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**ORIGINAL ARTICLE** ***Reproductive endocrinology***

# Anti-Müllerian hormone is a more accurate predictor of individual time to menopause than mother's age at menopause

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**STUDY QUESTION:** In the prediction of time to menopause (TTM), what is the added value of anti-Müllerian hormone (AMH) when mother's age at natural menopause (ANM) is also known?

**SUMMARY ANSWER:** AMH is a more accurate predictor of individual TTM than mother's age at menopause.

**WHAT IS KNOWN ALREADY:** Mother's ANM is considered a proxy for daughter's ANM although studies on its predictive accuracy are non-existent. AMH is a biomarker with a known capacity to predict ANM. However, its added value on top of known predictors, like mother's ANM, is unknown.

**STUDY DESIGN, SIZE, DURATION:** Population-based cohort studies were used. To assess any additive predictive value of mother's ANM, 164 mother–daughter pairs were used (Group 1). To assess the added value of AMH, a second group of 150 women in whom AMH and mother's ANM were recorded prior to a 12-year follow-up period during which daughter's ANM was assessed was used (Group 2).

**PARTICIPANTS/MATERIALS, SETTING, METHODS:** Group 1 consisted of participants of the DOM cohort (an ongoing breast cancer study). Group 2 was a pooled cohort of women with regular menstrual cycles from two independent published studies. Cox proportional hazards analysis estimated uni- and multivariate regression coefficients for female age at study entry, mother's ANM and AMH in the prediction of TTM. Discrimination of models was assessed with C-statistics. Clinical added value of AMH was quantified with a net reclassification index (NRI).

**MAIN RESULTS AND THE ROLE OF CHANCE:** A model with female age and mother's ANM had a c-statistic of 79 and 85% in groups 1 and 2, respectively. Both age and mother's ANM were significantly associated with TTM (HR 1.54 and HR 0.93 for age and mother's ANM in Cohort 1 and HR 1.59 and HR 0.89 in Group 2, respectively. *P*-value for all $<0.001$). In Group 2, the multivariate model with age, mother's ANM and AMH had a c-statistic of 92%, and only female age and AMH remained significantly associated with TTM (HR 1.41 $P < 0.0001$; HR 0.93 $P = 0.08$ and HR 0.06 $P < 0.0001$ for age, mother's ANM and AMH, respectively). The mean weighted NRI suggests that a 47% improvement in predictive accuracy is offered by adding AMH to the model of age and mother's ANM. In conclusion, AMH and mother's ANM both have added value in forecasting TTM for the daughter based on her age. In comparison, AMH is a more accurate added predictor of TTM than mother's ANM.

**LIMITATIONS, REASONS FOR CAUTION:** The cohort of women is relatively small and different cohorts of women were pooled.

**WIDER IMPLICATIONS OF THE FINDINGS:** This study shows that AMH is a more accurate predictor of ANM than mother's ANM. However, before achieving clinical applicability, the certainty with which a woman's prediction is made must improve. The association between mother's ANM and TTM in daughters did not appear to be influenced by whether ANM was recorded by mothers or daughters—an important finding because in the clinical setting daughters usually provide this information.

**STUDY FUNDING/COMPETING INTEREST(S):** No funding was received and there were no competing interests in direct relation to this study.

**Key words:** ovarian reserve / anti-Müllerian hormone / menopause

# Introduction

Menopause marks the definite end of the fertile lifespan. The average age at which a woman in the more developed countries enters menopause is 51 years. However, chronologic age at menopause shows considerable individual variation and ranges between the ages of 40 and 60 years, with ~10% of women becoming menopausal before 45 years of age (Powell *et al.*, 1994; te Velde and Pearson, 2002).

A fixed temporal relationship between age at menopause, the end of natural fertility and the start of subfertility is thought to be present (te Velde and Pearson, 2002; Broekmans *et al.*, 2009). Predicting age at menopause is therefore clinically relevant as it could give women a more accurate idea of the length of their fertile life span, which, in turn, may be used during informed decision-making about timing of childbearing. The large variability in menopausal age has prompted researchers to find a more reliable marker than chronological age in predicting age at natural menopause (ANM).

