Anti-Müllerian Hormone Predicts Menopause: A Long-Term Follow-Up Study in Normoovulatory Women


Department of Reproductive Medicine and Gynecology, Division of Woman and Baby (S.L.B., M.J.C.E., G.J.S., I.A.J.R., E.R.T.V., B.C.F., F.J.M.B.), and Julius Center for Health Sciences and Primary Care (M.J.C.E.), Division of Reproductive Medicine, Department of Obstetrics and Gynecology (A.d.V., J.S.E.L.), and Division of Endocrinology, Department of Internal Medicine (A.P.N.T., F.H.d.J.), University Medical Center, 3508 GA Utrecht, The Netherlands

Context: It has been hypothesized that a fixed interval exists between age at natural sterility and age at menopause. Both events show considerable individual variability, with a range of 20 yr. Correct prediction of age at menopause could open avenues of individualized prevention of age-related infertility and other menopause-related conditions, like cardiovascular disease and breast carcinoma.

Objective: The aim of this study was to explore the ability of ovarian reserve tests to predict age at menopause.

Design and Setting: We conducted a long-term follow-up study at an academic hospital.

Participants: A total of 257 normoovulatory women (age, 21–46 yr) were derived from three cohorts with highly comparable selection criteria.

Interventions: Anti-Müllerian hormone (AMH), antral follicle count, and FSH were assessed at time 1 (T1). At time 2 (T2), approximately 11 yr later, cycle status (strictly regular, menopausal transition, or postmenopause) and age at menopause were inventoried.

Main Outcome Measures: Accuracy of the ovarian reserve tests in predicting time to menopause was assessed by Cox regression, and a nomogram was constructed for the relationship between age-specific AMH concentrations at T1 and age at menopause.

Results: A total of 48 (19%) women had reached postmenopause at T2. Age, AMH, and antral follicle count at T1 were significantly related with time to menopause \((P < 0.001)\) and showed a good percentage of correct predictions (C-statistic, 0.87, 0.86, and 0.84, respectively). After adjusting for age, only AMH added to this prediction (C-statistic, 0.90). From the constructed nomogram, it appeared that the normal distribution of age at menopause will shift considerably, depending on the individual age-specific AMH level.

Conclusions: AMH is highly predictive for timing of menopause. Using age and AMH, the age range in which menopause will subsequently occur can be individually calculated. (J Clin Endocrinol Metab 96: 0000–0000, 2011)
Menopause, defined as the final menstrual period, marks the end of the female reproductive life span. This event occurs at a median age of about 51 yr, but age at menopause varies between 40 and 60 yr (1). The definitive loss of natural fertility is experienced at a median age of 41 yr, with a distribution and age variation range highly similar to that for age at menopause (2–4). These reproductive events are dictated by the decline in the number of follicles in the ovaries (the ovarian reserve) with increasing age. When follicle numbers fall below a critical threshold of a few thousand, the menstrual cycle pattern becomes irregular (5). At menopause, fewer than 1000 follicles are left (6–8). For human fertility, optimal conditions are present until an average age of 31 yr, followed by gradual decline until natural sterility (9, 10). It has been postulated that these events follow a time sequence with a more or less fixed interval, with the end of natural fertility occurring some 10 yr before menopause (1).

Because the rate of decline of the ovarian reserve varies considerably between individual women, the development of tests that correctly forecast an individual’s reproductive life span would represent a major step forward (1, 4). It has been shown that the number of antral follicles in the ovaries is proportionally related to the size of the primordial follicle pool from which they were recruited (11). A marker correctly reflecting the number of antral follicles is therefore potentially suitable for the prediction of ovarian senescence. Current candidate markers for such purpose are anti-Müllerian hormone (AMH) (12), the antral follicle count (AFC) as measured by transvaginal ultrasound (13), and early follicular FSH concentration (14).

In case correct individual prediction of menopause would be feasible, several options emerge for the preventive management of age-related female infertility and other female health conditions influenced by timing of menopause (15). Predicted early menopause could emphasize the need for timely prevention of bone demineralization and cardiovascular and neurological disease (16–18), whereas the prediction of late menopause would open options for preventive management of breast and intestinal cancer (19).

In the current long-term follow-up study, we therefore aim to explore the ability of endocrine and ultrasound markers to predict the timing of the occurrence of menopause and age at menopause in a group of normoovulatory female volunteers.

