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REVIEW ARTICLE

Anti-Mullerian hormone – a marker of upcoming menopause or a questionable guesswork?

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Abstract

Anti-Müllerian hormone (AMH) is a protein produced by pre-antral and small antral ovarian follicles. It is an acknowledged marker of ovarian reserve and remaining reproductive capacity, commonly used in reproductive medicine. From the third decade of life, AMH serum levels decrease consecutively up to menopause. Since the standardization of commercial assays, novel contributions of that parameter are being observed. Up to date, there is no screening tool for predicting the age of natural menopause (ANM). The following literature review evaluates the utility of AMH measurement in predicting ANM. Eleven studies met the inclusion criteria (original study with at least 9 years follow-up, 150 or more participants and the usage of ELISA assay for measuring AMH).

The main finding from all of those studies is that there is an undeniable correlation between lower AMH and time to menopause (TTM). Single measurement of AMH is characterized by up to 0.86 predictive capacity, 86% to 92% accuracy which may be enhanced with additional parameters. AMH level below critical threshold strongly correlates with TTM and may become undetectable few years before menopause. The highest effectiveness was proved in short-term (up to 3 years) prediction. AMH seems to be a better predictor of TTM than FSH or inhibin B. Additionally, patterns in AMH changes are individual and the evaluation of those dynamics may lead to a higher accuracy in predicting ANM.

AMH has a significant potential to become a useful tool in clinical practice as a predictor of TTM and ANM, especially with regard to family planning. More studies are required before proposed models may be implemented.

INTRODUCTION

Anti-Müllerian hormone (AMH) is a signaling dimeric protein classified in the great superfamily of transforming growth factors (TGF-β), members of which are involved in tissue differentiation and immunological system response in mammals (Johnson & Newfeld 2002; Johnston *et al.* 2016). The protein, primarily thought to be produced by Sertolli's cells, is considered to be an intracellular communicator, previously described in 1947 as a factor responsible for Müllerian duct regression during male sex differentiation (Jost 1947). Further studies proved that AMH is also produced in the ovaries by granulosa cells of pre-antral and antral follicles (2–8mm in diameter) and its concentra-

tion corresponds to the number of follicles developing at the same time (Kevenaar *et al.* 2006). The knowledge of molecular functions of anti-Müllerian hormone is constantly being broadened and the attention of investigators focuses on its role in the ovarian physiology. AMH seems to play a crucial role in folliculogenesis, coordination of the estrogen production by growing follicles and the regulation of female fertility (Dewailly *et al.* 2014). Main conclusions suggest that this protein is involved in the interactions between growing ovarian follicles: inhibiting the development of too many in the same cycle and preventing from rapid exhaustion of the pool of the reproductive potential (Durlinger *et al.* 1999).

AMH and ovarian reserve

Other authors suggest that there is a strong correlation between ovarian reserve, defined as the remaining reproductive capacity of a woman and AMH serum concentrations (Gleicher *et al.* 2011). Obviously, after postnatal period, germ cells cannot proliferate and the depletion of follicles remaining in the ovaries can be observed over the lifetime. The gonadal ability to recruit new follicles decreases slowly from the age of 25, which implicates gradual reduction of granulosa cells producing estradiol and AMH. It is worth emphasizing that AMH levels are stable within a single and in subsequent cycles (Tsepelidis *et al.* 2007). In the huge study on 6763 Chinese women from birth to menopause the authors evaluated how the AMH concentrations changed in consecutive time intervals. From birth to the third decade of life AMH levels increased, and then decreased consequently, indicating changes of ovarian maintenance (Cui *et al.* 2016). The hypothesis that AMH serum concentration could be a quantitative equivalent of ovarian aging was confirmed in many clinical trials (Hansen *et al.* 2011). For this reason AMH is a well-established predictor used in reproductive medicine.

According to the current opinion of American College of Obstetricians and Gynecologists, the measurement of AMH serum concentration is one of the most appropriate tools to evaluate ovarian reserve (Committee on Gynecologic Practice 2015). The concentration correlates with the effectiveness of infertility treatment and may be useful for individualizing therapy or detecting patients at risk of ovarian hyperstimulation syndrome (OHSS) (Broer *et al.* 2011; Szafarowska *et al.* 2014).

Nevertheless, AMH concentrations should be interpreted carefully, especially if measured under interfering conditions. Oral contraceptives, for example, significantly reduce the ovarian reserve parameters defined by AMH (20% decrease), while they come back to adequate levels after 3–6 months of discontinuation (Birch Petersen *et al.* 2015). That particular parameter may be doubled in patients with polycystic ovaries syndrome (PCOS) (Pellatt *et al.* 2010). The relationship between smoking or inflammatory diseases and AMH levels has also been reported (Henes *et al.* 2015; Plante *et al.* 2010). However, there is no correlation between AMH and body mass index, fasting blood glucose, fasting insulin or lipid profile at any phase (Cui *et al.* 2016).