Heritability of age at menopause has been recorded to be substantial, with heritability rates varying between 30 and 85% (Torgerson *et al.*, 1997; Snieder *et al.*, 1998; de Bruin *et al.*, 2001; van Asselt *et al.*, 2004; Murabito *et al.*, 2005). Although genetic studies on variation in ANM have delivered interesting results, currently only 2.5–4.1% of natural variability can be explained by involved common genetic loci. It is expected that in the near future, using more refined genetic techniques, more rare variants will be discovered which might predict more accurately the ANM (Stolk *et al.*, 2012). For this reason, the age at which a woman's mother reached menopause may be useful as a tool to indicate in what age range a woman herself will become menopausal. Interestingly, no studies have formally assessed the true predictive value of mother's ANM for the forecasting daughter's ANM.

More recently, ovarian reserve tests, such as the serum concentration of anti-Müllerian hormone (AMH), have been suggested as valuable markers for predicting the size of the primordial follicle pool, i.e. the ovarian reserve (de Vet *et al.*, 2002). As such, AMH serves as a proxy for the number of follicles remaining in an individual's ovaries. Since the exhaustion of the primordial follicle pool coincides with the ANM, AMH might constitute a marker for menopausal age as well (Broer *et al.*, 2011; Tehrani *et al.*, 2011, 2013; Freeman *et al.*, 2012; Dolleman *et al.*, 2013a,b). Interestingly, mother's ANM has recently also been found to be a determinant of AMH levels in the daughters (Bentzen *et al.*, 2013). This paper aims to answer two important questions: First, what is the predictive value of mother's ANM in the prediction of daughter's ANM and second, what is the added value of AMH in this prediction when mother's age at menopause is already known?

# Methods

## Participants and study design

Two study groups of women, from different individual cohorts, contributed information to this study. Firstly, a group of women (Cohort 1) in whom both mother's ANM and daughter's ANM were prospectively collected was used to assess the predictive value of mother's ANM in forecasting daughter's ANM. A second, pooled group of women (cohorts 2 and 3) with recorded information on AMH and mother's ANM at baseline who were followed up for >10 years was used to assess the *added value* of AMH when mother's ANM is already known. Group 1 was used for two reasons. The large number of mother–daughter pairs allows calculation of reliable regression coefficients for mother's ANM in the prediction of time to menopause (TTM). Secondly, Group 1 was used to verify the magnitude of regression coefficients in Group 2 so that the added value of AMH on mother's ANM could be adequately studied without the risk of overestimation due to a smaller study population in Group 2.

### *Study Group 1: Cohort 1*

Cohort 1 consisted of female volunteers participating in a prospective follow-up study on determinants of the development of breast cancer (Miltenburg *et al.*, 1998). This study consisted of four birth cohorts, DOM1 1911–1925; DOM2 1926–1931; DOM3 1932–1941 and DOM4 1942–1945. For this study, mothers were selected from the oldest, and daughters from youngest, birth cohorts. Probabilistic linkage was used to identify mother–daughter pairs on the basis of: date of birth of the mother, date of birth of the children, birth order, and part of the (maiden) name, as previously documented and successfully applied (de Bruin *et al.*, 2001; van Asselt *et al.*, 2004). Information on age at menopause, and whether this was natural or iatrogenic menopause, was collected from questionnaires. Upon first screening the majority of mothers were already post-menopausal. Either the daughters were post-menopausal at inclusion or menopausal age was assessed in a follow-up round. In total, 164 mother–daughter pairs were identified in which both females experienced natural menopause (van Asselt *et al.*, 2004). Written informed consent was received from all women and the study was approved by the Institutional Review Board of the University Medical Center Utrecht, The Netherlands.

### *Study Group 2: Cohort 2*

Study Group 2 is a pooled group from cohorts 2 and 3. Cohort 2 consists of 265 women aged 21–46 years with a regular cycle, who had not taken contraceptive medication for at least 3 months and who had no history of infertility or ovarian surgery at inclusion. For more details please refer to Broer *et al.* (2012). At cohort recruitment, AMH was measured and the age at which the participants' mothers became menopausal was recorded. At the two follow-up rounds, ~11 and 13 years later, women were assessed with

questionnaires. The questionnaires pertained to menstrual cycle characteristics, the occurrence of menopause, use of hormones or other medication, as well as reproductive history. Menopause was defined as the absence of menstrual periods for 12 consecutive months. The studies were approved by the Medical Ethical Review Committee of the University Medical Center Utrecht or the Erasmus Medical Center Rotterdam, and written informed consent was received from all women.