Subjects and Methods

Participants

This study group is comprised of three cohorts of participants. The first cohort of women was derived from an ongoing prospective longitudinal study on ovarian function (20). A total of 172 healthy female volunteers were recruited in 1996 and 1997. Women could be included if they were between 25 and 46 yr of age and had a regular menstrual cycle with a mean length of 21–35 d and the next menstrual period was predictable within a 7-d time frame. All women had proven natural fertility, which was defined as having established at least one pregnancy within 1 yr after discontinuing contraceptives, resulting in a normal delivery at term. If a woman used hormonal contraceptives, this had to be discontinued at least 3 months before the start of the study. Exclusion criteria were ovarian surgery or ovarian abnormalities.

The second cohort consisted of 90 healthy volunteers that were recruited between 1999 and 2001 for a prospective longitudinal study on pregnancy prediction in the normal population. Inclusion criteria were: age between 18–46 yr, two ovaries, no adnexal surgery in the past, and a regular menstrual cycle with a mean length between 21 and 35 d. Couples attempting both first and second pregnancy could participate as long as no previous history of infertility was present. Hormonal contraceptives were discontinued at least 3 months before the measurement of the ovarian reserve tests (ORT).

The third cohort of 40 normoovulatory women were recruited between 1983 and 1992 as normal controls for studies in relation to ovarian dysfunction in polycystic ovary syndrome (21–23), and they were subsequently asked to participate in a prospective longitudinal study on ovarian function in the year 2000 (24). Inclusion criteria were: age 20–35 yr, regular menstrual cycle (mean cycle length, 26–31 d), body mass index of 19–26 kg/m², absence of endocrine disorders or any other relevant disease, no hormonal treatment for at least 3 months before the study, and no prior treatment for infertility.

All three studies had been approved by the institutional review boards of the University Medical Center Utrecht or the Erasmus Medical Center Rotterdam. Written informed consent was obtained from each participant.

Study design

Volunteers visited the clinic for the first time [time 1 (T1)] during the early follicular phase of the menstrual cycle (on cycle d 2, 3, or 4) for assessment of the number of antral follicles (2–10 mm) by transvaginal ultrasonography and to provide blood samples. The ultrasound scans were performed by a limited group of physicians, well trained in transvaginal sonography. The ovary was examined by scanning from the outer to the inner margin. Round or oval echo-free structures in the ovaries were regarded as follicles and were counted and measured as such. The numbers of follicles in both ovaries were added to compute the antral follicle count. Serum and plasma samples were separated and stored at −20 C until assay of AMH and FSH.

In the period 2008–2010 [time 2 (T2)], all women were contacted again and asked to fill out a standardized questionnaire. Participants were questioned on whether they were still menstruating, on the mean cycle length, and the variability of the cycle length. In addition, data on the use of hormones, medication, surgical treatment on the uterus or ovaries, and reproductive history were collected. All completed questionnaires were judged independently by two medical doctors before recording in an electronic database. Both medical doctors were blinded for the results of the ORT. All participants were then placed in one of five subgroups, according to their cycle status or use of sex...
steroid hormones: regular cycle, menopausal transition, menopause, use of exogenous estrogens, or surgical removal of uterus and/or ovaries.

Definitions

Menopause was defined as no menstrual period in the last 12 consecutive months. No uniform definition for the transition to menopause (cycle irregularity) is available, but some definitions based upon increasing variability in cycle patterns have been proposed (25). We defined menopausal transition according to these Stages of Reproductive Aging Workshop criteria, as follows: 1) mean cycle length less than 21 or more than 35 d during the previous half year or longer; or 2) mean cycle length between 21 or 35 d, but the next menstrual period not predictable within a 7-d time frame. A regular cycle was defined as a mean cycle length of 21–35 d with the next menstrual period predictable within a 7-d time frame. Women who were using hormone therapy for medical reasons or as contraceptives or hormonal replacement therapy were excluded. Also, women who underwent surgery leading to removal of the uterus and/or one or both ovaries were excluded from the analysis.

