Cognition, estradiol, and proximity to menopause tested again

Results do not find change in relationship of estradiol levels and facets of cognition based on time from menopause


Summary. Researchers examined 643 healthy postmenopausal women, divided into early (<6 y after menopause) and late (10+ y after menopause) groups. They found that endogenous sex steroid levels were not associated with cognitive composites, but sex hormone binding globulin was positively associated with verbal memory. Mood was not significantly related to hormone concentrations. These results did not support the idea that time from menopause changes the relationship of endogenous serum levels of estradiol to facets of cognition.

Comment. Cognitive disturbance is an important and distressing symptom for women during the menopause transition and early postmenopause. Although many studies have not observed diminution of cognitive performance in menopause, some have noted a transient reduction in verbal learning during the perimenopause. Varying levels of endogenous estrogens and other reproductive hormones have been hypothesized to underlie menopause-associated cognitive changes based on animal models of cognitive performance but not human studies. In this baseline analysis of the Early versus Late Intervention Trial with Estradiol (ELITE), Henderson and colleagues examine verbal memory and executive function in relation to endogenous levels of estrogens (estradiol, estrone), testosterone, progesterone, and steroid hormone-binding globulin (SHBG) in 643 postmenopausal women who were more or less proximal to their final menstrual period (FMP; 6+ months to <6 y vs 10+ y). Hormone correlations with depressive symptoms were analyzed using the same approach.

The intervention phase of the ELITE trial will address the critical window hypothesis for cognitive response to estrogen therapy; namely, that there may exist in menopause a period of vulnerability to cognitive and affective sequelae and thereby a window of opportunity for women closer to their FMP to more robustly respond to exogenous estrogens. The current analysis from the baseline studies of this trial aimed to support this hypothesis by correlating cognitive performance and depressive symptoms with endogenous estrogen levels. By failing to demonstrate any difference between cohorts (early vs late postmenopause) in the association
between endogenous estrogen levels and cognitive performance or mood, results of the present study do not provide support for the critical-window hypothesis. Ancillary findings from this baseline analysis warranting further exploration include better verbal memory correlating with higher SHBG levels overall and, within the early postmenopause group specifically, better verbal memory and global cognitive performance correlating with higher progesterone levels.

The ELITE trial included a large and well-characterized study population that underwent a standardized battery of cognitive performance testing concurrent with serum testing of key endogenous sex steroids. The stratification into early and late postmenopause groups provided important contrasts in proximity to endogenous exposure to estrogens. However, by restricting the early postmenopause group to those with 6+ months of amenorrhea and serum estradiol levels below 25 pg/mL for the purpose of the trial, this group consequently had little variability in estradiol or other reproductive hormone levels, thereby minimizing opportunities to correlate endogenous hormone levels with cognitive performance or mood in the early postmenopause group at baseline. For example, the interquartile range for this group was 11.4 pg/mL for estradiol and 0.3 ng/mL for progesterone. The late postmenopause group similarly included women with consistently low levels of endogenous estrogens and progesterone. There was more of a range of testosterone levels in both groups as expected. In addition, cross-sectional studies using single time points to measure reproductive hormone levels have rarely observed correlations of hormones with any menopause-related symptom. Taken together, it is not surprising that the endogenous estrogen levels were not associated with cognitive or mood symptoms.

Results of this baseline analysis set an important context for the eagerly awaited ELITE trial results. Results of the trial will provide empiric data about the critical-window hypothesis for the effect of estrogen therapy on critical cardiovascular endpoints as well as cognitive performance and affective symptoms.

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Depression rates around natural menopause

Results differ in pre- and postmenopausal women


Summary. Researchers examined depressive symptoms and the rate of change in
reproductive hormones during a 14-year period around menopause in 203 late-reproductive-aged women who were premenopausal at baseline and reached natural menopause. There was higher risk of depressive symptoms before the FMP and lower risk afterwards. A history of depression increased risk before and after. No history of depression before the menopause transition was associated with a low risk of depressive symptoms 2 or more years after the FMP.

