INTRODUCTION

Women in high-income countries live the last 30%-40% of their lives in an essentially oophorectomized state. To a varying extent, this long period is beset by somatic, psychological, and psychosocial complaints, mostly due to consequences of hypoestrogenemia. Menopause has been regarded as the definite end of a woman’s reproductive life and the onset of a persistent hypoestrogenic state. This postmenopausal period will for most women last several decades. Although mean menopausal age seems to have increased somewhat during the last century, there is a significant individual variation in age at natural menopause. With efficient contraception, women of reproductive age can now, to some extent, choose when they want to have children. As a consequence of this and other sociodemographic changes, age at first birth has increased significantly over the last 50 years. It is well documented that long before a woman enters the menopausal transition and subsequent menopause, fertility declines and finally ceases. Being able to predict when a woman will enter menopause would therefore, from a reproductive perspective, be of major interest. Several sociodemographic, morphometric, and endocrine factors are associated with age at menopause or time to menopause. Unfortunately the sensitivity and specificity of these in predicting time to or age at menopause are low. Therefore, with the exception of anti-Müllerian hormone measurements, either alone or in combination with chronological age close to menopause, there are as of now no reliable ways of predicting when a woman will enter menopause.

1 | INTRODUCTION

Women in high-income countries live the last 30%-40% of their lives in an essentially oophorectomized state. To a varying extent, this long period is beset by somatic, psychological, and psychosocial complaints, mostly due to consequences of hypoestrogenemia. Menopause has been regarded as the definite end of a woman’s reproductive lifespan, and it is marked by loss of functional ovarian follicles that produce oocytes for fertilization, synthesize estrogens and progesterone to allow reproduction, and maintain physical, cognitive and mental well-being. Many years before natural menopause, however, fertility and fecundity are already lost. In a study on a natural fertility population from the nineteenth century, it was shown that the mother’s age at last birth was 38.3 years.¹ Those women who gave birth later during their fertile period lived longer and even their offspring had prolonged longevity. Late birth therefore seems to have a beneficial health effect. The age when a woman loses fertility and the age when she enters natural menopause vary
considerably. To foresee when a woman is no longer capable of producing an offspring would be highly interesting clinically, but such a prediction is challenging, because loss of fertility is not necessarily accompanied by irregular menstrual periods or symptoms of hypoestrogenemia. The menopausal transition from regular menstrual periods to irregular and later on to infrequent periods until permanent amenorrhea usually takes several years, but again, with substantial individual variation. To plan for late childbearing because of career or social circumstances would have considerable practical utility, but is it possible to predict when individual women will enter menopause? Here we review the demographics of perimenopausal transition and natural menopause and discuss if it is possible to predict the onset of demise of ovarian function based on demographic data, morphometric analysis of the ovaries, and endocrine assessment of ovarian function.

2 | MATERIAL AND METHODS

We searched PubMed, MEDLINE, Embase, and the Cochrane Library through February 2021 using the keywords and MeSH terms menopause, menarche, anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), inhibin, follicle and ovary to identify relevant literature. We also searched relevant clinical guidelines. The search was restricted to sources in the English language and mostly from Western European countries as there are significant differences in age at natural menopause (ANM) based on ethnicity, race, socio-economic conditions, and place of residence. Whenever possible, studies from this millennium, large observational studies, and meta-analyses were selected.

3 | DEMOGRAPHICS

Menopause marks the permanent cessation of menstruation, defined as the time-point 12 months after the last menstrual period. Last menstrual period occurs when there are too few functioning ovarian follicles left to synthesize sufficient estrogen and progesterone to sustain proliferation and cyclical transformation of the endometrium. Last menstrual period therefore marks the definite end to a woman’s reproductive period, which is usually defined as the time interval from menarche to menopause. The true window of fertility is nonetheless smaller, as during the first 1-2 years after menarche most ovarian cycles will be anovulatory because of an immature hypothalamo-pituitary-ovarian axis—thereby making many adolescents infertile. Similarly, during the last years before menopause, the cycles are increasingly irregular and infrequent indicating anovulation, probably caused by loss of sensitivity of the hypothalamus or pituitary to the positive feedback of estrogen.