Hormone assays

Blood sampling was performed on the same day as the transvaginal sonography at T1 (1991/2001). Hormone concentrations were measured in plasma (FSH) and serum (AMH). Specimens were stored at −20°C until processing. Concentrations of FSH were measured with the use of the MEIA technology on a fully automated AxSYM immunoanalyzer (Abbott Laboratories, Abbott Park, IL) according to the manufacturer’s instructions. The World Health Organization Second International Reference Preparation for human FSH (78/549) was used as a standard in the FSH assay. For FSH, interassay coefficients of variation were found to be 5.7, 5.7, and 7.8% at the levels of 5, 26, and 79 IU/liter, respectively (n = 80). The detection limit for the FSH assay was 0.03 IU/liter.

In the first cohort, the AMH levels were measured using an enzyme-immunometric assay [Diagnostic Systems Laboratories (DSL), Inc., Webster, TX]. Interassay and intraassay coefficients of variation were less than 5% at the level of 3.0 ng/ml and less than 11% at the level of 13.0 ng/ml. The detection limit of the assay was 0.026 ng/ml. Repeated freezing and thawing of the samples or storage at 37°C for 1 h did not affect the results of the assay (26). In the second and third cohorts, AMH levels were measured with an ultrasensitive immunoenzymometric assay (Immunotech-Coulter, Marseille, France) (27). The limit of detection (defined as blank + 3 SD of blank) was 0.05 ng/ml. Intra- and interassay coefficients of variation were less than 5% and less than 8%, respectively.

For the comparison and pooling of the AMH levels, a correction coefficient was applied. The AMH levels measured with the Beckman Coulter assay had to be corrected with a factor of 0.5 to be translated into the AMH levels measured using the DSL assay, as we described in an earlier study (28).

Statistical analysis

Based on the average age at follow-up and the expected number to be excluded because of the use of hormones or surgical removal of uterus and/or ovaries, a number of 50 women in menopause was anticipated. This number would be sufficient to allow for reliable analysis of five predictive variables for the association with age at menopause, according to the 10 events per variable rule of thumb (29).

First, baseline characteristics of the women in the three cohorts were compared using the Kruskal-Wallis test or the χ² tests. Moreover, the baseline characteristics and ORT were compared for women divided into subgroups according to their cycle status at T2.

Then, univariate and multivariate Cox regressions for time to menopause, with follow-up time from T1 to menopause or T2 as time axis and the occurrence of menopause as event, were performed to assess the predictive capacity of age and ORT. For the multivariate analysis, a forward selection with a P value of less than 0.05 for entry was applied. The effects of the variables were expressed as hazard ratios per 1 SD change to allow for a better comparability between the effect sizes of the different tested variables. The C-statistic was calculated to inform on the ability to correctly predict the time to menopause.

For ORT that significantly added to female age in the prediction of timing of menopause, a prediction model was built. We used a Weibull survival model having age of the women on the time axis, with delayed entry at the age at T1, and percentiles of the ORT as a single covariate. Participants were divided into percentiles for their age-specific ORT level by fitting a flexible spline function to the scatter plot of the ORT with age at T1 and assuming a normal distribution of residuals around this fitted curve. Therefore, before this analysis, ORT values were log-(AMH) or square root- (AFC) transformed. For each percentile, the curve of the predicted distribution of age at menopause was plotted. Per age category, ORT levels corresponding with the different percentiles will be shown, as well as the corresponding median, p5, p25, p75, and p95 of the predicted age at menopause distribution. Data were analyzed with SPSS 15.0 (SPSS Inc., Chicago, IL) and R version 2.9.0. (http://www.r-project.org/).

Results

The three cohorts together comprised 302 women. The questionnaire could not be sent to 21 women because they had died during the follow-up period or moved abroad or because correct contact address information could not be obtained. The questionnaire was thus sent to 281 women. Of these women, 24 were either not willing to participate or did not respond to the questionnaire, despite repeated mailing and efforts to make telephone contact. In total, 257 women could be included, for a follow-up rate of 91.5%. The baseline characteristics of these women are shown in Table 1. It becomes clear that the women in the three cohorts differ in age distribution, whereas other possible confounders for age at menopause, such as smoking, were not different. Strong confounders such as ovarian abnormalities or surgery have been controlled for by the selection criteria.