*Study Group 2: Cohort 3*

Cohort 3 was recruited for a study that assessed whether age at menopause was different between women who did and did not have a history of a trisomy-21 pregnancy. Cohort 3 consisted of 220 women aged 25–40 years with regular menstrual cycles. All participants had experienced two or more spontaneous menstrual cycles after discontinuation of breastfeeding or the use of oral contraceptives, and no women had gynaecological surgery at inclusion.

For more information please refer to van der Stroom *et al.* (2011). AMH and mother's age at menopause were recorded at cohort recruitment. At follow-up, ~11 years later, the cohort was approached with a questionnaire on general medical and gynaecological/obstetric history with which age at menopause was assessed. Menopause was defined as the absence of menstrual periods for at least 12 consecutive months. Approval for this study was received from the VU Medical Center's scientific review board and ethics committee and written informed consent was obtained from all participants.

### Hormone assays

AMH was measured in baseline samples as previously described in the original studies (Broer *et al.*, 2011; van der Stroom *et al.*, 2011). In short, in Cohort 2 two different AMH assays were used (Diagnostic Systems Laboratories (DSL) and Immunotech Coulter) and in Cohort 3 the same Immunotech Coulter assay was used as in Cohort 2. The AMH measures from cohorts 2 and 3 were determined in the same laboratory in Rotterdam, The Netherlands, during the same time period. A laboratory-specific conversion factor was calculated with which AMH levels between the two assays were made comparable: AMH levels from the DSL assay were multiplied by a factor of 2 to allow comparison with the Immunotech Coulter assay as previously successfully described and applied in the original study (Broer *et al.*, 2011). The DSL (Webster, TX, USA) had a detection limit of 0.026 ng/ml and inter- and intra-assay coefficients of variation were <5 and <11%, respectively. The immunosorbent assay from Immunotech Coulter (Marseille, France) had a detection limit of 0.05 ng/ml and intra and inter-assay coefficients of variation were <5 and 8%, respectively.

## Data Analysis

All participants from Group 2 had to have complete information on age, AMH and mother's ANM at the start of follow-up. Figure 1 shows which 150 of the original 522 women from cohorts 2 and 3 remained eligible for analysis after exclusion of women with missing values. Baselines characteristics were described as median (interquartile range: IQR) or mean (95% confidence interval (CI)). To analyse whether the sample of women in Group 2 in which we knew mother's ANM differed from those in which ANM was missing, baseline characteristics between these women were compared with independent sample *t*-tests. To justify pooling of AMH values from cohorts 2 and 3, age-specific AMH values were compared. Three AMH values were under the assay's detection limit; these values were included as 0.05 ng/ml.

The age at which a woman enters the cohort has intrinsic predictive value on the TTM prediction. While a young woman at entry will have a low *a priori* probability of entering menopause in a follow-up period of 10–15 years, a 45-year old will have a high probability in the same follow-up period. Additional factors may fine-tune these expectations; therefore, the added value of mother's ANM and AMH on top of age