According to historical data, women in medieval Europe reached menarche at 12-15 years and menopause at 50 years of age. Due to poor living conditions in primarily urban areas, age at menarche increased in conjunction with the start of the industrial revolution, but started to decrease again during the twentieth century, in response to improving socio-economic conditions. With regard to secular trends in ANM, there is considerable heterogeneity across countries. In several Northern European countries, however, a decrease followed by a steady increase in menopausal age has been observed since the beginning of the twentieth century, probably related to an era of initial deprivation followed by decades of increasing prosperity. Although both age at menarche and ANM are partly heritable traits, age at menarche also seems to be related to extrinsic factors such as socio-economic conditions, nutritional status, and energy balance. In addition to a genetic component, ANM is associated with birthweight, age at menarche, reproductive history, smoking, education, occupation, body mass index, and history of hormonal treatment.

In 2017, life expectancy for women in the European Union was 83.5 years, an increase of more than 3 years since the millennial shift and approximately 10 years during the last 50 years. A longer life expectancy reflects healthier life and possibly also brings on an increased reproductive lifespan. The reproductive period of a woman’s life from menarche to natural menopause may, therefore, have been extended. However, whether this is due to more primordial follicles being developed during fetal life, more follicles surviving until menarche, or a reduced attrition of the ovarian reserve during the reproductive period is to our knowledge unknown. As oocyte aneuploidy increases with chronological age, it remains to be shown whether recent delay in menopausal age extends the fertile window, or whether impaired oocyte quality offsets the effects of sustained ovarian function, as has been suggested in polycystic ovarian syndrome, a condition associated with sustained ovarian reserve at higher ages.

On the other hand, a conceivably increased reproductive lifespan has not increased population fertility. Indeed, total fertility rate (ie, number of births per woman) has been well below the replacement level for many decades across the Western world, mostly because of access to efficient contraception and family planning. The replacement level, ie, the number of live children each woman has to give birth to in order to keep a steady-state population, is 2.1, supposing no net migration and constant life expectancy, both of which have, however, changed considerably. In 2017, the total fertility rate in the European Union was 1.59 live births. In addition to fewer offspring being born per woman, women’s age at first birth has increased to 29.1 years in the European Union in 2017, Figure 1. There is every reason to assume that this reduction in number of children, delay in

Key message

Women’s age at first childbirth is increasing, shortening an individual’s effective reproductive period. It would be of considerable interest to predict the onset of fertility decline and age at menopause, but such prediction models remain elusive.
birth of the first child, and less frequently having more than two children are related to individual choices of the couple, socio-economic conditions, and efficient contraception; not to impaired biological fertility.19,20

As ANM can vary significantly, it would be of considerable clinical interest to predict the individual trajectory of reproductive decline, limits of the fertile window, and menopausal age—however, is it possible given our present knowledge?

4 | FOLLICULAR DYNAMICS

Ovarian primordial germ cells develop in the yolk sac of the fetus at approximately 5 weeks of gestation and migrate into the urogenital ridges, which are thickenings of the coelomic epithelium close to the mesonephroi. As the cells proliferate, the developing ovary will be populated by approximately six million oogonia, which will form, together with somatic cells, the primordial follicle pool of the ovary. From week 20 of gestation, however, atresia and apoptosis start to deplete the initial pool, so that about one million primordial follicles are present at birth. Atresia of follicles continues throughout childhood, and at menarche about 400,000 ovarian follicles remain.21 On average, approximately 1000 of these enter a growth phase during each menstrual cycle, but fewer with increasing age.22 In women in their early 20s, approximately 50 early pre-antral follicles enter growth daily, but this number is reduced to one-third 10 years later, and by their early 40s the daily number of recruited follicles is reduced to only three.23 Hence, the pool of primordial follicles at menarche can sustain approximately 400 menstrual cycles, but when the number of follicles is depleted to approximately 500, cyclical release of estrogens ceases as the result of the highly variable uncoordinated response of the remaining follicles to FSH, and regular menstrual bleedings will not take place because of the lack of estrogen stimulation of the endometrium.4

