Modeling age at menopause


Summary. Researchers attempted to improve their previous prediction of age at menopause in a population-based cohort of 1,015 women (the Tehran Lipid and Glucose Study) through additional follow-up time. Serum concentration of anti-Mullerian hormone (AMH) was measured at the time of recruitment, and date of menopause was determined over a 10-year follow-up. Actual ages at menopause were compared with the predicted ages. There were 277 occurrences of menopause and median age was 50 years.

Comment. AMH is a homodimeric, 140K Dalton member of the TGF-β family. There has been an explosion of publications relating to AMH in the past few years, evaluating its utility as a marker of ovarian reserve and assessing ovarian aging. Several of these reports have prospectively or retrospectively constructed age-specific curves for the decline of AMH with aging in various populations. In this recent report by Tehrani and colleagues, statistical modeling has been employed in 1,015 women who were followed for approximately 10 years, with the observation of the occurrence of menopause in 277 of these women. Their data suggest that prediction based on the AMH level and age showed a median difference of only 0.5 years. However the standard deviation was quite large at 2.5 years, with a range of 10 or more years. Also, age alone was 84% adequate in predicting the age of menopause, and only increased to 92% when AMH was added to the model.

The clinical application of AMH has been hampered by lack of precision in the various assays employed. To date, this remains an issue and calls out for an international standard to be used. For this and other reasons, when NAMS put together the latest version of the Stages of Reproductive Aging (STRAW+10), measurements but not specific levels of AMH were included in the scheme, and it was merely suggested that they would be “low” prior to menopause. There also is some concern about the stability of AMH with some blood collections. In the Tehrani paper, levels of AMH which were included in this model ranged from 0.1 to 4.5 ng/mL. While the authors did not include or discuss “undetectable” levels, the sensitivity of the assay and the low limit of detectability are key in providing an accurate prediction for the age of menopause. Values in the high end can be misleading and can include women who have polycystic ovaries, an important variable that was not taken into account.
account in this model. Thus, for example, in this model a woman at age 34 years with an AMH of 3.1 ng/mL was predicted to have menopause at over 65 years, an impossibility, and the absolute ranges around each of the predicted ages spans 10 or more years. This is quite different from the approach of predicting menopause once levels are undetectable (usually <0.05 ng/mL), and with this, it was shown that menopause would be expected to occur within 5 years.\(^3\)

At the crux of the issue, given some concerns with the assay, particularly its sensitivity and reproducibility, do we really need to accurately predict menopause? The major value of assaying AMH is in the reproductive age group, to help determine ovarian reserve, determine appropriate protocols and regimens for treatment, and provide advice in terms of how distant or close women may be to natural menopause. An inherent problem with prediction models is that we do not have precise information concerning the rapidity of the decline in ovarian follicles or AMH, which probably is not parallel in all women. Also, it has to be remembered that, in this setting, levels of AMH are not infallible, and there are several reports of pregnancies occurring with undetectable levels.\(^4\) It could be argued that, other than this, there is limited value for a woman to know when she will stop menstruating. Clearly the importance of this will be dictated by other clinical signs, such as vasomotor symptoms and irregular menstrual bleeding. Other risks that may ensue after menopause will be dictated by clinical circumstances once menopause has been established.

Roger A. Lobo M.D.
Professor of Obstetrics and Gynecology
Columbia University
New York

References:

Levonorgestrel IUS vs usual medical treatment for menorrhagia


Summary. This randomized trial compared a levonorgestrel-releasing intrauterine system (IUS) with usual medical treatment in 571 women with menorrhagia presenting to their primary care providers. The primary outcome was patient-reported score on the Menorrhagia Multi-Attribute Scale (MMAS; ranging from 0 to 100, with lower scores indicating greater severity) over a 2-year period. Secondary outcomes were quality-of-life and sexual-activity scores and surgical intervention.

MMAS scores improved after 6 months in both groups, but levonorgestrel IUS was more effective than usual medical treatment in reducing heavy menstrual bleeding and improving quality of life. Maintenance of improvements over a 2-year period were also greater with levonorgestrel IUS. MMAS improvements were significantly greater in the levonorgestrel-IUS group as well as for seven of eight quality-of-life measurements.

