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The following news items present reviews of important, recently published scientific articles selected by The North American Menopause Society (NAMS), the leading nonprofit scientific organization dedicated to improving women's health and quality of life through an understanding of menopause. Each has a commentary from a recognized expert that addresses the clinical relevance of the item. Note that opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS. Published news items may be viewed on the NAMS Web site (www.menopause.org/news.html).

Recurrent vasomotor symptoms common for EPT users in WHI after study was discontinued

Ockene JK, Barad DH, Cochrane BB, et al. Symptom experience after discontinuing use of estrogen plus progestin. *JAMA* 2005;294:183-193. **Evidence level: II-2.**

Postmenopausal women who discontinue estrogen-progestogen therapy (EPT) are significantly more likely to experience recurrent vasomotor symptoms than placebo recipients, especially women who had symptoms before starting EPT, according to a cross-sectional survey of participants in the Women's Health Initiative (WHI). Approximately 8 to 12 weeks after the WHI trial was stopped, investigators mailed a questionnaire to postmenopausal women who were still taking the study pills, either placebo or estrogen plus progestin therapy (0.625 mg/day conjugated equine estrogens plus 2.5 mg/day medroxyprogesterone acetate), when the trial was stopped. A total of 8,405 women completed the survey, a response rate of 89.9%. Their mean age at study discontinuation was 69.1 years. The primary end points were vasomotor symptoms and pain or stiffness.

After discontinuing the study pills, 21.2% of all EPT users experienced moderate or severe vasomotor symptoms compared with 4.8% of placebo users. Conversely, 36.7% of the EPT-withdrawal group and 59.5% of placebo recipients had no vasomotor symptoms. Among women who were experiencing these symptoms at baseline (n = 950), the rates for symptoms after therapy withdrawal were 55.5% and 21.3%, respectively. Among women with no vasomotor symptoms at baseline, 6.4% had symptoms after stopping EPT versus 1.2% of placebo recipients.

The adjusted odds ratio (OR) showed that the presence of symptoms at baseline was the most important factor influencing symptom occurrence after treatment withdrawal. Overall, 91.1% of the EPT withdrawal group who reported vasomotor symptoms had experienced them in the past. Among women who had these symptoms at baseline, the adjusted ORs were 5.36 (95% CI, 4.51-6.38) and 3.21 (95% CI, 2.90-3.56) for recurrence of vasomotor and pain or stiffness symptoms, respectively, for the EPT group compared with the placebo group. Women whose symptoms had been relieved by EPT also were likely to suffer symptoms after EPT withdrawal: OR, 5.82 (95% CI, 4.92-6.89) for vasomotor symptoms, and OR, 2.16 (95% CI, 1.90-2.40) for pain or stiffness.

Nearly half of the women with symptoms after treatment withdrawal reported use of at least one management strategy. Lifestyle management strategies included drinking more fluids, exercising, using fans, changing diet, using layered or cotton clothing, and drinking less caffeine or alcohol. Medical management strategies included talking to their clinician, taking vitamin E, using vaginal lubricants, or taking other medications.

Comment. This is a very interesting paper, despite limitations described by the authors. In this study, women discontinuing EPT or placebo in the WHI trial were followed up 8 to 12 months later to determine their symptom profile and actions they had or had not taken.

It is certainly not surprising that more than half of the women with vasomotor symptoms at randomization to active EPT also reported these symptoms after discontinuing use of them. This has always been a dilemma of clinical practice — we advise women to take EPT for "the shortest duration, etc." But if symptoms recur, they may need to go back on treatment, and despite the best intentions, short-term therapy inevitably becomes long-term therapy. The problem remains as to how to deal with the situation.

To me, one of the most interesting findings is the withdrawal placebo effect. Women on placebo reported a 21.3% increase in symptoms after placebo was discontinued. We all know that studies of postmenopausal therapies for vasomotor symptoms show a significant placebo response, with 30% to 50% of participants reporting reduced symptoms. What has not been reported before is the recurrence of symptoms with discontinuation of placebo, an area ripe for further research.

The 30% to 50% response with placebo is about the same level of response as reported in studies of soy, isoflavones, and other herbal products. It is, therefore, not surprising that the authors state, "The use of herbal or natural hormones by respondents in the current study was reported as one of the least effective strategies." This supports recommending against expensive but largely ineffective over-the-counter remedies.

The overall lesson from this article appears to be a suggestion that part of the counseling of women considering ET/EPT is to note that symptoms may only be delayed, and they have at least a 50-50 chance of recurring when such therapy is discontinued.

