Back to the basics of ovarian aging: a population-based study on longitudinal anti-Müllerian hormone decline

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Abstract

Background: Anti-Müllerian hormone (AMH) is currently used as an ovarian reserve marker for individualized fertility counseling, but very little is known of individual AMH decline in women. This study assessed whether the decline trajectory of AMH is uniform for all women, and whether baseline age-specific AMH levels remain consistently high or low during this trajectory.

Methods: A total of 3326 female participants from the population-based Doetinchem Cohort Study were followed with five visits over a 20-year period. Baseline age was 40 ± 10 years with a range of 20–59 years. AMH was measured in 12,929 stored plasma samples using the picoAMH assay (AnshLabs). Decline trajectories of AMH were studied with both chronological age and reproductive age, i.e., time to menopause. Multivariable linear mixed effects models characterized the individual AMH decline trajectories.

Results: The overall rate of AMH decline accelerated after 40 years of age. Mixed models with varying age-specific AMH levels and decline rates provided the significantly best fit to the data, indicating that the fall in AMH levels over time does not follow a fixed pattern for individual women. AMH levels remained consistent along individual trajectories of age, with an intraclass correlation coefficient (ICC) of 0.87. The ICC of 0.32 for AMH trajectories with time to menopause expressed the large variation in AMH levels at a given time before the menopause. The differences between low and high age-specific AMH levels remained distinguishable, but became increasingly smaller with increasing chronological and reproductive age.

Conclusions: This is the first study to characterize individual AMH decline over a long time period and broad age range. The varying AMH decline rates do not support the premise of a uniform AMH decline trajectory. Although age-specific AMH levels remain consistently high or low with increasing age, the converging trajectories and variance of AMH levels at a given time before menopause shed doubt on the added value of AMH to represent individualized reproductive age.

Background

Women are born with an endowment of oocytes, which decreases as they age. The decline in oocyte quantity eventually leads to menopause, marking the end of the reproductive lifespan [1]. The ability to achieve spontaneous pregnancies ceases several years before the onset of menopause [2], and is thought to be related to the quality of remaining oocytes. With an ever-expanding societal tendency to delay childbearing to a later age, more women may thus unknowingly surpass their window of fertile years due to a decline in oocyte quality and quantity.

Over the past decades, many research efforts have aimed at quantifying the remaining pool of oocytes, otherwise known as the ovarian reserve. Anti-Müllerian hormone (AMH), produced by follicular granulosa cells, has recently emerged as a promising biomarker representing the number of remaining follicles in the ovaries [1]. Herein, AMH levels are suggested to provide an estimation of...
`reproductive age`, irrespective of chronological age [3–11]. In other words, a woman with a low AMH level would have a lower ovarian reserve, and thus a shorter time to menopause than a woman with a higher AMH level of the same (chronological) age. This concept has found its way into clinical practice, as women are currently receiving personalized family planning or fertility treatment counseling based on their AMH levels. Although this may seem like an advancement in reproductive healthcare, evidence to support this practice is lacking. Current knowledge of AMH is scarce, and limited by the use of a single measurement [12–18], small study populations [5, 8, 19], selected study groups rather than a population-based approach [5, 8, 12–18], theoretical rather than empiric models [20, 21], and restricted age ranges [12, 15]. The individualized use of AMH as an indicator of the reproductive lifespan is therefore still hampered by two main questions.

First, little is known about whether the rate by which AMH declines is the same for all women. In other words, are individual AMH decline trajectories parallel to one another, or not? Secondly, the value of a single AMH measurement remains elusive, can a woman with a high age-specific AMH level at 20 years be expected to also have a high age-specific value at age 35, and what does this mean for her trajectory with reproductive age, i.e., time to menopause? We aimed to answer these two questions by characterizing the longitudinal decline trajectories of AMH in relation to both chronological age and time to menopause in a large population-based study.

**Methods**

**Study population**

Our study population consisted of the female participants of the Doetinchem Cohort Study. The Doetinchem Cohort is a population-based cohort, whose participants were randomly recruited from the Doetinchem area of the Netherlands in 1987 [22]. The objective of the Doetinchem Cohort Study is to observe the impact of lifestyle and biological factors on chronic disease occurrence and quality of life [22]. At the time of recruitment, participants were aged between 20 and 59 years. After the baseline visit (round 1), participants were invited for follow-up every 5 years. At the time of the study, rounds 1 through 5 had been completed, leading to an approximate follow-up time of 20 years.

