Can we predict menopause and premature ovarian insufficiency?

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The prediction of menopause and premature ovarian insufficiency (POI) involves understanding the factors that contribute to the timing of these events. Menopause is a natural biological process marked by the cessation of menstrual periods, typically occurring around the age of 51. On the other hand, POI refers to the loss of ovarian function before the age of 40. Several factors have been used to predict menopause and POI such as age, anti-Müllerian hormone, inhibins and follicle-stimulating hormone serum levels, antral follicle counts, menstrual cycle length, and, recently, some genetic markers. It seems that age has the best predictive power and all the other ones are only adding in a very limited way to the prediction of menopause. Low levels of anti-Müllerian hormone in young women might indicate a greater risk for POI and could facilitate early diagnosis. It is, however, important to note that predicting the exact timing of menopause and POI is challenging, and individual variations are significant. Although these factors can provide some insights, they are not foolproof predictors. Advances in medical research and technology may lead to more accurate methods for predicting menopause and POI in the future. (Fertil Steril® 2024;■:■–■. ©2024 by American Society for Reproductive Medicine.)

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The age-related decrease in ovarian antral follicle numbers dictates the onset of cycle irregularity and the final cessation of menses. The parallel decay in oocyte quality contributes to the gradual decline in fertility and the final occurrence of natural sterility. The average age at which natural menopause (ANM) worldwide occurs is estimated to be approximately 51 years and is due to a nearly total depletion of the primordial follicle pool depletion (1). The latter causes the cessation of menstrual cyclicity, with the final menstrual period serving as the indicator of natural menopause. Although menopause signifies a woman's ovarian senescence, her reproductive life span typically concludes approximately 1 decade before ANM and fertility experiences a substantial decline as early as 15 years before reaching ANM (2). However, the onset of the menopausal transition appears to vary between different races and ethnicities and is influenced by sociodemographic and lifestyle factors. Demographic, menstrual, reproductive, familial, genetic, and lifestyle factors seem to be important in this timing (3).

Therefore, aside from predicting ANM and reproductive outcomes in the general population, forecasting the anticipated timeframe of ovarian senescence becomes a crucial tool for cancer survivors. This is also applicable in specific cases such as disorders of sex development like Turner's syndrome, as well as for women with suspected POI or early menopause on the basis of their family history. In addition, in an era where many couples are increasingly delaying the conception of their first child, the prediction of ANM and consequently, the conclusion of the reproductive lifespan, emerges as significant in preventing involuntary childlessness. Finally, it's worth noting that the timing of natural menopause serves as a clinically important indicator of longevity and the risk of morbidity and mortality (1). Hence, because of the potential social and clinical implications of ANM, tools and methods to predict ANM have been a topic of great interest in menopause-related research in recent years.

PREDICTORS FOR ANM AND POI

Age

According to a recent review, age has been studied most in models to predict ANM (4). Age as a single predictor for ANM was used in a number of studies and showed a reasonable efficacy in predicting the onset of menopause with a (concordance-statistic) C-statistic ranging from 0.82 to 0.88 (4). The C-statistic, serves as an indicator of the discriminatory power of a predictive model. The C-statistic is similar to the area under the receiver operating characteristic curve. Models are generally deemed acceptable when the C-statistic surpasses 0.7, whereas values exceeding 0.8 signify strong discriminative power. Univariable Cox regression analysis demonstrated age and ovarian reserve tests to be significantly correlated with ANM. In such models, age represents the most significant

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predictor with a hazard ratio of 1.39 (95% confidence interval [CI]: 1.30–1.49) and a C-statistic of 85% (5). Another study of the same group looked at the hazard ratio of the mother's ANM as a predictor for ANM in daughters. Next to the baseline age, the mother's ANM was a significant predictor for time to menopause with a hazard ratio of 0.91 (95% CI: 0.84–0.97). In this initial analysis a C-statistic of 85% was found. In a second analysis, in an extended larger cohort, the mother's ANM next to baseline age, was also a highly significant predictor with a hazard ratio of 0.93 (95% CI: 0.90–0.96). However, the C-statistic in this cohort amounted to only 79% which was moderate and less than age (6). Generally speaking, age is a good predictor for ANM especially in older women. In all models, C-statistics are better in women over 50 years of age. This phenomenon is called proportionality since over 50 years of age menopause is inevitably happening in that decade in all women (5).

