Does AMH Relate to Timing of Menopause? Results of an Individual Patient Data Meta-Analysis

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Context: Anti-Müllerian hormone (AMH)–based age at menopause predictions remain cumbersome due to predictive inaccuracy.

Objective: To perform an individual patient data meta-analysis, regarding AMH-based menopause prediction.

Design: A systematic literature search was performed using PubMed, Embase, and Cochrane databases. Prospective cohort studies regarding menopause prediction using serum AMH levels were selected by consensus discussion. Individual cases were included if experiencing a regular cycle at baseline. Exclusion criteria were hormone use and gynecological surgery.

Results: This meta-analysis included 2596 women, and 1077 experienced menopause. A multivariable Cox regression analysis assessed time to menopause using age and AMH. AMH predicted time to menopause; however, added value on top of age was poor [age alone: C-statistic, 84%; age + AMH: hazard ratio (HR), 0.66; 95% CI, 0.61 to 0.71; C-statistic, 86%). Moreover, the capacity of AMH to predict early (≤45 years) and late menopause (≥55 years) was assessed. An added effect of AMH was demonstrated for early menopause (age alone: C-statistic 52%; age + AMH: HR, 0.33; 95%, CI 0.24 to 0.45; C-statistic, 80%). A Weibull regression model calculating individual age at menopause revealed that predictive inaccuracy remained present and increased with decreasing age at menopause. Lastly, a check of nonproportionality of the predictive effect of AMH demonstrated a reduced predictive effect with increasing age.

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Abbreviations: AMH, anti-Müllerian hormone; BMI, body mass index; HR, hazard ratio; IPD, individual patient data.

Conclusion: AMH was a significant predictor of time to menopause and especially of time to early menopause. However, individual predictions of age at menopause demonstrated a limited precision, particularly when concerning early age at menopause, making clinical application troublesome. (***J Clin Endocrinol Metab*** **103: 3593–3600, 2018)**

In recent years, more data have become available regarding the prediction of age at natural menopause based on anti-Müllerian hormone (AMH) levels (1–12). It is suggested that these menopause forecasts can be extrapolated to predict the end of natural fertility. This extrapolation is based on the hypothesis that a fixed interval exists between the end of natural fertility and the onset of menopause (13). According to this construct, both events occur within a 20-year window, menopause between the ages 40 and 60 and the end of natural fertility 10 years prior to this event. Considering this broad age interval for the end of natural fertility, it is understandable that many women are facing age-related infertility at the time they hope to conceive (14). This is especially the case because an increasing number of women are delaying childbearing due to an ever-growing participation in the workforce and a wide availability of effective contraceptives (15).

To prevent age-related infertility, a marker accurately assessing the limits of an individual woman's fertile lifespan is needed. Currently, there is no marker available reflecting actual fertility, and the end of natural fertility is an event that goes by unnoticed. Thus, based on the presumed fixed interval of 10 years between menopause and the end of natural fertility, menopause predictions are extrapolated to forecast the end of natural fertility.

Menopause occurs when the number of primordial follicles falls below a critical threshold at which the ovary loses the ability to produce mature oocytes and is therefore unable to maintain a menstrual cycle (16). Markers reflective of the number of primordial follicles have been researched to assess their capacity in the prediction of menopause. Of these putative markers for the true ovarian reserve currently researched (*i.e.*, the antral follicle count, FSH, and AMH), AMH is the most promising one. Studies providing longitudinal data on AMH-based menopause prediction available today all suggest that AMH is a substantial predictor of age at natural menopause (3–7, 9, 10, 17, 18). As unanimous as these suggestions may be, pitfalls regarding the precision of AMH-based menopause predictions have prevented the buildup of sufficient support for clinical applicability. Currently, the major problems surrounding AMH-based age at menopause forecasts are the fact that individualized predictions do not cover the full age range of menopause, the fact that prediction intervals are wide, and the observation that the predictive capacity of AMH declines with increasing age. Pooling of data, hereby performing analyses on the largest possible cohort to date, was thought to solve these problems regarding AMH-based menopause prediction. The aim of this study therefore was to perform an individual patient data (IPD) meta-analysis researching the true capacity of AMH in the prediction of age at menopause and thus the end of natural fertility.

