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Anti-Müllerian hormone for the diagnosis and prediction of menopause: a systematic review

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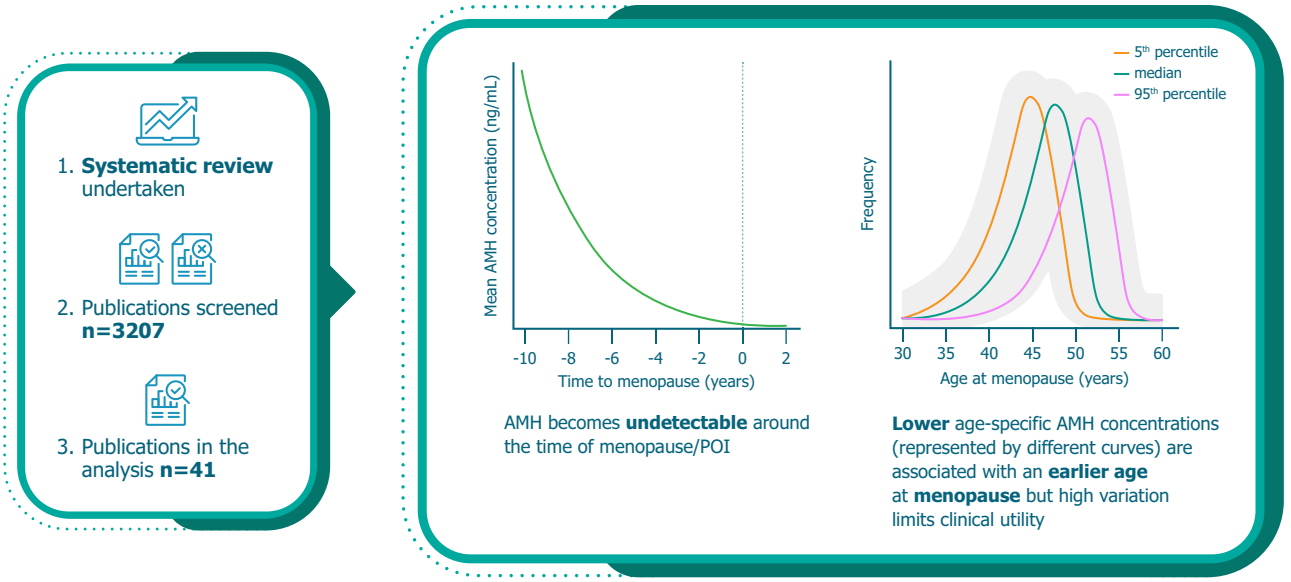
GRAPHICAL ABSTRACT



Prediction of age at menopause remains imprecise when not imminent, but very low AMH in young women can indicate increased risk of developing POI. AMH, anti-Müllerian hormone; POI, premature ovarian insufficiency.

BACKGROUND: The early onset of menopause is associated with increased risks of cardiovascular disease and osteoporosis. As a woman's circulating anti-Müllerian hormone (AMH) concentration reflects the number of follicles remaining in the ovary and declines towards the menopause, serum AMH may be of value in the early diagnosis and prediction of age at menopause.

OBJECTIVE AND RATIONALE: This systematic review was undertaken to determine whether there is evidence to support the use of AMH alone, or in conjunction with other markers, to diagnose menopause, to predict menopause, or to predict and/or diagnose premature ovarian insufficiency (POI).

SEARCH METHODS: A systematic literature search for publications reporting on AMH in relation to menopause or POI was conducted in PubMed®, Embase®, and the Cochrane Central Register of Controlled Trials up to 31 May 2022. Data were extracted and synthesized using the Synthesis Without Meta-analysis for diagnosis of menopause, prediction of menopause, prediction of menopause with a single/repeat measurement of AMH, validation of prediction models, short-term prediction in perimenopausal women, and diagnosis and prediction of POI. Risk-of-bias was evaluated using the Tool to Assess Risk of Bias in Cohort Studies protocol and studies at high risk of bias were excluded.

OUTCOMES: A total of 3207 studies were identified, and 41, including 28 858 women, were deemed relevant and included. Of the three studies that assessed AMH for the diagnosis of menopause, one showed that undetectable AMH had equivalent diagnostic accuracy to elevated FSH (>22.3 mIU/ml). No study assessed whether AMH could be used to shorten the 12 months of amenorrhoea required for a formal diagnosis of menopause. Studies assessing AMH with the onset of menopause (27 publications [n = 23 835 women]) generally indicated that lower age-specific AMH concentrations are associated with an earlier age at menopause. However, AMH alone could not be used to predict age at menopause with precision (with estimates and CIs ranging from 2 to 12 years for women aged <40 years). The predictive value of AMH increased with age, as the interval of prediction (time to menopause) shortened. There was evidence that undetectable, or extremely low AMH, may aid early diagnosis of POI in young women with a family history of POI, and women presenting with primary or secondary amenorrhoea (11 studies [n = 4537]).

WIDER IMPLICATIONS: The findings of this systematic review support the use of serum AMH to study the age of menopause in population studies. The increased sensitivity of current AMH assays provides improved accuracy for the prediction of imminent menopause, but diagnostic use for individual patients has not been rigorously examined. Prediction of age at menopause remains imprecise when it is not imminent, although the finding of very low AMH values in young women is both of clinical value in indicating an increased risk of developing POI and may facilitate timely diagnosis.

Key words: AMH / anti-Müllerian hormone / fertility / menopause / ovarian reserve / premature ovarian insufficiency

Introduction

A principal characteristic of a woman's reproductive function is that it has a distinctly finite duration. The terminal transition to a post-reproductive phase of life is overtly apparent to individual women in the form of the menopause when menstruation ceases, although this is preceded by subtle changes, including a decline in fertility being apparent from approximately a decade and a half earlier (Te Velde and Pearson, 2002). Thus, with increasing life expectancy and the average age of the menopause being ~49, ranging from 46 to 52 years, and depending on ethnicity (Gold, 2011; Schoenaker *et al.*, 2014), women will spend nearly half their lives in a postmenopausal state. However, for some, this will be substantially greater as ~4% of women experience premature ovarian insufficiency (POI; menopause before the age of 40 years) (Golezar *et al.*, 2019) and 8% experience early menopause (menopause before the age of 45 years) (Mishra *et al.*, 2017).

The transition to menopause is accompanied by several diverse and adverse outcomes (Lambrinoudaki *et al.*, 2022); thus, the ability to predict and identify when a woman's fertility and reproductive lifespan will end becomes increasingly relevant and clinically important the earlier this occurs. For example, untreated POI is characterized by progressive bone loss (leading to osteoporosis and fragility fractures), central adiposity and predisposition to type 2 diabetes, early cardiovascular disease and premature death, as well as infertility (Shuster *et al.*, 2010; Torrealday, Kodaman, and Pal, 2017; Anagnostis *et al.*, 2019a). Although POI reflects the extreme of the spectrum, the observed associations between age of onset of menopause and adverse outcomes are continuous. Therefore, being able to predict the age of natural menopause, including both POI and early menopause, in a timely fashion is critical. Similarly, the ability to diagnose menopause or POI prospectively, rather than making a retrospective diagnosis requiring, respectively, 12 months of amenorrhoea or 4 months with increased FSH concentrations as is currently used (European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI *et al.*, 2016; Panay *et al.*, 2020), would facilitate diagnosis and enable earlier interventions.

The classic tests of ovarian function relate to later stages of follicle growth and ovulation, while the menopause reflects the depletion of ovarian reserve. Studies have shown that serum anti-Müllerian hormone (AMH) is produced by granulosa cells of growing follicles (predominantly from follicles <8 mm in diameter) (Weenen *et al.*, 2004; Jeppesen *et al.*, 2013), that the concentration reflects the number of follicles remaining in the ovary (Hansen *et al.*, 2011), and that AMH declines before the menopause (de Vet *et al.*, 2002), in advance of elevated FSH concentrations, which are currently the key biochemical marker (Fig. 1). While the primordial follicle pool constitutes the ovarian reserve, as an indirect quantitative proxy, AMH has emerged as the current best biomarker. The term 'functional ovarian reserve' has been suggested to indicate the number of growing follicles that AMH reflects, with potential value for the diagnosis and prediction of the menopause. However, uncertainty remains as to the utility and accuracy of AMH for predicting age at spontaneous menopause and, importantly, the onset of POI, and current guidelines do not recommend routine use of AMH for the diagnosis of the menopause (Harlow *et al.*, 2012; NICE, 2019) or of POI (European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI *et al.*, 2016).