Comment. This trial is interesting in that it is referred to as a “pragmatic” randomized trial. Unlike most randomized trials comparing efficacy and other outcomes of specific treatment options, this trial conducted in the United Kingdom randomized 571 women with menorrhagia to either the levonorgestrel IUS (N
versus usual medical treatments (N = 286), which included mefenamic acid, tranexamic acid, norethindrone, combination oral contraceptives, progestin-only oral contraceptives, or medroxyprogesterone acetate injections. Unfortunately, nowhere in the article does it state percentages of patients in each medical treatment group or the exact doses of medications prescribed.

Women in the levonorgestrel-IUS group were almost twice as likely as the usual treatment group to still be receiving their assigned treatment at 2 years (64% vs 38%). Half the subjects (80) who discontinued usual medical treatment switched to the levonorgestrel IUS. The primary outcome measure was the MMAS, which measures effect of menorrhagia on aspects of daily life, including practical difficulties, social life, psychological health, physical health, work and daily routine, and family life and relationships. Although total scores on the MMAS improved significantly in both groups, the improvement was significantly greater in the levonorgestrel-IUS group.

Despite the better measured outcomes in the levonorgestrel-IUS group than in the usual medical management group, the frequency of surgical intervention for heavy menstrual bleeding did not differ between the two groups, with hysterectomy performed in 6% of both groups. In addition, at 2 years, 36% in the levonorgestrel-IUS group had the device removed because of lack of efficacy and irregular bleeding. Bottom line: the levonorgestrel IUS is widely used in the United Kingdom, the United States, and other countries for management of heavy menstrual bleeding and is more effective at improving numerous aspects of daily life affected by bleeding than numerous other medical options.

Patricia J. Sulak, MD
Dudley P. Baker Endowed Professor of
Research & Education in Obstetrics and Gynecology
Texas A&M Health Science Center
Scott & White Healthcare
Temple, TX

---

**Maternal menopause age, AMH, & antral follicle count**


**Summary.** Is mother’s age at menopause associated with ovarian reserve in daughters? This study included 527 women from a prospective cohort study whose mothers’ age at natural menopause was known. Researchers demonstrated a significant, positive association between maternal menopause age and serum anti-Mullerian hormone (AMH) and antral follicle count (AFC) in daughters. Rate of decline in AMH and AFC was also associated with maternal menopause age. Researchers used an analysis of covariance model with serum-AMH and AFC as outcomes, age as the quantitative predictor, and onset of maternal menopause as the categorical predictor, with adjustments for BMI, oral contraceptive use, and smoking.

**Comment.** AMH was named originally for its role in differentiation of the male reproductive system in the fetus but has achieved widespread recognition for its role in women. It is produced by small antral follicles, and its concentrations reflect the size of the ovarian follicle pool, ie, ovarian reserve, which can also be assessed by means of the ultrasonically determined AFC. AMH concentrations decline with increasing reproductive age and, with present assays, become undetectable 3 to 5 years prior to menopause. Levels are increased in women with polycystic ovaries and can be used as markers of ovarian response to ovulation induction in assisted reproductive programs. Levels are generally reasonably stable throughout the menstrual cycle, though some degree of variation has been reported. Several recent articles describe the predictive value of AMH levels for determining age at menopause, although the confidence intervals for an individual prediction are wide.
Because it has been established that maternal age at menopause (MMA) is moderately highly associated with a daughter’s age at menopause, it was logical to examine ovarian reserve (as measured by AMH and AFC) in daughters as a function of MMA. As would have been predicted, the present report describes a statistically significant association and further shows that the rates of decline in AMH and AFC are related to MMA being either early (<45 years), average (46-54 years), or late (>55 years), with the rates slowing with increasing MMA. The authors describe limitations of the study in some detail, including retrospective determination of MMA; the population, which consisted of Danish healthcare workers, who may be healthier than the general population; and the cross-sectional rather than longitudinal design. The evidence itself is somewhat challenging for the average reader, particularly the interpretation of the main Table III.

Whilst this is an elegant confirmation of the physiology underlying the relationship of MMA to the daughter’s age at menopause, it is difficult to envisage a practical application of the information. Women wishing to predict their age at menopause can use family history and AMH or AFC to assist in the prediction, though the confidence intervals are too wide to make that prediction practically useful.2

Henry G. Burger, MD, FRACP
Emeritus Director
Prince Henry’s Institute of Medical Research
Clayton, Victoria, Australia

References:

Screening mammograms in older women: annual or biennial?