From the questionnaires, it appeared that 57 women (22%) were using hormonal therapy and that 15 (6%) women had undergone surgical removal of the uterus or at least one ovary. These 72 women were excluded from the
The remaining 185 women were subdivided into groups of women who still had a strictly regular cycle \([n = 95\ (37\%)]\), women in the menopausal transition \([n = 42\ (16\%)]\), and women in the postmenopause \([n = 48\ (19\%)]\). The proportion of postmenopausal women at T2 was 19\%, with a mean age at T2 for the study population of 46.5 yr. This is in line with estimates from existing studies on age at menopause distributions, where the proportion of women that had reached menopause at the age of 46 yr was 16\% (30). The mean interval between T1 and T2 was 11.2 yr and did not differ significantly across the different subgroups \((P = 0.051)\). The women that were excluded from the analysis were comparable to the women that were included in the analysis, except that the women using hormones were somewhat younger. Twelve participants with missing data were discarded from the analysis. Missing data occurred in AFC, AMH, and FSH in eight, eight, and five participants, respectively.

Patient characteristics and ORT at T1 were compared between the subgroups based on the cycle status at T2. A significant difference in age upon initial screening was found between the women with a regular cycle, in menopausal transition, or in postmenopause at T2 \((P < 0.001)\). AMH levels and the AFC were significantly lower with increasing loss of cyclicity, whereas basal FSH concentrations were higher \((P\ value for all ORT, <0.001)\). There were no differences in body mass index and percentage of smokers.

The results of the Cox regression of the predictive power of age and the ORT for time until the occurrence of menopause are depicted in Table 2. In the univariate analysis, it is clear that age, AMH, AFC, and basal FSH are all significantly correlated with the time to menopause. Moreover, age, AMH, and AFC demonstrated an adequate predictive capacity \(\text{(C-statistic for proportion of correct predictions of 0.87, 0.86, 0.84, respectively)}\). FSH only showed a moderate predictive capacity \(\text{(C-statistic of 0.70)}\). From the two most significantly predicting tests \(\text{(AMH and AFC)}\), AMH revealed the strongest hazard ratio per unit of SD, indicating the strength of this predictor.

The analysis of independent effects of the ORT next to age at T1 in the prediction of time until menopause revealed that only AMH significantly added predictive information \((P < 0.001)\), with an improvement of the C-statistic to 0.90. FSH also showed a significant association; however, the C-statistic did not improve in comparison to the prediction based on age alone, demonstrating the lack of

<table>
<thead>
<tr>
<th>TABLE 1. Baseline characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Age at T1 (yr)</td>
</tr>
<tr>
<td>Age at menarche (yr)</td>
</tr>
<tr>
<td>BMI (\text{(kg/m}^2))</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
</tr>
</tbody>
</table>

All three cohorts consist of healthy volunteers, with a regular menstrual cycle, age 18–46 yr, with no history of ovarian abnormalities or surgery, absence of endocrine disease, and no steroid hormonal treatment for at least 3 months before the study. Only age differs significantly between the cohorts, which is corrected for in the Cox regression by delayed entry for age. Data are expressed as means ± SD or number (percentage). \(P\) values were calculated between the different cohorts using Kruskal-Wallis or \(\chi^2\) test.

FIG. 1. Nomogram for the relation between age-specific AMH concentrations and the distribution of age at menopause. In the upper panel, the AMH levels measured at entry of the study for women at the given age are shown, measured approximately 11 yr before cycle status assessment. The lines represent the upper margins of the different percentiles of AMH. Women can thus be placed in a percentile category based on their AMH concentration at a given age. The lower panel depicts the variation of age at menopause for different percentiles of AMH. Women with a low AMH level for their age will enter a low percentile—for example, the P5 that is represented in the small-dotted line. For women in a low percentile, the predicted distribution of age at menopause shifts toward a younger age. Women with a high AMH level for their age will enter a high percentile—for example, the P95 that is represented in the big-dotted line. For women in a high percentile, the predicted distribution of age at menopause shifts toward an older age. Note that the median age at menopause in this population is 52 yr; this is due to the selection based on cycle regularity at the entry of the study for women up to 46 yr old, which will shift the overall age at menopause to a later time.
added value for this test. Because smoking could be a potential confounder, these analyses were also performed with smoking taken into account. Smoking was not significantly associated with time to menopause ($P = 0.075$) in a model with AMH and age, and it did not change the predictive capacity of AMH.