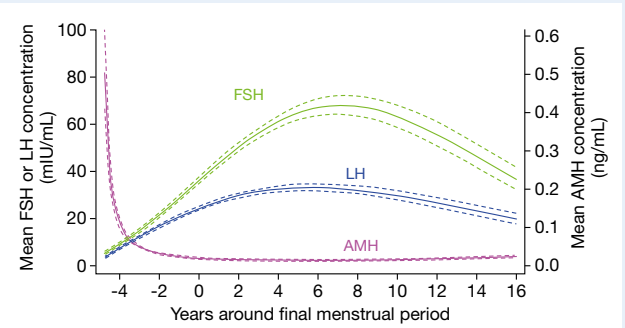


Figure 1. There is a steep decline in AMH prior to the final menstrual period. Solid lines represent the average predicted population means whilst 95% confidence intervals are indicated by dashed lines. Data are from the Avon Longitudinal Study of Parents and Children (ALSPAC) and reproduced from Soares *et al.* (2020), CC-BY. AMH, anti-Müllerian hormone.

There have been several narrative reviews of the potential role of AMH in the prediction of menopause (Depmann *et al.*, 2016a; Kruszyńska and Słowińska-Srzednicka, 2017; Victoria *et al.*, 2019; Moolhuijsen and Visser, 2020; de Kat *et al.*, 2021). To date, a systematic review of the relevant literature pertaining to either pathological or natural menopause diagnoses has not been conducted. To address this gap, this systematic review was undertaken to determine whether there is evidence that AMH can be used alone or in conjunction with other markers to diagnose menopause, whether AMH can be used to predict menopause and whether AMH can be used to predict and/or diagnose non-iatrogenic-related POI.

Methods

Data sources and searches

This study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and registered with the international prospective register of systematic reviews (PROSPERO) under the registration number: CRD42020161316. This review is reported in accordance with the PRISMA statement. No amendments were made to the protocol (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020161316) after the registration other than the exclusion of non-English language publications, use of an alternative bias evaluation tool (described below), and extension of the search date up to 31 May 2022.

PubMed®, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for longitudinal studies of premenopausal women and cross-sectional studies that included premenopausal women and women with POI who were not undergoing fertility treatment or assisted reproduction (Supplementary Data File S1).

Exclusion criteria

In summary, we excluded: non-clinical (animal or *in vitro*) studies; non-English language studies; studies of women with other

pathologies (including PCOS, Turner syndrome, or cancer); studies where AMH or ovarian reserve were not measured; fertility or genetic studies; studies of fewer than 10 subjects; studies judged to be of poor quality (for example, those with inconsistent reporting of results); and those that were deemed not relevant (for example, those concerned with therapeutic treatments, pregnancy, and hysterectomy). Non-primary publications, such as review articles, meta-analyses, trial protocols, and congress abstracts (poster and oral), were also excluded.

Study selection and bias analysis

After duplicate articles were removed, search results were screened consecutively by title, abstract, and full text as per the protocol (briefly, members of the project team screened articles, with the primary and senior authors reviewing the screening results). Relevant publications requiring evaluation of full text to determine inclusion underwent bias review via the Tool to Assess Risk of Bias in Cohort Studies protocol (CLARITY Group at McMaster University, 2017). Bias was assessed by the lead author, with conclusions verified by a second author; any disagreements were mediated by discussion with a third author. Publications with an overall bias judgement of low or moderate were included in the systematic review. All authors approved the final selection.

Data synthesis and analysis

Data were extracted by one of the project team and verified by a second team member. Synthesis was in accordance with the Synthesis Without Meta-analysis (SWiM) in systematic reviews: reporting guideline (Campbell et al., 2020). Certainty of evidence was based on vote counting (i.e., the number of positive versus the number of negative studies) for association of AMH with menopause/POI. Extracted data also included description of study types, year of publication, cohort mean/median age, mean/median AMH levels, timing of AMH measurement, and type of AMH assay used in each study. Where there were multiple studies reporting the same cohort with different durations of follow-up, thereby resulting in a different number of participants depending on the specific study, the details of each study are provided with an overall evaluation of the performance of serum AMH for the outcomes of interest. AMH values were converted to ng/ml or pg/ml where required. We categorized the publications into those concerned with the diagnosis of menopause, prediction of menopause, or diagnosis and prediction of POI. Studies are ordered by year (oldest to newest) within Tables I, II, and III.

Table I Summary of the findings of the three studies examining the role of AMH in the diagnosis of menopause.

Study	Study design	Total no. participants	Subjects	AMH assay	Outcomes
de Vet et al. (2002)	Longitudinal and prospective	54	Normo-ovulatory premenopausal women (n = 41) and postmenopausal women (n = 13). Premenopausal women (mean age 29 ± 4 years) were followed up with a mean of 2.6 ± 1.7 years	EIA AMH/MIS, Immunotech	AMH decreased over time (median 2.1 μg/l at Visit 1 versus 1.3 μg/l at Visit 2). AFC, FSH, and inhibin B did not change. AMH correlated with age, AFC, and FSH, but not with inhibin B. All postmenopausal women had undetectable AMH
Shin et al. (2008)	Cross-sectional	144	Healthy, ovulatory women (20–49 years) (n = 111) and postmenopausal women (n = 33). Median age premenopausal: 31 years; Postmenopausal: 56 years	Active MIS/AMH ELISA, DSL	AMH was lower in older women and undetectable in 20 of 33 postmenopausal women. The diagnostic accuracy of AMH (AUROC = 0.943) for menopausal status was similar to an FSH >22.3 mIU/ml (AUROC = 0.998) and LH >8.7 mIU/ml (AUROC = 0.996)
Zhang et al. (2021)	Cross-sectional	288	Women were categorized into three menopausal stages: late reproductive (n = 169), menopausal transition (n = 63), and early postmenopausal (n = 56). Median age was 48 years	Access AMH, Beckman Coulter	Age and menopause stage were associated with AMH level. Age had a greater impact on AMH than menopausal stage

Assay name is standardized as per Supplementary Table SII.
AFC, antral follicle count; AMH, anti-Müllerian hormone; MIS, Müllerian-inhibiting substance; AUROC, area under the receiver operating characteristics curve; DSL, Diagnostic Systems Lab; EIA, enzyme immunoassay.

Table II Summary of the findings of the 27 studies examining the role of AMH in prediction of menopause.

Study	Study design	Total no. participants	Subjects	AMH assay	Outcomes
van Rooij *et al.* (2004)	Prospective longitudinal cohort	81	81 normal women between 25 and 46 years, with follow-up at an average interval of 4 years	EIA AMH/MIS, Immunotech	Lower AMH was associated with onset of cycle irregularity. AMH, AFC and age had the highest predictive accuracy for cycle irregularity (AUROC 0.87, 0.80 and 0.82, respectively). After adjusting for age, only AMH and inhibin B were significantly associated with cycle irregularity
van Disseldorp *et al.* (2008)	Pooled (n = 2) prospective cross-sectional cohort	3384	Prospect-European Prospective Investigation into Cancer and Nutrition study (Prospect-EPIC). Healthy, regularly cycling women, plus a subgroup of women aged 58 years and older who had undergone natural menopause	Active MIS/AMH ELISA, DSL; EIA AMH/MIS, Immunotech Conversion factor applied	There was a good level of concordance between the distribution of observed age at menopause and the predicted distribution based on a modelled mean decline of AMH with age and the application of a menopausal threshold AMH level of 0.086 μg/l
Sowers *et al.* (2008)	Prospective longitudinal cohort	50	Michigan Bone Health and Metabolism Study. Subgroup of 50 women with regular cycle and FSH <14 mIU/ml. Mean age of women at baseline was 42 years	Active MIS/AMH ELISA, DSL	Longitudinal AMH profiles declined to values around the LOD at a time point 5 years prior to the FMP. Baseline AMH profiles were also significantly associated with age at FMP
Tehrani *et al.*, (2009)	Prospective longitudinal cohort	147	Tehran Lipid and Glucose Study (TLGS). 60 of the 147 women entered the menopause during 6 years of follow-up. Mean age at baseline was 44.8 years	Active MIS/AMH ELISA, DSL	Baseline AMH was associated with menopause. In women 40–49 years, for a threshold AMH level of 0.39 ng/ml, PPV was 0.90 and NPV was 0.76. Stratified results were similar for women aged 40–44 and 45–49 years
Broer *et al.* (2011)	Pooled (n = 3) prospective longitudinal cohorts	257	Three cohorts, 257 women available for analysis. Cohort 1: 172 women aged 25–46 years who had a regular menstrual cycle; Cohort 2: 90 women aged 18–46 years, two ovaries, no adnexal surgery in the past, and a regular menstrual cycle; Cohort 3: 40 normo-ovulatory women	Cohort 1: Active MIS/AMH ELISA, DSL Cohort 2 and 3: EIA AMH/MIS, Immunotech Conversion factor applied	AMH was associated with age at menopause. In an age-adjusted model, the hazard ratio for time to menopause was 0.092 (95% CI: 0.025–0.340) per 0.89 ng/ml change in AMH
Tehrani *et al.* (2011)	Prospective longitudinal cohort	266	Tehran Lipid and Glucose Study (TLGS). 266 women with three repeat measurements of AMH at around 3-year intervals. 63 women entered menopause over 6 years of follow-up. Mean age at baseline was 37.6 years	Active MIS/AMH ELISA, DSL	AMH was associated with age at menopause. A single AMH measurement at baseline showed the best model performance, with no enhancement of model performance with repeat AMH measurements. Level of agreement between predicted and observed age of menopause declined at extremes of age
Freeman *et al.* (2012a)	Prospective longitudinal cohort	293	Penn Ovarian Aging Study. Subgroup of 293 late reproductive age premenopausal women who had detectable AMH at baseline and at least one further AMH measurement.	AMH Gen II ELISA, Beckman Coulter	Rate of change of AMH was strongly associated with TTM and provided greater precision when included with baseline AMH rather than a single measure of AMH or age alone (HR

