Andrew M. Kaunitz, MD, NCMP
Dr. Kaunitz is University of Florida Term Professor and Associate Chairman, Department of Obstetrics and Gynecology, University of Florida College of Medicine–Jacksonville; Medical Director and Director of Menopause and Gynecologic Ultrasound Services, UF Women's Health Specialists at Emerson, Jacksonville. He serves on the OBG MANAGEMENT Board of Editors.

Deanna C. McCullough, MD
Dr. McCullough is Assistant Professor, Department of Obstetrics and Gynecology, University of Florida College of Medicine–Jacksonville.

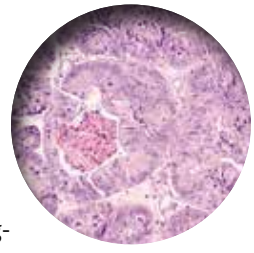
Dr. Kaunitz reports receiving grant or research support from Allergan and Mithra and that he is a consultant to AMAG, Merck, and Pfizer. Dr. McCullough reports no financial relationships relevant to this article.

What is the risk of endometrial cancer in women with postmenopausal bleeding, and who should be evaluated? Plus, consensus guidance on managing GSM in breast cancer survivors and addressing depression in perimenopausal women.

Among peri- and postmenopausal women, abnormal bleeding, breast cancer, and mood disorders represent prevalent conditions. In this Update, we discuss data from a review that provides quantitative information on the likelihood of finding endometrial cancer among women with postmenopausal bleeding (PMB). We also summarize 2 recent consensus recommendations: One addresses the clinically important but controversial issue of the treatment of genitourinary syndrome of menopause (GSM) in breast cancer survivors, and the other provides guidance on the management of depression in perimenopausal women.

IN THIS ARTICLE

Endometrial cancer is associated with a high prevalence of PMB



Clarke MA, Long BJ, Del Mar Morillo A, et al. Association of endometrial cancer risk with postmenopausal bleeding in women: a systematic review and meta-analysis. JAMA Intern Med. 2018;178:1210-1222.

Endometrial cancer is the most common gynecologic malignancy and the fourth most common cancer among US women. In recent

years, the incidence of and mortality from endometrial cancer have increased.[1] Despite the high prevalence of endometrial cancer, population-based screening currently is not recommended.

PMB affects up to 10% of women and can be caused by endometrial atrophy, endometrial polyps, uterine leiomyoma, and malignancy. While it is well known that PMB is a common presenting symptom of endometrial cancer, we do not have good data to guide counseling patients with PMB on the likelihood that endometrial cancer is present. Similarly, estimates are lacking regarding what proportion of women with endometrial cancer will present with PMB.

To address these 2 issues, Clarke and colleagues conducted a comprehensive systematic review and meta-analysis of the prevalence of PMB among women with endometrial cancer (sensitivity) and the risk of endometrial cancer among women with PMB (positive predictive value). The authors included 129 studies—with 34,432 women with PMB and 6,358 with endometrial cancer—in their report.

Cancer prevalence varied with HT use, geographic location

The study findings demonstrated that the prevalence of PMB in women with endometrial cancer was 90% (95% confidence interval [CI], 84%–94%), and there was no significant difference in the occurrence of PMB by cancer stage. The risk of endometrial cancer in women with PMB ranged from 0% to 48%, yielding an overall pooled estimate of 9% (95% CI, 8%–11%). As an editorialist pointed out, the risk of endometrial cancer in women with PMB is similar to that of colorectal cancer in individuals with rectal bleeding (8%) and breast cancer in women with a palpable mass (10%), supporting current guidance that recommends evaluation of women with PMB.[2] Evaluating 100 women with PMB to diagnose 9 endometrial cancers does not seem excessive.