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Suboptimal vitamin D levels common among women using osteoporosis therapy

Holick MF, Siris ES, Binkley N, et al. Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *J Clin Endocrinol Metab* 2005;90:3215-3224. **Evidence level: II-2.**

More than half of North American women receiving osteoporosis therapy have low serum levels of vitamin D, according to this cohort study. Serum levels were obtained from 1,536 postmenopausal women older than age 55 years (mean age, 71) who had been receiving osteoporosis therapy for at least 3 months. Participants were evenly distributed across geographic regions based on latitude.

The mean serum level of 25-hydroxyvitamin D was 30.4 ng/mL. Approximately 52% of the women had suboptimal vitamin D levels, defined as below 30 ng/mL; 36% were below 25 ng/mL, and 18% were below 20 ng/mL. A multivariate analysis found eight variables associated with low vitamin D levels: older than age 80, nonwhite race, body mass index greater than 30 kg/m^2, use of therapeutic agents known to decrease vitamin D levels, lack of exercise, physician did not discuss importance of vitamin D supplements with patient, low education level (did not finish high school), and taking a daily vitamin D supplement with less than 400 IU.

Comment. Holick and colleagues provide important evidence that the public health message on the benefits of vitamin D has not been delivered successfully to physicians or patients. More than 50% of women already receiving therapy for the treatment or prevention of osteoporosis did not reach adequate serum 25-hydroxyvitamin D levels of 30 ng/mL (75 nmol/L). This is not surprising when 40% of women reported that they consumed less than 400 IU of vitamin D per day. In fact, despite being treated for osteoporosis, about one-third never discussed the importance of vitamin D in bone health with their physicians.

Based on recent evidence from two meta-analyses of well-designed randomised controlled trials, consumption of at least 700 to 800 IU/day vitamin D is needed for optimal prevention of both fracture [Bischoff-Ferrari *JAMA* 2005] and falls. [Bischoff-Ferrari *JAMA* 2004] A recent pragmatic trial suggests that even more vitamin D may be needed

for individuals starting at 25-hydroxyvitamin D levels below 16 ng/mL (40 nmol/L) [Grant *Lancet* 2005] to reach the target serum 25-hydroxyvitamin D level of 30 ng/mL (75 nmol/L). [Dawson-Hughes *Osteoporos Int* 2005] Every strategy for the prevention or treatment of osteoporosis should include vitamin D in a dose of at least 700 to 800 IU/day. This is especially attractive as vitamin D is well-tolerated and inexpensive.

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Studies find no substantial link between low androgen levels and sexual function or androgen levels and natural menopause

Davis SR, Davison SL, Donath S, Bell RJ. Circulating androgen levels and self-reported sexual function in women. *JAMA* 2005;294:91-96. **Evidence level: II-2.**

Low serum androgen levels are not associated with low levels of female sexual function, according to this cross-sectional, community-based study from Australia. Serum levels of total and free testosterone, androstenedione, and dehydroepiandrosterone sulfate (DHEAS) were obtained from 1,423 randomly selected women aged 18 to 75 years, 85% of whom were older than 35. Women were excluded if they were pregnant, taking psychiatric medications or oral contraceptives, had abnormal thyroid function, or had diagnosed polycystic ovarian syndrome. Self-reports on the Profile of Female Sexual Function were used to assess sexual function.

A comparative analysis found no clinically significant relationship between low levels of total or free testosterone or androstenedione and sexual function scores. A low score for sexual responsiveness in women aged 45 years and older was significantly associated with the lowest DHEAS levels (odds ratio [OR], 3.90; 95% CI, 1.54-9.81). For women aged 18 to 44 years, the lowest DHEAS levels were significantly associated with low sexual desire (OR, 3.89; 95% CI, 1.27-11.67), sexual arousal (OR, 6.39; 95% CI, 2.30-17.73), and sexual responsiveness (OR, 6.59: 95% CI, 2.37-18.34).

Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause, and oophorectomy. *J Clin Endocrinol Metab* 2005;90:3847-3853. **Evidence level: II-2.**

An analysis of data from the same study indicates that although serum androgen levels decline sharply in the early postmenopausal year, the decline is not a result of natural menopause, and the postmenopausal ovary appears to continue to produce testosterone. For this analysis, serum levels of total testosterone (T), calculated free T, DHEAS, and androstenedione were compared from both the study population and a reference population of 595 women free of factors known to affect androgen levels.