At each visit, lifestyle, general health, and reproductive history were assessed through extensive questionnaires, and biometric and laboratory measurements were performed. In addition to the laboratory measurements that were performed directly after each consecutive blood withdrawal, aliquots with additional plasma samples of each participant were immediately stored for future use. All participants provided written informed consent and ethical approval was granted by the Medical Ethics Committee of the Netherlands Organization of Applied Scientific Research. The use of stored sample specimens was ethically approved by the Ethical Committee for Biobank Studies of the University Medical Center Utrecht.

Only female participants from the Doetinchem Cohort with at least one available stored plasma sample, regardless of their age or menopausal status, were eligible for the current study. Of the total number of 4128 participating women, 3326 had an available plasma sample for at least one of the follow-up rounds. Rounds 1–5 comprised plasma samples of 3133, 2914, 2507, 2324, and 2051 women, respectively.

**AMH measurements**

The plasma samples from round 1 were stored in EDTA aliquots at −80 °C. The samples derived from rounds 2–5 were stored in EDTA aliquots at −30 °C. Prior to the current study, the samples were thawed once for additional measurements and immediately refrozen. For the current study, stored plasma samples of rounds 1–5 were utilized. In March 2015, all the available samples of each participant had been retrieved from storage and were shipped on dry ice to AnshLabs (Webster, Texas, USA), where they were temporarily stored at −20 °C until the analyses were performed. AMH levels were measured with the picoAMH assay (AnshLabs), because of its low limit of detection and the small aliquot size necessary, which is crucial for cohort studies with a limited pool of biological samples. The plasma samples of each individual were measured in a single assay run, by a single laboratory operator. In total, two laboratory operators performed all measurements. At a mean level of 91.2 pg/mL, the coefficient of variation was 4.0 %. At 290.3 pg/mL, the coefficient of variation was 4.8 %. The limit of quantification was 3.0 pg/mL and the limit of detection 1.8 pg/mL. There were no indications of plate drift, with all coefficients of variation within plate columns and rows under 5 %.

**Time to menopause**

Age at the time of the final menstrual period (FMP) was assessed by taking into account questionnaire information of cycle regularity, number of menstrual periods in the prior 12 months, oral contraceptive (OC) use, pregnancy, reproductive surgery, and self-reported age at menopause. Due to slightly differing questionnaires throughout the follow-up rounds, the assessment of the timing of the FMP differed per round. The earliest estimation of the timing of the FMP was considered to be the most accurate, being the most proximate to the event. Time to menopause was calculated by subtracting a participant’s age at the FMP from her age at follow-up. Women who ever underwent a bilateral oophorectomy were excluded from this calculation in order to obtain the time to natural
menopause at each follow-up round. Women who underwent a hysterectomy before the onset of natural menopause were considered to have an unknown age at menopause.

**Missing data**

For information on smoking, OC use, menstrual cycle regularity in rounds 1, 4, and 5, age at menarche, and body mass index (BMI), the percentage of missing information was below 2%. In rounds 2 and 3, missing information for cycle status was 6.8% and 14.6%, due to missing information of the date of the last menstrual period. Missing information for hormone replacement therapy use increased with each round, and varied between 7.1% and 59.8%. Multiple imputation through predictive mean matching with 10 iterations was performed for these variables, including participant ID, age, and AMH levels solely as predictor variables, and all remaining variables both as predictors and outcomes. Multiple imputation was performed with R (http://www.R-project.org), using the ‘mice’ library (http://www.jstatsoft.org/v45/i03/).

**Assessment of individual decline rate: parallel or non-parallel trajectories**

To assess whether the decline rate of AMH differed for individuals, AMH trajectories in relation to age and time to menopause were fitted with a mixed model approach using the ‘lme4’ package in R. Mixed models enable the evaluation of multilevel longitudinal data, and are thus able to take into account multiple measurements over time for each participant, with varying AMH levels (i.e., random intercept) and decline rates (i.e., random slope) for each individual. As AMH had a skewed distribution, AMH levels were logarithmically transformed. Levels below the detection limit of 0.0018 ng/mL were set at this level for the purpose of logarithmic transformation.

\[ \log_{10}(AMH) \]

was used as the outcome of the mixed models, with chronological age or time to menopause as the time variable and participant ID as the group indicator variable. We modeled age and time to menopause with non-linear natural splines and checked the significance of non-linearity (a P value of < 0.05 indicated significant non-linearity). Models were adjusted for current OC use and OC use 5 years prior, hormone replacement therapy use, and current smoking and smoking 5 years prior, as these determinants were associated with the longitudinal AMH levels (data not shown). To decide whether women had differing age-specific AMH levels, differing decline rates, or both, the multivariable-adjusted models with a random intercept, slope or both, were compared to models with only fixed terms for these two parameters. The Akaike Information Criterion (AIC) of the models was used for this purpose. A lower AIC by at least 2 points represented a significantly better fit of the data.