Because only AMH showed a significant added value to age, a nomogram of age and AMH for the prediction of age at menopause was constructed using a Weibull model. There was good agreement between the Weibull model and the nonparametric Kaplan-Meier curve for age at menopause. Women were divided into percentiles of AMH level for their age category. Women with a relatively low AMH level for their age are in the lower percentiles, and women with a relatively high AMH level for their age are in the higher percentiles. The distribution of age at menopause was then plotted for each percentile (Fig. 1). Figure 1 shows that an age-specific AMH level will shift the normal expected distribution of age at menopause to a considerable extent. This becomes more obvious when the data are presented in a forecast table where combined information from age and AMH was linked to predicted age at menopause (Table 3). Per age category, AMH levels associated with a certain AMH percentile. For each percentile, the predicted $p_5$, $p_25$, $p_50$ (median), $p_75$, and $p_95$ of age at menopause are presented.

For example, a 30-yr-old woman with an AMH concentration close to 0.15 ng/ml is associated with the fifth percentile; therefore, her predicted median age at menopause will be 48.8 yr ($p_5$ to $p_95$ is 42.1–53.0 yr). On the other hand, a 30-yr-old woman with an AMH concentra-

<table>
<thead>
<tr>
<th>TABLE 2. Predictive capacity for ORT for time to menopause</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>$P$ value</th>
<th>C-statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per 5.85 yr)</td>
<td>7.989</td>
<td>4.649–13.730</td>
<td>&lt;0.001</td>
<td>0.87</td>
</tr>
<tr>
<td>AMH (per 0.89 ng/ml)</td>
<td>0.033</td>
<td>0.010–0.110</td>
<td>&lt;0.001</td>
<td>0.86</td>
</tr>
<tr>
<td>AFC (per 6.94)</td>
<td>0.126</td>
<td>0.068–0.230</td>
<td>&lt;0.001</td>
<td>0.84</td>
</tr>
<tr>
<td>FSH (per 4.47 IU/liter)</td>
<td>1.725</td>
<td>1.464–2.030</td>
<td>&lt;0.001</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Multivariate analysis (adjusted for age)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMH (per 0.89 ng/ml)</td>
<td>0.092</td>
<td>0.025–0.340</td>
<td>&lt;0.001</td>
<td>0.90</td>
</tr>
<tr>
<td>AFC (per 6.94)</td>
<td>0.559</td>
<td>0.260–1.200</td>
<td>0.135</td>
<td>0.88</td>
</tr>
<tr>
<td>FSH (per 4.47 IU/liter)</td>
<td>1.350</td>
<td>1.112–1.640</td>
<td>0.002</td>
<td>0.88</td>
</tr>
</tbody>
</table>

The hazard ratio, as estimated with the Cox regression, is the effect of the variable on the risk of menopause occurring at a certain time point in the observation period (mean 11 yr). The C-statistic is the proportion of correctly predicted events. Effects are depicted per unit of so of age and ORT. CI, Confidence interval.

| $a$ Significant difference in comparison to age alone. |

Results of prediction of menopause are represented in a tabular form in which women can combine their current age and AMH level to find their AMH percentile with its corresponding range of predicted age at menopause. AMH levels are represented in nanograms per milliliter as measured by the DSL assay. Given a certain age frame, the AMH level closest to the concentration measured in a particular woman can be found; to the right, find the corresponding percentile of age corrected AMH level, which further to the right will give a prediction of the $p_5$, $p_25$, median ($p_50$), $p_75$, and $p_95$ of age at menopause for women in that percentile.
In the present study, as well as in the earlier report by van Rooij et al. (34), however, the AFC as well as basal FSH failed to show a significant capacity in predicting age at menopause compared with prediction on the basis of age alone. Age at menopause is linked to loss of natural fertility, occurring at a mean age of 41 yr, with a distribution curve very similar to the one for menopausal age (1, 4, 37). If individualized predictions of the menopausal age range could be given early in life, a tool for individualized preventive management of age-related infertility could be developed. Such advanced knowledge could lead to important strategy decisions, such as individual planning to attempt conception earlier or preservation of fertility by banking oocytes (38).