It is worth mentioning that the most appropriate method to measure serum AMH levels, recommended by scientific committees, is the second generation enzyme-linked immunosorbent assay (ELISA), which has been widely available in practice since 2010 (Wallace *et al.* 2011).

AMH and menopause

The term menopause in common clinical practice refers to the last menstrual bleeding in women's life. According to the World Health Organization, the scientific definition classifies the menopause as the absence of spontaneous menstrual bleeding for over 12 months, while other pathological or physiological causes can be excluded ("Research on the menopause in the 1990s. Report of a WHO Scientific Group," 1996).

The anticipation of climacterium has multiple implications for women's health and reproductive potential (Radowicka *et al.* 2015). The time of menopause varies greatly in individual cases and spreads physiologically from 40 to 60 years of age (Skałba 2014). Among Polish women the average age at natural menopause was estimated to be 51.25 years (Kaczmarek 2007). Various studies were performed to prove the influence of genetic factors on the age of the menopause. The mother-daughter or twin-twin comparisons set the genetic factor as probable in playing the major role in determining the variation of menopausal age. However, due to the variety of genes and molecules involved in that process, it is difficult to draw a clear conclusion which are the most important (Voorhuis *et al.* 2010).

Various procedures, such as iatrogenic oophorectomy, aggressive chemotherapy and radiotherapy during cancer therapy, poor life conditions or other idiopathic factors may additionally shorten the reproductive period, approximating the time to menopause (Stangel-Wojcikiewicz *et al.* 2012; Thomas-Teinturier *et al.* 2013; Yasui *et al.* 2012). The relationship between menopause and morbidity seems to be bilateral. The evidence for higher and earlier prevalence of civilization diseases in patients with an early menopause is unquestionable – greater risk of type 2 diabetes, increased risk of developing heart failure or all types of strokes and increased risk of osteoporosis in the elderly (Rahman *et al.* 2015; Rocca *et al.* 2012; Svejme *et al.* 2012).

Up to date there is no screening tool for predicting the age of menopause in the individual patient in common clinical practice. It can only be speculated basing on the mother's or sister's age at that same time. In the era of successive exploration of AMH biological significance and standardization of commercial assays, intensive efforts in evaluating the role of AMH in novel contributions are being observed. These trends are additionally enhanced by dynamically developing field

of reproductive medicine, where serum AMH concentration has already become a routine in daily practice.

AIM OF THE STUDY

Is it possible that in the near future a single measurement of AMH could provide various information at the same time?

The following systematic review is an attempt to briefly summarize and evaluate the most recent literature data referring to the new contributions for the AMH measurement. The increasing number of clinical trials provides the evidence of essential correlation between AMH serum levels and the time remaining to the natural menopause. Some of these studies aim at following different prospective or retrospective mathematical models with more or less predictive value.

MATERIALS AND METHODS

The authors searched Pubmed database with the different combinations of the key words: 'menopause', 'AMH', 'POF' and 'ovarian reserve'. The established inclusion criteria for the following review were: an original study with the mean of 9 years or longer follow-up period, the study group of at least 150 participants and the use of ELISA assay for measuring AMH levels. Only eleven trials met the inclusion criteria. Strengths and limitations of the above are pointed out in Table 1.

LITERATURE REVIEW

Dolleman *et al.* stated that a single serum AMH concentration had a higher predictive value in estimating age of natural menopause (ANM) in comparison with mother's ANM (86% vs. 63%) (Dolleman *et al.* 2014). Basing on 150 women's data the authors designed a formula using both previously mentioned parameters and patient's actual age (at the time of AMH measurement) – it resulted in 92% accuracy in predicting women's ANM. In view of those findings AMH serum level seems to increase the accuracy of clinical judgement by up to 47% in comparison with only patient's anamnesis. However, the limitation of the study cannot be neglected: the sample size was relatively small, AMH was measured with two different assays and the authors had some problems with gaining information about mothers' menopausal age (one of the inclusion criteria). Therefore, the authors concluded that calculating several parameters together gave the highest effectiveness in predicting ANM (Dolleman *et al.* 2014).