Materials and Methods

Method of systematic review of literature

To detect all papers regarding AMH-based age at menopause prediction, we systematically searched the PubMed, Embase, and Cochrane databases. Eligible studies reported on time to menopause or age at menopause using serum AMH levels. Individual cases within the studies were only included if experiencing a regular cycle at the time of sampling, if women were not using hormone therapy, and if they had no history of uterine or ovarian surgery. Searches were confined to papers published up to May 2017, with no language restriction. Titles, abstracts, and full-text papers retrieved were evaluated, and, where necessary, consensus discussion between M.D. and F.J.M.B. determined eligibility of the paper.

Authors of studies that were considered eligible for inclusion in our IPD meta-analysis were invited to join our project and share their data. When willing to participate, authors received a study protocol, including a data request form, and a collaboration contract. Data received was harmonized and reformatted into a single format.

Statistical analyses of IPD meta-analysis

Baseline characteristics comparing women per cohort of origin were analyzed using the Kruskal-Wallis or χ^2 test. Single, within cohort, imputation was performed for cases with missing data on AMH. Summary statistics depicting time between baseline (*i.e.*, AMH measurement) and the event menopause, as well as medians and interquartile ranges of time between baseline measurement and menopause, were assessed to provide insight into the data. Kaplan-Meier curves depicting the distribution of age at natural menopause were drawn for each cohort.

Next, and to model individual, AMH-based time to menopause, the available cohorts needed to be pooled. Before starting the analyses on menopause prediction, heterogeneity potentially arising from publication bias and due to AMH assay differences and study of origin had to be evaluated.

A funnel plot was created depicting the hazard ratios (HRs) for AMH on the x-axis and the standard error for these estimates on the y-axis (Supplemental Fig. 1).The asymmetry seen in this plot indicates some publication bias to be present. Because, as explained in the Results section, not all invited authors were willing to participate in this IPD, selection bias cannot be

excluded in the selected papers. However, in view of the differences in the studies included, due to different populations examined and different AMH assays used, much of the asymmetry observed in the funnel plot is likely to stem from between-study heterogeneity.

For the assessment of heterogeneity due to the AMH assay, we applied a linear regression analysis for AMH in relation to age, using a natural spline with 3 degrees of freedom for age due to nonlinearity. The variable "study of origin" was added to the regression analysis to assess the between-study heterogeneity of AMH levels. This analysis, depicted in Supplemental Fig. 2, revealed that the shape of the curve is similar for all cohorts included. However, only five out of the six studies showed similarity in AMH levels, whereas one study differed in AMH levels. This implies that substantial heterogeneity is present, which prevents pooling of raw data. Therefore, age-specific AMH percentiles were calculated per original data set. These study- and age-specific categories were then used to pool the AMH data.

For the assessment of heterogeneity due to study origin, a frailty Cox regression analysis was performed. This Cox model was adjusted for female age and "study of origin." The effect of "study of origin" was also added as a frailty variable to the Cox model, which expresses the differences due to study of origin as the standard deviation of $_{\log}$hazard scale. The analysis revealed significant heterogeneity from study of origin (variance of random effects: 0.46); however, this effect was small. Therefore, pooling the data at this level was deemed feasible.

To assess whether AMH predicts time to menopause in a model next to age, a Cox regression analysis assessing time to menopause was performed. For this model, the C-statistic was calculated to reflect the capacity of the model to discriminate between women with a short or longer time to menopause. To further assess the effect of age at baseline (*i.e.*, at AMH measurement), the Cox regression analysis mentioned above was repeated in three age groups at AMH sampling (18 to 30 years, 31 to 40 years, and 41 to 50 years).

To assess the capacity of AMH in predicting early and late menopause, the Cox regression analysis was repeated. This time early menopause ($\leq$45 years of age) or late menopause ($\geq$55 years of age) was defined as the event. These analyses too were repeated using the abovementioned age groups at baseline, to further assess the effect of baseline age.