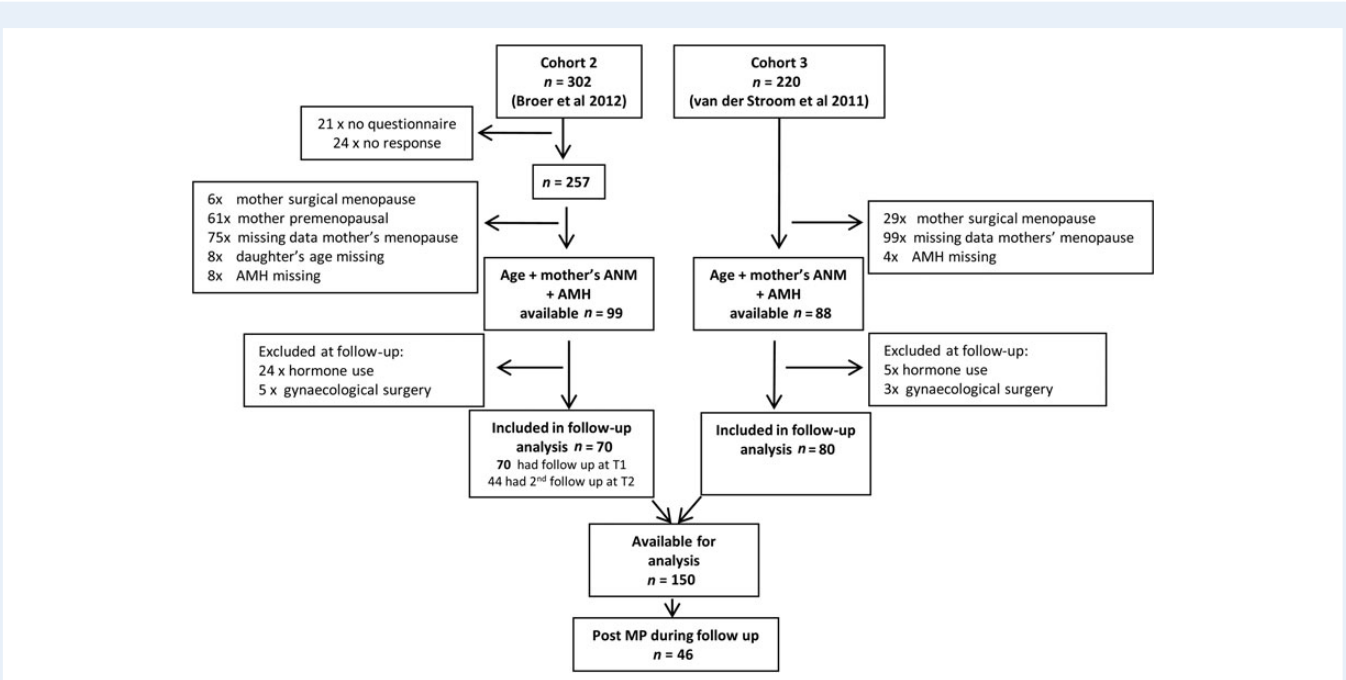


**Figure 1** Flowchart of eligible participants from cohorts 2 and 3 in the study to determine whether anti-Müllerian hormone (AMH) is a more accurate predictor of individual time to menopause than mother's age at natural menopause (ANM).

at entry (henceforth referred to as 'age') was assessed. Cox proportional hazards analysis was used, with follow-up time on the time-axis, to estimate the univariate regression coefficient for age in the prediction of TTM and the multivariate regression coefficients for age, mother's ANM and AMH in the prediction of TTM. Follow-up time was described as the number of years until menopause was reached or as the total number of years until the most recent follow-up for women who were premenopausal at the last assessment (at which they were censored). Women who underwent gynaecological surgery were censored at the time of operation, and women taking hormonal medication were censored at the age at treatment initiation. If this information was missing, these women were excluded (Fig. 1). The shape of the associations was assessed and where necessary, data were transformed with restricted cubic splines. Regression coefficients with standard errors were transformed to Hazard Ratio's (HR, 95% CI) to simplify interpretation. The discrimination of the univariate and multivariate models was assessed with c-statistics (95% CI).

A net reclassification index (NRI) was calculated for the different models with age, mother's ANM and AMH. An NRI quantifies the improvement offered by new markers by examining the extent to which a new marker reclassifies subjects at a higher or lower risk of having an event during follow-up (Pencina *et al.*, 2011). A continuous NRI (cNRI) was chosen as no risk categories for the occurrence of menopause exist. The cNRI counts the direction of change per individual instead of counting the percentage that crosses a particular risk threshold. Each patient is counted as +1 or −1 depending on whether the change in calculated risk was in the correct direction (higher for those with events, lower for those without events) (Pickering and Endre, 2012). The NRI is the sum of the 'event NRI' and the 'non-event NRI', where the event NRI is the net proportion of patients who did experience menopause during a 10-year follow-up who had an increase in calculated risk and the non-event NRI is the proportion of women without menopause who had a decrease in calculated risk. The maximum possible cNRI is 200% as, theoretically, all women with an event and all without an event can be correctly reclassified. For ease of interpretation we also reported the average of the two net percentages. In a sensitivity analysis we excluded daughters with a history of a trisomic pregnancy to see whether this affected the prediction (Pencina *et al.*, 2011).

A *P*-value of $<0.05$ was considered significant. Data were analysed with the Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, IL, USA) and with R version 2.13 (http://www.r-project.org/).

# Results

Baseline characteristics are shown in Table I. From the women in Group 2 in whom no mother's ANM was recorded, 61 indicated that their mothers were still premenopausal and 35 indicated that their mothers experienced surgical menopause. The women in whom mother's ANM was missing were younger than women in whom mother's ANM was known (33.3 versus 35.5 years, *P*-value $<0.001$). All other baseline characteristics were comparable. Supplementary data, Fig. 1 shows the comparability of age-adjusted AMH values between cohorts 2 and 3, especially at 30–45 years, thus justifying the pooling of these AMH values.