(continued)

Table II Continued

Study	Study design	Total no. participants	Subjects	AMH assay	Outcomes
			Mean age: 40.93 years at baseline. 14 years of follow-up. 146 became postmenopausal		for TTM with 1 SD change in AMH = 1.82, 95% CI: 1.56–2.14)
Freeman et al. (2012b)	Prospective longitudinal cohort	401	Penn Ovarian Aging Study. Subgroup of 401 premenopausal women with a baseline AMH measurement. Mean age at baseline: 41.5 years. 198 women reached natural menopause over 14 years of follow-up	AMH Gen II ELISA, Beckman Coulter	AMH strongly predicted TTM, with age further improving predictions. For women with baseline AMH <0.20 ng/ml, the median TTM was 5.99 years and 9.94 years for those aged 45–48 years and 35–39 years, respectively. For women with higher baseline AMH levels (>1.50 ng/ml), median TTM was 6.23 years in the oldest age group and >13.01 years in the youngest age group
Tehrani et al. (2013)	Prospective longitudinal cohort	1015	Tehran Lipid and Glucose Study (TLGS). 277 women reached the menopause over mean of 10 years of follow-up. Mean age at baseline: 36.7 years	AMH Gen II ELISA, Beckman Coulter	In an accelerated failure time model, AMH at baseline was associated with age at menopause and improved an age alone model. The median (SD) of differences between the actual age at menopause and the age predicted by a model was 0.5 (2.5) years. The accuracy of prediction of age at menopause using the model was 92% vs 84% for age alone
Iino et al. (2013)	Prospective longitudinal cohort	44	Subgroup of 44 women (>40 years old) from 595 women in Japan. Annual AMH measurements for 6 years. 29 women experienced menopause during the study	AMH Gen II ELISA, Beckman Coulter	Longitudinal reductions in AMH across the perimenopause; AMH may be a marker for defining menopausal transition
Dólleman et al. (2014)	Prospective cohort study	314	Three study groups: Cohort 1: 164 mother–daughter pairs from four birth cohorts: DOM1, DOM2, DOM3 and DOM4 (median age at baseline: 39.0 years); Cohort 2: 70 women (median age at baseline: 37.0 years); Cohort 3: 80 women (median age at baseline: 34.7 years); Follow-up over 12 years	Active MIS/AMH ELISA, DSL; EIA AMH/MIS, Immunotech	Maternal age at menopause predicts daughter's age at menopause. AMH independently adds value to this prediction and is suggested to be more accurate prediction than maternal age at natural menopause
Ramezani Tehrani et al. (2014)	Prospective longitudinal cohorts (n = 2)	424	Scheffer, van Rooij, de Vet (SRV) cohort: 158 of 257 women at baseline followed up 11 years later; 48 became menopausal during follow-up. Tehran Lipid and Glucose Study (TLGS): 266 women randomly selected from 1265 women; 63 became menopausal during follow-up	SRV: Active MIS/AMH ELISA, DSL; TLGS: AMH Gen II ELISA, Beckman Coulter Conversion factor applied	External validation of cohort-specific models for AMH prediction of age at menopause. Both models showed good agreement between predicted risk and observed menopausal age
Tehrani et al. (2014)	Prospective longitudinal cohort	1015	Tehran Lipid and Glucose Study (TLGS). 277 women reached the menopause over a mean of 10 years of follow-up. Mean age at baseline: 36.7 years	AMH Gen II ELISA, Beckman Coulter	Development of a nomogram of age-specific estimates of AMH in a large sample of naturally fertile women

(continued)

Table II Continued

Study	Study design	Total no. participants	Subjects	AMH assay	Outcomes
Dólleman *et al.* (2015)	Prospective longitudinal cohort	1163	Doetinchem Cohort Study. Assessment of menopause at 5 and 10 years of follow-up. 169 became postmenopausal at 5 years and 527 at 10 years of follow-up. Mean age at baseline: 40.8 years	AMH Gen II ELISA, Beckman Coulter	Inclusion of AMH improved prediction of age at menopause. *C*-statistic increased from 0.89 to 0.91 for TTM by adding AMH to model including age, BMI, years of smoking and menstrual cycle status
Nair *et al.* (2015)	Prospective longitudinal cohort	716	Coronary Artery Risk Development in Young Adults (CARDIA) Women's Study. Median age at baseline was 42 years, with 9 years of follow-up. 207 women reached natural menopause during follow-up	Ultra-Sensitive AMH/MIS ELISA, Ansh Labs	AMH was independently associated with age at menopause, and exhibited strongest prediction in the identification of women at risk within 3 years. No women with AMH >2.0 ng/dl (20 pg/ml) experienced menopause within 6 years
de Kat *et al.* (2016)	Prospective longitudinal cohort	3326	Doetinchem Cohort Study. Assessment of menopause at baseline, 5, 10, 15 and 20 years of follow-up. Repeat AMH measurements at 5-year intervals. In total, 1882 became menopausal. Mean age at baseline was 40 ± 10 years	picoAMH ELISA, Ansh Labs	Age-specific AMH was associated with the onset of menopause. 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 ICC of 0.87. 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. 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
Depmann *et al.* (2016b)	Pooled (n = 3) prospective longitudinal cohorts	155	265 women at baseline between 1992 and 2001, with 216 followed up between 2008–2010 or 2012–2013 and 155 available for analyses. Mean age at baseline: 36 years. 81 women were postmenopausal, with a mean follow-up of 14 years	Active MIS/AMH ELISA, DSL EIA AMH/MIS, Immunotech	Age-specific AMH levels were predictive of menopause (*C*-statistic 0.86, HR 0.70 [95% CI: 0.56 – 0.86]); however, the predictive effect reduced with increasing age
Ramezani Tehrani *et al.* (2016)	Prospective longitudinal cohort	1015	Tehran Lipid and Glucose Study (TLGS). 277 women reached the menopause over a median of 9.8 years of follow-up	AMH Gen II ELISA, Beckman Coulter	Use of age-specific AMH percentiles in a flexible parametric survival model improved model performance for menopause prediction. The difference between actual and predicted age at menopause was 1.9 years
Gohari *et al.* (2016)	Prospective longitudinal cohort	266	Tehran Lipid and Glucose Study (TLGS). 63 of the 266 women entered the menopause during an average of 6.5 years of follow-up, with AMH measured every 3 years. Mean age at baseline: 37.55 years	Active MIS/AMH ELISA, DSL	Rate of decline of AMH (AMH trajectory) using 2 or 3 measurements improved baseline AMH prediction of age of menopause
Kim *et al.* (2017)	Prospective longitudinal cohort	426	Coronary Artery Risk Development in Young Adults (CARDIA) Women's Study. 30 years of follow-up; mean age: 43 years	Ultra-Sensitive AMH/MIS ELISA, Ansh Labs	AMH improved age-based prediction of menopause within the next 5 years. AMH >2.0 ng/dl was associated with minimal probability of menopause within the next 5 years, irrespective of age. AMH concentrations below LOD were associated with >60% chance of menopause among women ≥45 years