Interestingly, among women with PMB, the prevalence of endometrial cancer was significantly higher among women not using hormone therapy (HT) than among users of HT (12% and 7%, respectively). In 7 studies restricted to women with PMB and polyps (n = 2,801), the pooled risk of endometrial cancer was 3% (95% CI, 3%–4%). In an analysis stratified by geographic region, a striking difference was noted in the risk of endometrial cancer among women with PMB in North America (5%), Northern Europe (7%), and in Western Europe (13%). This finding may be explained by regional differences in the approach to evaluating PMB, cultural perceptions of PMB that can affect thresholds to present for care, and differences in risk factors between these populations.

The study had several limitations, including an inability to evaluate the number of years since menopause and the effects of body mass index. Additionally, the study did not address endometrial hyperplasia or endometrial intraepithelial neoplasia.

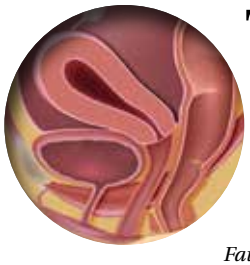
CONTINUED ON PAGE 24

WHAT THIS EVIDENCE MEANS FOR PRACTICE

PMB accounts for two-thirds of all gynecologic visits among perimenopausal and postmenopausal women.[3] This study revealed a 9% risk of endometrial cancer in patients experiencing PMB, which supports current practice guidelines to further evaluate and rule out endometrial cancer among all women presenting with PMB[4]; it also provides reassurance that targeting this high-risk group of women for early detection and prevention strategies will capture most cases of endometrial cancers. However, the relatively low positive predictive value of PMB emphasizes the need for additional triage tests with high specificity to improve management of PMB and minimize unnecessary biopsies in low-risk women.

WATCH FOR... ›› Update on abnormal uterine bleeding
Howard T. Sharp, MD, and Marisa R. Adelman, MD

CONTINUED FROM PAGE 22



Treating GSM in breast cancer survivors: New guidance targets QoL and sexuality

Faubion SS, Larkin LC, Stuenkel CA, et al. Management of genitourinary syndrome of menopause in women with or at high risk for breast cancer: consensus recommendations from The North American Menopause Society and The International Society for the Study of Women's Sexual Health. Menopause. 2018;25:596-608.

FAST TRACK

Management of GSM should be individualized based on shared decision-making involving the patient and her oncologist

More than 3 million breast cancer survivors reside in the United States. Accordingly, ObGyns see survivors on a frequent basis. For several reasons, genitourinary syndrome of menopause (also known as vulvovaginal atrophy) is particularly prevalent in women who have been treated for breast cancer. Chemotherapy, for example, often induces ovarian failure. For some premenopausal women, bilateral salpingo-oophorectomy may be performed or gonadotropin-releasing hormone agonists may be prescribed as part of breast cancer treatment. In postmenopausal survivors with hormone receptor–positive tumors, adjuvant aromatase inhibitor (AI) therapy may be used for up to 10 years. Treatment with AIs is associated with GSM symptoms.[5] Although vaginal estrogen is an effective treatment for GSM, package labeling for all estrogens, including vaginal estrogens, lists a personal history of breast cancer as a contraindication.

Given that there is little evidence addressing the safety of vaginal estrogen, other hormonal therapies, and nonprescription treatments for GSM in breast cancer survivors, many survivors with bothersome GSM symptoms are not appropriately treated.

Expert panel creates evidence-based guidance

Against this backdrop, The North American Menopause Society and the International Society for the Study of Women's Sexual Health convened a group comprised of menopause specialists (ObGyns, internists, and nurse practitioners), specialists in sexuality, medical oncologists specializing in breast cancer, and a psychologist to create evidence-based interdisciplinary consensus guidelines for enhancing quality of life and sexuality for breast cancer survivors with GSM.