## Accuracy of mother's age at natural menopause

Results of uni- and multivariate analyses are presented in Table II. In Group 1, both age at entry and mother's ANM appeared predictive of TTM in the daughter. In the multivariate model, both predictors remained significantly associated with TTM. The HR for age was 1.54 (95% CI 1.42–1.66) meaning that an increase in age at baseline increased the hazard of menopause during follow-up by 1.5 times, while an increase in mother's ANM by 1 year decreased the hazard of menopause by 7% (HR = 0.93; 95% CI 0.90–0.96). The c-statistic of this two factor model was 79% (95% CI 76–82%), meaning that it can discriminate between women who enter menopause early and women who enter menopause late during follow-up with an accuracy of 79%.

## Added value of AMH on mother's age at natural menopause

In a multivariable model with age and mother's ANM, both predictors were significantly associated with TTM: HRs 1.58 (95% CI 1.41–1.78) and 0.91 (95% CI 0.84–0.97), for age and mother's ANM, respectively. The c-statistic of this model was 85% (95% CI 79–91%). In a model with all three predictors, female age at entry and AMH remained significant

**Table I Baseline characteristics of women included in a study of factors that predict age at natural menopause (ANM).**

| | Study Group 1 | Study Group 2 | | Study Group 2 Pooled |
|---|---|---|---|---|
| | Cohort 1 | Cohort 2 | Cohort 3 | Cohorts 2 + 3 |
| *n* | 164 | 70 | 80 | 150 |
| Age (years) at inclusion [median (IQR)] | 39.0 (37.0–41.0) | 37.0 (32.8–42.2) | 34.7 (33.2–36.6) | 35.5 (33.0–38.5) |
| Age (years) at follow-up [median (IQR)] | 49.5 (47.0–52.0) | 51.6 (47.0–54.5) | 47.2 (45.1–48.6) | 48.4 (45–51.4) |
| Years of Follow-up [mean (SD)] | 10.1 (5.6) | 12.5 (11.6–14.9) | 12.1 (11.6–12.9) | 12.4 (11.6–13.2) |
| AMH [median (IQR)] | NA | 0.6 (0.3–2.4) | 1.8 (1.0–3.5) | 1.5 (0.5–2.9) |
| Age (years) at menopause [mean (SD)] | 48.8 (4.2) | 50.8 (3.5)[a] | 49.9 (3.0)[a] | 50.7 (4.1)[a] |
| Mother's age (years) at menopause [mean (SD)] | 49.8 (4.1) | 49.8 (4.3) | 49.1 (4.3) | 49.4 (4.3) |
| Menopausal at follow-up (*n*) | 164 | 33 | 13 | 46 |

AMH, anti-Müllerian hormone; IQR, interquartile range.
[a]Means calculated on the basis of the survival analysis.

**Table II Univariate and multivariate Cox regression analysis for time to menopause prediction in the daughters.**

| | Study Group 1 (Cohort 1) | | | | | Study Group 2 (Cohorts 2 + 3) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Regression analysis | | | C-statistic | | Regression Analysis | | | C-statistic | |
| | HR | 95% CI | *P*-value | C-index | 95% CI | HR | 95% CI | *P*-value | C-index | 95% CI |
| Univariate regression | | | | | | | | | | |
| Daughter's age | 1.54 | 1.42–1.67 | <0.0001 | 0.77 | 0.73–0.81 | 1.59 | 1.42–1.78 | <0.0001 | 0.84 | 0.78–0.90 |
| Mother's ANM | 0.93 | 0.90–0.96 | <0.0001 | 0.59 | 0.51–0.67 | 0.89 | 0.75–1.06 | 0.001 | 0.63 | 0.54–0.72 |
| Daughter's AMH | | | | | | 0.02 | 0.01–0.10 | <0.0001 | 0.86 | 0.81–0.91 |
| Multivariate regression | | | | | | | | | | |
| Daughter's age + mother's ANM | | | | | | | | | | |
| Age | 1.54 | 1.42–1.66 | <0.0001 | 0.79 | 0.76–0.82 | 1.58 | 1.41–1.78 | <0.0001 | 0.85 | 0.79–0.91 |
| Mother's ANM | 0.93 | 0.90–0.96 | <0.0001 | | | 0.91 | 0.84–0.97 | 0.01 | | |
| Daughter's age + daughter's AMH | | | | | | | | | | |
| Age | | | | | | 1.40 | 1.25–1.57 | <0.0001 | 0.91 | 0.88–0.94 |
| AMH | | | | | | 0.05 | 0.01–0.22 | <0.0001 | | |
| Daughter's age + mother's ANM + daughter's AMH | | | | | | | | | | |
| Age | | | | | | 1.41 | 1.26–1.59 | <0.0001 | 0.92 | 0.88–0.96 |
| Mother's ANM | | | | | | 0.93 | 0.87–1.01 | 0.08 | | |
| AMH | | | | | | 0.06 | 0.02–0.24 | <0.0001 | | |