Anti-Müllerian hormone

Anti-Müllerian hormone (AMH) stands out as the extensively examined biomarker for predicting menopause, early menopause, and POI. A recent comprehensive review demonstrated that in all the examined studies, a singular AMH measurement exhibited robust predictive capability for estimating ANM. In addition, at any given age, a reduced AMH level correlated with an earlier ANM and the onset of perimenopausal symptoms. Notably, lower serum AMH levels strongly correlated with the likelihood of early menopause, and this association remained significant irrespective of other established risk factors for premature ovarian senescence (7). Reduced serum AMH levels consistently indicated a heightened risk of early ANM, regardless of the measurement method employed or the demographic characteristics of the studied population—whether comprising women with a history of infertility, menstrual cycle irregularities, or oligomenorrhea. Nevertheless, in most, if not all, of the studies, the confidence intervals were notably broad, making it challenging to make a precise prediction of ANM solely on the basis of a single AMH measurement (8–10). Various efforts have been made to determine whether consecutive assessments of serum AMH concentrations could enhance predictive accuracy. Regardless of the mathematical methodologies applied, the findings are inconclusive. Some studies, which included AMH measurements taken over several years, indicated no improvement in the predictive capability of ANM (11, 12). Although some studies reported that the decline rate in AMH values was a stronger predictor for ANM repeated measurements only slightly increased the accuracy of the prediction of menopause (9–12). Interpreting results of studies addressing the role of AMH in predicting ANM should have noted that the added value of AMH on top of a model using age is very modest (13). As stated before, another factor to consider is the predictive effect of AMH on top of age. With increasing age, the predictive capacity of AMH decreases. In addition, the predictive accuracy of AMH is lower for women at younger ages (13). So, the imprecision of AMH is even greater in younger women with a longer time to menopause (14). Finally, there are presently multiple assays for measuring AMH, and they exhibit notable variations in accuracy, particularly in lower concentrations. This complexity in accuracy makes comparisons between different assays challenging. In addition, the absence of an international standard further impedes the comparison of results across various studies (13, 15).

Because of the low prevalence of POI within the general population and the availability of appropriate cohorts, data assessing the value of AMH for the prediction of POI are limited as described in a recent review. The largest study to date included 410 women under age 40 and suggested that an AMH of $<$0.25 ng/mL (1.78 pmol/L) was diagnostic of POI with a sensitivity of 92.46% and specificity of 90% (16). However, this cross-sectional study also included women with follicle-stimulating hormone (FSH) levels $>$10 IU/L but $<$25 IU/L that could have introduced bias. In contrast to ANM, the rate of decline of AMH seems to be predictive for POI in patients with Turner syndrome with the mosaic karyotype. These patients suffer from accelerated loss of primordial follicles and AMH <-2 SD was predictive for failure to enter puberty in young girls with Turner syndrome as well as POI in adolescent and adult patients (17).

In summary, relying solely on AMH for predicting the age at menopause lacks precision. Estimated predictions and confidence intervals range widely, from 2 to 12 years for women under 40 years old. Although AMH holds diagnostic value for identifying those at an elevated risk of POI, its accuracy falls short in precisely predicting the onset timing of POI. Although the predictive value of AMH improves with age due to the shortened interval to ANM, it's important to note that menopause is virtually inevitable in the sixth decade of life for almost all women (7).