Tehrani *et al.* published the outcomes of the cohort study referring to the model of ANM calculation with the use of serum AMH concentration. Primarily the authors included 1015 patients and the follow-up period reached the average of 10 years. However, only 277 women reached the actual menopause within that time (Tehrani *et al.* 2013). Tehrani *et al.* measured serum AMH concentrations after each 3-year interval, from the beginning of the study to menopause. They created some models of correlation between AMH concentrations and particular age and further utilized them in their calculator reaching the accuracy of 92% for predicting ANM. Nevertheless, three years later the same group of authors introduced amendments to their own model for predicting age at menopause on the same study group. They obtained even higher efficacy basing on age-specific AMH percentiles. The average difference between the actual and predicted age at menopause was estimated to be only 1.9 years. Despite the fact that the obtained results are very promising, it is unknown whether they could be extrapolated to the European population. In addition, the usefulness of this method was not evaluated in patients with irregular cycles or with the history of ovarian surgery (exclusion criteria for the study) (Ramezani Tehrani *et al.* 2016).

Nair *et al.* published one of the best designed studies referring to the association between AMH and the age at natural menopause. They included 716 premenopausal women at a median age of 42 (39–45 years). The population was diverse with regard to age, race and education. Contrary to the previous studies, women with both regular and irregular menstrual cycles were taken into account. Their project was a part of another larger study called CARDIA Women's Study and the participants were recruited from the general population. Additional sociodemographic factors, obtained from the questionnaire were analyzed as well. AMH concentrations were measured every 3 years. 207 women (29%) reported natural menopause within 9 years of follow-up. AMH concentration of 0.5ng/dL was associated with higher risk of menopause. Hazard ratios for menopause were calculated to be 8.1 (2.5–26.1) within 0–3 years from AMH measurement, 2.3 (1.7–3.3) and 1.6 (1.3–2.1) for 3–6 and 6–9 years, respectively. The above association was independent on regular/irregular cycles. According to the presented results, AMH appears most useful in identifying women at risk of menopause in the near future (Nair *et al.* 2015).

La Marca *et al.* designed a study on 375 highly selected eumenorrheic Italian women aged 19–44 years, who served as a control group for the distribution of AMH values. The authors excluded patients with menstrual disorders, pregnancy, hormones or drugs usage (which could interfere with menstrual cycle), any history of hysterectomy, miomectomy, oopherectomy, or other surgery on the ovaries and women with chronic diseases. They created AMH-percentile charts and their logarithmic models significantly correlating with the age at menopause. The distribution of ages at menopause was obtained from another study group – 2635 women aged 41–61 (all menopausal). The authors suggested that the use of additional variables (BMI and smoking status) could improve the AMH-based prediction of age at menopause. AMH serum concentra-

Tab. 1. Strengths and limitations of the papers included in the study.

Author	Follow-up	AMH assay	Nationality	Sample size	Accuracy in predicting ANM	Calculation/ hazard analysis	Exclusion criteria	Limitations of the study
Dólleman M et al. 2014	12 years	DSL assay (Diagnostic Systems Laboratories) and Immunotech Coulte	Dutch	150	63% using only mother's ANM vs. 86% for only AMH measurement vs. **92%** when both previous parameters were evaluated together **47%** improvement in predictive accuracy by adding AMH, patient's age and mother's ANM	Cox proportional hazards analysis estimated uni- and multivariate regression coefficients for female age at study entry, mother's ANM and AMH	contraceptive medication for at least 3 months, history of infertility, ovarian surgery	small number of sample size, samples recruited from the cohorts in three other studies, different assays used for AMH concentration
Tehrani FR et al. 2013	10 years	Gen II kit (Beckman Coulter, Inc,) and the Sunrise ELISA reader (Tecan Co.)	Iranian	1015	92%	coefficients derived from accelerated failure time modeling involving current age and serum AMH	irregular menstrual cycles, unproved natural fertility (at least 1 term pregnancy within 1 year from discontinuation of contraception, endocrine disorders, hysterectomy, oophorectomy, or other kind of ovarian surgery	samples from the another study- Tehran lipid and glucose study, at the end of the study, only 277 patients from the study group reached menopause, different assays used for AMH concentration
Tehrani R et al. 2016	10 years	As above	Iranian	1015	mean difference between correct and predicted age at menopause was **1.9 years**	Flexible parametric survival models built on age-specific AMH percentiles	As above	retrospective study, the same population as in the previous one, at the end of the study, only 277 patients from the study group reached menopause
Nair S. et al. 2015	9 years	Ultra-Sensitive AMH ELISA	American differentiated according to age, race and education	716	AMH under 0.5 ng/dL was associated with 8.1-fold increase in risk of menopause within next 3 years	discrete-time hazard regression	natural menopause, History of hysterectomy	short-term follow-up, qualitative rather than quantitative association between AMH and upcoming menopause
Author	Follow-up	AMH assay	Nationality	Sample size	Accuracy in predicting ANM	Calculation/ hazard analysis	Exclusion criteria	Limitations of the study
La Marca A et al. 2013	Retrospective study	Gen II kit Beckman Coulter, Inc. (Chaska, MN, USA) AMH ELISA kit	Italian	375	AMH serum concentrations below estimated critical thresholds (differentiated by BMI and smoking status), had significant correlation with ANM ($p < 0.001$)	two-stage modelling and estimation process using AMH measurements and menopausal age residual variation from the regression model of AMH and age	menstrual disorders, pregnancy, hormones or drugs usage which could interfere with menstrual cycle, history of hysterectomy, miomectomy, oopherectomy, or any other ovarian surgery, chronic diseases	selected study group, retrospective study
Dólleman M et al. 2013	Retrospective study	DSL assay (ELISA provided by Diagnostic Systems Laboratories, Webster, Texas)	American, British	27 563	- age-related AMH concentration highly correlates with population distribution of ANM - AMH becomes undetectable (concentration <0.2 ng/mL) approximately five years before menopause onset	model of age-related AMH change was constructed using a robust regression analysis	fertile women, regular menstrual cycle pattern between 30 and 40 years of age Only subfertile women, recognized with questionnaire, were included in this study.	only one AMH measurement, AMH and ANM data derived from different sources, distribution of ANM was estimated from another cohort of women (Prospect-European Prospective Investigation into Cancer and Nutrition)
Freeman EW et al. 2012	14 years	Gen II kit (AMH ELISA kits- Beckman Coulter Inc.)	American (equal numbers of African-American and white women)	401	among women with AMH level under 0.2 ng/ml, mean TTM equaled 5.99 years in 45-48 yr age group, and 9.94 years in younger patients (35-39 yr) AMH was better predictor of TTM than FSH or inhibin B	AMH evaluated as a continuous variable and as a group variable, Kaplan-Meier estimations, uni- and multivariable Cox proportional hazards models	current use of psychotropic or hormonal medications, pregnancy or breast feeding, serious health problems known to compromise ovarian failure, alcohol or drug abuse	study group consists of women at late reproductive age (35 to 48 years old), selected study group involving only women in general good health

