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This e-newsletter presents 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 and healthy aging. Each review has a commentary from a recognized expert that addresses the clinical relevance of the item. Oversight for this e-newsletter issue was by Chrisandra L. Shufelt, MD, MS, NCMP, Chair-elect of the 2012-2013 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Shufelt.

## Is ET avoidance associated with early death in women with hysterectomy?

*Study covers decline in estrogen use, 2002-2011*

Sarrel PM, Njike VY, Vinante V, Katz DL. The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years. *Am J Public Health*. 2013 Jul 18. [Epub ahead of print] **Level of evidence: II-3.**

**Summary.** Over a 10-year period, researchers examined how estrogen therapy (ET) avoidance affected mortality rates among hysterectomized women aged 50 to 59 years. They applied a formula relating mortality in hysterectomized women assigned to placebo in the Women's Health Initiative (WHI) and the entire population of comparable US women, finding that a minimum of 18,601 and a maximum of 91,610 postmenopausal women died prematurely because of ET avoidance. Study authors concluded that for young postmenopausal women with hysterectomy an informed conversation with their healthcare provider about ET effects is of vital importance.

**Comment.** This study presents an oversimplified interpretation of the WHI estrogen-alone study. The decision about the use of hormone therapy is complex, and there are both

risks and benefits of estrogen for women in all age groups. For example, the risks of stroke and deep vein thrombosis were increased in women taking oral estrogen in the WHI, even among younger women close to the onset of menopause. Although a suggestion of reduced risk of heart disease and all-cause mortality was found with estrogen in younger women (aged 50-59 y), these findings were of only borderline statistical significance. Moreover, decision-making about ET must be individualized because the balance of risks and benefits is heavily dependent on the personal risk factor profile of the woman and her underlying health risks. Estrogen is appropriate for some, but not all, women. The WHI contributed enormously important information by clarifying the benefits and risks of hormone therapy and identifying high-risk groups who should avoid treatment. The findings have undoubtedly saved countless lives and have been linked to a reduced risk of breast cancer in this population.

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## Health & social factors affecting age at menopause in SWAN study

*Study finds no significant racial or ethnic differences*

Gold EB, Crawford SL, Avis NE, et al. Factors related to age at natural menopause: longitudinal analyses from SWAN. *Am J Epidemiol.* 2013;178(1):70-83. **Level of evidence: II-3.**

**Summary.** This analysis of data from more than 3,000 women in the Study of Women's Health Across the Nation (SWAN), a longitudinal study of a large, ethnically diverse population of pre- and perimenopausal women, aimed to uncover modifiable risk factors associated with age at final menstrual period (FMP). Later age at menopause was significantly associated with having graduated from college, having used oral contraceptives, being employed, not smoking, higher weight at the beginning of the study, consuming more alcohol, better self-reported health, and lower levels of physical activity.

There were no significant racial or ethnic differences. Former smokers had an age at FMP similar to that of nonsmokers, and greater height was not associated with later FMP. Greater physical activity was only modestly associated with earlier age at FMP, and there was no association with caloric intake. An association between age at FMP and maternal age at menopause was not retained in the study's adjusted models.

**Comment.** SWAN is a superb study of the menopausal transition, providing the results of up to 10 years of prospectively measured ages at natural menopause among 3,302 women from seven US sites. The importance of this study is made clear in the first sentence of the paper: age at FMP "holds intrinsic public health interest" because it is associated with numerous health outcomes. For cross-population comparisons, age at menopause is a marker of community health, albeit not as immediate as measures of infant mortality or age at menarche.

It is of particular interest to read that there is no ethnic variation in age at menopause after controlling for smoking, self-reported health, education, use of oral contraceptives, alcohol intake, employment, physical activity, and baseline weight. The same was not true when the cross-sectional data from this study were analyzed in 2001. We have been waiting for these prospective results, and it is worth the wait to see that health and socioeconomic factors are more important than ethnicity in relation to age at menopause.

The prospective nature of SWAN allowed investigators to avoid the error in recall that plagues researchers constrained by cross-sectional data. The prospective design also permits researchers to carefully examine previously established risk factors, including change in risk factors over time. The study is, however, a snapshot of menopause within a particular cohort. The next generation of women to reach menopause will have different childhood experiences, health habits, stress, levels of obesity, reproductive histories, and environmental exposures. The next SWAN will tell us more, as will the one after that.