(continued)

Table II Continued

Study	Study design	Total no. participants	Subjects	AMH assay	Outcomes
Whitcomb et al. (2018)	Nested case-control study	820	Nested case-control subgroup (n = 820) of premenopausal women (n = 108,811) from the prospective longitudinal Nurses' Health Study 2 (n = 116,429). Follow-up every 4 years. Mean age of sample: 33.8–34.2 years across the groups	picoAMH ELISA, Ansh Labs	Lower mean AMH was associated with a higher risk of early menopause
Bertone-Johnson et al. (2018)	Nested case-control study	818	Nurses' Health Study 2. Women reporting natural menopause between sample collection and age 45, n = 327. Control group who experienced menopause after age 45, n = 491. Mean age in all groups: 40 years	picoAMH ELISA, Ansh Labs	AMH level was significantly lower in women who subsequently experienced early menopause (0.40 ng/ml) than in matched controls (1.9 ng/ml; $P < 0.001$). For each 0.10 ng/ml decrease, there was a 14% higher risk of early menopause ($P < 0.001$). Accuracy of prediction was lower in women age ≤35 (*C*-statistic 0.68), compared with those at age 42 (*C*-statistic 0.93)
de Kat et al. (2019)	Prospective longitudinal cohort	2434	Doetinchem Cohort Study. Assessment of menopause at baseline, 5, 10, 15 and 20 years of follow-up. Repeat AMH measurements at 5-year intervals (367–736 women with 1–5 AMH measurements). In total, 1298 women became postmenopausal	picoAMH ELISA, Ansh Labs	In women over the age of 25 years, inclusion of repeat AMH measurements/AMH trajectory did not improve prediction of age of menopause or early menopause
Ramezani Tehrani et al. (2020)	Prospective longitudinal cohort	959	Tehran Lipid and Glucose Study (TLGS). 529 women reached menopause over a median follow-up period of 14 years. Mean age at baseline: 36 ± 7.1 years	AMH Gen II ELISA, Beckman Coulter	Including the AMH decline rate in the model improved the discrimination adequacy from 70% (95% CI: 67–71) to 78% (95% CI: 75–80) in terms of *C*-statistics, with improvements in median differences between actual and predicted age at menopause (from -0.48 years to -0.21 years). The predicted age at menopause for women with equivalent age-specific AMH was one decade lower in those with an annual AMH decline rate of the 95th percentile compared with those with a decline rate at 5th percentile
Soares et al. (2020)	Prospective longitudinal cohort	1608	Avon Longitudinal Study of Parents and Children (ALSPAC). Four clinics over 5–6 years. 1608 women with 4037 observations over 5–6 years. At baseline, 281 premenopausal, 493 perimenopausal and 547 postmenopausal. Median age at baseline was 48 years	Elecsys® AMH Plus, Roche Diagnostics	AMH decreased markedly before menopause and remained low subsequently. Women with earlier age at menopause had the highest levels of AMH about 4 years before the FMP, and the decline in AMH was slightly later than in those with menopause at on average 50 years
Finkelstein et al. (2020)	Prospective longitudinal cohort	1537	The Study of Women's Health Across the Nation (SWAN). Annual follow-up where possible until menopause (1537 women with 7407 blood samples) Mean age: 47.5 years	MenoCheck® picoAMH ELISA, Ansh Labs	AMH was able to predict the FMP within a window of 12–36 months in late-reproductive aged women. The probability that a woman with AMH <10 pg/ml would reach menopause within the next 12 months was

(continued)

Table II Continued

Study	Study design	Total no. participants	Subjects	AMH assay	Outcomes
					between 51% at <48 years old and 79% at ≥51 years old. The probability that a woman with AMH >100 pg/ml would not reach menopause within the next 12 months was between 97% in women <48 years old and 90% in women ≥51 years old
Ramezani Tehrani *et al.* (2021)	Prospective longitudinal cohort	901	Tehran Lipid and Glucose Study (TLGS). 522 women reached menopause over a median follow-up of 13 years. AMH levels were measured every 6 years. Mean age at baseline: 36 years	AMH Gen II ELISA, Beckman Coulter	A time-dependent Cox model showed that each unit increase in the AMH level could reduce the risk of menopause by 87%. The Cox proportional hazards model also improved the prediction of age at menopause by 3%. Multiple AMH measurements could improve the individual predictions of the risk of physiological menopause compared to single AMH measurements

Assay name is standardized as per Supplementary Table SII.
AMH, anti-Müllerian hormone; AFC, antral follicle count; AUROC, area under the receiver operating characteristic curve; DSL, Diagnostic Systems Lab; EIA, enzyme immunoassay; FMP, final menstrual period; HR, hazard ratio; ICC, intraclass correlation coefficient; LOD, limit of detection (as reported by authors); MIS, Müllerian-inhibiting substance (AMH); NPV, negative predictive value; PPV, positive predictive value; SRV, Scheffer, van Rooij, de Vet; TTM, time to menopause; TLGS, Tehran Lipid and Glucose Study.

Results

Characteristics of included studies

A total of 3207 publications were initially identified (Fig. 2). After removal of duplicates and assessment for quality and relevance to the study question at the title, abstract, and full text level, 44 were included for bias review.

Of these, a further three were assessed to be at severe or critical risk of bias and were excluded (Kelsey *et al.*, 2011; Moreau *et al.*, 2018; Nelson *et al.*, 2020), leaving 41 publications at low risk of bias including 28 858 participants for systematic review, published between February 2002 and December 2021 (Supplementary Table SI and Tables I, II, and III). Of these, 30 publications (n = 24 321 participants) were concerned with AMH and menopause (three focused on diagnosis [n = 486] and 27 [n = 23 835] focused on prediction), with several large cohorts (Tehran Lipid and Glucose Study [TLGS], Doetinchem Cohort Study and Nurses' Health Study 2) contributing multiple publications with different numbers of participants, periods of follow-up or analyses. Eleven studies (n = 4537) were concerned with POI, two investigating the use of AMH in diagnosis and nine the prediction of POI.

Assays used in studies

Across the 41 studies included in the analysis, circulating AMH concentrations were measured by different assays with substantial differences in assay performance characteristics (Supplementary Table SII; Wallace *et al.*, 2011; Ansh Labs, 2014; Lukaszuk *et al.*, 2014; Roche Diagnostics, 2014; Su *et al.*, 2014; Beckman Coulter, 2017, 2018, 2021; Roche Diagnostics, 2017, 2018, 2022; Ansh Labs, 2018; Sun *et al.*, 2018; Jiao *et al.*, 2021; Punchoo and Bhoora, 2021). Even for assays predicated on the same methodology, such as ELISA, the lower limit of the measurable range varied from 0.006 ng/ml (equivalent to 0.04 pmol/l) (picoAMH ELISA) to 0.16 ng/ml (1.2 pmol/l) (AMH Gen II ELISA), reflecting the differential construction and antibody selection within the assays. This may be of relevance to the diagnosis of menopause and POI. Only two studies used an electrochemiluminescence immunoassay (Soares *et al.*, 2020; Ma *et al.*, 2022).