**Assessment of the consistency of age-specific AMH levels: does high remain high and vice versa?**

To get an indication of whether individual AMH levels that were relatively low or high based on age remained comparatively low or high as time progressed, women were divided into age-standardized AMH quartiles in round 1. The CG-LMS method, previously described in detail by Dölleman et al. [23], was used for age standardization. The AMH decline trajectory of women in these four quartile groups was then plotted against chronological age and time to menopause.

In order to measure whether the AMH levels of the individual participants remained on a single trajectory, and did not vary between the 95th and 5th percentile over time for example, the variance of AMH measurements within and between individuals was assessed for the final mixed models. By dividing the between-individual variance by the total variance (between-individual + within-individual variance), the intraclass correlation coefficient (ICC) was calculated. The ICC gives an indication of the correlation of AMH measurements on each individual’s trajectory, which is directly relative to the amount of variation between individuals. For AMH decline with age, we hypothesized that women would follow a consistent high or low trajectory, i.e., that the variance of their AMH levels around a trajectory would be low. We therefore postulated that most of the variance would arise from differences in AMH levels between individuals, in which case the ICC would approach 1. For AMH decline with time to menopause, we hypothesized that there would be little variance of AMH levels between individuals; for example, we expected that the AMH level at 10 years before menopause would be roughly similar across the whole group. In this case, the ICC would approach 0.

**Participant involvement**

Participants of the Doetinchem Cohort were not directly involved in the formulation of the study question or realization of the study design. As this was a population-based study design, patients were not involved.

**Results**

**Population characteristics**

On average, women in the study population completed 3.1 visits, and 79% of the participants completed two or more visits. The longest follow-up time was 21 years. In Table 1, the participant characteristics per follow-up round are presented. The number of women and their characteristics at each visit are listed per 5-year age groups in Additional file 1: Tables S1–S6. The youngest age at baseline was 20 years and the highest age at the end of follow-up was 81 years. At baseline, 18% of the women were aged between 20 and 30 years, and 32% were aged between 30 and 40 years. At each visit, the
percentage of OC users and smokers decreased with increasing age (Table 1, Additional file 1: Tables S1–S3). The percentage of smokers within the same age categories (thus comprising different women at each visit) decreased over time. BMI levels increased both with age and over time within the same age categories, meaning that, on average, a 40-year-old woman had a lower BMI in 1987 than in 2007 (Table 1, Additional file 1: Table S4). Within the entire study population, the median (interquartile range (IQR)) ages at menarche and FMP were 13 (12–15) and 50 (48–53), respectively.

By the end of follow-up (visit 5), there were 1882 women with a known age at menopause. In total, 440 women (13.2 %) underwent a hysterectomy, 139 women (4.2 %) had a unilateral oophorectomy, and 77 women (2.3 %) had a bilateral oophorectomy. The women with no available blood samples had similar baseline characteristics to the study population with regards to age, age at menarche, age at FMP and OC use. They smoked more frequently at baseline (41.9 % vs. 33.6 %, \(P < 0.001\)) and had a higher average BMI (25.9 vs. 24.6 kg/m\(^2\), \(P < 0.001\)).

**Assessment of individual decline rate: parallel or non-parallel trajectories**

**Chronological age**

For AMH decline with age, the best fitting mixed models incorporated a random slope and random intercept and were significantly non-linear. The random slopes indicate that individual women had differing decline rates, and the non-linearity indicates that the overall rate of decline varied with age. Based on the multivariable-adjusted AMH levels, the rate of change in various age intervals was assessed per participant (Table 3). The average rate of AMH decline was greatest between 45 and 50 years of age. Because the AMH decline rates with age differed between participants, we plotted the adjusted AMH levels at age 20 against the decline rate at different age intervals in order to estimate whether there was a relationship between AMH levels and rate of decline. As seen in Fig. 2a, women who had a higher adjusted AMH level at age 20 had a slower decline rate between the ages of 20 and 25. This was also true between the ages of 25 and 40 years, whereas between the ages of 40 and 45 all women had approximately equal decline rates, regardless of their adjusted AMH levels at age 20. In contrast, after age 45, women with higher AMH levels at age 20 had a faster decline rate.
Time to menopause

For time to menopause, the best fitting mixed models incorporated a random slope and random intercept and were significantly non-linear. Thus, individual women had differing AMH levels and decline rates, and the rate of decline varied with time to menopause. In Table 3, the multivariable-adjusted rate of change per time to menopause interval is displayed, indicating that the average decline rate gradually decreased closer to the menopause.