Next, study- and age-specific AMH percentiles were used to estimate individual age at natural menopause, using a Weibull survival model with age on the time axis. The parametric Weibull survival model produces smoother curves when using age-specific AMH percentile lines. This model was preferred over a Cox model because this model cannot produce this type of curve. Per age-specific AMH category, the median predicted age at menopause and the corresponding age ranges were depicted in a nomogram. Furthermore, and derived from the Weibull model, the distribution of the occurrence of the event menopause was tabulated per age at menopause category ($\leq$45 years, 45 to 55 years, and $\geq$55 years) and per age-specific AMH percentile category.

Lastly, a check of nonproportionality of AMH was performed for the risk of reaching menopause with increasing age. Therefore, the Schoenfeld residuals (method for assessing the assumption of proportional hazard) of the Cox model were plotted against age, and a smoothed line was fitted on these plotted data, representing the time-varying regression coefficient of AMH [β(t)]. In case of significant nonproportionality, the shape parameter of the Weibull model, determining the width of the distribution, was also made dependent on the AMH percentiles (19).

Data analysis was performed using SPSS 20 (SPSS, Inc., Chicago, IL) and RStudio Team 2015 (RStudio, Inc., Boston, MA)

Results

Systematic review of literature and data acquisition

Twelve full-text papers reported analyses regarding AMH-based age at menopause (or time to menopause) prediction and were thus potentially eligible for inclusion in this IPD (3–10, 17, 18) (Supplemental Fig. 3). These 12 papers reported on the prediction of individual age at menopause in seven different cohorts. Corresponding authors of the seven eligible cohorts were contacted and asked to join this IPD meta-analysis. Authors from six cohorts were willing to participate. Therefore data from six of the seven available cohorts could be included. In Supplemental Fig. 3, the number of cases present in the source data, the number of cases lost due to inclusion and exclusion criteria, and the final number of cases included in the IPD data set were depicted.

IPD meta-analysis

The six cohorts participating in this IPD analysis provided data on 2596 women with a regular cycle at AMH measurement. Baseline characteristics of women available for analysis were depicted per cohort of origin in Table 1. As outlined in this table, statistically significant differences were present in all baseline parameters, demonstrating the dissimilarity of the available cohorts. For cases with missing data on AMH (n = 31, 0.01%), single imputation within the original cohort was performed.

A total of 1077 menopause events were observed across the studies with a range of 0.1 to 15.7 years between baseline (*i.e.*, AMH measurement) and the event menopause (mean: 7.1, median: 7.1, SD: 3.5). Median age at inclusion in the overall cohort was 39.3 years. Median age at inclusion ranged from 34.1 to 42.7 years in the different cohorts.

In Supplemental Fig. 4, Kaplan-Meier curves of the distribution of age at natural menopause were depicted for each of the participating cohorts. As illustrated, the distribution of menopausal ages is quite comparable, although two studies consistently reported a shift to later ages at menopause (6, 9).

As stated above, the checks for heterogeneity resulted in the use of study- and age-specific AMH percentile curves in the final analyses.

The results of the different Cox regression analyses assessing time to menopause based on age and AMH are

Table 1. Baseline Data of IPD Cohort

	Vd Stroom (n = 166)	Freeman (n = 374)	Sowers (n = 277)	Tehrani (n = 1005)	Dólleman (n = 595)	Broer/Depmann (n = 152)	*P* Value
Characteristics baseline							
Age , y (SD)	33.9 ± 3.1	41.5 ± 3.5	38.2 ± 4.8	36.9 ± 7.3	42.2 ± 5.8	37.2 ± 6.0	<0.05
Age menarche, y (SD)	13.0 ± 4.8	12.7 ± 1.8	12.6 ± 1.3	NA	13.3 ± 1.4	13.0 ± 1.9	<0.05
AMH, ng/mL (SD)	2.41 ± 2.1	1.1 ± 1.1	3.1 ± 2.8	1.6 ± 1.7	1.06 ± 1.4	2.3 ± 2.6	<0.05
AMH assay	BC 100%	Gen II 100%	Gen II 7.9% Gen II 78.7% DSL 13.4%	Gen II 100%	Gen II 100%	Gen II 100%	
BMI, kg/m^2 (SD)	25.2 ± 5.3	29.2 ± 7.5	26.3 ± 5.6	27.1 ± 4.5	24.3 ± 3.9	23.9 ± 3.8	<0.05
Smoking[a]							<0.05
Ever, %	NA	38.6	5.9	4.5	31.1	31.9	
Never, %	NA	61.4	NA	95.5	68.9	68.1	
Yes, %	NA	NA	27.1	NA	NA	NA	
No, %	NA	NA	67.0	NA	NA	NA	
Characteristics at last follow-up							
Cycle state							<0.05
MP, %	9.6	50.3	63.9	27.6	57.1	52.0	
MT, %	16.9	26.5	9.0	72.4	19.6	20.4	
Regular, %	73.5	23.2	27.1	0	23.3	27.6	
BMI, kg/m^2 (SD)	NA	29.4 ± 7.5	28.4 ± 6.4	NA	NA	24.9 ± 4.1	<0.05

