28.60-35.28)	35.48(30.87-38.07)	38.29(33.31-41.08)	41.32(35.94-44.33)	44.59(38.79-47.84)	48.12(41.86-51.63)	51.92(45.17-55.71)

2.0							
P5%	44.22(38.47-47.44)	47.72(41.51-51.20)	51.49(44.79-55.25)	55.57(48.34-59.62)	59.96(52.16-64.34)	64.71(56.29-69.43)	>65
P25%	43.22(37.60-46.37)	46.64(40.57-50.04)	50.33(43.78-54.00)	54.31(47.25-58.27)	58.61(50.98-62.88)	63.24(55.02-67.86)	>65
P50%	41.47(36.07-44.49)	44.75(38.93-48.01)	48.29(42.01-51.81)	52.11(45.33-55.91)	56.23(48.92-60.34)	60.68(52.79-65.11)	>65
P75%	39.30(34.19-42.17)	42.41(36.89-45.50)	45.76(39.81-49.10)	49.39(42.96-52.99)	53.29(46.36-57.18)	57.51(50.03-61.71)	62.06(53.99-66.59)
P95%	34.44(29.96-36.95)	37.16(32.33-39.88)	40.11(34.89-43.03)	43.28(37.65-46.44)	46.70(40.63-50.11)	50.40(43.84-54.08)	54.39(47.31-58.35)
2.5							
P5%	46.32(40.29-49.70)	49.98(43.48-53.63)	53.94(46.92-57.87)	58.20(50.63-62.45)	62.81(54.64-67.39)	>65	>65
P25%	45.27(39.38-48.57)	48.85(42.50-52.41)	52.72(45.86-56.56)	56.89(49.49-61.04)	61.39(53.40-65.87)	>65	>65
P50%	43.43(37.78-46.60)	46.87(40.77-50.29)	50.58(44.0054.27)	54.58(47.48-58.56)	58.90(51.24-63.20)	63.56(55.29-68.20)	>65
P75%	41.16(35.81-44.17)	44.42(38.64-47.66)	47.94(41.70-51.43)	51.73(45.00-55.50)	55.82(48.56-59.89)	60.24(52.40-64.63)	>65
P95%	36.07(31.38-38.71)	38.93(33.86-41.77)	42.01(36.54-45.07)	45.33(39.44-48.64)	48.92(42.56-52.49)	52.79(45.92-56.64)	56.97(49.56-61.12)
3.0							
P5%	48.51(42.20-52.05)	52.35(45.54-56.17)	56.49(49.15-60.62)	60.96(53.03-65.41)	65.79(57.23-70.59)	>65	>65
P25%	47.42(41.25-50.88)	51.17(44.51-54.90)	55.22(48.03-59.24)	59.59(51.83-63.93)	64.30(55.94-68.99)	>65	>65
P50%	45.49(39.58-48.81)	49.09(42.7152.68)	52.98(46.09-56.84)	57.17(49.73-61.34)	61.69(53.67-66.20)	>65	>65
P75%	43.12(37.51-46.26)	46.53(40.4849.92)	50.21(43.68-53.87)	54.18(47.14-58.14)	58.47(50.86-62.74)	63.10(54.89-67.70)	>65
P95%	37.79(32.87-40.54)	40.77(35.47-43.75)	44.00(38.28-47.21)	47.48(41.31-50.95)	51.24(44.57-54.98)	55.29(48.10-59.33)	59.67(51.91-64.02)
3.5							
P5%	50.81(44.20-54.52)	54.84(47.70-58.84)	59.17(51.48-63.49)	63.86(55.55-68.52)	>65	>65	>65
P25%	49.67(43.21-53.29)	53.59(46.62-57.51)	57.84(50.31-62.06)	62.41(54.29-66.97)	>65	>65	>65
P50%	47.65(41.45-51.13)	51.42(44.73-55.18)	55.49(48.27-59.54)	59.88(52.09-64.25)	64.62(56.22-69.34)	>65	>65
P75%	45.16(39.29-48.46)	48.74(42.40-52.29)	52.59(45.75-56.43)	56.75(49.37-60.89)	61.24(53.28-65.71)	>65	>65
P95%	39.58(34.43-42.47)	42.71(37.15-45.83)	46.09(40.09-49.45)	49.74(43.27-53.36)	53.67(46.69-57.59)	57.92(50.38-62.14)	62.50(54.37-67.06)
4.0							
P5%	53.23(46.30-57.11)	57.44(49.97-61.63)	61.98(53.92-66.50)	>65	>65	>65	>65
P25%	52.02(45.25-55.82)	56.14(48.84-60.23)	60.58(52.70-65.00)	>65	>65	>65	>65
P50%	49.91(43.42-53.56)	53.86(46.86-57.79)	58.12(50.56-62.37)	62.72(54.57-67.30)	>65	>65	>65
P75%	47.30(41.15-50.76)	51.05(44.41-54.77)	55.09(47.92-59.11)	59.45(51.71-63.78)	64.15(55.81-68.83)	>65	>65
P95%	41.46(36.06-44.48)	44.74(38.92-48.00)	48.28(42.00-51.80)	52.09(45.32-55.90)	56.22(48.90-60.32)	60.66(52.77-65.09)	>65
4.5							
P5%	55.75(48.50-59.82)	60.16(52.34-64.55)	>65	>65	>65	>65	>65

P25%	54.49(47.40-58.46)	58.80(51.15-63.09)	63.45(55.20-68.08)	>65	>65	>65	>65
P50%	52.28(45.48-56.10)	56.42(49.08-60.53)	60.88(52.96-65.32)	>65	>65	>65	>65
P75%	49.55(43.10-53.16)	53.47(46.51-57.37)	57.70(50.20-61.91)	62.27(54.17-66.81)	>65	>65	>65
P95%	43.42(37.77-46.59)	46.86(40.76-50.28)	50.57(43.99-54.25)	54.57(47.47-58.55)	58.88(51.22-63.18)	63.54(55.28-68.18)	>65

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