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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.

**HT does not affect cognition in younger WHI women**


**Summary.** Researchers examined the effect of conjugated equine estrogens (CEEs) on cognitive function when initiated in postmenopausal women aged 50 to 55 years. The study population of 1,326 women from the Women’s Health Initiative (WHI) trials (using 0.625 mg CEE with or without 2.5 mg medroxyprogesterone acetate [MPA] over a mean of 7.0 years) was assessed for cognitive function with telephone-administered tests measuring global and domain-specific cognition. Testing occurred after an average of 7.2 years, when the women were a mean of 67.2 years old, and was repeated 1 year afterwards.

Primary outcome was global cognitive function, and secondary outcomes were verbal memory, attention, executive function, verbal fluency, and working memory. Results were similar among women assigned to CEE and women assigned to placebo. No overall differences were found for any cognitive domain. CEE produced neither benefit nor risk to cognitive function.

**Comment.** The critical window hypothesis has been proposed to explain apparently discrepant findings regarding the impact of hormone therapy (HT) on memory and risk for Alzheimer’s disease. Meta-analyses of observational studies revealed a significant 29% decreased risk of Alzheimer’s disease in women who used HT. In contrast, the WHI Memory Study (WHIMS) revealed a doubling of the risk of all-cause dementia in older women (mean age, 72 years) randomized to receive CEE/MPA and no increased or decreased risk of all-cause dementia in women randomized to receive CEE alone. The discrepancy between the observational studies and WHIMS has been attributed to differences in the timing of treatment initiation, with younger age at initiation (around the time of the final menstrual period) in the observational studies versus a much older age in WHIMS.

To date, all observational cohort studies that specifically examined the timing of HT initiation on the risk for Alzheimer’s disease have provided support for the timing hypothesis. Now an ancillary study, the WHIMS of Younger Women (WHIMSY), reveals no impact of either CEE or CEE/MPA on a measure of global cognitive function or other cognitive outcomes. Those data were interpreted as suggesting that treatments may be safer when initiated at a younger age.
As acknowledged by the authors, WHIMSY does not address whether initiating hormone therapy during menopause and maintaining therapy until symptoms pass affects cognitive function, either in the short or longer term. The average years since final menstrual period in the CEE group at the time of randomization was 9 years, but the average time since menopause is unclear since roughly 40% of women in the WHI had bilateral oophorectomy. Although WHIMSY suggests no benefit from CEE/MPA even with early treatment initiation, this is not surprising in light of evidence that CEE/MPA actually can have a small negative impact on verbal memory even when given to healthy early postmenopausal women.

The current findings raise the reassuring possibility that any negative impact of early use CEE/MPA may not be sustained. Critical and unanswered questions are: 1) whether other combination estrogen/progestogen treatments may confer cognitive benefits; and 2) whether estrogen alone confers benefits when used in the critical window.

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References:

Long-term outcomes of abdominal sacrocolpopexy for prolapse


Summary. This long-term follow-up of the randomized, masked 2-year Colpopexy and Urinary Reduction Efforts (CARE) trial aimed to describe anatomic and symptomatic outcomes up to 7 years after abdominal sacrocolpopexy (ASC) and to examine whether they are affected by Burch urethropexy, a concomitant anti-incontinence surgery. It examined 215 (92%) of eligible 2-year CARE trial completers. Of these, 181 (84%) and 126 (59%) completed 5 and 7 years of follow-up. After a median follow-up of 7 years, abdominal sacrocolpopexy failure rates increased in both groups. Urethropexy prevented stress urinary incontinence longer than no urethropexy. Researchers concluded that long-term risks of mesh or suture erosion should be considered with abdominal sacrocolpopexy.

Comment. Pelvic floor disorders are extremely common, affecting 46% of women aged 40 to 59 years, 37% of women aged 60 to 79 years, and more than 50% of women over age 80. Approximately 166,000 operations are performed each year in the United States for pelvic organ prolapse, and a woman’s lifetime risk of
surgery for prolapse is 7%.\textsuperscript{2-3} Success rates after prolapse surgery can vary from 19% to 97% depending on the outcome measure used to define success.\textsuperscript{4}

CARE\textsuperscript{5} is a landmark trial from the National Institute of Child Health and Human Development’s Pelvic Floor Disorders Network. It was one of the first clinical trials to evaluate the effect of a prophylactic concomitant anti-incontinence procedure (Burch urethropexy) at the time of an ASC. The ASC procedure with mesh has long been considered the gold-standard prolapse operation; however, limited long-term data exist. This extended CARE study is remarkable for its 7-year follow-up, double-blind trial design, and use of validated quality-of-life questionnaires and well-defined outcomes. Findings show that the number of women with long-term anatomic and symptomatic failure nearly doubled between years 2 and 7 (anatomic failure increased from 9% to 21%). Nevertheless, reoperation for prolapse recurrence was infrequent. The probability of mesh exposure through the vaginal epithelium by year 7 was 10.5%; about half of these received further treatment by study end. The Burch procedure continued to have a protective effect against stress urinary incontinence; however, the study was underpowered to confirm that there is no difference in prolapse outcomes over time in the Burch versus no Burch groups.