Age at menopause is also related to women’s health in general. It has been shown that bone loss accelerates after menopause. The earlier menopause occurs, the lower bone density will be later in life (15, 16). Furthermore, data have also consistently shown an increased risk for cardiovascular disease for women experiencing premature menopause (17). Also, an increased risk for cognitive impairment or dementia was shown for women experiencing premature menopause (18). At the other end of the spectrum, late age at menopause increases the risk for development of breast and endometrial cancer (19). From this knowledge, preventive management regarding cardiovascular, reproductive, and neurological health could be targeted, based on menopause prediction at an early stage of life.

In the current study, women between the ages of 21 and 46 with still regular cycles at T1 were included. This is likely to explain both the somewhat higher predicted median age at menopause of 52 yr in this cohort and the strong predictive effect of age at T1 in the prediction of menopause. If women with any cycle status would have been included in the cohort, the relation between age at T1 and time to menopause would have been weaker. For AMH, the relationship with menopause timing would have become reinforced by also selecting women with both lower AMH and earlier menopausal ages.

A possible limitation of this study is that it is composed of three separate, although quite similar, cohorts. Each of the cohorts had been set up for studies on the status and decline of normal fertility in humans. Moreover, the protocols for the selection of these volunteers were highly comparable. All three cohorts reflect healthy volunteers with a regular cycle, age between 18 and 46 yr, no history of ovarian surgery, no previous or current ovarian abnormalities, and no hormonal treatment for at least 3 months before entrance into the study. The difference in age distribution between the cohorts will not affect the comparability of the cohorts. Moreover, this distribution difference is taken into account in the analysis by delayed entry
for age in the Cox regression. Furthermore, subgroup analyses have been performed, showing no differences in the predictive performance of the ORT within the three subgroups (AMH, P = 0.58; AFC, P = 0.65; and FSH, P = 0.95, test for interaction). As such, we feel that it is justified to combine these three cohorts into a single study population. Another limitation for both research and clinical practice is the usage of two different AMH assays. However, subgroup analysis comparing the performance of AMH measured with the different assays revealed no significant difference (P = 0.28, test for interaction). In previous studies, the results of Beckman Coulter and DSL assays showed a good correlation, although the translation of results from one assay to the other is not based on large bodies of published data (39, 40). In our own laboratory setting a consistent correction factor of 2 has also been used in previous studies (28, 41). Interpretation of the data in the forecast Table 3 may only be translated freely into clinical practice after a thorough assay standardization has taken place. At present, it offers insight into the possible future use of this marker.

In summary, AMH is highly predictive for the time interval until the occurrence of menopause. Using age and AMH, the age range in which menopause will occur can be individually predicted. Correct prediction of age at menopause could open avenues of individualized prevention of age-related infertility and menopause-related conditions, like cardiovascular disease and breast carcinoma. Long-term follow-up studies starting at age 20 need to show whether predictions over periods longer than 11 yr will be possible, using not only endocrine and ultrasound factors but also genetic information to be linked to future reproductive events.

Acknowledgments

Hereby we thank all participants for volunteering and putting time and effort into this longitudinal study. Thanks to you, research on natural fertility in healthy women is possible.

Address all correspondence and requests for reprints to: S. L. Broer, M.D., Department of Reproductive Medicine and Gynecology, University Medical Center Utrecht, Room F05.126, P.O. Box 85500, 3508 GA Utrecht, The Netherlands. E-mail: S.L.Broer@umcutrecht.nl.

Disclosure Summary: F.J.J.M.B. is a member of the external advisory board for Ferring Pharmaceuticals, Hoofddorp, The Netherlands. He receives no monetary compensation. B.C.F. has advisory board for Ferring Pharmaceuticals, Hoofddorp, The Netherlands. He receives no monetary compensation. B.C.F. has advisory board for Ferring Pharmaceuticals, Hoofddorp, The Netherlands. E-mail: S.L.Broer@umcutrecht.nl.

References

8. Wallace WH, Kelsey TW 2004 Ovarian reserve and reproductive age may be determined from measurement of ovarian volume by transvaginal sonography. Hum Reprod 19:1612–1617


27. van Rooij IA, Tonkelaar I, Broekmans FJ, Looman CW, Scheffer GJ, de Jong FH, Themmen AP, te Velde ER 2004 Anti-Mullerian hormone is a promising predictor for the occurrence of the menopausal transition. Menopause 11:601–606