A higher AMH level at 20 years before the FMP was associated with a slower decline rate of AMH between 20 and 15 years before the FMP (Fig. 2b). In the last 5 years before the FMP, this relationship reversed, such that a high AMH level at 20 years before the FMP was associated with a faster AMH decline rate.

Assessment of the consistency of age-specific AMH levels: does high remain high and vice versa?

Chronological age

According to the distribution of AMH with age at baseline, women were divided into age-specific AMH quartiles. The overall decline trajectory of each quartile group with chronological age is depicted in Fig. 3a. The difference between low and high age-specific AMH levels was maintained with increasing age, but the absolute difference became smaller. The ICC of the mixed model for AMH decline with age was 0.87, indicating that 13% of the total variance could be accounted for by variability within individual AMH decline trajectories with age. Including only regularly cycling women at baseline (n = 2070), the ICC was 0.93, leaving 7% of the total variance to be explained by variability within individual trajectories.

Time to menopause

The overall decline trajectory of each age-specific AMH quartile group with time to menopause is depicted in Fig. 3b. The difference between low and high age-specific AMH levels was distinguishable from 20 years before menopause to the FMP, but the absolute differences became smaller as women neared their FMP. The ICC for

### Table 3

| Age period (years) | 5-year rate of change | 1-year rate of change |
|--------------------|-----------------------|-----------------------|
| 20–25              | 0.05 ± 0.86 (−3.1 to 3.3) | 0.01 ± 0.17 (−0.63 to 0.66) |
| 25–30              | −0.12 ± 0.78 (−2.9 to 2.8) | −0.02 ± 0.16 (−0.59 to 0.56) |
| 30–35              | −0.46 ± 0.60 (−2.6 to 1.9) | −0.09 ± 0.12 (−0.51 to 0.37) |
| 35–40              | −0.97 ± 0.35 (−2.0 to 0.42) | −0.19 ± 0.07 (−0.40 to 0.08) |
| 40–45              | −1.65 ± 0.13 (−2.3 to −0.3) | −0.33 ± 0.03 (−0.46 to −0.05) |
| 45–50              | −2.2 ± 0.37 (−3.5 to 0.3) | −0.43 ± 0.08 (−0.71 to 0.05) |
| 50–55              | −1.9 ± 0.46 (−3.6 to 0.3) | −0.38 ± 0.09 (−0.71 to 0.06) |
| 55–60              | −0.95 ± 0.37 (−2.4 to 0.4) | −0.19 ± 0.07 (−0.47 to 0.07) |

| Time to menopause period (years) | 5-year rate of change | 1-year rate of change |
|----------------------------------|-----------------------|-----------------------|
| 20–15                            | −2.18 ± 0.65 (−3.75 to −0.30) | −0.44 ± 0.13 (−0.75 to −0.06) |
| 15–10                            | −2.11 ± 0.48 (−3.25 to −0.70) | −0.42 ± 0.10 (−0.65 to −0.14) |
| 10–5                             | −1.98 ± 0.17 (−2.58 to −1.39) | −0.39 ± 0.03 (−0.52 to −0.28) |
| 5–0                              | −1.78 ± 0.32 (−2.87 to −0.80) | −0.36 ± 0.06 (−0.57 to −0.16) |

Numbers indicate mean ± standard deviation (range) difference in individual logAMH levels between specified age and time to menopause intervals
time to menopause was 0.32 for the whole group \((n = 1882)\) and 0.31 for only the baseline regular cyclers \((n = 1046)\), meaning that approximately one-third of the total variance arose from between-individual differences in AMH levels. Thus, differences between high and low age-specific AMH levels were also distinguishable before menopause, but there was more overlap of AMH trajectories with time to menopause than with chronological aging.

**Discussion**

With this longitudinal study, we are able to shed light on the individual decline of AMH. We found that AMH trajectories with age and time to menopause were not identical, as the rate of decline differed between individuals. The rate of AMH decline was dependent on initial AMH levels, and this relationship differed with age and time to menopause. The evident differences between women with relatively high and low age-specific AMH levels at baseline became increasingly smaller as time progressed. The AMH levels of an individual woman correlated well with one another and thus did not deviate far from her trajectory. Contrary to our expectations, there was considerable variation of AMH levels between individuals with time to menopause. Taken together, these
inhibitory effect of AMH on follicle recruitment [28–30] is effective up to a certain age or ovarian reserve threshold. This concept was previously brought up in a mouse study, in which the decline of growing follicles and AMH levels accelerated only later in reproductive life [31], leading to the hypothesis that compensatory mechanisms are present earlier on. In any case, this observation may prove detrimental for the hopes of improved reproductive age estimation with repeated AMH measurements.