Author	Follow-up	AMH assay	Nationality	Sample size	Accuracy in predicting ANM	Calculation/ hazard analysis	Exclusion criteria	Limitations of the study
Freeman EW et al. 2012	14 years	Gen II kit (AMH ELISA kits- Beckman Coulter Inc.)	American (equal numbers of African-American and white women)	293 randomly-identified women from population-based cohort	dynamics in AMH changes was an independent, significant predictor of TTM TTM differed in women with similar AMH levels (by approximately 2 years), depending on the dynamics in AMH changes	uni- and multivariable Cox proportional hazards models	As above and additionally: detectable baseline serum level of AMH (≥0.2 ng/ml),	study group consisted of women at late reproductive age (35 to 48 years old) in general good health the possibility of misclassification of dynamics in AMH changes, due to unequal time intervals between following measurements and in particular participants.
Author	Follow-up	AMH assay	Nationality	Sample size	Accuracy in predicting ANM	Calculation/ hazard analysis	Exclusion criteria	Limitations of the study
Broer SL et al. 2011	11 years	Cohort 1. DSL assay Cohort 2. and 3. ultrasensitive immuno-enzymometric assay	Dutch	257	baseline AMH level significantly correlated with the time to menopause, with predictive capacity of 0.86	Cox regression for evaluating predictive capacity of age and ovarian reserve tests in predicting time to menopause the relationship between AMH and ANM was assessed using specially constructed normograms	Cohort 1. age <25 or .>46 years, irregular menstrual cycles, unproven natural fertility, ovarian surgery or any ovarian abnormalities, Cohort 2. age <18 or >46 years, irregular menstrual cycles, history of infertility, lack of at least one ovary, Cohort 3. age <20 or .>35 years, BMI <19 or >26 kg/m^2, irregular menstrual cycles, endocrine disorders	participants recruited from three separate studies with heterogeneous inclusion and exclusion criteria, following outcomes concerns finally very small sample size (from the output cohort of 257 patients, the onset of menopause occurred in only 48 (19%) of them) single measurement of baseline AMH, different assays used for AMH concentration
Depmann M et al. 2016	extended follow-up of previous study, up to 14 years	Cohort 1. DSL assay Cohort 2. and 3. ultrasensitive immune-enzymo-metric assay	Netherlanders	155	age-specific AMH level is an independent predictor of time remaining to menopause (predictive capacity of 0.86) predictive effect decline with increasing age	Cox regression analysis of age and ovarian reserve tests to calculate TTM, Weibull survival model predicting ANM	As above	heterogeneous inclusion and exclusion criteria, heterogeneous population (study group consists of samples from three researches, carried out in different time intervals), single measurement of AMH, different assays used for AMH concentration
De Kat AC et al. 2016	20 years	picoAMH ELISA assay (AnchLabs)	Netherlanders	3326	AMH decreased slowly until the age of 40 , then the rate of decline accelerated patterns in AMH changes are individual single measurement of AMH characterize insufficient accuracy in order to predict TTM	AMH trajectories in relation to age and time to menopause were fitted with a mixed model approach using the 'lme4' package in R'	Randomly recruited female participants from a cohort study, who had at least one stored serum sample.	long-term storage of blood samples which were additionally thawed and refrozen prior to the study