5 | AGE-RELATED REDUCTION IN FERTILITY

Women’s fertility decreases with increasing age beginning in the first part of their 30s.24 Age-related fertility decline is not only explained by loss of ovarian follicles, but also by chromosomal errors in the remaining oocytes, in particular premature separation of sister chromatids and reverse segregation, which increase significantly from the late 30s.17 The likely molecular cause of increased meiotic errors is weakening of cohesion between sister chromatids and altered chromatin structure in aged oocytes.25 Consequently, the risk of miscarriage increases in women of advanced maternal age, whereas the probability of live birth decreases.26 Indeed, a mathematical model on age-related fertility decline indicated that 75% of women who attempted pregnancy at 30 years of age will conceive within 12 months, but only 66% and 44% of women will conceive who attempt pregnancy at 35 and 40 years, respectively.27 According to a recent meta-analysis on patients trying to conceive naturally after a 2-year history of primary, unexplained infertility, a 35-year-old woman has 24% probability to conceive during the first following year of trying whereas a 42-year-old woman has a modest 13% chance to conceive during the same period.28 Demographic data from the end of the 1800s and beginning of the 1900s gave rise to the “fixed interval hypothesis”, which postulates that women are sterile, i.e., unable to conceive and give birth to a live offspring, during the last 10 years before ANM, and that fertility is impaired ~10 years before the onset of sterility.29 According to this hypothesis, a woman who enters natural menopause at 50 years will be unable to complete a pregnancy and give birth to a child beyond

FIGURE 1  Fertility rate and age at first birth during the last decades are shown for the Nordic countries, Great Britain and Germany
40 years of age, and during the period between 30 and 40 years her fertility will be impaired. For women experiencing early menopause, however, the fertile window is closing later than would be predicted by the fixed interval hypothesis.30

6 | PREDICTION OF REPRODUCTIVE DECLINE

6.1 | Sociodemographic and anthropometric data

Age at natural menopause is known to be associated with a range of socio-economic, health-related, and genetic factors.15,31 The role of some factors has been unambiguously established, whereas the evidence of others has been contested. Socio-economic conditions are established determinants of menopausal age, as greater educational attainment, urban living, lack of financial strain, and current employment are associated with later menopausal age. Living in a marital relationship, increasing parity, and moderate physical activity are also associated with later ANM. Long menstrual intervals are associated with later ANM than short intervals. Most studies investigating a possible link between the use of oral contraceptives and late ANM show a positive association. There is also a positive relationship between a mother’s and a daughter’s ANM, and genome-wide association studies have identified multiple genetic loci that are associated with ANM, including genes that are involved in DNA repair and immune function.13 Race and ethnicity are also linked to ANM, as African American and Hispanic women enter natural menopause earlier than European and White American women. Women who were breastfed and who were overweight before puberty have later ANM, and the relation between increased weight and ANM continues throughout reproductive life. Smokers enter menopause 1–2 years earlier than non-smokers, but the longer the time since cessation of smoking, the larger the benefit. The effect of passive smoking on ANM is uncertain. Frequent night shifts reduce age of menopause compared with regular working hours.32 In summary, ANM seems to be affected by a combination of genetic, reproductive, lifestyle, and environmental factors. Factors associated with shift towards earlier menopause are shown in Table 1.