AMH and diagnosis of menopause

No studies formally examined whether AMH could be used as a diagnostic marker for menopause in accordance with an international framework for the assessment of diagnostic tests (Ferrante di Ruffano *et al.*, 2012). Two cross-sectional studies and one longitudinal observational study assessed the age-related decline of AMH prior to the menopause (Table I). These studies included postmenopausal participants and demonstrated that undetectable AMH was strongly associated with menopausal stage (de Vet *et al.*, 2002; Shin *et al.*, 2008; Zhang *et al.*, 2021). In a study of 144 women, undetectable AMH had equivalent diagnostic accuracy to elevated FSH (where 22.3 mIU/ml was the optimal cut point) (Shin *et al.*, 2008). However, this study included women with an established, rather than recent, menopause (Shin *et al.*, 2008), and therefore, the diagnostic accuracy may have been overestimated. However, in a further cross-sectional analysis of 288 healthy women aged 40–55 years, while AMH was progressively lower in women at later menopausal stages, age was found to have a greater impact on AMH levels than menopausal stage (Zhang *et al.*, 2021). No prospective studies undertaken in women prior to

Table III Summary of the findings of the 11 studies examining the role of AMH in the diagnosis and prediction of premature ovarian insufficiency.Retrospective case-control study

Study	Study design	Total no. participants	Subjects	AMH assay	Outcomes
Méduri *et al.* (2007)	Cross-sectional, case-control study	48	250 women with POF, of whom 93 had ovarian biopsy and 48 were eligible as no gonadotoxic therapy and normal karyotype. Mean age: 27.2 ± 7.2 years	EIA AMH/MIS, Immunotech	AMH levels correlated with the number of follicles in women with POF. In the absence of follicles, the mean AMH level was 0.42 ± 0.65 ng/ml, increasing to 2.16 ± 1.66 ng/ml in those with 15 or more follicles
Knauff *et al.* (2009)	Prospective cohort study	342	Women < 40 years in four groups: –Controls, n = 83 –IOF, n = 68 –TOF, n = 79 –POF, n = 112 Mean age: 34–35.2 years across the groups	Active MIS/AMH ELISA, DSL; EIA AMH/MIS, Immunotech was used for controls, with values converted to DSL calibration	AMH values in POF patients were below the fifth percentile for their age and detectable in 6% of the POF group, despite fluctuations in FSH levels and incidental vaginal bleeding. The IOF group showed intermediate AMH levels. AMH discriminated at every age group, with greater differences with increasing age
Kallio *et al.* (2012)	Case-control study	135	Several groups of patients with different phenotypes of ovarian insufficiency, controls, and TS (n = 135). Ages: FSHRO, 22–43 years (n = 12); PA, 18–42 years (n = 11); SA, 19–41 years (n = 20); controls, 18–44 years (n = 23); TS, 6–43 years (n = 35); healthy controls, 7–44 years (n = 34)	Active MIS/AMH ELISA, DSL	AMH level identified patients with decreasing ovarian reserves and POI: AMH was lower in women with PA (0.05 ± 0.04 ng/ml; $P < 0.001$) or SA of unknown origin (0.12 ± 0.20 ng/ml; $P < 0.001$) than controls (3.77 ± 2.36 ng/ml). TS girls/women with 45, X or SCA had low AMH levels (0.13 ± 0.09 or 0.27 ± 0.19 ng/ml, respectively) compared with their controls (3.34 ± 2.23 ng/ml) or subjects with mosaicism (2.33 ± 2.81 ng/ml)
Li *et al.* (2011)	Retrospective case-control study	150	Women with SA: Hypogonadotropic hypogonadism (n = 24); PCOS (n = 33); POF (n = 23); Hyperprolactinaemia (n = 22); Normally ovulating women with regular cycles for controls (n = 26); Women with normogonadotropic normogonadic (WHO group 2) anovulation (n = 22)	EIA AMH/MIS, Immunotech	AMH was decreased to very low levels in POI. The diagnostic accuracy was high (AUROC 0.977).
Sahmay *et al.* (2014)	Cross-sectional retrospective study	175	Women with POI and secondary amenorrhoea (n = 38); women with elevated FSH levels (n = 48); control group (n = 89). Mean age controls: 30.7 years; elevated FSH: 33.0 years; POI: 30.4 years	Active MIS/AMH ELISA, DSL	AMH significantly discriminated controls from patients with elevated FSH or POI (best AMH cut-off point was 0.955 ng/ml for the FSH group and 0.945 ng/ml for the POI group). AMH did not significantly discriminate between POI and women with high FSH
Guzel *et al.* (2017)	Prospective observational study	963	Women aged <30 years (n = 963). Mean age: 20.1 years. Occult POI as determined by AMH ≤1.1 ng/ml at baseline (n = 43) and 920 women with AMH >1.1 ng/ml. Follow-up of 12.2 months for the 43 women with occult POI	Active MIS/AMH ELISA, DSL	A large percentage (20.9%) of women with AMH ≤1.1 ng/ml had a mother and/or sister with POF as compared to 7.2% in women with an AMH > 1.1 ng/ml

(continued)

Table III Continued

Study	Study design	Total no. participants	Subjects	AMH assay	Outcomes
Sun *et al.* (2018)	Case-control study	282	142 women with POF and 140 controls. Mean age: 29.2 years	AMH ELISA, Shanghai Ximin Biotechnology Co. Ltd	AMH was lower than 2.51 ± 1.4 ng/ml but still detectable in women with POF compared to age-matched controls (4.92 ± 0.42 ng/ml)
Desongnis *et al.* (2021)	Cross-sectional, longitudinal cohort study	47	From an initial cohort of 92 women, 47 had clinical assessments, 21 had further AMH measurement 5–10 years later. Median age at baseline: 29.0 years; median age at follow-up: 36.0 years. 8 women experienced POI during follow-up	At baseline: EIA AMH/MIS Immunotech At follow-up: Access AMH, Beckman Coulter	In women with low AMH (<8 pmol/l before the age of 36 years), the prevalence of POI after at least 5 years was 17% [95% CI: 8–31]
Jiao *et al.* (2021)	Retrospective case-control study	1998	Women were classed NOR (n = 987), pre-POI (n = 410), early POI (n = 147), and POF (n = 454) based on FSH levels. Age <40 years.	Unspecified ELISA, Kangrun Biotech	AMH of ≤0.25 ng/ml was diagnostic of POI, with sensitivity 92.46% and specificity 90%. AMH concentrations were lower in genetic POI than with other aetiologies
Ma *et al.* (2022)		378	169 patients with POI and 209 healthy controls were assessed. All participants were aged <45 years and most were aged between 30 and 40 years	Unspecified ECLIA, Roche Diagnostics	AMH was significantly ($P < 0.001$) lower in women with POI vs controls. FSH was significantly higher in women with POI than controls. In 169 patients with POI, age at menopause was <30 years in 20.7%
Kasahara *et al.* (2021)	Retrospective observational	19	Patients with POI who underwent cyclic hormonal therapy. Age <40 years	MenoCheck® picoAMH ELISA, Ansh Labs	FSH levels were lower and AMH levels were higher in cycles with follicle growth compared with those without

Assay name is standardized as per Supplementary Table SII.
AMH, anti-Müllerian hormone; AUROC, areas under the receiver operating characteristic curve; ECLIA, electrochemiluminescence; EIA, enzyme immunoassay; DSL, Diagnostic Systems Lab; FSHRO, FSH-resistant ovaries; IOF, incipient ovarian failure; TOF, transitional ovarian failure; MIS, Müllerian-inhibiting substance (AMH); NOR, normal ovarian reserve; PA, primary amenorrhoea; POF, premature ovarian failure; POI, premature ovarian insufficiency; SA, secondary amenorrhoea; SCA, structural chromosome abnormalities; TS, Turner's syndrome; WHO, World Health Organization.

completion of 12 months of amenorrhoea to determine whether AMH could shorten the diagnostic timeframe of menopause, from the conventional 12 months of amenorrhoea, were identified. Similarly, none of the studies assessed whether AMH could be incorporated with other biomarkers to improve the diagnostic accuracy of the menopause.

AMH and prediction of menopause

The twenty-seven publications that examined the role of AMH in the prediction of menopause are summarized in Table II. In all of these studies, for any given age, a lower AMH was associated with earlier menopause or onset of menopause-related symptoms. Similarly, lower AMH exhibited strong associations with the risk of early menopause (Bertone-Johnson *et al.*, 2018), and this association was independent of established risk factors for early reproductive decline. Assessment of age-specific AMH values suggested that lower AMH at younger ages was more strongly associated with an increased risk of younger age at menopause than a non-age-adjusted AMH value (Gohari *et al.*, 2016). For example, in one study, an AMH of 0.1 ng/dl at age 26 years was predicted by the model to be associated with age of menopause of 36 years (95% CI: 30–40), but at age 44 years, the same AMH level was associated with a predicted age of menopause of 48 years (95% CI: 40–54) (Tehrani *et al.*, 2013).

