Case

A 56-year-old postmenopausal woman who had a successful endometrial ablation at age 42 presents with abnormal uterine bleeding (AUB). An ultrasound showed a thickened endometrium but no endometrial biopsy was performed because of scarring from the ablation. A hysteroscopy was performed showing hyperplasia without atypia. The woman did not want further surgery, but conservative management with oral progestin did not alleviate the problem, and after several months of treatment, she continued to have AUB. What are the management options going forward?

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Commentary by

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Abnormal uterine bleeding (AUB) is one of the most common complaints of women of reproductive age. There are many causes, including structural (fibroids, polyps) and nonstructural (anovulation, infectious, malignancy). Heavy menstrual bleeding is the most common form of AUB, and treatment can be managed either medically or surgically.

For women with symptomatic heavy menstrual bleeding and who have completed child-bearing, surgical management with either endometrial ablation or hysterectomy can be considered. Endometrial ablation, using second-generation, global ablation devices, is a low-risk, quick procedure that may be completed in an outpatient setting. Ablation of the endometrium results in a decrease in menstrual flow, and some women will experience amenorrhea.

There are no clinical guidelines for management of postmenopausal AUB after endometrial ablation. Identifying endometrial lesions such as endometrial hyperplasia or cancer can be difficult because the endometrium is altered in women after ablation procedures.

Studies have found that nearly all women who undergo endometrial ablation have residual endometrium. One retrospective study that examined magnetic resonance imaging in women after endometrial ablation (mean follow-up time, 34 mo) found that most women (56/59) had residual
endometrium, mainly in the uterine fundus, near the tubal ostia.\(^1\)

In postmenopausal women who experience AUB, an endometrial thickness greater than 4 mm warrants endometrial sampling. Endometrial thickness is less reliable in women with a history of ablation. A retrospective study of 63 women who had endometrial ablation before menopause found the postmenopausal endometrial thickness to be 5 mm to 10 mm (mean, 7.7 mm ± 3.0 mm) in 36 women and more than 10 mm in 15 women.\(^2\) Interestingly, amenorrheic women had thicker stripes than women with postmenopausal AUB (8.3 mm vs 4.1 mm). The only woman who developed endometrioid adenocarcinoma did not experience AUB and had an endometrial fluid collection visualized on ultrasonography. This study suggests that neither AUB status nor endometrial thickness reliably predict endometrial lesions after ablation.

Endometrial biopsy with a Pipelle may prove difficult because of postablation uterine scarring. However, in a series review of endometrial cancer diagnosed after endometrial ablation, endometrial biopsy resulted in a correct diagnosis in 89% of cases.\(^3\) In the event that endometrial biopsy is not feasible, hysteroscopy remains a good alternative to survey the uterine cavity and obtain adequate endometrial tissue sampling. In postmenopausal women with AUB, the priority is to obtain a tissue diagnosis to exclude hyperplasia and malignancy.

A recent Finnish study found that endometrial ablation was not associated with an increased risk of endometrial cancer.\(^4\) Only 0.05% of study women treated with endometrial ablation subsequently developed endometrial cancer (a rate analogous to matched controls). A limitation of this study was that the Finnish population is mostly of white ethnicity, with a lower incidence of endometrial carcinoma (14.2 per 100,000 age standardized woman-years)\(^4\) compared with the United States (19.5 per 100,000 age standardized woman-years).\(^5\)

Endometrial hyperplasia without atypia in postmenopausal women can be managed with medical or surgical treatment. Medical management with progestins, either oral, intramuscular, or with a levonorgestrel intrauterine system, will counteract unopposed estrogen. Unopposed estrogen is the most common risk factor for development of endometrial hyperplasia.

Hysterectomy provides definitive management of endometrial hyperplasia. If progestin therapy is used, endometrial sampling should be completed every 3 to 6 months. If the hyperplasia resolves and postmenopausal AUB stops, then no further treatment is needed. If postmenopausal AUB continues, progestin therapy should be continued and hysterectomy considered if the woman is a good surgical candidate.