Current time to menopause estimations with single AMH measurements are based on the concept that comparatively high (or low) AMH levels for age will remain high (or low) with age. Following this principle, a lower age-specific AMH level at any age should be associated with a shorter time to menopause [4, 6, 7, 9–11, 32]. While we did indeed observe differences between women in different baseline age-specific quartiles, it was surprising that there was such variability of AMH levels between women at a given time before menopause. This may in part explain the currently limited discriminatory capacity of AMH for time to menopause [32]. A related finding in this study is the 62.9 % observed AMH levels above the limit of detection within a year of the FMP. While this may partly be attributed to the high sensitivity of the assay, measurement error or recall bias for the timing of the FMP, earlier research has also suggested that the follicle pool is not entirely depleted at the time of menopause [2, 26, 33]. It may well be that this critical threshold differs between women, or that in the minority of the cases other causes such as hypothalamic dysregulation are at the root of the cessation of menses [2].

Prior longitudinal studies of AMH decline with age at menopause are in disagreement on whether AMH decline rate is associated with time to menopause [5, 8]. Contrary to our current findings, these studies assumed a linear decline of logAMH with time to menopause. The rate of decline was assessed over a maximum period of 14 years in 293 women [8], and over six annual intervals in 50 women [5]. A striking difference with our current study is the difference in age; Freeman et al. [8] included women aged between 35 and 48 (mean 41) years and Sowers et al. [5] included women with a mean age of 42 ± 2.7 years (no range provided). This age difference may explain the perceived linear decline, as we found the decline rate of AMH to be highest between the ages of 40 and 55, at which time the overall decline trajectory did appear more or less linear. Importantly, if AMH is ever to be used for individual estimations of the remaining number of fertile years in the light of family planning, the AMH measurements should occur at a far earlier age than in these studies. Our results indicate that the currently available prediction models with AMH decline rate cannot be extrapolated to the ages at which the measurement of AMH would be most useful.
The added value of multiple AMH measurements for studies measuring the true feasibility of the individualized clinical use of single and multiple AMH measurements. Until then, AMH levels with regard to the reproductive lifespan should be interpreted with caution.

Additional file

Additional file 1: Table S1. Number of women in each age category per follow-up round. Table S2. Current oral contraceptive users per age group and follow-up round (n (%)). Table S3. Current smokers per age group and follow-up round (n (%)). Table S4. Body mass index levels per age group and follow-up round (mean ± SD). Table S5. Current estrogen users for climacteric complaints per age group and follow-up round (n (%)). Table S6. Anti-Müllerian hormone (AMH) levels per age group and follow-up round in ng/mL (median [IQR]). Table S7. Number (% of women with undetectable AMH levels (<1.8 pg/mL) per age category and follow-up round. (DOCX 22 kb)

Funding

No funding from external parties was received for this study. AnshLabs performed the AMH measurements free of charge. AnshLabs was not involved in the data analysis, interpretation, or reporting, nor was it financially involved in any aspect of the study.

Authors’ contributions

ACdK, YTvdS, MV, MICE, and FJMB designed the study. MV was in charge of data collection and design of the cohort. ACdK analyzed the data. GCHG provided support for part of the analyses. ACdK, YTvdS, MV, MICE, FJMB, and JV interpreted the data. ACdK wrote the first draft of the manuscript, which was revised by all authors. All authors approved the final version of the manuscript. All authors had full access to the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and analyses. ACdK is guarantor.

Competing interests

All authors declare no financial support for any part of this submitted work. FJMB has received fees and grant support from Merck Serono, Gedeon Richter, Ferring BV, and Roche.

Ethics approval and consent to participate

Patients provided written informed consent for each follow-up round. Ethical approval to utilize the stored plasma samples was obtained from the Ethical Committee for Biobank Studies of the University Medical Center Utrecht, number 14-580.

Transparency declaration

The lead authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing

Full dataset and statistical code available on request, in liaison with the National Institute of Public Health and the Environment.

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Received: 26 July 2016 Accepted: 17 September 2016
Published online: 03 October 2016

In conclusion, this study provides an insight into the physiology of ovarian reserve decline and paves the way for studies measuring the true feasibility of the individualized clinical use of single and multiple AMH measurements. Until then, AMH levels with regard to the reproductive lifespan should be interpreted with caution.
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