Serum levels of all four androgen measures declined with age (P <0.001), with the decline being greater in the earlier decades than in later decades. In women aged 45 to 54 years, androgen levels were similar in both premenopausal women and postmenopausal women of the same age, indicating that natural menopause does not have a significant effect on androgen levels. In postmenopausal women older than 55 years, those who had undergone bilateral oophorectomy had significantly lower levels of total T and free T (but not DHEAS or androstenedione) than those who had experienced natural menopause, suggesting ongoing ovarian production, the authors note.

Comment. While *endogenous* serum androgen concentrations (ie, testosterone or androstenedione) are highly correlated with erectile function in men and some small studies demonstrate an association with female sexual function, other studies have suggested that endogenous estrogens are paramount in this regard. The improbability that any hormonal relationship determines sexual function might best be explained by the poor correlation between serum androgen levels and intracellular concentrations. Further, sexual function in human females is highly dependent on external, nonhormonal factors including prior sexual history, availability of a partner, emotional intimacy, privacy, mood, etc.

These two articles from an experienced group of Australian investigators describe the changes in endogenous androgens that accompany aging and the menopause transition and whether these hormonal changes were associated with changes in sexual function. They did not find "clinically important" associations between these hormonal

changes and sexual function, except in specific subgroups of women. Women aged 18 to 44 years with the lowest DHEAS levels had lower sexual desire, sexual arousal, and sexual responsiveness; women aged 45 years and older with the lowest DHEAS levels had lower sexual function.

While the "holy grail" of the psychoneuroendocrinologist would be to prove that a hormone (ie, an androgen) could direct a behavior, the likelihood of making such a finding in this study seems extremely remote. Given the provisos listed above (eg, biological, psychological, social, situational) and the extremely complex nature of sexual function combined with the primitive nature of our instruments for assessing sexual function (ie, The Profile of Female Sexual Function [PFSF]), it is more surprising that these investigators found any correlations between the hormones and behaviors they assessed.

The absence of strong associations of hormones with aging or menopause should not be confused with the results of treatment studies of women with low sexual desire or other sexual dysfunctions. Several published randomized controlled trials indicate that *exogenous* testosterone in both oral and nonoral formulations have a positive effect on sexual function, primarily desire, arousal, and orgasmic response, in women after spontaneous or surgically induced menopause.

The studies under review here should also give the clinician great pause when considering whether to measure androgens in a clinical setting as an index or a marker of sexual dysfunction. Laboratory testing of testosterone levels, for example, should be used only to monitor for supraphysiologic testosterone concentrations before and/or during therapy, not to diagnose testosterone insufficiency or sexual dysfunction.

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Rates of less severe lupus flares increased by CEE/MPA

Buyon JP, Petri MA, Kim MY, et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. *Ann Intern Med* 2005; 142:953-962. **Evidence level: I.**

Combined estrogen and progestin therapy (EPT) is associated with a modest, but statistically significant, increase in mild to moderate flares in women with systemic lupus erythematosus (SLE), according to this randomized, double-blind, placebo-controlled trial. In all, 351 postmenopausal women (mean age, 50 years) with inactive or stable-active SLE were assigned to 12 months of treatment with either placebo or oral EPT (0.625 mg/day conjugated equine estrogens [CEE] with 5 mg/day medroxyprogesterone acetate [MPA] added 12 days per month). The end point was flare rate during the trial.

At 12 months, mild to moderate flares were significantly increased in the EPT group compared with placebo. The rate per person-year was 1.14 for EPT and 0.86 for placebo, yielding a 34% increased relative risk for EPT ($P = 0.01$). However, the rate of severe flare was low in both groups: 0.081 for EPT and 0.049 for placebo, a nonsignificant between-group difference. Overall, the probability of experiencing any type of flare was significantly increased for EPT recipients: 0.64 vs 0.51 for placebo ($P = 0.01$).

Comment. General dogma suggests that in women with SLE, hormone therapy increases the risk of flare. The results of this study can be characterized as "good news-bad news" — although so-called severe flares were not increased, mild to moderate flares were increased.

I am concerned that the study presentation tends to minimize the risk to patients. What was described as moderate flares were clinically significant (pleuritis, pericarditis, need for significant steroid increase, etc). Furthermore, 82% of the women randomized to this study had inactive disease at baseline, which leads one to wonder what the results would have been if EPT had been given to women with more active disease at onset.

Nevertheless, as the authors note, the story remains essentially the same — estrogen-containing hormone

therapy can be considered in women with SLE if the gains outweigh the risks.

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Comment. Use of estrogen therapy by women with SLE has been controversial owing to data from both animal and human studies on the ability of estrogen to either induce or exacerbate lupus. Retrospective and prospective studies have found that estrogen use either has no effect on the rate of lupus flare or it produces a modest increase in disease frequency.