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## Positive & negative estrogen effects on urothelial defense

*Estrogen plays two different roles in UTIs*

Lüthje P, Brauner H, Ramos NL, et al. Estrogen supports urothelial defense mechanisms. *Sci Transl Med.* 2013; 5(190):190ra80. **Level of evidence: II-3.**

**Summary.** This study looked at the influence of estrogen on urinary tract infections (UTIs) in women and in mice and found that while estrogen improves two urothelial defense mechanisms against UTI—the production of antimicrobial peptides and maintaining the

urothelial barrier—it also helps promote bacterial invasion into urothelial cells.

**Comment.** UTIs are the most common outpatient bacterial infection. One in three women will develop a UTI by age 24, and more than half of all women will have at least one UTI in their lifetime. The higher incidence of UTI in women is probably related to a number of factors, including a shorter female urethra and colonization of urinary tract pathogens at the vaginal introitus. Generally considered to be self-limited and treated easily with antibiotics, UTIs frequently recur. For example, a woman who gets one UTI has a 25% risk of getting another within 6 months and a 46% risk of recurrence within 1 year.<sup>1</sup> There are many complex recurrence mechanisms, including bacterial strain characteristics, deficiencies in host defense mechanisms, bacterial epithelial invasion, and ultimately the establishment of intracellular bacterial communities (IBCs) within the bladder mucosa.<sup>2</sup>

Topical vaginal estrogen has long been used to prevent recurrence of UTIs in postmenopausal women but without a good understanding of how it works.<sup>3</sup> This study elucidates possible positive and negative estrogen effects on urothelial defense systems and microbial activity. The authors used a multidimensional approach that includes measuring human serum antimicrobial peptides and evaluating human urothelial cell characteristics to demonstrate estrogen-induced changes. They then used a UTI mouse model to assess in vivo effects of estrogen in the establishment of IBCs. Their findings suggest that estrogen may reduce recurrent infection by increasing the presence of antimicrobial peptides, strengthening the intracellular barrier to reduce bacterial invasion of urothelial cells, and restricting bacterial proliferation. However, estrogen may also increase superficial urothelial shedding in response to infection that then exposes the more easily invaded deeper epithelial cells or more directly enhances bacterial epithelial invasion. These apparently opposing estrogen effects may

simultaneously provide additional mechanisms for why UTIs are more common in women than in men and explain why topical estrogen can reduce recurrent UTIs in postmenopausal women.

Studies like this demonstrate the great potential for translational research. As scientists and clinicians work to dissect the complex relationship between host endocrine and immune systems in the urinary tract, they will develop better clinical strategies for UTI prevention and treatment. For clinicians caring for women, learning about the various cellular mechanisms by which UTIs occur and recur aids in developing and communicating with their patients a rational approach to managing recurrent UTIs.

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3. Barber AE, Norton JP, Spivak AM, Mulvey MA. Urinary tract infections: current and emerging management strategies. *Clin Infect Dis.* 2013 May 23. [Epub ahead of print]

## Hyaluronic acid vaginal gel effective for vaginal dryness

*Performs as well as estriol cream*

Chen J, Geng L, Song X, Li H, Giordan N, Liao Q. Evaluation of the efficacy and safety of hyaluronic acid vaginal gel to ease vaginal dryness: a multicenter, randomized, controlled, open-label, parallel-group, clinical trial. *J Sex Med.* 2013;10(6):1575-1584.

**Level of evidence: I.**

**Summary.** A hyaluronic acid vaginal gel performed as well as an estriol (not estradiol) cream to relieve vaginal dryness in this randomized, controlled but open-label trial in

postmenopausal women. A total of 133 women completed the study (67 who used hyaluronic acid and 66 who used estriol cream). Both groups applied the treatments every 3 days for a total of 10 applications. Mean vaginal dryness scores improved 84% in the hyaluronic acid group and 89% in the estriol group by the final visit, demonstrating no significant difference. The improvements in dyspareunia were not as strong but were not significantly different (24% in the hyaluronic acid group and 27% in the estriol group). Improvements in vaginal itching (63% and 67%, respectively) and burning (86% and 88%, respectively) were also not significantly different. The vaginal microflora and endometrial thickness also did not differ significantly, but vaginal pH was significantly lower in the estriol group. Adverse events included vulvovaginal candidiasis and bacterial vaginosis in the hyaluronic acid group and mild increased endometrial thickness, vulvar itching, asymptomatic and mild bacterial vaginosis, and vaginal itching in the estriol group. The authors concluded that the gel is a valid and safe option for patients unwilling or unable to consider an estrogen therapy.