Measures to help enhance quality of life and sexuality

The group's key recommendations for clinicians include:

- Sexual function and quality of life (QoL) should be assessed in all women with or at high risk for breast cancer.
- Management of GSM should be *individualized* based on shared decision-making involving the patient and her oncologist.
- Initial treatment options include:
  - —over-the-counter vaginal moisturizers used several times weekly on a regular basis
  - —lubricants used with intercourse
  - —vaginal dilator therapy
  - —pelvic floor physical therapy.
- Low-dose vaginal estrogen therapy may be appropriate for select women who have been treated for breast cancer:
  - —With use of vaginal estrogen, serum estradiol levels remain in the postmenopausal range.
  - —Based on limited data, use of vaginal estrogen is associated with a minimal risk for recurrence of breast cancer.
  - —Because their use is associated with the lowest serum estradiol levels, vaginal tablets, rings, or inserts may be preferable to creams.
  - —Decisions regarding use of vaginal estrogen in breast cancer survivors

CONTINUED ON PAGE 30

CONTINUED FROM PAGE 24

should involve the woman's oncologist. Appropriate candidates for off-label use of vaginal estrogen may be survivors:

- who are at relatively low risk for recurrence
- with hormone receptor–negative disease
- using tamoxifen rather than an AI
- who are particularly concerned about quality of life.

—Given that AIs prevent recurrence by lowering estrogen levels, oncologists may be reluctant to consider use of vaginal estrogen in survivors using adjuvant agents.

—With respect to use of vaginal estrogen, oncologists may be more comfortable with use in patients taking tamoxifen.

- Neither intravaginal dehydroepiandrosterone (DHEA; prasterone) nor the oral selective estrogen receptor modulator ospemifene has been studied in breast cancer survivors.

In women with metastatic disease, QoL, comfort, and sexual intimacy are key considerations when weighing potential therapies; optimal choices will vary with probability of long-term survival.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Although more data addressing the safety of vaginal estrogen as well as prasterone and ospemifene in breast cancer survivors clearly are needed, these guidelines should help clinicians who care for breast cancer survivors with GSM.

Framework provided for managing depressive disorders in perimenopausal women

Maki PM, Kornstein SG, Joffe H, et al; Board of Trustees for The North American Menopause Society (NAMS) and the Women and Mood Disorders Task Force of the National Network of Depression Centers. Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. Menopause. 2018;25:1069-1085.

Although perimenopausal women are more susceptible to the development of depressive symptoms and major depressive episodes (MDE), there is a lack of consensus regarding how to evaluate and treat depression in women during the menopausal transition and postmenopausal period.

Recently, an expert panel comprised of representatives from The North American Menopause Society and the National Network of Depression Centers Women and Mood Disorders Task Group developed clinical guidelines addressing epidemiology, clinical presentation, therapeutic effects of antidepressants, effects of HT, and efficacy of other therapies. Here we provide a summary of the expert panel's findings and guidelines.

Certain factors are associated with higher risk for depression

The perimenopause represents a time of increased risk for depressive symptoms and major depressive disorder (MDD), even in women with no prior history of depression. Several characteristics and health factors

are associated with the increased risk during the menopause transition. These include a prior history of MDD, current antidepressant use, anxiety, premenstrual depressive symptoms, African American race, high body mass index, younger age, social isolation, upsetting life events, and menopausal sleep disturbances.

Although data are inconclusive on whether surgical menopause increases or decreases the risk for developing depression compared with women who transition through menopause naturally, recent studies show an elevated risk of depression in women following hysterectomy with and without oophorectomy.[6,7]

Menopausal and depressive symptoms can overlap

Midlife depression presents with classic depressive symptoms that commonly occur in combination with menopausal symptoms, including vasomotor symptoms, sleep and sexual disturbances, and weight and energy changes. These menopausal symptoms can complicate, co-occur, and overlap with the clinical presentation of depression.

Conversely, depression may affect an individual's judgment of the degree of bother from menopausal somatic symptoms, thereby further magnifying the effect of symptoms on quality of life. The interrelationship between depressive symptoms and menopausal symptoms may pose a challenge when attempting to parse out contributing etiologies, relative contributions of each etiology, and the potential additive effects.