Prediction of menopause with a single AMH measurement

Modelling the predicted age at menopause using a single serum measurement of AMH was undertaken by several authors (Table II). Approaches included prospective longitudinal cohort studies with back derivation of nomograms (Tehrani *et al.*, 2011, 2013), graphical representation of age-specific AMH percentiles to estimated distribution of menopause (Depmann *et al.*, 2016b), and defined time periods for the onset of menopause, e.g., within 5 years (Kim *et al.*, 2017). Others reported overall associations (e.g., hazard ratios) of AMH concentrations with time to menopause (Freeman *et al.*, 2012b; Dólleman *et al.*, 2014, 2015; Depmann *et al.*, 2016b) or early menopause (Whitcomb *et al.*, 2018). An alternate indirect approach of modelling techniques to show good levels of conformity between the distribution of the

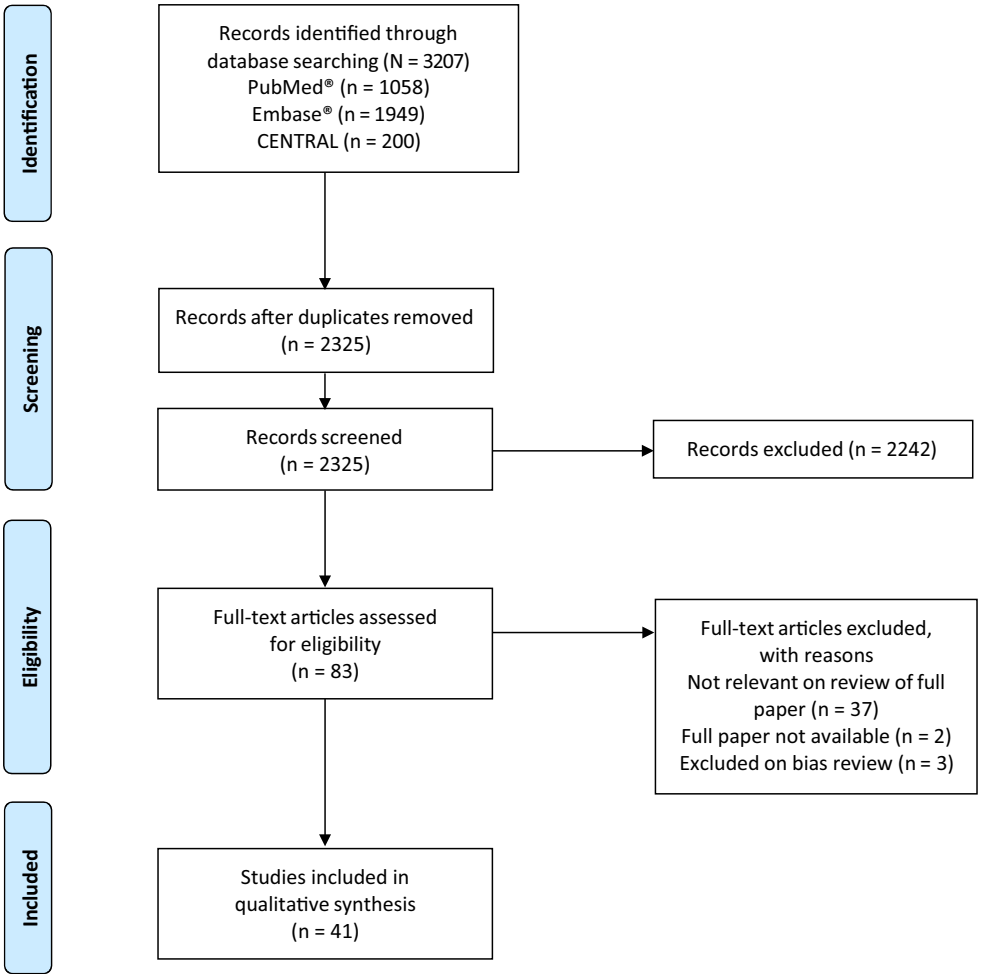


Figure 2. PRISMA flow chart.

observed age at menopause and the predictive distribution based on a modelled decline of AMH with age and the application of a menopausal threshold AMH level was also used (van Disseldorp *et al.*, 2008). Irrespective of the approach used, or the population studied, [regularly cycling women (Freeman *et al.*, 2012b; Tehrani *et al.*, 2013) or women with a history of infertility, menstrual irregularity, or oligomenorrhoea (Nair *et al.*, 2015)], all studies utilizing a single AMH value confirmed that the risk of spontaneous menopause was high if AMH values were low or undetectable. However, the CIs for estimates and associated time frames were generally wide—for example, the 95% CI for a serum AMH measurement of 2.1 ng/dl measured in a woman 30 years of age was 44–59 (Tehrani *et al.*, 2013)—precluding clinical use.

Prediction of menopause with repeat AMH measurements

Several studies assessed the utility of repeat AMH measures, incorporating a variety of different mathematical approaches to try to model the menopausal transition or improve the prediction of time to menopause compared with single measurements. These included differences in absolute values (Iino *et al.*, 2013), Weibull accelerated failure time models (Tehrani *et al.*, 2013), flexible parametric survival models (Tehrani *et al.*, 2013; Ramezani Tehrani *et al.*, 2016), mixed models (de Kat *et al.*, 2016), Kaplan–Meier estimations (Freeman *et al.*, 2012a), and Cox proportional hazards models with time-varying covariates (de Kat *et al.*, 2019; Ramezani Tehrani *et al.*, 2021). The findings are inconsistent. Two studies reported that the use of two different AMH measurements several years apart did not improve prediction of menopause, or early menopause, compared with a single value in some age groups (25–30, 30–35 years), but did in women aged 20–25 years (Sowers *et al.*, 2008; de Kat *et al.*, 2019). In the Penn Ovarian Aging Study (POAS), both a lower baseline AMH level and a more rapid rate of decline were associated with a shorter time to menopause for all ages (Freeman *et al.*, 2012a). Similarly, in the TLGS cohort, the serum AMH trajectory was a strong predictor for age at menopause (Gohari *et al.*, 2016), with subsequent analyses demonstrating that the addition of the AMH annual decline within models

significantly improved the prediction of age at menopause over AMH and age alone (Ramezani Tehrani *et al.*, 2020). Analysis of that study using Cox proportional hazards showed that repeated measurement of AMH only slightly improved prediction of age at menopause; the best model for predicting menopause only generated a 3% improvement in prediction, with the *C*-statistic increasing from 0.71 (95% CI: 0.69–0.73) at baseline to 0.74 (95% CI: 0.71–0.76) when a second measurement and calculation of the annual decline were included (Ramezani Tehrani *et al.*, 2021). These contradictory results may be partly due to the different modelling used, the variation in time to menopause, the different time periods between repeat AMH measures, and/or the heterogeneity in populations. A consistent finding was that while there were strong links between AMH and age at menopause, the accuracy of prediction for an individual woman was sufficiently imprecise to be of little clinical value, except at extremes of values.

Validation of menopause prediction models

Prediction of an event in the future, such as menopause, is ideally validated in accordance with international guidelines for prognostic models (Hemingway *et al.*, 2013). Of the included studies, only two prognostic models from two cohorts, the Scheffer, van Rooij, de Vet (SRV) (Broer *et al.*, 2011) and the TLGS cohorts (Tehrani *et al.*, 2011, 2013), underwent cross-validation (Ramezani Tehrani *et al.*, 2014). Both models used a single measure of AMH, and either age-specific AMH percentiles or age at AMH measurement as the predictor (Broer *et al.*, 2011; Tehrani *et al.*, 2013; Ramezani Tehrani *et al.*, 2014). The models demonstrated good discrimination between women at risk of early menopause and women likely to be of older age at menopause, with discriminatory capacity of both models in excess of 70% (Ramezani Tehrani *et al.*, 2014). However, the SRV cohort model slightly overestimated age of menopause when applied to the TLGS cohort, and conversely, the TLGS model underestimated the age at menopause of the SRV cohort (Ramezani Tehrani *et al.*, 2014). This may reflect the similar proportion of women undergoing menopause in the two cohorts despite shorter follow-up time and lower age at follow-up in the TLGS study, higher AMH values observed in the TLGS study despite age at AMH measurement being slightly older, potential differences between ethnicities, and how age and AMH were incorporated into the models (Ramezani Tehrani *et al.*, 2014). Whether age-specific AMH percentiles yield a more realistic prediction of age at menopause than absolute AMH values that are age-corrected in the model where age is already on the time axis will require further study. Age-specific AMH percentiles may also be more limited in their ability to predict the extreme ends of the spectrum for menopausal age, which may be of more clinical interest; this also requires further clarification.

