Care of Women During Menopause

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Introduction

This Clinical Update series is intended to help providers stay up to date on important articles that have been published on topics relevant to the care of women. In this update on menopause, we review the relationship between breastfeeding and early menopause, the effect of childhood abuse on vasomotor symptoms (VMS), and intriguing results from several early trials for a new medication class for nonhormonal vasomotor symptom treatment. We also highlight some new analyses from the Women’s Health Initiative and Nurses’ Health Study pertaining to estrogen therapy (ET) after oophorectomy and risks associated with vaginal estrogen (VE) use.

Early Menopause


What we know

Early menopause has been associated with adverse health outcomes such as cognitive decline, osteoporosis, and increased risk of cardiovascular disease.1 Prior studies that have examined the association between breastfeeding and menopause have been limited by study design (case–control or cross-sectional). Langton et al. studied this association using a large prospective cohort.

Study results

The study authors used the Nurses’ Health Study II Cohort that comprised 108,887 women who were followed from 1989 to 2015. In this prospective cohort, 2,571 women experienced early menopause, defined as 12 consecutive months of amenorrhea before the age of 45 years. Multivariate modeling was performed to look at risk factors associated with early menopause. When compared with nulliparous women, risk of early menopause decreased with increasing number of pregnancies (one pregnancy hazard ratio [HR] 0.92, 95% confidence interval [CI] 0.79–1.06; three pregnancies HR 0.78, 95% CI 0.67–0.92; p for trend 0.006). Longer breastfeeding duration was also associated with lower risk of early menopause. When compared with women who breastfed for <1 month, adjusting for parity, women who breastfed 25 months or longer had significantly lower risk of early menopause (HR 0.73, 95% CI 0.63–0.85, p<0.001). Those who breastfed for shorter durations showed a trend toward decreased risk (1–6 months HR of 0.95, 95% CI 0.85–1.07; 7–12 months HR 0.72, 95% CI 0.62–0.83; p for trend <0.001). When stratified by parity, risk of early menopause was lowest for those who exclusively breastfed (no other liquids or solids) for 7–12 months at each level of parity. Age at first birth was not associated with early menopause.

What this changes or adds

This study confirms prior data that nulliparous women are at increased risk of early menopause,2 and also suggests that some of the risk reduction with parity may actually be related to breastfeeding. Future study should explore the directionality of this association further, as to clarify whether parity and breastfeeding lead to less early menopause, or if women whose underlying biology will result in earlier menopause also are more likely to be nulliparous and/or unable to breastfeed.

Risk Factors for VMS


What we know

Retrospective cohort studies have shown an association between self-reported VMS and childhood abuse,3 as well as posttraumatic stress disorder.4 The mechanism of the relationship is unclear, although it has been suggested that those with history of childhood abuse and trauma are more likely to have anxiety disorders as adults, and increased anxiety predicts greater self-report of VMS.3 In this study, Carson et al. set out to examine the association between childhood trauma and VMS through both self-report and physical measurement of hot flashes.

Study results

The authors prospectively examined the relationship between childhood trauma (sexual, physical, or emotional

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abuse: physical or emotional neglect) and VMS. Data were evaluated from 295 women who were originally part of the MsHeart Study, conducted between 2012 and 2015. Childhood trauma and abuse were measured using a validated questionnaire. VMS were measured by self-report and by physiological measurement of sternal skin conductance. Sleep was also measured by both self-report and objectively with wrist actigraphy. Most women in the study were white and obese (mean body mass index 29), with a mean age of 54 years. Almost half of the sample (n = 129, 44%) reported childhood abuse or neglect. In women who reported having VMS at baseline, women with history of childhood sexual or physical abuse had significantly increased frequency of physiologically measured sleep VMS than women without history of abuse (yes sexual abuse = 4.49 sleep VMS vs. no sexual abuse = 2.45 sleep VMS, p < 0.01; yes physical abuse = 3.78 sleep VMS vs. no physical abuse = 2.47, p < 0.05). Childhood abuse was not associated with self-reported VMS frequency.

What this changes or adds

This study is unique in that it does not rely entirely on self-report of VMS, adding validity to its findings. Also, it highlights that in addition to performing the U.S. Preventative Services Task Force-recommended screening for intimate-partner violence,5 clinicians should consider screening for a history of trauma as well, particularly in symptomatic midlife women. A positive screen may serve as a potential predictor of a worse menopause experience and thus help guide anticipatory guidance on menopause management in this population.