Some argue that women with risk factors for endometrial cancer, such as hyperplasia, postmenopausal AUB, or anovulatory cycles, should be counseled against endometrial ablation. In one review, 82% of women with endometrial cancer after endometrial ablation had a prior diagnosis of endometrial hyperplasia with atypia or other significant risk factors, including postmenopausal status.\(^3\)

My approach to women with postmenopausal AUB in the setting of endometrial ablation is individualized. Preprocedure counseling is imperative so that women are aware of their personal risk factors for endometrial hyperplasia and subsequent difficulty in evaluation of the endometrium. If
hyperplasia is identified, management with either progestin therapy or hysterectomy is appropriate. In the event that hyperplasia persists, I would offer hysterectomy. If the woman is a poor surgical candidate or is not accepting of a surgical approach, I would continue progestin therapy and biopsy again in 3 to 6 months.

References

Disclosure: Dr. Roach reports no relevant financial relationships.

Question
A 50-year-old white female has severe hot flashes as well as severe migraines with significant aura. She has been admitted to a local hospital for full evaluation for possible stroke, but the final diagnosis was migraine with aura. The migraines are being treated with Botox and Topamax. Her sister had a stroke at age 39. She is already taking venlafaxine for depression. She is intolerant to gabapentin (dizziness and nausea). Any ideas for treatment of her incapacitating hot flashes?

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Vasomotor symptoms (VMS), may affect up to 80% of menopausal women and can significantly affect a woman’s life. Risk factors such as obesity, inactivity, ethnicity and smoking increase a woman’s risk of having VMS. Data from the Study of Women Across the Nation indicate that the median duration of VMS is 7.4 years.

Hot flashes appear to be a result of thermoregulatory dysfunction induced by fluctuating levels of estrogen; thus, estrogen therapy may be the treatment of choice because estrogen alleviates VMS symptoms and has some beneficial effects related to bone health and possibly to cardiovascular health and mood. Unfortunately, hormone therapy (HT) is contraindicated in a subset of women.

Women who should likely avoid HT for menopause symptoms include those with a history of breast cancer, coronary heart disease, previous venous thromboembolic event, stroke, and migraine with aura.

Nonhormone options can be used to treat VMS. These include pharmacologic options—serotonin norepinephrine-reuptake inhibitors (SNRIs), selective serotonin-reuptake inhibitors (SSRIs), gabapentin, and clonidine. A woman’s medication list should be reviewed before prescribing new medicines to ensure that there are no potential drug-drug interactions. For
example, women taking tamoxifen should not be prescribed paroxetine or fluoxetine because they are both potent inhibitors of CYP2D6 and decrease the serum concentrations of the active metabolite of tamoxifen.⁶

Women should also be counseled on possible adverse effects of medications. For example, venlafaxine and paroxetine can be associated with significant “withdrawal”-type symptoms such as nausea/vomiting, palpitations, and diaphoresis if the medications are stopped abruptly or doses are missed. Some women may be unable to tolerate medications or may desire alternative treatments. Nonpharmacologic options include cognitive-behavioral therapy (CBT) and clinical hypnosis.⁷

In reviewing this case, there are key elements to this woman’s history that affect which therapies we can offer. First, she has a history of migraine with aura and her sister suffered a stroke at age 39 years; therefore, she is not an ideal candidate for HT. She is currently taking venlafaxine, an SNRI, for depression (although it does not appear to be helping with her VMS). She was unable to tolerate gabapentin because of its adverse effects. Additional current medications include Topamax and Botox. There appears to be no significant drug interactions between Topamax and medications used to treat VMS; therefore, we have several choices of treatment for this woman.

Before discussing possible nonhormone treatments, it may be worthwhile to briefly explore HT. There is some literature showing that it may be acceptable to treat a perimenopausal woman who suffers from migraine with aura with transdermal estrogen at low doses, consistent with physiologic estrogen levels.⁵ Therefore, if this woman only had migraine with aura and debilitating hot flashes, a healthcare provider could consider discussing this option with her. However, she has an additional risk factor—a sister who suffered a stroke when aged 39 years.