Hazard ratios (HR) are displayed with their 95% confidence intervals (CI) and the corresponding *P*-value for the predictor. A value of $P < 0.05$ was considered significant. ANM, age at natural menopause.

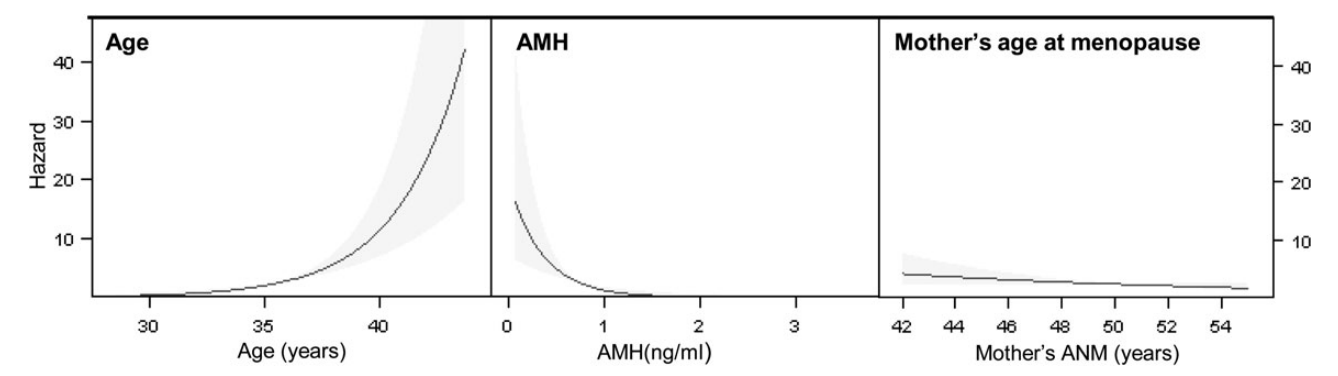


**Figure 2** Hazard ratios of menopause according to female age, AMH and mother's ANM. Solid black lines show the log relative hazard with the confidence intervals shown in grey. ANM, age at natural menopause

predictors but mother's ANM was no longer significant: HRs for age, mother's ANM and AMH were 1.41 (95% CI 1.26–1.59), 0.93 (95% CI 0.87–1.01) and 0.06 (95% CI 0.02–0.24), respectively. This model had an accuracy of 92% (95% CI 88–96%), which is similar to a model with only age and AMH (c-statistic 91%; 95% CI 88–94%) and better than a model with age and mother's ANM.

In the sensitivity analysis excluding the 44 women who had a history of a trisomy-21 pregnancy (Cohort 3), the results were almost identical to the results in the whole group (HR 1.39 for age, 0.93 for mother's ANM and 0.08 for AMH). Figure 2 illustrates the HRs for age, AMH and mother's ANM in the model with all three parameters over the relevant range per parameter.

The NRIs per model are shown in Table III. The model with AMH in addition to age and mother's ANM correctly reclassified an extra 55% of women who did become post-menopausal during follow-up to a higher risk category (event NRI) and correctly reclassified an extra 39% of women who did not become post-menopausal to a lower risk level (non-event NRI) in comparison with a model with only age and mother's ANM. This corresponds to an average weighted improvement of 47% or a NRI of 95% (Table III). Another way to evaluate improvement