Treating the Symptoms of Menopause


What we know

Estrogen decline at the menopausal transition is thought to lead to loss of thermoregulatory control, with the result being VMS. The thermoregulatory control center is in the hypothalamus; it is stimulated by neurokinin B (NKB) and inhibited by estrogen, so in menopause with declining estrogen levels, NKB activity is unopposed. The receptor for NKB is the neurokinin 3 receptor (NK3R). A new oral drug, fezolinetant, is an NK3R antagonist currently in development as a selective antagonist for both the NK3R and NK1R, and the RELENT-1 trial, whose results were presented by Trower et al., set out to explore the efficacy and safety of NT-814 in the treatment of VMS.

Study results

Depypere et al. performed a double-blind randomized placebo-controlled study comparing fezolinetant 90 mg twice daily to placebo. A mean daily total VMS score was calculated as a composite of severity and frequency data, where the number of mild, moderate, or severe VMS events during a time period were multiplied by 1 for mild, 2 for moderate, or 3 for severe, and the sum of the values divided by the number of days in the time period. At baseline, the mean daily total VMS score was 28.8 in the fezolinetant group and 25.8 in the placebo group; the mean frequency of moderate/severe VMS was 80.7 episodes per week in the fezolinetant group and 72.0 episodes in the placebo group. In total, 87 women (43 fezolinetant, 44 placebo) were studied, with mean age 53.5 years and mean body mass index 25.8 kg/m². After 12 weeks of treatment, the fezolinetant group had a significantly greater reduction in daily total VMS score than the placebo group, with a reduction of 26.5 points in the treatment group compared with reduction of 12.2 points in the placebo group (p < 0.001). The mean frequency of moderate/severe VMS was also significantly reduced from baseline, with 76.1 fewer episodes per week in the fezolinetant group compared with 35.3 fewer episodes per week in the placebo group (p < 0.001). The most common treatment-related adverse effects in the fezolinetant group were gastrointestinal (not specified further), affecting 14% of subjects in the fezolinetant group compared with none in the placebo group.

Fraser et al. performed a phase 2b randomized, double-blind, placebo-controlled study evaluating seven dosing regimens for fezolinetant for a 12-week period. Primary outcomes of the study were mean change in frequency and severity of moderate/severe VMS from baseline to various points of the 12-week study. Frequency was measured as number of moderate/severe VMS in a 24-hour period, and severity score was calculated as the number of moderate VMS multiplied by 2, plus the number of severe VMS multiplied by 3, and the sum divided by the total number of moderate and severe VMS in a 24-hour period. The seven dosing regimens studied included daily dosing (30, 60, 120 mg daily) and twice daily dosing (15, 30, 60, 90 mg twice daily). A total of 356 women were randomized in the trial, with mean age 54.6 years and baseline average of 9–11 moderate/severe VMS daily. When compared with placebo, all seven fezolinetant regimens significantly reduced severity of VMS at week 4; however, only the fezolinetant 60 mg BID, 90 mg BID, and 60 mg QD regimen significantly reduced severity of VMS when compared with placebo at week 12. Rates of treatment-emergent adverse events were no different between placebo and the seven dosing regimens, with the most common being diarrhea, nausea, and headache. Nine participants had elevated liver function tests, which normalized after treatment was discontinued; one participant had drug-induced liver injury attributed to fezolinetant 60 mg QD and one had cholelithiasis attributed to fezolinetant 60 mg QD.
Trower et al. presented the results of RELENT-1, which was a phase 1 multicenter randomized multidose placebo-controlled study of NT-814 that enrolled 76 women, with average age of 55 years. Women were admitted to a clinical research unit for days 1–8 of the trial, readmitted for day 14 pharmacokinetic assessments, and followed until day 21 for a safety assessment. The patients received either placebo or NT-814 at 50, 100, 150, or 300 mg daily. The most common adverse events were mild somnolence and headache, and no serious events led to study drug discontinuation. Adverse event rates were similar between placebo and all doses except for the 300 mg dose, which had a higher frequency. Self-reported hot flash frequency and severity, as well as frequency of waking due to night sweats, was evaluated. At day 14, there was reduction in hot flash frequency and waking due to night sweats for all doses of NT-814, with significant reductions at higher doses. For example, when compared with baseline, mean reduction in awakening due to night sweats in NT-814 group was 20% at the 50 mg dose (p = 0.059), 55% at the 100 mg dose (p = 0.135), 81% at the 150 mg dose (p < 0.001), and 63% at the 300 mg dose (p = 0.031); for comparison, the placebo group had a 32% mean reduction. Pharmacokinetic studies showed a plateau effect on measured outcomes with plasma NT-814 concentrations achieved with doses of 150 mg or higher.