Some women enter natural menopause early: one 1% before the age of 30 years, 1% before the age of 40, and 5%–10% before the age of 45 years.33,34 Many women do not have the possibility or wish to have children before they are well into their 30s, so early menopausal age may imply that the fertile window is closing early for these women. Prediction of early menopause from sociodemographic and anthropometric data, however, has been elusive. For women entering menopause between 42 and 52 years of age, ANM can be predicted with approximately 1-year precision based on current age, menstrual cycle regularity, smoking status, and hormone measurements (FSH and estradiol).35 However, it may be assumed that for the majority in this age group it is of less interest to them to have their fertility assessed, for example by reproductive counseling, because many will already have the children they desire or they do not want children.36

| TABLE 1 | Selected factors associated with shift towards earlier menopause |
| Genetic factors | Early menopause in first- and second-degree relatives |
| | Being a twin |
| | Non-European, non-White ethnicity |
| | Variants in genes related to age at natural menopause |
| Reproductive factors | Early age at menarche |
| | Nulliparity |
| | Short menstrual cycles in early reproductive age |
| Lifestyle/health factors | Current cigarette smoking |
| | Underweight |
| | Malnutrition |
| | Over-exercising |
| | Chronic illness |
| | Type 2 diabetes |
| | Autoimmune diseases |
| | HIV infection |
| | Cytotoxic drugs |
| Early life | Poor early-life nutrition |
| | Poor childhood growth |
| | Childhood socio-economic deprivation |
| | Low cognitive scores in childhood |
| | Childhood sexual abuse |
| | Parental divorce before the age of 5 years |
| | Paternal absence |
| Sociodemographic factors | Low level of education |
| | Low occupational level |
| | Living in rural conditions |
| | Irregular working time and night shifts |
| | Intimate-partner violence |

6.2 | Morphometric studies

With advancing age, the density of primordial follicles in the ovarian cortex derived from autopsy or biopsy specimens declines and the spatial distribution of follicles becomes more clustered.37,38 Indeed, a relation exists between size of the primordial follicle pool and menopausal age.39 Assessment of primordial follicle density is impractical in an ordinary clinical setting, but several studies have related number of antral follicles (AFC) and ovarian volume to age at menopause.40–43 These studies indicate an association between reduced AFC and ovarian volume with early menopausal age. In one study, 456 women with a mean age of 42 years (range 34–49 years) were followed for 7 years after an initial AFC count. After adjustment for covariates, those who at baseline had an AFC of less than
or equal to four had almost double the risk of entering natural menopause during the 7 years of follow up compared with those who had five or more AFC. However, the specificity and sensitivity in all the studies are low, making morphometric evaluations of the ovarian primordial or antral follicle count, or ovarian volume inadequate in predicting ANM.

6.3 | Hormone analyses

During the last 10 years before menopause, FSH levels in the early follicular phase increase because of depletion of functional follicles, low estrogen levels, and hence reduced negative feedback. Nevertheless, serum FSH concentration is not a reliable predictor of ANM.

Inhibin A and B are dimeric hormones of the transforming growth factor β superfamily, mostly produced by the granulosa and theca cells of antral ovarian follicles. Inhibin B is mainly produced in the follicular phase, inhibin A in the luteal phase, and both inhibit the synthesis and secretion of FSH by the pituitary. In the later part of reproductive life, although estradiol concentrations are still in the normal range, secretion of inhibin B decreases with subsequent increase in FSH levels. Decline in inhibin A and inhibin B levels may therefore indicate perimenopausal transition, but with low predictive value.

Anti-Müllerian hormone is another glycoprotein hormone of the transforming growth factor β superfamily, secreted by the granulosa cells of maturing pre-antral and small antral follicles. AMH is not produced by granulosa cells from follicles that are in the FSH-dependent phase of development. AMH acts as a paracrine factor inhibiting the maturation of pre-antral and early antral follicles. Serum AMH concentration is therefore an expression of the number of maturing follicles. Although the AMH gene is not expressed by resting primordial follicles, there is a fair correlation between serum AMH concentration and the number of resting primordial follicles, which constitute the majority of the follicle cohort in women of reproductive age. AMH might therefore be a candidate marker of ovarian reserve. Furthermore, reduced AMH levels may be associated with increased blastocyst aneuploidy independent of age, suggesting that AMH is an indicator not only of follicle quantity but also of oocyte competence.