**Comment.** The topic of this year's Pre-Meeting Symposium at the NAMS Annual Meeting is "Vulvovaginal Health: Let's Talk About It." Vulvovaginal atrophy can cause vaginal dryness, dyspareunia, and resultant female sexual dysfunction and urogenital discomfort. It is a common, relevant, and undertreated problem for many women. NAMS does assert that nonestrogen, over-the-counter lubricants should be used first for vaginal atrophy.<sup>1</sup> I disagree, because this does not improve the integrity of the urogenital tissues. However, many women are concerned about using low-dose local vaginal estrogen creams, tablets, or vaginal rings. Local vaginal dehydroepiandrosterone has shown improvement in vulvovaginal atrophy, dyspareunia, and sexual dysfunction<sup>2</sup>; however, it remains in phase 3 trials. Recently, the first nonestrogen, oral agent to treat moderate to severe dyspareunia and vulvovaginal atrophy (ospemiphene [Osphepa

60 mg], taken daily with food) has been approved.<sup>3</sup>

Many women remain leery of any prescription medications to treat local vaginal dryness. Furthermore, not all vaginal dryness is caused by vaginal atrophy, and not all dyspareunia is caused by vaginal atrophy. Having a non-hormonal vaginal gel to reduce dryness is very helpful because it has a high safety profile and no hormone-like adverse effects. Hyaluronic acid, which is part of the extracellular matrix and one of the glycosaminoglycans secreted during tissue repair, was compared with vaginal estriol in this study. Although the hyaluronic gel did not reduce vaginal pH like the estriol, it rapidly reduced vaginal dryness symptoms.

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## What's old is new again: paroxetine for hot flashes?

US Food and Drug Administration. FDA approves the first non-hormonal treatment for hot flashes associated with menopause. [press release]. June 28, 2013. <http://viajwat.ch/12y1Jvd>. Accessed July 19, 2013.

**Summary.** On June 28, 2013, the FDA approved a 7.5-mg formulation of paroxetine

mesylate (Brisdelle) for treatment of moderate to severe menopausal hot flashes. Recommended dosing is one 7.5-mg oral capsule daily at bedtime.

To assess efficacy and safety, researchers conducted two randomized, double-blind, placebo-controlled trials in a total of 1,175 women who reported experiencing at least 7 to 8 moderate-to-severe hot flashes daily. Brisdelle reduced daily hot flash frequency more than placebo: The difference between the median changes from baseline was one to two hot flashes daily. The mechanism of action for alleviating hot flashes remains unknown.

**Comment.** Paroxetine is a selective serotonin reuptake inhibitor that has been used at higher doses for treatment of generalized anxiety disorder, major depressive disorder, obsessive-compulsive disorder, and other psychiatric conditions. Despite its lower dosing in Brisdelle, this medication is not without side effects (eg, nausea, headache, fatigue) and warnings (suicidality). Although it represents an important nonhormonal option for diminishing hot flashes, how beneficial this drug will be in practice remains to be seen.

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## **Menopause Editor's picks from July 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.

### **Patterns of use of oral adjuvant endocrine therapy in Australian breast cancer survivors 5 years from diagnosis.**

Bell, Robin J.; Schwarz, Max; Fradkin, Pamela; Robinson, Penelope J.; Davis, Susan R.

### **Classifying menopause stage by menstrual calendars and annual interviews: need for improved questionnaires.**

Paramsothy, Pangaja; Harlow, Siobán D.; Elliott, Michael R.; Lisabeth, Lynda D.; Crawford, Sybil L.; Randolph, John F. Jr.

### **Comparison of follicle-stimulating hormone, estradiol, ovarian volume, and antral follicle count, based on the Stages of Reproductive Aging Workshop system, among community-based women in China.**

Sun, Ning; Lin, Shou-Qing; Lin, Hui-Jun; He, Zhong; Wang, Yan-Hong; Zhang, Ying; Chen, Feng-Ling; Jiang, Ying.

### **Elevated intraocular pressure is associated with metabolic syndrome in postmenopausal women: the Korean National Health and Nutrition Examination Survey.**

Park, Byoung-Jin; Park, Jin-Oh; Kang, Hee-Taik; Lee, Yong-Jae.

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

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- Information from the KEEPS, ELITE, and MsFLASH Trials
- Cancer survivorship
- The aging brain
- Musculoskeletal updates: The dynamic duo
- Menopause and sleep

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