Abbreviations: BMI, body mass index; MP, menopause; MT, menopause transition; NA, not available.

[a]Smoking at baseline either defined as current smoking: yes or no; or ever smoking: yes or no.

depicted in Table 2. The univariable Cox model demonstrated age to be an important predictor of time to (any age at) menopause (HR, 1.31; 95% CI, 1.29 to 1.33). The C-statistic of this univariable model was 84% (95% CI, 83% to 86%). The multivariable model, where an AMH-based time-to-menopause prediction was performed correcting for age, demonstrated AMH to be a significant predictor of time to menopause (HR, 0.66; 95% CI, 0.61

Table 2. Results of the Different Cox Models Assessing Time to Menopause

	Age			AMH + Age			
	HR (CI)	C-Statistic % (CI)	*P* Value	HR (CI)[a]	C-Statistic % (CI)	*P* Value	Median FU
Prediction of time to MP (all ages at MP)							
Cohort	1.31 (1.29–1.33)	84 (83–86)	<0.01	0.66 (0.61–0.71)	86 (85–87)	<0.01	9.5
By age at AMH sampling							
18–30 (MP in n = 4)	NE	NE		NE	NE		
31–40 (MP in n = 278)	1.32 (1.25–1.39)	70 (67–74)	<0.01	0.70 (0.64–0.78)	77 (74–80)	<0.01	10.2
41–50 (MP in n = 795)	1.25 (1.22–1.28)	68 (66–70)	<0.01	0.61 (0.55–0.69)	72 (70–74)	<0.01	7.2
Prediction of early MP (MP ≤45 y of age)							
Cohort	1.01 (0.97–1.04)	52 (48–55)	0.65	0.33 (0.24–0.45)	80 (75–85)	<0.01	9.5
By age at AMH sampling							
18–30 (MP in n = 4)	NE	NE		NE	NE		
31–40 (MP in n = 77)	1.06 (0.98–1.15)	59 (55–62)	0.16	0.34 (0.24–0.48)	80 (74–86)		10.2
Prediction of late MP (MP ≥55 y of age)							
Cohort	1.94 (1.82–2.06)	99 (99–99)	<0.01	1.19 (1.02–1.38)	99 (99–99)	<0.01	9.5
By age at AMH sampling							
18–30 (MP in n = 0)	NE	NE		NE	NE		
31–40 (MP in n = 4)	NE	NE		NE	NE		
41–50 (MP in n = 116)	1.90 (1.77–2.04)	96 (95–97)	<0.01	1.18 (1.00–1.39)	99 (95–97)	0.1	7.2

Results of Cox regression analyses assessing time to menopause. Analyses are depicted assessing time to any age at menopause in the entire cohort and per baseline age category. The bottom rows depict analyses assessing early and late menopause (defined as ≤45 and ≥55 y of age). The outermost right column displays the mean follow-up within the cohort of interest.

Abbreviations: FU, follow up; MP, menopause; NE, no estimation possible due to lack of (sufficient number of) events.

[a]HR for AMH in AMH + Age model.

to 0.71). However, the added value on top of age was quite limited, as reflected by the minor rise in the C-statistic (86%; 95% CI, 85% to 87%).