Diagnosis and treatment options

Diagnosis involves identifying the menopausal stage, assessing for co-existing psychiatric and menopause symptoms, appreciating the psychosocial factors common in midlife, and considering the differential diagnosis. Validated screening instruments can be helpful. Although a menopause-specific mood disorder scale does not yet exist, several general validated screening measures, such as the Patient Health Questionnaire-9, or PHQ-9, can be used for categorical determination of mood disorder diagnoses during the menopause transition.

Antidepressants, cognitive-behavioral therapy, and other psychotherapies are considered first-line treatments for perimenopausal major depressive episodes. Only desvenlafaxine has been studied in large randomized placebo-controlled trials and has proven efficacious for the treatment of MDD in perimenopausal and postmenopausal women.

A number of small open-label studies of other selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and mirtazapine to treat MDD in perimenopausal and postmenopausal women have demonstrated a positive effect on mood, and several SSRIs and SNRIs also have the added benefit of improving menopause-related symptoms.

In women with a history of MDD, a prior adequate response to a particular antidepressant should guide treatment selection when MDD recurs during the midlife years.

Although estrogen is not approved by the US Food and Drug Administration specifically for the treatment of mood disturbances, some evidence suggests that unopposed estrogen therapy has efficacy similar to that of antidepressant medications in treating depressive disorders in *perimenopausal women*,[8-11] but it is ineffective in

CONTINUED ON PAGE e53

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The findings from this expert review panel demonstrate that women in the perimenopausal transition are at increased risk for depressive symptoms, major depressive episodes, and major depressive disorder. The interrelationship between symptoms of depression and menopause can complicate, co-occur, overlap, and magnify one another. Clinicians treating perimenopausal women with depression that is unresponsive to conventional antidepressant therapy should consider concurrent use of estrogen-based hormone therapy or referring the patient to a clinician comfortable doing so.

FAST TRACK

SSRIs, SNRIs, and mirtazapine to treat MDD in peri- and postmenopausal women have been shown to have a positive effect on mood, and several SSRIs and SNRIs have the added benefit of improving menopause-related symptoms

CONTINUED FROM PAGE 31

treating depressive disorders in *postmenopausal* women. Estrogen therapy also may augment the clinical response to antidepressants in midlife and older women.[12,13] The data on combined HT (estrogen plus progestogen) or for different progestogens in treating depressive disorders in perimenopausal women are lacking and inconclusive. ●

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin.* 2017;67:7-30.
2. Matteson KA, Robison K, Jacoby VL. Opportunities for early detection of endometrial cancer in women with postmenopausal bleeding. *JAMA Intern Med.* 2018;178:1222-1223.
3. van Hanegem N, Breijer MC, Khan KS, et al. Diagnostic evaluation of the endometrium in postmenopausal bleeding: an evidence-based approach. *Maturitas.* 2011;68:155-164.
4. American College of Obstetricians and Gynecologists. ACOG Committee Opinion no. 734 summary. The role of transvaginal ultrasonography in evaluating the endometrium of women with postmenopausal bleeding. *Obstet Gynecol.* 2018; 131:945-946.
5. Baumgart J, Nilsson K, Evers AS, et al. Sexual dysfunction in women on adjuvant endocrine therapy after breast cancer. *Menopause.* 2013;20:162-168.
6. Chou PH, Lin CH, Cheng C, et al. Risk of depressive disorders in women undergoing hysterectomy: a population-based follow-up study. *J Psychiatr Res.* 2015;68:186-191.
7. Wilson L, Pandeya N, Byles J, et al. Hysterectomy and incidence of depressive symptoms in midlife women: the Australian Longitudinal Study on Women's Health. *Epidemiol Psychiatr Sci.* 2018;27:381-392.
8. Schmidt PJ, Nieman L, Danaceau MA, et al. Estrogen replacement in perimenopause-related depression: a preliminary report. *Am J Obstet Gynecol.* 2000;183:414-420.
9. Rasgon NL, Altshuler LL, Fairbanks L. Estrogen-replacement therapy for depression. *Am J Psychiatry.* 2001;158:1738.
10. Soares CN, Almeida OP, Joffe H, et al. Efficacy of estradiol for the treatment of major depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. *Arch Gen Psychiatry.* 2001;58:529-534.
11. Cohen LS, Soares CN, Poitras JR, et al. Short-term use of estradiol for depression in perimenopausal and postmenopausal women: a preliminary report. *Am J Psychiatry.* 2003;160:1519-1522.
12. Schneider LS, Small GW, Hamilton SH, et al. Estrogen replacement and response to fluoxetine in a multicenter geriatric depression trial. Fluoxetine Collaborative Study Group. *Am J Geriatr Psychiatry.* 1997;5:97-106.
13. Schneider LS, Small GW, Clary CM. Estrogen replacement therapy and antidepressant response to sertraline in older depressed women. *Am J Geriatr Psychiatry.* 2001;9:393-399.