ANM- age at natural menopause; TTM- time to menopause

tions below estimated critical thresholds, differentiated according to BMI and smoking status, significantly correlated with ANM (p-value <0.001). Generally, menopausal age would be lower in women with low BMI and in current / past smokers (La Marca *et al.* 2013).

Contrary to the previous investigations, Dolleman *et al.* included all women attending fertility clinics to measure AMH concentrations and correlate them with the age at menopause. Basing on 27563 participants, the authors constructed a model of age-related AMH change using a robust regression analysis. They observed that AMH becomes undetectable (concentration <0.2 ng/mL) approximately five years before menopause and concluded that its concentration seems to be an excellent marker for predicting ANM. The main strength of the study was a large sample size. Nevertheless, there are also limitations: ANM data were collected from another study group (participants in Prospect-European Prospective Investigation into Cancer and Nutrition; n=2249) and based on self-reporting questionnaires. Additionally, AMH assays used in the study are nowadays replaced with the new ones – second generation AMH assays. They may differ, therefore it is hard to extrapolate created normograms into current clinical practice (Dolleman *et al.* 2013).

Freeman *et al.* published a study with the longest follow-up period of 14 years. The authors tried to assess the correlation between AMH serum concentration and time remaining to menopause. Numerous inclusion and exclusion criteria (described in Table 1) allowed the investigators to create a homogenous study group. They included only women at late reproductive age – 35 years or older. AMH serum levels were measured at each visit every 9 months for 5 years and then once a year. Such frequent appointments allowed for the precise insight into AMH changes during comparatively long period preceding menopause. The authors proved that AMH is a much better predictor than the other hormones (FSH, inhibin B). The age of women was also a significant and independent contributor to AMH predictions. AMH threshold level of 0.2ng/ml correlated significantly with ANM – it predicted 9.94 years to menopause in patients aged 35–39 years and 5.99 years in 45–48 years group. The authors suggested that considering patient's age in addition to AMH concentration could improve the predictive value. The evaluation of other parameters and their influence on ANM showed that smoking significantly decreased the age at menopause (p=0.002), while patient's BMI had no significant impact (Freeman *et al.* 2012).

The same group of authors tried to improve the precision of predicting time remaining to menopause (TTM) by using the rate of AMH changes during the last few fertile years. The research was carried out on patients selected from the previously described cohort (293 participants). TTM differed by approximately 2 years in women with similar baseline AMH levels, depending on the dynamics in AMH changes. Introducing the AMH rate of change let the authors increase the efficacy of menopausal age prediction. The study also introduced a novel finding – the dynamics in AMH serum concentration changes seemed to be an independent, significant predictor of TTM (p<0.0001) (Freeman *et al.* 2012).

Broer *et al.* evaluated the utility of different ovarian reserve tests (AMH level, antral follicle count (AFC) and FSH) in predicting ANM. A selected cohort of 257 women aged 21–46 years, was followed-up for 11 years. Only 48 (19%) of them reported menopause after the above mentioned period, which makes the study sample quite small. The additional limitation of the study was a single measurement of baseline ovarian reserve tests (AMH, AFC and FSH) only at the beginning of the investigation. The participants were recruited from three different studies in which the inclusion and exclusion criteria differed from each other and different AMH assays were used.

According to their results, baseline AMH serum levels significantly correlated with TTM.

Age, AMH, and antral follicle count were significantly related to time to menopause (p<0.001) and showed a good percentage of correct predictions. However, after adjusting for age, only AMH added to this prediction. According to the obtained results, AMH may become a useful tool in predicting ANM. Nevertheless, the results must be assessed in the view of several shortcomings occurring in that study (Broer *et al.* 2011).

The results of the extended follow-up period from the previous study were recently published by Depmann *et al.* During additional three years, 33 women experienced menopause (in total 81 patients during 14-years observation) and 31 suffered from menopausal transition. Weibull survival model was performed to predict the end of the fertile period. As it was concluded before, age-specific AMH level seems to be an independent indicator of time remaining to menopause (with predictive capacity of 0.86). The investigators also suggested that different AMH assays used in the study do not interfere with the correctness of those predictions. However, high accuracy of such proceeding is still lacking and more studies are required before AMH will be implemented in that purpose into common clinical practice. The precision of those assessments additionally decline with increasing patient's age (Depmann *et al.* 2016).