Numerous studies have shown that AMH levels decline with increasing age, but with large variation within age cohorts. The trajectory of decline is S-shaped, and its pace is highly variable across time and among women.

Most of the studies comparing AMH with ANM are based on spot analyses, whereas some more recent studies report on the value of repeated measurements of AMH on ANM. A meta-analysis summarized individual patient data from six prospective studies, of which five related single AMH levels (n = 2292) in women with regular periods to menopausal age. In addition one small study (n = 50) with annual measurements for 6 years was also included. Median age of the participants at inclusion was 39.3 (34.1–42.7) years, and 1077 reached menopause at a median of 7.1 years later. Both age and AMH were found to be significant predictors of menopausal age, although AMH had limited additional value over age and the overall predictive power was poor. Indeed, women with age-adjusted AMH levels corresponding to the 50th centile had a 77.7% chance of entering natural menopause at age 46–54 years, whereas 8% would enter menopause before the age of 45 years. Women who had an age-adjusted AMH level at the fifth centile, had 28.1% risk of menopause at 45 years or earlier, but almost 70% had menopause at 46–54 years. When time to early menopause (<45 years) was assessed, age was not a predictor of ANM, but when adding AMH to the statistical model, the predictive effect became significant. Conversely, when assessing time to late menopause (>55 years), age alone was a significant factor, whereas adding AMH to the model gave no additional effect. The authors conclude that AMH was a significant predictor of time to menopause, but the precision, especially concerning age at menopause before 45 years, was limited.

Spot AMH assessments only weakly predict menopausal age, so some studies have examined whether repeated assays over time, and thereby calculation of a decline rate, might be a superior predictor of ANM. A summary of the studies is given in Table 2. All studies had observational design, and with few exceptions only included women in their late reproductive years. The decline rate of AMH was compared with spot analysis of AMH and age at study start in prediction of ANM. In all studies, spot analyses of AMH were associated with time to menopause or ANM. In some studies the decline rate of AMH was also associated with time to menopause or ANM, and combinations of spot AMH and AMH decline rate often increased the predictability. In one study the AMH decline rate in the age group 20–25 years tended to improve prediction of ANM compared with spot AMH, but also tended to underestimate the risk of early menopause. Beyond 25 years, the decline rate did not improve prediction of time to menopause or early menopause. In general, fair prediction of mean menopausal age in study cohorts failed to translate into robust clinically applicable models, as the predicted individual menopausal age varies in a wide range.

7 | ON PREDICTION OF MENOPAUSE IN SPECIFIC SITUATIONS

Chemotherapy and pelvic irradiation during cancer treatment may severely damage the ovarian follicle pool with devastating effects on future fertility and a shortening of the time to menopause. In many cases such treatments result in permanent ovarian failure with subsequent hypergonadotropic amenorrhea. Unfortunately, the utility of post-treatment AMH or other factors to predict menopausal age after cancer treatment remains to be demonstrated. Furthermore, conditions requiring ovarian surgery like severe endometriosis may influence time to menopause. Removal of one ovary will shorten the time to menopause by approximately 1 year. Freezing a woman’s oocytes can extend her fertile period even until after she has entered natural menopause, but for ethical reasons this is strongly debated.
### TABLE 2  Summary of papers studying the predictive value of repeated anti-Müllerian hormone measurements on age at final menstrual period, age at natural menopause, time to final menstrual period, or time to menopause