The ASC effectively relieves prolapse symptoms in most women. Adding an anti-incontinence operation decreases but does not eliminate the risk of stress urinary incontinence. Even though pelvic support deteriorates over time, most women do not choose to undergo repeat prolapse surgery. The recurrence of urinary incontinence and prolapse may reflect the natural history of pelvic floor disorders with aging and hormonal changes. The use of synthetic mesh, even when placed abdominally as opposed to vaginally, may still cause problems over time. Findings from this trial are important when counseling patients with prolapse about the surgical approach and timing.

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References:

OCs reduce risk of microsatellite unstable endometrial tumors


Summary. Endometrial cancer risk is modulated by hormonal and reproductive factors. The relationship between these factors and the microsatellite status of endometrial tumors is unknown. Microsatellite instability is a condition of genetic hypermutability resulting from impaired DNA Mismatch Repair. In this population-based case-control study from Alberta, Canada, researchers examined the association between hormonal factors and risk of microsatellite stable (MSS) and microsatellite unstable (MSI) endometrial cancer in postmenopausal women (MSS = 258, MSI = 103, ...
controls = 742) from 2002 to 2006. They found a significant risk reduction for MSI (\(P = .005\)) but not MSS (\(P = .23\)) cancer with oral contraceptive use. With over 5 years of oral contraceptive (OC) use, risk reduction was greater for MSI than MSS cancer. For OC use within the last 30 years, risk reduction was also greater for MSI than MSS cancer.

**Comment.** This is a preliminary report of some basic science likely previously unknown to most NAMS clinicians. In colonic cancers, MSI is considered to be present when tumor cells show base-pair repeats in DNA different from the patient’s normal cells. Apparently, this MSI is an underlying aspect in hereditary nonpolyposis colorectal cancer (HNPCC), a syndrome associated with both colon and endometrial cancers. MSI also occurs in 30% of nonhereditary (ie, sporadic) cases of endometrial cancer. The authors state that cases of MSI colon cancer have different hormonal risks than MSS cases. This paper examines this same phenomenon in endometrial cancer.

This epidemiologic study, including only sporadic postmenopausal endometrial cancers, showed that, overall, endometrial cancers were reduced with oral contraceptive use and increased parity, consistent with previous studies. Endometrial cancers were increased with earlier menarche and later menopause. In addition, menopausal use of estrogen plus progestogen reduced overall endometrial cancer risk (not universally demonstrated in prior studies) compared with controls. In terms of MSI versus MSS cancers, the only positive finding was that OC use greater than or equal to 5 years or use within the past 30 years reduced the risk of MSI but not MSS cancers. While this particular finding itself may not have current clinical relevance, the authors speculate that in the future this may have significance for a phenomenon called the mismatch repair system (MMR), which is an early step in the repair of DNA damage. If MMR is defective, there is an increase in spontaneous mutation and a predisposition to tumor development. This has been studied in HNPCC but may also play a role in sporadic tumors. The authors speculate that reduction of risk with OC use may be attributable to a long-lasting positive effect on this MMR system in the endometrium. This study is certainly interesting, although complex, and should not yet affect clinical management.

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**Effects of BMI changes on estradiol and testosterone in regard to breast cancer risk**


**Level of evidence:** II-3.

**Summary.** From a cohort study of over 100,000 UK women, a sample of 177 postmenopausal women aged over 45 years provided blood samples at two intervals between 2004 and 2011. The percentage change in plasma estradiol and testosterone levels per 1 kg/m² change in body mass index (BMI) and per 1 ng/ml change in plasma leptin were measured.

Results were as follows:

1. In women whose BMI decreased, estradiol decreased 12.7% per kg/m², and testosterone decreased 10.7% per kg/m².
2. In women whose BMI increased, estradiol increased 6.4% and testosterone increased 1.9%.
3. In women with decreases in leptin, estradiol decreased by 3.9% per ng/mL and testosterone decreased by 4.8% per ng/mL.
4. In those with leptin increases, estradiol increased by 1.7% and testosterone increased by 0.3%.
These results suggest that fat loss results in substantial decreases in estradiol and testosterone levels in postmenopause. Researchers suggest that their results support weight management as a way to lessen breast cancer risk.

**Comment.** The Breakthrough Generations Study, a long-term, UK cohort study to investigate breast cancer etiology, was initiated in 2003. Cohort members were recruited to assemble a large group (112,049) of women who could answer detailed questionnaires and give blood samples repeatedly over decades. Women aged 16 to 102 years from a broad geographic and socioeconomic distribution within the United Kingdom constitute this cohort; funding was provided by the Breakthrough Breast Cancer charity.

Although the emphasis on breast cancer risk modification is not readily apparent from the title of this paper, the potential relevance of changes of serum estradiol and testosterone levels resulting from increases or decreases in BMI quickly becomes evident. As already summarized, this report focuses on findings in 177 women (mean age 59.6 y) who experienced menopause after age 45, were more than 2 years postmenopausal (either natural or surgical), were not taking hormone therapy, had a BMI below 40 (average 26.1), and had not reported cancer. The final criteria involved a change in BMI over a 5 to 6 year period: an increase of 2 or more units, a decrease of the same degree, or a less-than-2-unit change.