The utility of AMH measurement in predicting time remaining to menopause was considered by De Kat *et al.* Population-based cohort study over randomly recruited 3326 Dutchwomen was aimed to evaluate changes in that parameter during 20 years observation period. Blood samples were collected every five years and then stored in –80 °C up to March 2015. The authors observed that AMH decreased slowly until the age of 40 and then the rate of decline accelerated significantly. Similar dependency was observed also 10 years before menopause. Pattern of AMH decline is individual in

each case and does not fit all. The general conclusion is that those trajectories depend on initial age-specific AMH concentration. According to the investigators, predicting remaining fertile lifespan using only single AMH measurement, characterize prominent discrepancies. Although AMH individual curves overlap with time to menopause more than chronological age, the authors suggest that multiple AMH evaluations require further investigation (de Kat *et al.* 2016). Those results should be carefully interpreted in the view of a few factors which may interfere with correctness of those measurements. The influence of long-term blood storage on AMH concentration in the samples remains unknown. Additionally, prior thawing and refreezing episodes, may result in different AMH levels in comparison with fresh serum (Li *et al.* 2016).

CONCLUSIONS

The above described researches were designed to answer one common question – could AMH serum levels become a useful factor in predicting age at natural menopause? Although each of the investigating groups used different models and evaluated different additional parameters, the general findings seem to be comparable. There is an undeniable correlation between lower AMH and upcoming menopause. Several proposals of different, specially designed formulas and percentile charts based on population's distribution of AMH concentrations at various points of reproductive age are described in the literature. Some of them also tried to evaluate different confounding factors which could interfere with the relevance of forecasting ANM. It seems that irregular cycles, only one ovary or fertility disorders do not interfere with the accuracy of prediction, while BMI and smoking status should be taken into account.

Two new fully automated anti-Müllerian hormone immunoassays have been available since 2014. Their effectiveness in clinical practice is comparable (correlation coefficient of 0.99). Both are based on ELISA method, but in contrast to the previous assays the results are obtained much faster, which is very important in clinical practice. These tests are also more efficient in discrimination between subfertile women and upcoming menopause (van Helden & Weiskirchen 2015).

The described correlation between AMH and ANM was characterized by the highest effectiveness in short-term prediction, up to 3 years (Nair *et al.* 2015). However, some authors suggest that created models could help women to plan more conscious motherhood in the future. At the moment 14 years was the longest follow-up period. The participants were usually in their fourth decade of life, when the baseline fertility was already decreased. The prediction charts could be useful especially for women with premature ovarian insufficiency (POI) – forecasting the age at menopause only few years before, or even the probability of such a diagnosis in the future, might help them in family planning. Although the qualitative correlations between AMH and the age at natural menopause are undeniable, the quantitative evaluations of AMH levels seem to be a remarkable aim for further studies, especially in more diversified populations. AMH has significant potential to become a useful tool in clinical practice for a brand new purpose.