In the model assessing time to early menopause (*i.e.*, ≤45 years), age was not predictive of time to menopause (HR, 1.01; 95% CI, 0.97 to 1.04; C-statistic, 52%; 95% CI, 48% to 55%). When adding AMH to the model, the predictive capacity became significant (HR, 0.33; 95% CI, 0.24 to 0.45), and the predictive accuracy improved to 80% (95% CI, 75% to 85%). Due to lack of sufficient events in most age groups, this effect almost completely resulted from women aged 31 to 40 years at baseline.

The model assessing time to late menopause (*i.e.*, ≥55 years of age) demonstrated no added effect of AMH to the model assessing age alone (age alone: HR, 1.94; 95% CI, 1.82 to 2.06; C-statistic, 99%; 95% CI, 99% to 99% vs age + AMH: HR, 1.19; 95% CI, 1.02 to 1.38; C-statistic, 99%; 95% CI, 99% to 99%).

A further individual age at menopause analysis was performed based on age-specific AMH percentiles using a Weibull survival model (Table 3; Fig. 1, top panel). This analysis revealed that for women with the lowest age-specific AMH percentile levels, an increased risk of early menopause could be predicted (Table 3; risk of menopause ≤45 years in the <p5 group: 28.1%, in the p95 group: 3.8%). Moreover, it becomes clear that women with high age-specific AMH levels experienced menopause later in life. However, the range of predicted ages was limited and did not cover early and late age at menopause, whereas the accompanying prediction intervals remained wide.

A check of nonproportionality of AMH-based age at menopause prediction was performed and outlined in Supplemental Fig. 5. This figure revealed that for younger women, a more solid AMH effect in prediction is observed, whereas this effect becomes negligibly small in older women. This implies that at higher ages, the chance of becoming menopausal is more poorly predicted by a woman's AMH percentile category.

Because nonproportionality of the AMH effect was observed, the previously stated Weibull survival model was redone, this time making the shape parameter of the model dependent to the AMH percentile categories (see Fig. 1, bottom panel). As depicted in this Weibull plot, when correcting for the nonproportionality of the AMH effect, the prediction interval became increasingly wide with decreasing age at menopause. Hence, individual predictions of age at menopause are less precise at younger ages at menopause. Unfortunately, it was this age range in which the most solid AMH effect in the Cox regression model could be observed.

Discussion

In this IPD meta-analysis, AMH was a significant predictor of time to menopause and especially of time to early menopause (*i.e.*, ≤45 years). However, individual predictions of age at menopause demonstrated a limited precision, especially when concerning early age at menopause, making clinical application troublesome. Moreover, the predictive capacity of AMH decreased with increasing age.

By creating the largest data set to date, this study aimed to overcome the limitations in menopause prediction previously observed and mentioned above (20). The first problem surrounding AMH-based menopause predictions is the wide prediction interval accompanying the predicted ages at menopause, which makes the clinical application cumbersome. Unfortunately, in this IPD meta-analysis, the prediction intervals remained wide, especially when concerning younger ages at menopause (Fig. 1). This might be due to the fact that AMH alone cannot capture all variation in age at menopause. Adding other factors potentially predictive of age at menopause, such as lifestyle factors [*i.e.*, body mass index (BMI) or smoking] or genetic factors, might narrow this

Table 3. Proportion of Women in Each AMH Percentile Category With Early, Normal, or Late Age at Menopause, as Derived From the Weibull Predicted Age at Menopause Distribution

Baseline AMH	Menopause ≤Age 45 y (9.6%)	Menopause Age 46–54 y (79.3%)	Menopause ≥Age 55 y (11.1%)
p5	28.1%	68.2%	3.8%
p10	25.3%	70.4%	4.3%
p25	17.7%	75.8%	6.5%
p50	8.0%	77.7%	14.2%
p75	2.7%	66.4%	30.9%
p90	1.2%	53.1%	45.6%
p95	0.9%	48%	51.1%

The outer left column displays the age-specific AMH percentile categories. The top two rows display the age categories at which the event menopause occurred and their respective incidence. The incidence of the event menopause for each age category is displayed (irrespective of AMH levels). The seven bottom rows of the table display the distribution of age at menopause per AMH percentile category calculated using the Weibull model.