Short-term prediction of menopause in perimenopausal women

While most studies examined long-term prediction, several specifically assessed perimenopausal women and limited the duration of follow-up to either 3 years (Finkelstein *et al.*, 2020) or 5 years (Kim *et al.*, 2017) (Table II). In the Study of Women's Health Across the Nation (SWAN) of 1537 pre- or perimenopausal women with mean age 47.5 years at first assessment, the areas under the receiver operating characteristic curves utilizing AMH as the primary predictor were significantly greater than FSH-based models for predicting time to final menstrual period (FMP) for both 24- and 36-month predictions (0.891 versus 0.877 at 24 months, $P < 0.05$) (Finkelstein *et al.*, 2020). The strength of the association of AMH with the FMP was modified by age, such that the probability that a woman with low AMH levels (<10 pg/ml) would undergo her FMP within the next 12 months varied between 51% at <48 years old and 79% at ≥51 years old (Finkelstein *et al.*, 2020). Conversely, if AMH was high (>100 pg/ml), the probability that the woman would not reach menopause within the next 12 months was high but still exhibited an independent effect of age, with estimates ranging from 97% in women <48 years old to 90% in women ≥51 years old. Predicting that menopause was not imminent was thus substantially more accurate than predicting imminent menopause.

An ancillary study of the CARDIA cohort assessed the probability of menopause in the following 5 years in women with a mean age of 43 years and also found that a model incorporating AMH and age better predicted the odds of menopause within the next 5 years than models incorporating age with FSH or antral follicle count (AFC), or both (Kim *et al.*, 2017). The inclusion of other biomarkers (FSH or AFC) did not improve prediction over AMH and age alone (Kim *et al.*, 2017). Among women aged 45–49 years, undetectable AMH concentrations, albeit with a less sensitive assay (limit of detection 23 pg/ml; 0.16 pmol/l), was associated with a 60% probability of menopause within 5 years (Kim *et al.*, 2017). Although the UK's National Institute for Health and Care Excellence guidelines currently recommend against FSH testing in women over 45 years (NICE, 2019), appreciation of the timeline for individual women who may be experiencing a range of clinical symptoms may be useful.

AMH and diagnosis and prediction of POI

Eleven publications examined the use of AMH in women with POI in various contexts, as summarized in Table III. Two studies reported AMH levels to be significantly lower in women with POI compared with age-matched controls (Sahmay *et al.*, 2014; Ma *et al.*, 2022), and another study reported that most women with POI have undetectable or very low levels of AMH (Méduri *et al.*, 2007). In women without POI, AMH has been shown to positively correlate with follicle numbers (Hansen *et al.*, 2011), and, similarly, AMH concentrations were higher in women with a higher number of ovarian follicles than in those with fewer or no ovarian follicles (Méduri *et al.*, 2007). Ovarian biopsies of some women with POI were found to contain 15 or more follicles, reflecting the often fluctuating nature of this condition (Méduri *et al.*, 2007). Furthermore, differences in AMH concentrations, although all low, were reported in a study of different phenotypes of POI; AMH concentrations were lower in women who experienced primary amenorrhoea than in those with secondary amenorrhoea (Kallio *et al.*, 2012).

With regard to the utility of AMH for the diagnosis of POI, several studies have reported detectable AMH in women with POI (Knauff *et al.*, 2009; Li *et al.*, 2011; Kallio *et al.*, 2012; Sun *et al.*, 2018), with estimates suggesting that AMH is detectable in approximately 6% of the POI population (Knauff *et al.*, 2009). In general, AMH was reduced to very low levels, with an albeit relatively high threshold of 8 pmol/l

(1.12 ng/ml) associated with optimal sensitivity of 85% and specificity of 100% in diagnosing POI in a cohort of 124 women with mixed causes of secondary oligomenorrhoea and 26 controls (Li et al., 2011). A subsequent study, using a similar threshold at a mean age of 20 years, demonstrated that a large proportion of women with AMH levels below the threshold had a mother or sister with POI compared with those above the threshold (20.9% versus 7.2%, respectively; $P < 0.01$) (Guzel et al., 2017). Furthermore, a longitudinal cohort study reported that if women had an AMH <8 pmol/l before the age of 36 years, the prevalence of POI after at least 5 years was 17% (Desongnis et al., 2021). The largest study to date (including 410 women with pre-POI [defined as FSH >10 IU/l but ≤25 IU/l], 147 with early POI [defined as FSH >25 IU/l but ≤40 IU/l], 454 women with POI [defined as FSH >40 IU/l], and 987 controls) 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% (Jiao et al., 2021). However, this was a cross-sectional study with enrichment for pre- and early POI.

Discussion

The studies included in this systematic review provide strong evidence that women with low AMH concentrations during the reproductive years have an increased risk of earlier age at menopause. However, robust evidence for the use of serum AMH for the diagnosis of the menopause was lacking, although, in older, late reproductively aged women, the predictive value of AMH for menopause increased with age, as the time to menopause shortened. These principal findings were replicated across different populations, different study designs, including cross-sectional, case–control and prospective longitudinal cohorts, and different AMH assays, indicating generalizability.

The clinical diagnosis of menopause in women is principally based on a period of amenorrhoea of 12 months and hence is made in retrospect (NICE, 2019). Furthermore, the diagnosis for amenorrhoeic women (including after hysterectomy or endometrial ablation, in those using a hormonal intrauterine system or systemic hormonal ovarian suppression) can be challenging. Notably, only two studies that evaluated AMH as a diagnostic marker of the menopause were identified (de Vet et al., 2002; Shin et al., 2008). Both were small and neither robustly evaluated the role of AMH as a formal diagnostic criterion. The SWAN study showed that a very low/undetectable AMH concentration in late reproductive-age women to be predictive of imminent menopause, but the accuracy of this was substantially lower in women up to the age of 48 years compared with women over 51 years (Finkelstein et al., 2020). Conversely, the SWAN investigators reported that a low, but detectable, AMH much more accurately predicted that menopause was not imminent (Finkelstein et al., 2020). These findings highlight the difficulties of detecting the small and variable number of actively growing follicles in the ovary in late reproductive years where there is a less robust association between the number of preantral and small antral follicles, which produce AMH (Jeppesen et al., 2013), and the need for only one dominant follicle to emerge and produce sufficient oestrogen to cause menstruation, or ameliorate menopausal symptoms (Broekmans et al., 2009). Further refinement of assay sensitivity may increase the accuracy of AMH to reflect clinically important ovarian activity during late reproductive life. Meanwhile, studies are greatly needed to determine whether combining AMH measurement with symptoms, or other biomarkers, will shorten the time interval to menopause diagnosis.

This systematic review found strong evidence that lower age-specific AMH concentrations are predictive of a younger age at spontaneous menopause (Fig. 3), although the actual estimates of age at menopause were wide (Freeman et al., 2012b; Tehrani et al., 2014). Initial refinements of the use of AMH for the prediction of menopause included interpretation of AMH relative to age, either by inclusion of age in the model (Freeman et al., 2012b; Tehrani et al., 2013), or by the use of age-specific centiles (Broer et al., 2011; Depmann et al., 2016b). These measures add context, particularly given the convergence of AMH trajectories with increasing age and depletion of the ovarian reserve (Wallace and Kelsey, 2010; Almog et al., 2011; Nelson et al., 2011). Several studies also investigated whether an individual's rate of change or decline in AMH, rather than a single value, provided a more accurate picture of the trajectory towards the menopause and reduced within-subject variation by providing an overall summary rather than a single snapshot in time (Freeman et al., 2012b; Gohari et al., 2016). In one cohort, the inclusion of AMH concentrations at 25 and 30 years, when it might be considered most important to have accurate information, underestimated the risk of becoming postmenopausal before age 45 years (de Kat et al., 2019). In contrast, for women aged 35–48 years at recruitment to the POAS, both a low baseline AMH concentration and swift decline rate were associated with a shorter time to menopause (Freeman et al., 2012a). This may reflect differences in methodology, or the age range of participants. Although the time interval between sampling was similar between the two studies (Freeman et al., 2012a; de Kat et al., 2019), the POAS modelled the rate of decline to undetectable values which are known to precede the menopause, and which may have contributed to the better performance of that model (Freeman et al., 2012a). It is therefore possibly the move to undetectable AMH values, or further decline on a background of very low AMH, that gives the maximal prediction and suggests follicular depletion and impending menopause, all of which are associated with increasing age. Further prospective studies are required to assess whether this finding from modelling can be translated into clinical use. In addition to the decline in follicle number, the ageing ovary shows changes in stromal function (e.g., increasing fibrosis) associated with changes in collagen and hyaluronan content (Amargant et al., 2020), with likely consequences for follicle activation and growth. This provides a physical basis for the increased accuracy of identification of near menopause with later age. The development of biomarkers assessing this may markedly improve understanding and analysis of stromal/follicle interactions, with consequences for the interpretation of AMH in this context. Overall, however, it appears that multiple AMH measurements do not increase the accuracy of prediction.