**Table III Elements of the continuous net reclassification index (NRI) which show the improvement offered by adding AMH or mother's ANM to a model with age only, and the improvement offered by adding AMH to a model with daughter's age and mother's ANM.**

| Model | Event NRI | Non-event NRI | NRI | Average NRI |
|---|---|---|---|---|
| Daughter's age | Reference | | | |
| Daughter's age + mother's ANM | 11% | 32% | 43% | 21.50% |
| Daughter's age | Reference | | | |
| Daughter's age + daughter's AMH | 48% | 41% | 89% | 44.5% |
| Daughter's age + mother's ANM | Reference | | | |
| Daughter's age + mother's ANM + daughter's AMH | 55% | 39% | 95% | 47% |

ANM, age at natural menopause.

offered by AMH can be described in terms of the increase in the accuracy with which a model discriminates between women who enter menopause early or late during follow-up. The c-statistic of 85% of the model with age and mother's ANM has 15% to gain in accuracy to attain a perfect c-statistic of 100%. Through addition of AMH to this model the c-statistic rises by 7 of these 15%, which represents almost half of the total amount of accuracy that can possibly be gained by addition of any other marker of TTM.

# Discussion

## Main findings

The current study demonstrates that mother's ANM provides specific information in forecasting the TTM of the daughter. This information adds to the predictive ability of female age itself in estimating the probability of the occurrence of menopause within the next 10–15 years with an accuracy of ~80%. AMH is shown to independently add value to this prediction, and is suggested to be a more accurate added predictor than mother's ANM.

## Findings in view of existing literature

We have shown that mother's ANM has reasonable accuracy in the prediction of daughter's TTM. Although the c-statistics between groups 1 and 2 are not directly comparable due to differences in follow-up duration and the incidence of menopause in the daughters, the HRs are directly comparable. In the multivariate analyses in both groups the HRs for age and AMH were very comparable (HR 1.54 versus 1.58 for age and 0.91 versus 0.93 for mother's ANM in groups 1 and 2, respectively). This similarity implies two important things: firstly, that despite the small sample size of Group 2 and the large number of women that had to be excluded, the estimated HRs are reliable and secondly, that the association between mother's ANM and TTM does not seem to be influenced by whether mother's ANM was recorded by the mothers themselves (Group 1) or by the daughters (Group 2). Considering that in the clinic, the daughters provide such information, this is an important finding.

It is commonly understood that ANM is a heritable characteristic with a 40–85% heritability (Torgerson *et al.*, 1997; Snieder *et al.*, 1998; de Bruin *et al.*, 2001; van Asselt *et al.*, 2004; Murabito *et al.*, 2005). Up to now, however, no study has assessed the predictive value of mother's ANM on daughter's ANM. This is surprising, as clinicians may base their therapeutic approach on this information (e.g. by early initiation of IVF in women whose mothers experienced early menopause) especially when found in combination with slightly lower measures of ovarian reserve.

The best prediction of TTM involved age and AMH, or age, mother's ANM and AMH with c-statistics of 91 and 92%, respectively. The event NRI suggests that in 55% of women who will enter menopause within 10 years, their predicted risk is adequately increased through addition of AMH. This corresponds to an increase in accuracy from 85 to 92% with which women with a short TTM can be discriminated from women with a long TTM. Together, these results advocate AMH as a useful added marker for menopause prediction. The present findings are in line with existing literature that demonstrate the interdependency of genetic variants within the AMH molecule as well as in the AMH type II receptor on one hand and variations in ANM on the other hand (Kevenaar *et al.*, 2007). A recent study has revealed mother's ANM to be a determinant of AMH (Bentzen *et al.*, 2013). The stronger role for AMH in predicting TTM compared with mother's ANM may be explained by several observations. Firstly, it has been shown that AMH is influenced by environmental determinants, such as smoking, which may also influence menopausal age (Dolleman *et al.*, 2013a,b). Information on mother's ANM, on the other hand, will limit itself to the genetic factors shared by mother and daughter. Second, it is likely that reproductive longevity is influenced by both genetic and environmental influences with the genetic component reflecting both a maternal and paternal genetic contribution. Therefore, whilst information from mother's ANM only reflects the maternal half of the genetic influence, AMH may reflect the sum total of genetic and environmental influences.

Recently, retrospective as well prospective studies have emerged that advocate AMH as a prognosticator of ANM (van Disseldorp *et al.*, 2008; Broer *et al.*, 2011; Tehrani *et al.*, 2011, 2013; Freeman *et al.*, 2012; Dolleman *et al.*, 2013a,b). Although providing promising results, none established the added value of AMH on top of patient history information, such as mother's ANM. Although our results favour AMH over mothers ANM for forecasting TTM, considering the relatively small number of women in this study, our findings need confirmation in studies with a long follow-up period allowing improvement of TTM predictions for young women at the beginning of their fertile lifespan.