REFERENCES

1 Birch Petersen K, Hvidman HW, Forman JL, Pinborg A, Larsen EC, Macklon KT, Sylvest R, Andersen AN (2015). Ovarian reserve assessment in users of oral contraception seeking fertility advice on their reproductive lifespan. Hum Reprod. **30**(10): 2364–2375.
2 Broer SL, Dólleman M, Opmeer BC, Fauser BC, Mol BW, Broekmans FJ (2011). AMH and AFC as predictors of excessive response in controlled ovarian hyperstimulation: a meta-analysis. Hum Reprod Update. **17**(1): 46–54.
3 Broer SL, Eijkemans MJ, Scheffer GJ, van Rooij IA, de Vet A, Themmen AP, Laven JS, de Jong FH, Te Velde ER, Fauser BC, Broekmans FJ (2011). Anti-mullerian hormone predicts menopause: a long-term follow-up study in normoovulatory women. J Clin Endocrinol Metab. **96**(8): 2532–2539.
4 Committee on Gynecologic Practice (2015). Committee opinion no. 618: Ovarian reserve testing. Obstet Gynecol. **125**(1): 268–273.
5 Cui L, Qin Y, Gao X, Lu J, Geng L, Ding L, Qu Z, Zhang X, Chen ZJ (2016). Antimullerian hormone: correlation with age and androgenic and metabolic factors in women from birth to postmenopause. Fertil Steril. **105**(2): 481–485, e481.
6 de Kat AC, van der Schouw YT, Eijkemans MJ, Herber-Gast GC, Visser JA, Verschuren WM, Broekmans FJ (2016). Back to the basics of ovarian aging: a population-based study on longitudinal anti-Mullerian hormone decline. BMC Med. **14**(1): 151.
7 Depmann M, Eijkemans MJ, Broer SL, Scheffer GJ, van Rooij IA, Laven JS, Broekmans FJ (2016). Does anti-Mullerian hormone predict menopause in the general population? Results of a prospective ongoing cohort study. Hum Reprod. **31**(7): 1579–1587.
8 Dewailly D, Andersen CY, Balen A, Broekmans F, Dilaver N, Fanchin R, Griesinger G, Kelsey TW, La Marca A, Lambalk C, Mason H, Nelson SM, Visser JA, Wallace WH, Anderson RA (2014). The physiology and clinical utility of anti-Mullerian hormone in women. Hum Reprod Update. **20**(3): 370–385.
9 Dólleman M, Depmann M, Eijkemans MJ, Heimensem J, Broer SL, van der Stroom EM, Laven JS, Van Rooij IA, Scheffer GJ, Peeters PH, van der Schouw YT, Lambalk CB, Broekmans FJ (2014). Anti-Mullerian hormone is a more accurate predictor of individual time to menopause than mother's age at menopause. Hum Reprod. **29**(3): 584–591.
10 Dólleman M, Faddy MJ, van Disseldorp J, van der Schouw YT, Messow CM, Leader B, Peeters PH, McConnachie A, Nelson SM, Broekmans FJ (2013). The relationship between anti-Mullerian hormone in women receiving fertility assessments and age at menopause in subfertile women: evidence from large population studies. J Clin Endocrinol Metab. **98**(5): 1946–1953.
11 Durlinger AL, Kramer P, Karels B, de Jong FH, Uilenbroek JT, Grootegoed JA, Themmen AP (1999). Control of primordial follicle recruitment by anti-Mullerian hormone in the mouse ovary. Endocrinology. **140**(12): 5789–5796.
12 Freeman EW, Sammel MD, Lin H, Boorman DW, Gracia CR (2012). Contribution of the rate of change of antimullerian hormone in estimating time to menopause for late reproductive-age women. Fertil Steril. **98**(5): 1254–1259, e1251–1252.
13 Freeman EW, Sammel MD, Lin H, Gracia CR (2012). Anti-mullerian hormone as a predictor of time to menopause in late reproductive age women. J Clin Endocrinol Metab. **97**(5): 1673–1680.
14 Gleicher N, Weghofer A, Barad DH (2011). Defining ovarian reserve to better understand ovarian aging. Reprod Biol Endocrinol. **9**: 23.