Studies have consistently shown that women who experience POI or early menopause, spontaneously or due to iatrogenic causes, are at increased risk of type 2 diabetes and cardiovascular disease, including ischaemic heart disease, as well as osteoporosis, fragility fractures and premature all-cause mortality (European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI et al., 2016; Muka et al., 2016; Anagnostis et al., 2019a,b; Okoth et al., 2020; Stevenson et al., 2021). Recent data from the Women's Health Initiative Study suggest that menopausal hormone therapy will reduce all-cause mortality in women with early surgical menopause (Manson

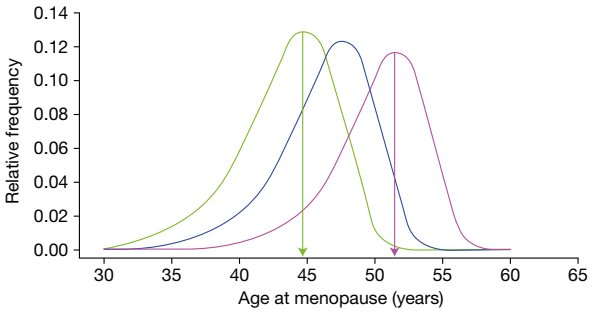


Figure 3. Age-specific AMH values can indicate the predicted age of menopause. Lines reflect indicative distribution of age at menopause for women with age-specific AMH concentrations that are low (green line), mid-range (blue), or in the higher (purple) normal range. From Nelson and Anderson (2021) (modified from Broer *et al.*, 2011). Prediction of premature ovarian insufficiency: foolish fallacy or feasible foresight? SM Nelson and RA Anderson, Climacteric, 2021 Taylor & Francis, reprinted by permission of the publisher (Taylor & Francis Ltd, http://www.tandfonline.com). AMH, anti-Müllerian hormone.

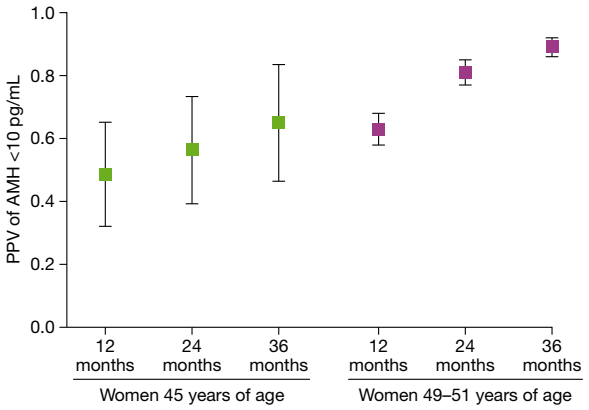


Figure 4. Positive predictive value of AMH <10 pg/ml for final menstrual period occurring within 12, 24, and 36 months for women aged 45 (green squares) and 49–51 (purple squares) years of age. Data are from the Study of Women's Health Across the Nation (SWAN), a multicentre, multiethnic, community-based longitudinal study of the menopause transition (Finkelstein *et al.*, 2020). 95% CIs are represented by vertical bars. AMH, anti-Müllerian hormone; PPV, positive predictive value.

et al., 2019). A meta-analysis of randomized controlled trials of oral menopausal hormone therapy (MHT) initiated within 10 years of the onset of menopause, and data from a Finnish register of women exposed to oral or transdermal MHT for 1–8 years, confirm a reduction in the risk of coronary heart disease and death by around 50% (Tuomikoski *et al.*, 2014; Boardman *et al.*, 2016), in addition to relief of vasomotor symptoms, leading to recent multidisciplinary recommendations to address excess cardiovascular disease risk (Maas *et al.*, 2021). We were unable to identify studies specifically examining relationships between AMH and early menopause, but given the potential ability of very low/undetectable AMH to both predict and diagnose menopause within a short-term time frame, future studies assessing its utility as part of the diagnostic criteria for early menopause would be valuable.

The diagnosis of POI is frequently delayed, with consequences for long-term health (European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI *et al.*, 2016; Panay *et al.*, 2020). We identified a small number of studies that have investigated the value of AMH in the diagnosis of POI, demonstrating a progressive decline in women across the stages of declining ovarian function to POI, although it remained normal in many women until POI was established (Knauff *et al.*, 2009; Li *et al.*, 2011; Desongnis *et al.*, 2021; Jiao *et al.*, 2021). Testing of diagnostic accuracy showed very good discrimination from other causes of oligo/amenorrhoea, notably PCOS, hypogonadotropic hypogonadism and hyperprolactinaemia, where AMH levels are characteristically normal or high (Li *et al.*, 2011; Barbakadze and Kristasashvili, 2014; Bradbury *et al.*, 2017; Bell *et al.*, 2021a). Thus, serum AMH may be useful in young women where there is diagnostic uncertainty of the cause of amenorrhoea, with the caveat that AMH can be normal in some women with incipient POI (Guzel *et al.*, 2017). While indirect evidence indicates AMH may be of value in assessing family members of a proband with POI (Guzel *et al.*, 2017), the Doetinchem Cohort Study (de Kat *et al.*, 2019) showed low discriminatory performance of AMH in menopause prediction in young women. Thus, the general utility of AMH in young women remains to be confirmed (Nelson and Anderson, 2021).

The concurrent use of systemic hormonal contraception impacts AMH levels, which are lower in women using systemic hormonal contraceptives than in women not taking any contraceptive (Kallio *et al.*, 2013; Hariton *et al.*, 2021). As the presence or absence of menstruation in such women is not of value in menopausal assessment, there is potential for the use of AMH in that context. Studies including women using systemic hormonal contraception were excluded from this analysis, but we are not aware of any studies formally addressing the diagnostic or predictive value of AMH in that context.

Although our study has a number of strengths, including restriction to age at spontaneous menopause, exclusion of POI secondary to iatrogenic or gonadotoxic therapies, robust bias ascertainment methodology, and the large number of participants included, we acknowledge several limitations. These include the use of multiple different assays from a variety of manufacturers, reflecting the evolution of AMH measurement across nearly two decades of research. These assays differ in their sensitivities, limits of detection, and limits of quantification and are not interchangeable (Iliodromiti *et al.*, 2017; Bungum *et al.*, 2018; Bell *et al.*, 2021b). This limited direct between-study comparisons of the number of women with undetectable AMH as well as comparisons of prognostic models. The importance of the sensitivity of the assay used is particularly relevant to the investigation of menopause, as exemplified by early studies identifying that AMH became undetectable 3–5 years before FMP (Sowers *et al.*, 2008; Soares *et al.*, 2020), whereas in a recent study using a substantially more sensitive assay, much shorter intervals were reported (Finkelstein *et al.*, 2020) (Fig. 4). The lack of an

international standard for AMH tests continues to hinder comparison between studies (Iliodromiti *et al.*, 2017; Magnusson *et al.*, 2017; American College of Obstetricians and Gynecologists, 2019). However, recent automated assays are beginning to show concordance for gonadotrophin prescribing (La Marca *et al.*, 2021), suggesting that the previously reported differences (Iliodromiti *et al.*, 2017) may now be attenuated and have minimal clinical significance. Some of the studies in our review have analysed small numbers of patients and many were of convenience samples from fertility clinics or otherwise enriched for target populations, potentially leading to outcomes which may not be applicable to the broader population. Despite this heterogeneity, the association between low AMH values with an increased risk of earlier menopause or POI persisted, strengthening our findings. While we were unable to undertake statistical evaluation of the different studies in a meta-analysis due to the study designs, different assays and outcome measures, the systematic review undertaken in accordance with PRISMA guidelines allowed objective analysis and limited the possibility of bias as far as practicable. In conclusion, while measurement of serum AMH shows promise as part of an endocrine panel to investigate women with oligo/amenorrhoea or perimenopausal symptoms, the use of AMH in individuals to predict their age at spontaneous menopause remains imprecise and cannot presently be recommended.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

Data availability

There are no new data associated with this article.

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Authors' roles

All authors developed the strategy for the literature search, reviewed the outputs of the searches, and reviewed and approved the manuscript. S.M.N. and R.A.A. wrote the drafts and guided the development of the article.

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Conflict of interest

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