The relationship between endogenous serum estradiol and testosterone levels and breast cancer risk in postmenopausal women has been well described. This study by Jones et al reports a reduction in both estradiol and testosterone serum levels associated with a reduction in BMI and an increase in both hormones, though of lesser magnitude, following a rise in BMI. Hormonal changes followed a similar pattern when the independent variable was leptin, rather than BMI, confirming the relationship between hormonal levels and adiposity. Changes in sex hormone-binding globulin were inversely associated with changes in BMI. The authors discuss their choice of estrogen assay, an indirect extraction-based radioimmunoassay. While they indicate that mass spectrometry is a more specific method, they emphasize percent change of estradiol rather than absolute levels, and in their methods, they took care to measure each woman’s baseline and follow-up sample in the same batch.

A number of questions regarding the subjects arise when considering the results of this study. It would be informative to know how many had experienced natural versus surgical menopause and whether the absence of ovarian steroid precursors in the women with surgical menopause affected the magnitude of the hormonal changes reported following weight loss. Also, it would be of interest to know the racial breakdown of this population. At least two recent reports suggest that postmenopausal African-American women have higher baseline levels of estrogen and testosterone than non-Hispanic white or Hispanic women and that weight loss has less effect on reducing steroid hormone levels in African-American women.

This study nevertheless provides an important piece of the emerging story about the hormonal implications of postmenopausal weight change and breast cancer risk. In addition to references cited by Jones et al, other recent studies reported a similar reduction in serum estrogens after weight loss in overweight or obese breast cancer survivors. Furthermore, the Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) study, a 4-year randomized trial of overweight/obese women with early-stage breast cancer diagnosed and treated within the previous 5 years, is designed to demonstrate the feasibility of achieving sustained weight loss and examining the impact on quality of life and co-morbidities. The goal is to establish biochemical mechanisms that link obesity to lower likelihood of disease-free
survival. It is possible that weight loss, and the resulting reduction in serum estrogen and testosterone levels, may emerge as a new standard of clinical care for postmenopausal women with a history or high risk of breast cancer. Careful attention to other potential sequelae of declining estrogen and testosterone levels will be important to monitor.

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References:

Is menopausal hormone therapy associated with excess risk for ovarian cancer?


**Summary.** Epidemiologic studies have indicated an association between menopausal hormone therapy (HT) and ovarian cancer risk. Investigators used information on 171,142 incident ovarian cancers in the North American Association of Central Cancer Registries database to estimate incidence rate changes before and after publication in 2002 of the Women’s Health Initiative (WHI) report on risks and benefits of combined HT, at which time HT use declined markedly.

In women 50 and older, age-standardized ovarian cancer incidence declined by 0.8% annually before the WHI report and by 2.4% after the report. Incidence of ovarian cancer in younger women decreased steadily (by 2.2%) throughout the study period. The change in incidence among older women was greatest in those most likely to use HT (ie, aged 50-69 years, white, and living in US regions where HT use was most prevalent), and was most pronounced for the endometrioid histologic subtype.

**Comment.** The authors suggest that these data are consistent with the hypothesis that menopausal HT raises risk for ovarian cancer, noting that similar data for breast cancer incidence support the broader idea of a link between HT and hormonally sensitive cancers. Undoubtedly, the development of these cancers involves multiple factors; furthermore, alternative explanations that are not immediately apparent may emerge. To me, this analysis is not sufficiently persuasive to convince me to alter my administration of HT, which remains indicated for those with severe menopausal symptoms who have no other contraindications.

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References:

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**Menopause Editor’s picks from June 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.

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**Estrogen alone and joint symptoms in the Women’s Health Initiative randomized trial.**
Chlebowski, Rowan T.; Cirillo, Dominic J.; Eaton, Charles B.; Stefanick, Marcia L.; Pettinger, Mary; Carbone, Laura D.; Johnson, Karen C.; Simon, Michael S.; Woods, Nancy F.; Wactawski-Wende, Jean.

**Comparative study of the quality of life associated with menopause in Tunisia and France.**
Ferrand, Farida; Hajri, Selma; Benzineb, Sarah; Draoui, Dorra Mahfoudh; Hassoun, Danielle; Delanoë, Daniel; Zins, Marie; Ringa, Virginie.

**Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy.**
Portman, David J.; Bachmann, Gloria A.; Simon, James A.; and the Ospemifene Study Group.

**Disruptions in ovarian function are related to depression and cardiometabolic risk during premenopause.**
Bleil, Maria E.; Bromberger, Joyce T.; Latham, Melissa D.; Adler, Nancy E.; Pasch, Laurie A.; Gregorich, Steven E.; Rosen, Mitchell P.; Cedars, Marcelle I.
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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- Cancer survivorship
- The aging brain
- Musculoskeletal updates: The dynamic duo
- Menopause and sleep

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