Inhibins and FSH

Although as discussed earlier AMH seems a reliable marker of declining numbers of primordial follicles, FSH constitutes also such a marker. The decay in follicle numbers eventually leads to a decrease in inhibin-B levels, thereby releasing the negative feedback on FSH secretion from the pituitary leading to the so-called monotropic rise in FSH (18). FSH levels have been used in numerous prediction models. In univariable models, the C-statistic ranged from 66% to 72% with broad confidence intervals. After adjustments for baseline age at first assessment, the performance in most models improved and C-statistics improved accordingly ranging between 0.84 and 0.88 when FSH was added to the model (4). However, the added value of a single serum FSH measurement in terms of hazard ratios does not add significantly to the prediction of ANM. Hazard ratios vary between 1.03 and 1.02 with confidence intervals overlapping 1.0 and no increases in C-statistics (4, 6).

In line with the above, inhibin B and FSH/lutheinizing hormone ratio had no additive effects in the prediction of POI compared with AMH in the very early stage of ovarian insufficiency (16, 19).

Antral follicle count

Fluctuations in anti-Müllerian hormone levels parallel fluctuations in antral follicles, suggesting that AMH levels are closely linked to variation in the antral follicles. This knowledge adds to the basic understanding of the origin of AMH and could aid in the interpretation of individual anti-Müllerian hormone levels (20). In a fairly large cohort study, antral follicle count (AFC) was correlated among others with age at menopause. Compared with AFC higher than 4, those with an AFC of 4 or less were nearly twice as likely to have undergone menopause during 7 years of follow-up (hazard ratio, 1.89; 95% CI: 1.19–3.02) after adjustment for covariates (21). Similarly, in a large cross-sectional study, a significant, positive association between age at maternal menopause and serum AMH levels and AFC in daughters was found. Moreover, the rate of decline in serum AMH level and AFC is also associated with age at maternal menopause (22). The predictive usefulness of this relationship in a clinical setting may be more marginal, except in the case of women who have low AFCs for their age (23). Likewise, ovarian volume exhibits variations on the basis of age in both premenopausal and postmenopausal women. Although menopausal status holds greater significance than age alone in determining ovarian volume, the combination of age and ovarian volume proves to be highly accurate in predicting menopausal status (24). However, sonographic data on AFC and ovarian volume seem to be of less predictive value compared with other markers such as age and AMH (25).

Menstrual cycle length

The menopausal transition is characterized by the appearance of irregular menstrual cycles, which become shorter and more frequent as menopause approaches. The transition from late reproductive life to early menopausal transition appears to begin in the late thirties when variability of cycle length increases. Patterns of change in menstrual function during the menopausal transition do not differ by age at menopause (26). Menstrual cycle shortening, a physiologic occurrence preceding the menopausal transition, is not usually perceived as an indicator of decreased ovarian reserve in the general population. In a recent meta-analysis, shorter menstrual cycles were associated with significantly lower AMH serum levels, lower AFCs, and a reduced fecundability. Similarly in artificial reproductive technology procedures, fewer oocytes were retrieved and pregnancy rates were significantly lower in women with short menstrual cycles (27). Differences in menstrual cycle length, however, are not solely dependent on age but are also influenced by body mass index and ethnicity (28). As menstrual cycles shorten toward the menopausal transition FSH levels rise and inhibin levels decrease leading to increased FSH/inhibin ratios (29). Although menstrual cycles became more variable and longer closer to the final menstrual period they cannot predict the ANM (30).