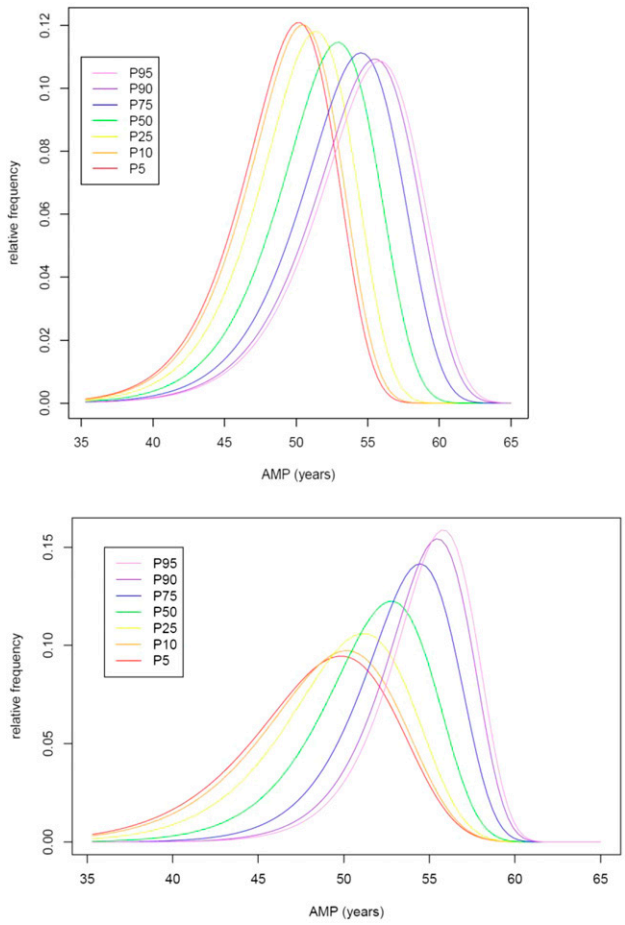

Figure 1. Nomogram depicting the estimated distribution of age at menopause (AMP) per AMH percentile line, assuming a stable predictive performance across age groups at AMH assessment (top panel) or applying a Weibull model including dependency of the shape on the AMH percentiles (bottom panel). The *x*-axis represents age at menopause. Each curve represents the distribution of ages at menopause for an age-specific AMH percentile category. As demonstrated, the lower the age-specific AMH category is, the younger the predicted mean age at menopause. Moreover, when correcting for the nonproportionality of the AMH effect (bottom panel), it appears that the younger the predicted age at menopause is, the wider the accompanying prediction interval, making predictions less precise at lower ages.

prediction interval. Unfortunately, we could not incorporate these factors because these data were not available in the majority of the cohorts. Data for BMI was available in most of the cohorts except for one, where data were missing in half of the subjects. We therefore decided to keep BMI out of the main analysis, because, otherwise, data from half of a cohort needed to be imputed or discarded as missing data. To review the BMI effect though, we performed a sensitivity analysis in which BMI was added to the Cox regression analysis when available. For this sensitivity analysis, data on 2343 women were available. As depicted in Supplemental Table 1 and compared with Table 2, when comparing the C-statistic of the main analysis with the C-statistic of the sensitivity analysis, including BMI, a small added effect could be observed because the C-statistic rose 1% to 2%, making BMI a possible interesting predictor in age at menopause.

The wide prediction intervals could also originate from the different AMH assays that were used (11). When combining six cohorts, using four different assays, assay-related problems increase rather than decrease, potentially resulting in model imprecision. We have attempted to bypass this problem by performing age at menopause predictions using age- specific AMH percentiles calculated within the data set of origin.