This study by Buyon and colleagues is the largest randomized, placebo-controlled trial of EPT in SLE patients to date. It uses rigorous standardization of patient assessments to increase accuracy between centers when determining the presence of mild, moderate, and severe disease flares. Results indicate that while EPT increased the frequency of all flares, there was no difference between groups in the number of severe flares, the most significant outcome. If EPT is deemed necessary in postmenopausal women with SLE, the data on induction of severe flares should not discourage its use. However, clinicians need to be aware that EPT may increase the risk of mild to moderate flares.

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Genetic traits have substantial effects on age at menopause

Murabito JM, Yang Q, Fox C, Wilson PWF, Cuples LA. Heritability of age at natural menopause in the Framingham Heart Study. *J Clin Endocrinol Metab* 2005; 90:3427-3430. **Evidence level: II-3.**

More than half of the individual difference in age at menopause appears to be attributable to inherited factors, according to these data from the Framingham Heart Study, a community-based, epidemiologic study. Family correlations regarding age at natural menopause were evaluated in 1,500 women from the original cohort and 932 women in an offspring cohort. The study sample included the following pairs: mother-daughter (n = 622), sister-sister (n = 474), grandmother-granddaughter (n = 29), aunt-niece (n = 258), and first cousins (n = 165) from 1,296 extended families.

The mean age at menopause was 49.1 years for the original cohort and 49.4 years for the offspring cohort. According to results from a multivariable-adjusted analysis (adjusted for body mass index, cigarette smoking, and number of children), genetic factors accounted for 52% of the variation in age at menopause for the overall study population (95% CI, 0.35-0.69; P <0.0001). It accounted for 74% of the variation in age at menopause in the original cohort (95% CI, 0.31-1.00; P <0.002) and 48% of the offspring cohort (95% CI, 0.15-0.81; P = 0.003). The estimates of heritability for specific pairs were 0.42 for mother-daughter, 0.44 for sister-sister, and 0.48 for aunt-niece.

Comment. This is the first study of genetic influences on age at menopause in a population-based sample of U.S. women. Using data from the Framingham Heart Study, the investigators found evidence that age at natural menopause can be explained, in large part, by knowing the age at which one's mother experienced menopause. The Framingham Heart Study is a prospective cohort study initiated in 1948. In 1971, offspring of the original cohort members and offspring spouses were enrolled in the Framingham Offspring Study. The large number of women (N = 2,432) for whom data are available makes the results of this study compelling and an excellent basis for comparison with studies from other countries.

Despite its strengths, the Framingham study has some limitations that we need to consider:

- The sample was primarily composed of Caucasian women.
- Age at natural menopause was ascertained by self-report from women who had already completed the menopause transition at the start of the study, and thus, relied on their memory.
- Parity was higher in the original cohort than in the U.S. population estimates for women born during the same period. Because nulliparity is associated with earlier menopause, the estimated age at menopause may be somewhat later than would be reflective of the entire U.S. population.
- Some offspring women had not yet reached menopause, thus, potentially underestimating the heritability of age at menopause.

Another consideration not noted by the authors is that genetic studies cannot differentiate genetics from family environmental factors. Lifestyle factors such as diet and activity and other household exposures shared among family members could have influenced the age at menopause.

Despite these limitations, the data in this report suggest that the mother's age at menopause is an important factor determining that for daughters, even when controlling for the effects of body mass index, cigarette smoking, parity, alcohol intake, oral contraceptive use, and age at menarche. Studies of other U.S. ethnic groups of women are needed to ascertain whether the heritability of age at menopause is predicted equally well by mother's age at menopause. In addition, the influence of contemporary environmental factors on age at menopause should be explored, including trends in obesity, smoking, activity patterns, parity, and oral contraceptive use.

The "Baby Boomers" are likely to differ from their mothers in each of these factors, and in turn, their daughters are likely to reflect secular trends in their behavior. Until work with a more diverse population of mother-daughter and sibling pairs is available, these data provide important evidence that age at menopause is heritable. Further studies are needed that address heritability of symptoms during the menopause transition.

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Low-dose aspirin provides women minimal cancer protection

Cook NR, Lee I-M, Gaziano JM, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. *JAMA* 2005;294:47-55. **Evidence level: I.**

Low-dose aspirin does not lower the risk of total cancer or of breast, colorectal, or other site-specific cancers, according to data from the Women's Health Study. In this randomized, placebo-controlled study, 39,876 women aged 45 years and older were assigned to receive either aspirin (100 mg) or placebo every other day. Participants did not have a history of cancer, cardiovascular disease, or other major chronic illness. Follow-up lasted an average of 10.1 years.