**Comment.** Numerous studies have shown that there is an increased likelihood of depressive symptoms during the menopause transition, but limited data address the likelihood of depressive symptoms after menopause. In the current analysis of the Penn Ovarian Aging (POA) longitudinal cohort study, Freeman and colleagues extend their previous work with a 14-year follow-up.

The observation of decreased likelihood of depressive symptoms after menopause among those with and without a history of clinical depression disorders provides reassuring data for those who experience mood disturbance during the menopause transition. It is especially important that women who first experienced significant depressive symptoms during the menopause transition also had a reduction in risk for depressive symptoms after menopause, although their risk remained elevated for the first 2 years after FMP. This latter observation buttresses the notion of a transient vulnerability during the period of most marked fluctuation in estradiol and follicle-stimulating hormone (FSH), given that levels of both remain more variable until 2 years after FMP when they begin to stabilize. These data argue for a more refined approach to the study of symptoms after menopause by dividing the postmenopause into an early and late phase, as recently established by the revised Stages of Reproductive Aging Workshop (STRAW+10) criteria.

Freeman and associates stratified their analysis by the presence or absence of prior history of clinical depressive disorders, because a prior depression history is the strongest predictor of significant depressive symptoms after menopause. Rate of change of FSH, estradiol, and inhibin B levels before the FMP was also examined in relation to risk for depressive symptoms after menopause. In contrast to previous POA results showing that vulnerability to depressive symptoms during the perimenopause correlated with greater variability in FSH and estradiol, the current analysis highlights that there are different hormonal correlates of depressive symptom risk after menopause because researchers observed that the risk of depressive symptoms after menopause decreased in relation to a faster rate of increase in FSH before the FMP. No associations were seen with changing levels of estradiol or inhibin B before the FMP. It is notable that this analysis focuses on hormone changes preceding rather than concurrent with the period of depressive symptom observation after FMP, as data are not reported for rates of change in FSH after FMP. Nonetheless, this finding suggests that the different trajectories of change in reproductive hormones observed during the menopause transition may provide important data about vulnerability to symptoms or health conditions after menopause.

This POA analysis provides important longitudinal data over an extended period of time surrounding the FMP. Clinicians can use these data to reassure patients that their risk for experiencing significant levels of depressive symptoms is reduced after their FMP, regardless of their mental health history or whether they experienced depressive symptoms for the first time during the menopause transition. However, as these data did not establish whether a clinical depression was present when depressive symptoms were assessed, caution must be used in translating these findings to those who develop a diagnosis of major depression during the menopause transition. To date, only the Study of Women’s Health Across the Nation provides such data, showing that the increased risk of experiencing a clinically
relevant depressive episode continues from the menopause transition through the first 2 years after FMP but is reduced thereafter both for those with and without a history of depression before midlife. Again, such data highlight the importance of stratifying analyses of the postmenopause into early and late, with careful characterization of the population under study during the first 2 years after FMP.

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References

HPV-based screening for cervical cancer prevention

In women aged 30 years and older, HPV-based screening resulted in less cervical cancer


Level of evidence: I.

Summary. Researchers evaluated a composite follow-up of four randomized clinical trials comparing HPV-based screening versus cytology-based cervical screening programs at four different institutions. Women recruited to all four trials had not had a hysterectomy and were attending for routine screening within organized population-based programs. Women in the control arm had either liquid-based or conventional cytologic testing. The endpoint of interest was how many women developed cervical cancer after a median of 6.5 years. After 2.5 years, the rate of cervical cancer was lower when HPV screening was used for women aged 30 years or older. Different methods of HPV testing were used at different sites. Management of abnormal results was handled according to guidelines but varied across the sites. After the first screening round was concluded, study participants were invited for further screening rounds within the organized programs at the routine interval (5 y in the Netherlands; 3 y in Italy, Sweden, and the United Kingdom).
Comment. This is an important article for anyone providing women’s health care. I recommend that readers review the entire article. One major strength of the study is excellent linkage between clinic visit and the outcome of cervical cancer. As in many practices, some patients did not return for follow-up; the researchers adjusted for this in the analysis.