The second problem for AMH-based menopause predictions that recently became apparent (18) is the fact that AMH loses its predictive capacity with increasing age. In the current analysis, we therefore performed a nonproportionality analysis for the predictive effect of AMH. We could confirm previous findings and showed that AMH has a notably reduced predictive capacity when assessed in older women. As seen in Supplemental Fig. 5, the predictive capacity of AMH is virtually lost for older women. This is understandable if you keep in mind that for women above 50 years of age, the occurrence of menopause within the next 10 years is inevitable, and no level of AMH will alter this fact. This effect is also observed in Fig. 1, where the results of the individual predictions of age at menopause are depicted. In this figure, it becomes clear that the higher the age at menopause, the narrower the prediction interval of individual age at menopause becomes. This effect is due to the fact that the occurrence of menopause is affected by a natural upper age limit of approximately 60 years (13). Consequently, the prediction interval accompanying the individual age at menopause is compressed at the highest ages.

The last problem regarding AMH-based menopause predictions is the incapacity to identify extreme ages at menopause (*i.e.*, early or late menopause). It was postulated that the lack of predictive capacity of early menopause stemmed from the rareness of the event in combination with small data sets. Regrettably, even in this large cohort, only 103 events of early menopause (≤45 years) were observed. This might be due to the fact that all women contributing data to this IPD had a regular cycle at baseline. Therefore, women experiencing irregular cycles at a young age, possibly destined for an early menopause, were excluded at baseline. Nonetheless, when evaluating these 103 events, an added value of AMH on top of predictions based on age alone was observed. In this subanalysis, the predictive capacity expressed by the C-statistic of the model rose from 52% to 80%. When looking at Table 3, where the distribution of ages at menopause are depicted derived from the Weibull model, these promising results are somewhat

tempered. In line with the Cox regression models, this table demonstrates an increased risk of early menopause for women with an AMH value in the lowest percentiles compared with woman with the highest AMH values (risk of menopause ≤45 years in the <p5 group: 28.1%; in the p95 group: 3.8%). And although a significant effect of AMH is observed when regarding the prediction of early age of menopause (in both models), it must be noted that even with the lowest age-specific AMH, the chances of not reaching menopause at an early age are still 72%. Moreover, and as previously stated, the prediction intervals surrounding the predictions of individual age at menopause are increasingly wide with decreasing age at menopause, making the predictions of early menopause the least precise.

Regarding late menopause (≥55 years of age), no predictive AMH effect could be demonstrated. On the one hand and as previously mentioned, this stems from the fact that age alone is such an important predictor of menopause in older women that AMH has virtually no added predictive capacity next to age in prediction models regarding late menopause. On the other hand, to observe late menopause in women included at a young age, a long follow-up time is needed. Because median time to follow-up was 9.5 years in the cohort, few women included at a young age could have experienced late menopause in the present cohort.

When looking at the results, even though AMH was proven to be a significant predictor of age at menopause, the remaining imprecisions and limited capacity of forecasting the extreme ages at menopause may jeopardize its clinical applicability as a tool to forecast reproductive lifespan. Additional research is needed to overcome the current limitations of AMH-based menopause predictions. The limited ability of AMH to identify women destined for extreme ages at menopause might be resolved by including women in a prospective study at a very young age, irrespective of cycle state and allowing for a long follow-up. The broad prediction intervals could be narrowed by subduing the effect of AMH assays, by using a rigid automated assay methodology. In addition, when measuring AMH more frequently, or at predetermined intervals, individual AMH decline trajectories could be calculated and consequently incorporated in the analyses, making them potentially more precise. Lastly, adding currently (un)known variables contributing to age at menopause (such as lifestyle factors or genetic factors) could improve prediction precision.

In conclusion, in this large IPD meta-analysis, AMH-based menopause prediction using all data currently available worldwide was evaluated. The capacity of AMH in the prediction of menopause was confirmed. Still, major problems in the precision of these predictions make clinical application troublesome. Future research designed as outlined above may make AMH a more relevant tool for clinical practice.

Acknowledgments

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Disclosure Summary: F.J.M.B. is a member of the external advisory board for Ferring BV, a member of the external advisory board for Merck Serono, and a consultant for Gedeon Richter and is involved in educational activities for Ferring BV, strategic cooperation with Roche on automated AMH assay development, and research cooperation with Ansh Laboratories. B.W.M. reports consultancy for ObsEva, Merck Serono, and Guerbet and is supported by National Health and Medical Research Council Practitioner Fellowship GNT1082548. The remaining authors have nothing to disclose.

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