15 Hansen KR, Hodnett GM, Knowlton N, Craig LB (2011). Correlation of ovarian reserve tests with histologically determined primordial follicle number. Fertil Steril. **95**(1): 170–175.
16 Henes M, Froeschlin J, Taran FA, Brucker S, Rall KK, Xenitidis T, Igney-Oertel A, Lawrenz B, Henes JC (2015). Ovarian reserve alterations in premenopausal women with chronic inflammatory rheumatic diseases: impact of rheumatoid arthritis, Behcet's disease and spondyloarthritis on anti-Mullerian hormone levels. Rheumatology (Oxford). **54**(9): 1709–1712.
17 Johnson AN, Newfeld SJ (2002). The TGF-beta family: signaling pathways, developmental roles, and tumor suppressor activities. ScientificWorldJournal. **2**: 892–925.
18 Johnston CJ, Smyth DJ, Dresser DW, Maizels RM (2016). TGF-beta in tolerance, development and regulation of immunity. Cell Immunol. **299**: 14–22.
19 Jost A (1947). The age factor in the castration of male rabbit fetuses. Proc Soc Exp Biol Med. **66**(2): 302.
20 Kaczmarek M (2007). The timing of natural menopause in Poland and associated factors. Maturitas. **57**(2): 139–153.
21 Kevenaar ME, Meerasahib MF, Kramer P, van de Lang-Born BM, de Jong FH, Groome NP, Themmen AP, Visser JA (2006). Serum anti-mullerian hormone levels reflect the size of the primordial follicle pool in mice. Endocrinology. **147**(7): 3228–3234.
22 La Marca A, Sighinolfi G, Papaleo E, Cagnacci A, Volpe A, Faddy MJ (2013). Prediction of age at menopause from assessment of ovarian reserve may be improved by using body mass index and smoking status. PLoS One. **8**(3): e57005.
23 Li HW, Wong BP, Ip WK, Yeung WS, Ho PC, Ng EH (2016). Comparative evaluation of three new commercial immunoassays for anti-Mullerian hormone measurement. Hum Reprod. **31**(12): 2796–2802.
24 Nair S, Slaughter JC, Terry JG, Appiah D, Ebong I, Wang E, Siscovick DS, Sternfeld B, Schreiner PJ, Lewis CE, Kabagambe EK, Wellons MF (2015). Anti-mullerian hormone (AMH) is associated with natural menopause in a population-based sample: The CARDIA Women's Study. Maturitas. **81**(4): 493–498.
25 Pellatt L, Rice S, Mason HD (2010). Anti-Mullerian hormone and polycystic ovary syndrome: a mountain too high? Reproduction. **139**(5): 825–833.
26 Plante BJ, Cooper GS, Baird DD, Steiner AZ (2010). The impact of smoking on antimullerian hormone levels in women aged 38 to 50 years. Menopause. **17**(3): 571–576.
27 Radowicka M, Szparaga R, Pietrzak B, Wielgos M (2015). Quality of life in women after menopause. Neuro Endocrinol Lett. **36**(7): 644–649.
28 Rahman I, Akesson A, Wolk A (2015). Relationship between age at natural menopause and risk of heart failure. Menopause. **22**(1): 12–16.
29 Ramezani Tehrani F, Mansournia MA, Solaymani-Dodaran M, Steyerberg E, Azizi F (2016). Flexible parametric survival models built on age-specific antimullerian hormone percentiles are better predictors of menopause. Menopause. **23**(6): 676–681.
30 Research on the menopause in the 1990s. Report of a WHO Scientific Group. (1996). World Health Organ Tech Rep Ser. **866**: 1–107.
31 Rocca WA, Grossardt BR, Miller VM, Shuster LT, Brown RD, Jr. (2012). Premature menopause or early menopause and risk of ischemic stroke. Menopause. **19**(3): 272–277.
32 Skałba P (2014). Przekwitanie. In P. Skałba (Ed.), Diagnostyka i leczenie zaburzeń endokrynologicznych w ginekologii (1 ed., pp. 283). Kraków: Medycyna Praktyczna.
33 Stangel-Wojcikiewicz K, Zdebik A, Jach R, Huras H, Wadowska-Jaszczynska K, Radon-Pokracka M, Kempisty-Zdebik E, Ludwin A, Ludwin I (2012). Hormone replacement therapy regimens in chemotherapy-induced premature ovarian failure and the subsequent correction of hormone levels. Neuro Endocrinol Lett. **33**(7): 697–702.
34 Svejme O, Ahlborg HG, Nilsson JA, Karlsson MK (2012). Early menopause and risk of osteoporosis, fracture and mortality: a 34-year prospective observational study in 390 women. BJOG. **119**(7): 810–816.
35 Szafarowska M, Molinska-Glura M, Jerzak MM (2014). Anti-Mullerian hormone concentration as a biomarker of pregnancy success or failure. Neuro Endocrinol Lett. **35**(4): 322–326.
36 Tehrani FR, Solaymani-Dodaran M, Tohidi M, Gohari MR, Azizi F (2013). Modeling age at menopause using serum concentration of anti-mullerian hormone. J Clin Endocrinol Metab. **98**(2): 729–735.
37 Thomas-Teinturier C, El Fayech C, Oberlin O, Pacquement H, Haddy N, Labbé M, Veres C, Guibout C, Diallo I, De Vathaire F (2013). Age at menopause and its influencing factors in a cohort of survivors of childhood cancer: earlier but rarely premature. Hum Reprod. **28**(2): 488–495.
38 Tsepelidis S, Devreker F, Demeestere I, Flahaut A, Gervy C, Englert Y (2007). Stable serum levels of anti-Mullerian hormone during the menstrual cycle: a prospective study in normo-ovulatory women. Hum Reprod. **22**(7): 1837–1840.
39 van Helden J, Weiskirchen R (2015). Performance of the two new fully automated anti-Mullerian hormone immunoassays compared with the clinical standard assay. Hum Reprod. **30**(8): 1918–1926.
40 Voorhuis M, Onland-Moret NC, van der Schouw YT, Fauser BC, Broekmans FJ (2010). Human studies on genetics of the age at natural menopause: a systematic review. Hum Reprod Update. **16**(4): 364–377.
41 Wallace AM, Faye SA, Fleming R, Nelson SM (2011). A multicentre evaluation of the new Beckman Coulter anti-Mullerian hormone immunoassay (AMH Gen II). Ann Clin Biochem. **48**(Pt 4): 370–373.
42 Yasui T, Hayashi K, Mizunuma H, Kubota T, Aso T, Matsumura Y, Lee JS, Suzuki S (2012). Factors associated with premature ovarian failure, early menopause and earlier onset of menopause in Japanese women. Maturitas. **72**(3): 249–255.