Some may argue that additional information is warranted. For example, was the stroke ischemic or hemorrhagic? Did the sister smoke cigarettes? Does the sister have a known thrombophilia for which the woman could be tested? If so, and she tests negative for the thrombophilia, does that decrease her risk?

When considering pharmacologic management, we should do our best to limit the number of medications needed and attempt to use a medication that could be helpful in the treatment of more than one medical condition. In this case, I would recommend further exploration of medications in the antidepressant category because these could be used to treat both the depressive symptoms and VMS.

Generally, both SNRIs and SSRIs may be beneficial in mitigating VMS. To date, the only FDA-approved antidepressant for treatment of hot flashes is low-dose paroxetine; however, other SSRIs/SNRIs, including citalopram, escitalopram, and venlafaxine, are commonly used.⁸,⁹

The duration of treatment required before an improvement in symptomatology is seen is shorter than that required for improvement in depressive symptoms. On average, women see an improvement in VMS within 1 month of starting treatment. In this case, the woman is currently taking an SNRI that may be managing depressive symptoms but not alleviating VMS. One could consider increasing the dose of the venlafaxine (depending on the current dosage). Alternatively, if the woman’s depression is
mild and she is naive to other antidepressants, she could be offered a switch from an SNRI to an SSRI.

Additional information as to the timing of the VMS (ie, whether they are worse at night) might help us to consider specific medications. For example, paroxetine can be sedating, thus this antidepressant could be used for the treatment of her depression, VMS, and VMS-related sleep disturbances.

Mirtazapine, an atypical antidepressant, has also been found to be helpful. As with paroxetine, it is also sedating (at lower doses) and can be used, preferably, in women who report significant sleep disturbances related to VMS. If venlafaxine is the only antidepressant that has worked for this woman, I would recommend considering the addition of mirtazapine, because this antidepressant is in a different class and works on different receptors.

Alternatively, we could consider a different group of medications, such as clonidine. Clonidine is a central-acting alpha-2 adrenergic agonist. There is only modest evidence that clonidine may be helpful in ameliorating VMS. If this drug is an option, I would recommend the transdermal route to ensure consistent levels. Adverse effects with this medication include dry mouth, sedation, and orthostatic hypotension.

Cognitive-behavioral therapy (both individual and group) has been well studied, especially in the treatment of survivors of breast cancer who have VMS, and has shown modest beneficial outcomes, not only in the treatment of VMS but also with mood, sleep, and quality of life. To a lesser extent, clinical hypnosis has been shown to be effective in reducing VMS. Clinical hypnosis is a mind-body therapy that involves a deeply relaxed state and individualized mental imagery and suggestion. It has been widely used to manage other chronic symptoms, such as pain and anxiety.

Acupuncture has been investigated for its possible role in the treatment of VMS. A meta-analysis investigating actual versus sham acupuncture concluded that acupuncture does not affect the frequency of VMS; however, in some studies it decreased the severity of VMS.

Given this woman’s comorbidities, there is not a clear “right answer” with respect to treatment of her VMS. However, in reviewing possible treatment options, we have several choices.

I would likely recommend the option of venlafaxine plus mirtazapine, switching to mirtazapine alone, or switching to an SSRI. Additionally I would recommend CBT alone or in combination with the above. And although acupuncture may not be helpful in decreasing VMS, it may reduce their severity and would thus be an option. I would encourage the woman to choose the option best suited to her needs but to be open to other options in the future.

I would like to acknowledge Dr. Andrew Kaunitz for his contribution to this commentary.

References
3. Thurston RC, Joffe H. Vasomotor symptoms and menopause: findings from the Study of Women’s
What do you think of trying nonpharmacologic treatments for vasomotor symptoms as a way to avoid using hormone therapy if contraindicated? Would you ever think of sending a woman to a clinical hypnotist? And even though acupuncture is still unproven, is it something you would ever consider trying if you thought it might offer her relief? Visit our Member Forum to discuss the February Menopause e-Consult.

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