### Strengths and weaknesses

The main strength of this paper lies in the uniqueness of the cohorts. The self-reported ANM from both mothers and daughters in Cohort 1 made it an ideal cohort in which to assess the accuracy of mother's ANM, a finding that has not been previously published. It also provided a reliable way to confirm findings from group 2, thereby verifying that despite the small numbers these models do not overestimate the predictive power of the studied predictors.

One limitation of this study is the use of several cohorts, one of which consisted of three studies. However, long-term follow-up studies on menopause are scarce, especially when information on both AMH and mother's ANM must be known. The biggest difference between cohorts is the recruitment of women on the basis of trisomic pregnancy in the obstetric history in Cohort 3; however, a sensitivity analysis without these women did not alter the accuracy of the predictions thus justifying their inclusion. Although the number of women that were available for the analyses on the added value of AMH was small, according to the rule of thumb that one candidate predictor may be assessed per 10 events (natural menopause at follow-up), only 30 events had to occur to have enough power to assess the value of the three candidate predictors. We had 46 events in 150 women. The main reason for this small number of women was due to poor registration of mother's ANM in cohorts 2 and 3. Comparison of the group in which mother's ANM was recorded to the group in which it was missing showed no substantial differences, apart from a younger age in those women where this information was missing. It is possible that mothers were not yet menopausal in these younger women. Nonetheless, these missing values may have led to selection bias about mother's ANM. However, the median ANM of the mothers was 50 years (IQR 47–52 years), which is well within the normal range of age at menopause suggesting that such bias is likely to be minimal. Another possible limitation is that AMH values were measured using two different assays. Recent studies have questioned the reproducibility of AMH values (Rustamov *et al.*, 2012). However, all measurements were carried out in the same laboratory by the same experienced lab technicians during the same time period, with a within-laboratory developed conversion of the two assay systems, thus justifying one-on-one comparison of these data. Furthermore, in the original study a subgroup analysis comparing the performance of AMH measured with different assays revealed no significant difference (Broer *et al.*, 2011).

### Clinical implications

Much variation exists in the rate of reproductive ageing amongst women of the same chronological age, as evidenced by the range of menopausal ages of 40–60 years (te Velde and Pearson, 2002). Considering a fixed temporal relationship this means that natural sterility would ensue at 30–50 years, with the *start* of subfertility occurring ~10 years prior (Broekmans *et al.*, 2009). With current trends in delayed childbearing it is conceivable that a considerable proportion of women who delay childbearing would require help to conceive. Therefore, prediction of future ANM may be a better forecaster of reproductive performance than chronological age alone (te Velde and Pearson, 2002) and women could use this information to make informed decisions about the age until which they can delay starting a family. This may reduce the need for assisted reproduction for age-related subfertility, which has a success rate of 50% at most. However, if this information is to be clinically applied, true predictive accuracy must be substantial. Our results describe reasonable accuracy and 95% CIs. However, previous studies that provide individual predictions of ANM have considerably large 95% CIs (Broer *et al.*, 2011; Tehrani *et al.*, 2013). Before achieving clinical applicability, the certainty with which a woman's prediction is made must improve.

## Conclusion

This study shows that mother's ANM provides additional information, on top of female age, in the prediction of TTM. Furthermore, we found AMH to be a more accurate predictor of individual TTM than mother's ANM. The optimal prediction is made using a combination of female age and AMH; adding mother's ANM does not further improve this prediction.

## Supplementary data

Supplementary data are available at http://humrep.oxfordjournals.org/.

## Authors' roles

M.Dó. was the primary investigator, and she analysed the data and wrote the article. J.S.E.L., I.A.J.v.R. and G.J.S. collected the baseline data for Cohort 2. M.De., S.L.B. and J.H. collected the follow-up data for Cohort 2 and helped with interpreting data. S.L.B. collected the round 1 follow-up data for cohort 2. C.B.L. and E.M.v.d.S. collected the data for Cohort 2 and helped with interpretation of the data. M.J.C.E. supervised the analysis and interpretation of the statistical work. Y.T.v.d.S. and P.H.M.P. are the representatives of the DOM cohort and they supervised interpretation of the data. F.J.M.B. supervised interpretation of the data

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## Conflict of interest

None declared.

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