Hormone therapy and multiple health outcomes: What 3 studies say about route of administration and treatment timing

Is vaginal estrogen used for GSM associated with a higher risk of CVD or cancer?[1]

Key takeaway. No. Vaginal estrogen use (average duration of use, 37.5 months) for genitourinary symptoms of menopause (GSM) was not associated with a higher risk of cardiovascular disease or cancer in nonusers of systemic hormone therapy in the Nurses' Health Study.

"Despite the boxed warning on vaginal estrogen, the findings from this study support the safety of vaginal estrogen use for effective relief of GSM in women with and without a uterus." —JoAnn V. Pinkerton, MD, NCMP
OBG Manag. 2019;31(2):51,52.

Does the type of menopausal HT used increase the risk of VTE?[2]

Key takeaway. Yes, according to a case-control study that analyzed data from 2 large UK databases. Use of oral conjugated equine estrogen or estradiol was associated with an elevated risk of venous thromboembolism (VTE) (OR, 1.49 and 1.27, respectively), while transdermal preparations were safest (OR, 0.96) when risk of VTE was assessed.

"Although randomized trials have not compared VTE risk with oral versus transdermal estrogen, prior observational studies have consistently suggested that transdermal estrogen does not elevate VTE risk; this is consistent with the results from this large UK study."
—Andrew M. Kaunitz, MD, NCMP
OBG Manag. 2019;31(2):14,16.

How does HT in recent and 10+ years past menopause affect atherosclerosis progression?[3]

Key takeaway. Secondary analysis of ELITE trial data among 596 women in early (<6 years) and late (≥10 years) postmenopause indicates that estradiol (E2) plasma levels resulting from oral E2 administration were inversely associated with atherosclerosis progression in the women in early menopause, but positively associated with atherosclerosis progression in those in late menopause.

"These new findings from a posttrial analysis of ELITE data provide yet further support for the hormone therapy (HT) 'timing hypothesis,' which postulates that HT slows atherosclerosis progression in recently menopausal women but has neutral or adverse effects in women who are at least a decade past menopause onset… These data…provide reassurance regarding the cardiovascular safety of HT when prescribed for recently menopausal women with bothersome vasomotor symptoms."
—Andrew M. Kaunitz, MD, NCMP
OBG Manag. 2019;31(1):51,52.

References

1. Bhupathiraju SN, Grodstein F, Stampfer MJ, et al. Vaginal estrogen use and chronic disease risk in the Nurses' Health Study. *Menopause.* December 17, 2018. doi: 10.1097/GME.0000000000001284.
2. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. *BMJ.* 109;364:k4810.
3. Sriprasert I, Hodis HN, Karim R, et al. Differential effect of plasma estradiol on subclinical atherosclerosis progression in early versus late postmenopause. *J Clin Endocrinol Metab.* 2019;104:293-300.