What this changes or adds

These early trials suggest that neurokinin receptor antagonism, through either the NK₃R or both the NK₁R and NK₃R, appears to be a promising pharmacotherapeutic pathway for effective nonhormonal treatment of VMS. We look forward to seeing the results of future fezolinetant and NT-814 trials. More importantly, these studies also underscore the importance of understanding the etiology and pathophysiology of hot flashes and night sweats, so that targeted treatments for VMS can be developed.


What we know

VE has an FDA black box warning due to class labeling based on data related to the risks associated with systemic menopausal hormone therapy (MHT). In 2018, an analysis of the Women’s Health Initiative Observational Study (WHI-OS) was published, which showed no increased risk of cancer or cardiovascular disease with low-dose VE use. However, one potential weakness of the WHI cohort was the older mean participant age of 64.8 years in the treatment group. Bhupathiraju et al. investigated the association between VE and cancer or cardiovascular disease and VE use in younger menopausal women.

Study results

Study authors evaluated >53,000 women in the Nurses’ Health Study (NHS), a prospective cohort that has been enrolling women since 1976. In total, 896 of the 52,901 post-menopausal women in the NHS cohort (mean age 54 years) reported VE use. Outcomes studied included cancer (all types, with specific analyses of invasive breast, ovarian, endometrial, and colorectal cancers), cardiovascular outcomes (such as myocardial infarct [MI], stroke, pulmonary embolism/deep vein thrombosis [PE/DVT]), and hip fracture. In multivariate modeling, there were no significant differences between women who used VE and those who did not with regard to all studied outcomes. Specifically, there was no increased risk of invasive breast cancer (HR 1.13, 95% CI 0.82–1.55), endometrial cancer (HR 1.62, 95% CI 0.88–2.97), or ovarian cancer (HR 1.17, 95% CI 0.52–2.66), and no increased risk of total MI (HR 0.71, 95% CI 0.45–1.10) or PE/DVT (HR 1.05, 95% CI 0.58–1.92).

What this changes or adds

This study adds to the growing body of evidence that low-dose VE therapy does not carry the same risk profile as systemic MHT, despite the label’s black box warning. Providers should feel comfortable offering VE to women with bothersome genitourinary symptoms from the hypoestrogenic state of menopause and can reassure patients that observational data have not shown an increased risk of adverse outcomes.


What we know

Bilateral salpingo-oophorectomy (BSO) has been associated with adverse health outcomes such as increased mortality and increased risk for heart disease; these adverse effects may possibly be mitigated by MHT use. Manson et al. examined data from the Women’s Health Initiative trials to assess whether MHT use in women with history of BSO conferred any benefit.

Study results

Subgroup analyses of the Women’s Health Initiative Estrogen-Alone Trial were performed on 9,939 women aged 50–79 years with a history of hysterectomy and known oophorectomy status. Women who used ET alone (oral conjugated equine estrogen [CEE] 0.625 mg daily) were compared with those who used placebo, and results were stratified by BSO status and by 10-year age group at time of CEE assignment (50–59, 60–69, and 70–79 years). Patients were studied both in the intervention phase and during the 18-year follow-up. The median duration of intervention was 7.2 years of CEE or placebo. Primary outcomes were coronary heart disease (CHD), invasive breast cancer, all-cause mortality, and a composite global index of adverse events that comprised CHD, invasive breast cancer, hip fracture, stroke, PE, colorectal cancer, and death.

There were no significant differences in primary outcomes between women using CEE compared with placebo, or when stratified by prior BSO status. However, when stratified by age at time of assignment to CEE or placebo, differences were noted in women with a history of BSO. Among older women (70–79 years) with prior BSO, those who took CEE had a greater global index versus placebo (HR for global index 1.42, 95% CI 1.09–1.86). However, in younger women
(50–59 years) with prior BSO, those who took CEE had reduced all-cause mortality in the 18-year cumulative follow-up compared with placebo (HR 0.68, 95% CI 0.48–0.96). Women aged 60 years and older with BSO who used CEE did not have any mortality benefit over placebo in the 18-year follow-up period (all-cause mortality, 60–69 years, HR 0.88, 95% CI 0.74–1.05; 70–79 years, HR 1.02, 95% CI 0.86–1.21).

**What this changes or adds**

The results of this study confirm that the risk to benefit balance of MHT, and specifically ET in this population of hysterectomized women, is most favorable in younger menopausal women who initiate therapy in their 50 seconds. ET is not only effective in relieving common menopausal symptoms such as hot flashes, night sweats, and sleep disturbances, it may even provide a mortality benefit, particularly for younger women with prior BSO.

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**References**


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