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>N</th>
<th>Study design</th>
<th>Age at inclusion (mean ± SD)</th>
<th>Response variables</th>
<th>Predictor variables</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sowers52</td>
<td>2010</td>
<td>50</td>
<td>Prospective cohort study, 15 years follow up</td>
<td>41 ± 2.6 years</td>
<td>FMP, TFM</td>
<td>AMH (six yearly measurements), FSH, inhibin B, smoking status, insulin resistance, BMI</td>
<td>The slope of AMH change was associated with age at FMP, with more rapid decline in smokers</td>
<td>Small study to reliably analyze possible interactions among various biomarkers</td>
</tr>
<tr>
<td>Freeman53</td>
<td>2012</td>
<td>146</td>
<td>Prospective cohort study, 14 years follow up</td>
<td>40.9 (35–48) years (mean (range))</td>
<td>TTM</td>
<td>Age, AMH—at least two measurements in median (interval) 4.9 (2.5–7.3) years</td>
<td>AMH slope was strongly associated with TTM and the precision increased further when baseline AMH and age was added to the analysis</td>
<td>The reliability of the AMH slope on predicting TTM depended on the interval between the two tests with an interval of 3.5 years having the highest reliability</td>
</tr>
<tr>
<td>de Kat54</td>
<td>2019</td>
<td>1298</td>
<td>Retrospective cohort study, 20 years follow up</td>
<td>36.1 ± 8.1 years</td>
<td>TTM</td>
<td>Age, AMH levels, AMH decline rate (AMH measured every 5. years), OC use, smoking</td>
<td>Spot AMH levels at age 20 or 25 years significantly predicted age at menopause and time to early menopause in this age group. AMH decline rate did not predict menopause</td>
<td>AMH spot levels cannot, because of low discriminative ability and underestimation, be used as a screening method to estimate ANM</td>
</tr>
<tr>
<td>Ramezani Tehrani55</td>
<td>2020</td>
<td>529</td>
<td>Retrospective cohort study. Median follow up 14 years</td>
<td>36 ± 7.1 years</td>
<td>ANM</td>
<td>Age, AMH, AMH decline rate (measured three times with six years intervals)</td>
<td>Baseline AMH and AMH decline rate significantly improves prediction of menopause compared to baseline AMH alone</td>
<td>The study includes a wide age range of women included (20–50 years of age). Difference between actual and predicted ANM was −0.21 year (range −2.24 to 3.75), indicating some practical predictive utility</td>
</tr>
<tr>
<td>Finkelstein46</td>
<td>2020</td>
<td>1537</td>
<td>Prospective cohort study. Mean time to FMP 57 ± 38 months</td>
<td>47.5 ± 2.6 (42–63) (mean ± SD (range))</td>
<td>FMP</td>
<td>Age, AMH and FSH measured annually</td>
<td>AMH had a higher probability for predicting FMP than FSH. For various levels of AMH the precision increased with time to FMP and age</td>
<td>No patients below 42 years of age, therefore of limited value for prediction of future fertility</td>
</tr>
</tbody>
</table>

Only data on study participants who did enter natural menopause during the observation period are included.

Abbreviations: AMH, anti-Müllerian hormone; ANM, age at natural menopause; BMI, body mass index; FMP, final menstrual period; FSH, follicle-stimulating hormone; OC, oral contraceptive; SD, standard deviation; TFM, time to FMP; TTM, time to menopause.
CONCLUSION

Although several factors have been found to be associated with menopausal age, including anthropometric, morphometric, and hormone analyses, and combinations of various factors, most of these have insufficient accuracy for clinical use and prediction of fertility among women in their late 20s to early 40s. Current data only support the prediction of ANM using age and AMH among women in their late 40s and with regular menstrual periods. Future studies, however unfeasible, should be prospective and include women from their 20s with regular follow up during perhaps 20 years, combining hormone assays with morphometric and anthropometric assessments.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Both authors contributed equally to all aspects of preparation of the manuscript.

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