Of interest is that comparative incidence screening was superior for the HPV methods after 2.5 years of follow-up. Adding cytology to HPV in follow-up was not helpful. There are many scenarios and different clinical dilemmas regarding screening and follow-up, depending on age and past gynecologic history. Practitioners should be aware that different organizations have different guidelines—professional organizations are constantly updating algorithms according to current research. This article should provide more unity among the guidelines. There is an app for the decision pathways available for download to your mobile device.

HPV screening methods are now more standardized and widely available compared with the time period covered in this study. It is reassuring that the interval needed for follow-up is now longer for most patients. Be alert that many patients equate an annual visit with an annual Papanicolaou smear. Be sure to inform your patients that preventive efforts are needed annually, even though cervical screening intervals have widened given the improved methods for screening and detection of cervical cancer.

Endometrial cancer: another reason to limit consumption of sugar-sweetened soda

Regardless of BMI, women who drank sugar-sweetened beverages had excess risk for estrogen-dependent endometrial neoplasia


Summary. Although the link between obesity and endometrial cancer is well established, how might intake of sugar-sweetened beverages (SSB) affect risk for this cancer? Beginning in 1986, researchers for the Iowa Women’s Health Study assessed participants’ health-related parameters, such as dietary intake. Incidence of type I (estrogen-related) and type II (estrogen-independent) endometrial cancer was determined annually using state and federal surveillance data.

As of 2010, among 23,039 evaluable women (mean age at baseline, 62 y), 592 incident, invasive endometrial cancers were identified (506 type I; 89 type II). After adjusting for body mass index and other confounders, placement in the top quintile for SSB consumption compared with the bottom quintile was associated with a 78% higher risk for type I endometrial cancer ($P=$.0005). Neither fruit juice nor sugar-free beverages were associated with risk for type I tumors. None of the dietary items studied were associated with risk for type II endometrial cancer.

Comment. Sugar-sweetened beverages are a major source of dietary sugar in the United States, affecting insulin and glucose levels more profoundly than sugars in whole foods. Furthermore, SSB consumption has been rising in parallel with obesity prevalence. By clarifying that consumption of SSB contributes to risk for type I endometrial cancer (regardless
of body weight), these findings point to the health benefits of avoiding sugary beverages.

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**Menopause Editor's picks from December 2013**

Objective cognitive performance is related to subjective memory complaints in midlife women with moderate to severe vasomotor symptoms.
Lauren L. Drogos, MA, Leah H. Rubin, PhD, Stacie E. Geller, PhD, Suzanne Banuvar, MHSA, Lee P. Shulman, MD, and Pauline M. Maki, PhD.

♦

Age-related changes in major ovarian follicular wave dynamics during the human menstrual cycle.
Heidi Vanden Brink, MSc, Donna Chizen, MD, FRCSC, Georgina Hale, MD, FRCSC, and Angela Baerwald, PhD.

♦

Quality of life and hypertension after hormone therapy withdrawal in New York City.
Michelle P. Warren, MD, Olivia Richardson, BA, Sonal Chaudhry, MD, Aimee D. Shu, MD, Yael Swica, MD, Valerie R. Sims, BA, and Nancy L. Sloan, DrPH.
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.

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<tr>
<th>Level</th>
<th>Description</th>
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<tr>
<td>Level I</td>
<td>Properly randomized, controlled trial.</td>
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<tr>
<td>Level II-1</td>
<td>Well-designed controlled trial but without randomization.</td>
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<tr>
<td>Level II-2</td>
<td>Well-designed cohort or case-control analytic study.</td>
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<tr>
<td>Level II-3</td>
<td>Multiple time series with or without the intervention (e.g., cross-sectional and uncontrolled investigational studies).</td>
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<tr>
<td>Level III</td>
<td>Meta-analyses; reports from expert committees; descriptive studies and case reports.</td>
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**New Member Forum on www.menopause.org**

What are your clinical challenges with vestibulodynia? Post on our Member Forum to discuss November’s *First to Know* papers: [https://www.menopause.org/member-login?ReturnUrl=%2fforum](https://www.menopause.org/member-login?ReturnUrl=%2fforum)