Genetic markers

Menopause is strongly influenced by genetic factors, with approximately 50% of the variation in age at menopause attributed to genetic variants. Various genetic studies, utilizing diverse techniques in both population studies and animal models, have attempted to elucidate this genetic background. Although genome-wide linkage studies have identified a limited number of genetic variants associated with menopause, many of these studies are hindered by methodological flaws. Replication in independent samples is often lacking, and a significant number of these studies are underpowered, resulting in conflicting results (31). Genome-wide association studies typically employ hypothesis-free methodologies to uncover the genetic factors associated with a particular disease or trait. Recent investigations of the entire genome have revealed that a substantial portion of the genes implicated in menopause is also integral to processes like double-strand break repair, mismatch repair, and base excision repair of DNA. The accumulation of DNA damage contributes to cellular senescence, leading to the depletion of somatic cell renewal capacity and eventual cellular dysfunction. This process ultimately accelerates cell death, commonly referred to as aging (32). A comparable degradation of the genome takes place in the germ cell line, affecting the ovaries accordingly. After this, the systemic response geared toward "survival" deliberately inhibits the production of sex-steroid hormones, potentially playing a role in triggering the onset of menopause. This phenomenon becomes more pronounced when there is an accumulation of age-dependent DNA damage. The combined effects of these processes are anticipated to work together, fostering ovarian suppression and ultimately leading to menopause (33). The latest Genome-Wide Association Study on menopause in more than half a million women identified loci implicated in a broad range of DNA damage response (DDR) processes and include loss-of-function variants in key DDR-associated genes. Integration with experimental models demonstrates that these DDR processes act across the life course to shape the ovarian reserve and its rate of depletion (34). The 290 common alleles that were identified were associated with extremes of ANM in such a way that women in the top first percentile had a hazard ratio of 5 approaching the risk of FMR1 carriership (34). Moreover, the manipulation of 2 important genes involved in apoptosis in animal models underpinned the crucial role of DDR-associated genes governing ovarian aging and establishing ovarian reserve (34). Hence, a gradual accumulation of unrepaired DNA damage leads to cellular senescence and cell death. This in turn affects cell renewal capacity leading to reduced cell numbers and dysfunction in all parts of the soma as well as in the germ cell line becoming obvious from the increased risk of trisomy 21 in pregnancies from older women (33). Together with the so-called systemic survival response which will suppress sex-steroid hormone output leading to the onset of menopause (35). Both of these processes synergize to promote ovarian silencing resulting in menopause. Certainly, in a recent Mendelian randomization study, approximately 55 traits were found to have a direct association with ANM. These traits encompassed liver function, kidney function, lung function, blood-cell composition, breast cancer, and bone and cardiometabolic health. Notably, these effects were particularly accentuated in women undergoing natural menopause at younger ages (36).

Recent approaches using next-generation sequencing, especially whole-exome sequencing, in large POI, pedigrees have identified new causatives and proposed relevant candidates, also mainly enriched in DNA damage repair, homologous recombination, and meiosis (37). Currently, international guidelines recommended diagnostic tests for women with POI include *FMR1* carriership and cytogenetic karyotyping (38). However, using a POI-associated gene panel, and extended whole-exome sequencing data, besides the recommended diagnostic investigations increased the determination of a potential etiological diagnosis of POI from 11% to 41% and will facilitate risk prediction for POI (39).

Sociodemographic and anthropometric markers

The role of certain factors has been unequivocally established, whereas the evidence for others remains a topic of debate. Socio-economic conditions are confirmed determinants of menopausal age, with higher educational attainment, urban residence, financial stability, and current employment linked to a later onset of menopause. Likewise, being in a marital relationship, having more children, and engaging in moderate physical activity are also associated with a later ANM. Race and ethnicity play a role in ANM, with African American and Hispanic women experiencing natural menopause earlier than European and White American women. Women who were breastfed and those who were overweight before puberty tend to have a later ANM, and the association between increased weight and ANM persists throughout reproductive life. Smoking is linked to menopause occurring several years earlier compared with nonsmokers, and frequent night shifts are associated with a reduced age of menopause compared with those with regular working hours (40).

CONCLUSION

Although various markers of ovarian reserve, including age, AMH, menstrual cycle length, inhibins, AFCs, ovarian volume, and various sociodemographic and anthropometric indicators, are undeniably correlated with the age at menopause, their precision in predicting the exact age of menopause remains inadequate. Recently identified genetic markers may emerge as promising indicators that could offer more accurate predictions of menopause in the near future.

CRediT Authorship Contribution Statement

Joop S.E. Laven: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Yvonne V. Louwers:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization.

Declaration of Interests

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