**Summary.** Controversy continues to surround recommendations about screening mammography intervals. Investigators prospectively collected data from 1999 through 2006 on women aged 66 to 89 at baseline who received screening mammograms in five U.S. regions in which mammography records could be linked with Medicare claims data.

Of 140,000 women, invasive breast cancer or ductal carcinoma in situ (either screen-detected or interval-detected) was diagnosed in nearly 3000. The percentage of invasive tumors with adverse characteristics (stage IIb or higher, size >20 mm, or positive lymph nodes) was similar among women receiving annual and biennial screens and did not vary significantly with respect to comorbidity scores. The 10-year cumulative likelihood of a false-positive recall was higher among women who underwent annual screening (48%) than among those who underwent biennial screening (28%). Likewise, the 10-year cumulative probability of a false-positive biopsy recommendation was higher with annual screening (10%) than with biennial screening (5%). These false-positive trends were similar, regardless of age or extent of comorbidity.

**Comment.** Conflicting guidance about the risks and benefits of screening mammography can be bewildering for women and their clinicians: The US Preventive Services Task Force recommends biennial screens for women aged 50 to 74, whereas the American Cancer Society recommends annual screens for women older than 40, with no upper age limit. As the authors point out, their findings are consistent with earlier reports that indicate biennial screening
retains the benefits of annual screening with fewer resulting harms. Although I anticipate that most of my patients aged 50 and older will continue to choose yearly screens for the time being, I will continue to be flexible with respect to the choice of screening interval in these women.

Andrew M. Kaunitz, MD
Professor and Associate Chairman
Department of Obstetrics and Gynecology
University of Florida College of Medicine-Jacksonville
Jacksonville, FL


**Menopause Editor’s picks from February 2013**

NAMS spotlights selections from the most recent issue of the Society’s official journal, *Menopause*, chosen by its Editor-in-Chief, Isaac Schiff, MD.

---

**Impact of denosumab on the peripheral skeleton of postmenopausal women with osteoporosis: bone density, mass, and strength of the radius, and wrist fracture.**

Simon, James A.; Recknor, Christopher; Moffett, Alfred H. Jr; Adachi, Jonathan D.; Franek, Edward; Lewiecki, E. Michael; McClung, Michael R.; Mautalen, Carlos A.; Ragi-Eis, Sergio; Nicholson, Geoffrey C.; Muschitz, Christian; Nuti, Ranuccio; Töring, Ove; Wang, Andrea; Libanati, Cesar.

Breast density changes in a randomized controlled trial evaluating bazedoxifene/conjugated estrogens.

Harvey, Jennifer A.; Pinkerton, JoAnn V.; Baracat, Edmund C.; Shi, Harry; Chines, Arkadi A.; Mirkin, Sebastian.

Initiating therapy with antidepressants after discontinuation of hormone therapy.

Citarella, Anna; Andersen, Morten; Sundström, Anders; Bardage, Carola; Hultman, Christina M.; Kieler, Helle.

Self-reported and accelerometer-derived physical activity levels and coronary artery calcification progression in older women: results from the Healthy Women Study.

Gabriel, Kelley Pettee; Matthews, Karen A.; Pérez, Adriana; Edmundowicz, Daniel; Kohl, Harold W. III; Hawkins, Marquis S.; Janak, Judson C.; Kriska, Andrea M.; Kuller, Lewis H.
The level of evidence indicated for each study is based on a grading system that evaluates the scientific rigor of the study design, as developed by the US Preventive Services Task Force. A synopsis of the levels is presented below.

Level I  Properly randomized, controlled trial.
Level II-1  Well-designed controlled trial but without randomization.
Level II-2  Well-designed cohort or case-control analytic study.
Level II-3  Multiple time series with or without the intervention (e.g., cross-sectional and uncontrolled investigational studies).

Level III  Meta-analyses; reports from expert committees; descriptive studies and case reports.

Accurate, Concise Summaries About Menopause

MenoNotes

Six free handouts summarize some of the most confusing menopause-related topics. Hot flashes, vaginal dryness, bioidentical hormone therapy, and a menstrual calendar (in English, French, and Spanish) are clearly explained with the most up-to-date information. More topics will be added regularly so check back often.

Free to download on the NAMS website at:
www.menopause.org/publications/publications-for-women/menonotes