Compared with placebo, aspirin had no effect on the relative risks (RR) for total cancer (RR, 1.01; 95% CI, 0.94-1.08), breast cancer (RR, 0.98; 95% CI, 0.87-1.09), colorectal cancer (RR, 0.97; 95% CI, 0.77-1.24), or any other site-specific cancer except lung cancer (RR, 0.70; 95% CI, 0.50-0.99). Analyses based on follow-up time or interaction with vitamin E found no differential effects for aspirin.

Comment. Animal research and epidemiologic studies have suggested that aspirin may prevent cancer development at various primary sites by 20% to 50%. Two small-scale randomized trials demonstrated no chemopreventive effect from low-dose and high-dose aspirin on colorectal cancer. However, large-scale, randomized controlled trials were needed to assess the effect of aspirin on cancers of all sites.

The study by Cook and colleagues is a well-conducted, large-scale, long-term, randomized, controlled, primary prevention trial. It provides strong evidence that in healthy women, low-dose aspirin does not reduce the incidence and mortality of total cancer, breast cancer, colorectal cancer, and other site-specific cancers, except for a trend in reducing lung cancer. These results do not necessarily refute previous research demonstrating that a higher dose of aspirin (≥325 mg/day) may prevent certain cancers. In addition, it cannot be extrapolated that other nonsteroidal anti-inflammatory agents will not be as useful as chemopreventive agents. Because it is possible that nonsteroidal agents may interfere in early events in the carcinogenesis process, it is important to note that participants were not women at high risk. Finally, this study did demonstrate a protective effect of low-dose aspirin on lung cancer, which may warrant further research.

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Presentation of POF diagnosis key to woman's emotional reaction

Groff AA, Covington SN, Halverson LR, et al. Assessing the emotional needs of women with spontaneous premature ovarian failure. *Fertil Steril* 2005;83:1734-1741. **Evidence level: II-3.**

How a clinician presents the diagnosis of premature ovarian failure (POF) can have a significant impact on the woman's emotional reaction, according to this observational study by the National Institutes of Health. For this study, structured telephone interviews were conducted with 100 women diagnosed with spontaneous POF (median age at diagnosis, 28 years; range, 13.5 to 39.0 years). The diagnosis was based on the woman having at least 4 months of amenorrhea before age 40, which was associated with two serum FSH levels in the postmenopausal range sampled at least 1 month apart. The structured interview used 40 questions, which were designed to determine the manner in which they were informed of the POF diagnosis, their emotional response, and the type of emotional support.

Overall, 71% were not satisfied with the manner in which their physician informed them of the diagnosis, and 89% reported experiencing moderate to severe emotional distress at the time, including anger, depression, and feeling older, less healthy, or less feminine. A direct correlation was found between their degree of emotional distress and the manner in which they were informed ($P = 0.01$). Women were significantly more satisfied with the clinician's presentation if they were emotionally prepared ($P < 0.001$), felt that the clinician spent enough time with them ($P < 0.001$), or perceived the clinician as knowledgeable ($P < 0.001$) or sensitive ($P < 0.01$).

Comment. The diagnosis of premature ovarian failure often comes as devastating news to young women. Infertility and amenorrhea are major concerns to them, but the diagnosis can cause an array of emotional responses, including those related to alterations in body image.

In this study, 84% of the women reported being unprepared for the diagnosis. Some 43% stated they were informed by telephone call, in many cases while at work. These results underscore the need for improvement in the professional response to this poorly understood and oft neglected condition. Clinicians are advised to provide results of diagnostic studies at a planned follow-up office visit where information can be conveyed in a supportive and caring context. During the discussion, the terms *ovarian insufficiency* or *ovarian decline* might be substituted for the term *ovarian failure* which, in itself, may reinforce a sense of defectiveness. The NAMS consumer education resource, *Early Menopause Guidebook*, can be a helpful adjunct to counseling.

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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 U.S. 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 (eg, cross-sectional and uncontrolled investigational studies).
Level III	Meta-analyses; reports from expert committees; descriptive studies and case reports.

(continued)

Counseling about Early Menopause?
There Is a Resource to Help

Today more women are reaching menopause earlier than the typical age – either spontaneously or through medical means, including bilateral oophorectomy or ovarian damage through chemotherapy or pelvic radiation therapy. These women have special needs, regarding not only menopause symptom relief and reducing long-term health risks, but also emotional support due to their loss of fertility earlier than planned.

The *Early Menopause Guidebook* is a comprehensive, affordable, 64-page booklet designed especially for this population.

Place your order today through the NAMS Web site (www.menopause.org).

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