Your menopausal patient’s breast biopsy reveals atypical hyperplasia

How do you now manage her menopausal symptoms, including bothersome hot flashes?

JoAnn V. Pinkerton, MD

JoAnn V. Pinkerton, MD, Professor, Department of Obstetrics and Gynecology, and Director, Division of Midlife Women’s Health, University of Virginia. Dr. Pinkerton is a North American Menopause Society (NAMS) past president and certified menopause practitioner. She also serves on the OBG MANAGEMENT Board of Editors.

CASE Atypical ductal hyperplasia

Your 56-year-old, married, white patient has been on hormone therapy (HT) since age 52 for the treatment of vasomotor symptoms. She is taking a low-dose oral estrogen and micronized progesterone combination as she has an intact uterus. Her family history is positive for breast cancer, as her mother was diagnosed at age 68.

Her most recent annual screening mammogram shows linear calcifications. Because fine, linear, branching or casting calcifications are worrisome for atypical ductal hyperplasia (ADH) or ductal carcinoma in situ, a biopsy is recommended.

She elects to wean off and discontinue HT during the evaluation of her abnormal mammogram. The mammographic-guided stereotactic biopsy reveals ADH. She undergoes an open excisional biopsy, the results of which reveal extensive ADH with negative margins.

Six weeks after a lumpectomy she returns to your office reporting moderate to severe hot flashes that occur seven to 10 times per day and impair her sleep, leading to fatigue and “brain fog.” In addition, she is noticing vaginal dryness and dyspareunia despite use of lubricants. She requests treatment for her symptoms and wonders if she can restart HT systemically or vaginally.

How do you manage her hot flashes?

What are the alternatives to HT for hot flashes?

Certain lifestyle changes have been reported to provide relief for hot flushes. These include:

- use of layered clothing
- maintenance of cool ambient temperature (particularly during sleep)
- consumption of cool foods or beverages
- relaxation techniques (such as deep breathing, or paced respirations, for 20 min three times per day).

Despite sparse data, avoiding triggers such as spicy or hot foods or alcohol may be helpful.

Therapies such as evening primrose oil, dong quai, ginseng, wild yam, magnet therapy, reflexology, and homeopathy have not been found more effective in treating hot flashes than placebo.

Dr. Kaunitz

I would add soy isoflavones, red clover, and black cohosh to this list of

Dr. Pinkerton discusses her approach to screening patients at increased risk for breast cancer, at obgmanagement.com
Layered clothing and relaxation techniques may help for less severe hot flashes. Therapies that have not been shown to be more effective than placebo.3

Phytoestrogens (such as equol), acupuncture, yoga, and hypnosis continue to be tested in randomized trials with mixed results.

Off-label drug options offer modest help. There are currently no FDA-approved nonhormonal pharmaceutical options for relief of hot flashes; the gold standard for treatment remains estrogen therapy. For moderate to severe bothersome hot flashes, potentially effective drug therapies used off label include clonidine, selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), and gabapentin (TABLE 1).2,4 In large, randomized, controlled trials, the following agents were modestly more effective than placebo: desvenlafaxine,5 low-dose paroxetine salt,6 escitalopram,7 and gastroretentive gabapentin.3 Participants in these trials included women with both spontaneous and surgically induced menopause.

Although sponsors have applied for approval for three of these agents, the FDA so far has declined to approve these agents for vasomotor treatment due to concerns about risks versus benefits. Benefits of these nonhormonal prescription therapies need to be weighed carefully against side effects, because the reduction in absolute hot flushes is modest.

Many small trials have assessed other medications and complementary and alternative therapies regarding management of menopausal symptoms. Most, however, are limited by small numbers of enrolled participants and shorter study duration (≤12 weeks). In addition, enrolled participants have variable numbers of hot flashes, often less than 14 per week.3

**TABLE 1** Nonhormonal treatment of vasomotor symptoms

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study Design*</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complementary/alternative medicines (black cohosh, St. John’s Wort, red clover, acupuncture, exercise)</td>
<td>Duration: 4–52 wk; OL and RPL trials; entry criteria for most trials: &gt;14 hot flashes/wk</td>
<td>Mixed results, mostly with no sustained improvement</td>
</tr>
<tr>
<td>SSRIs** (paroxetine, fluoxetine, sertraline, citalopram, escitalopram)</td>
<td>Duration: 4–36 wk; RPL trials with all agents; N = 20–90 in active arms; entry criteria for most trials: &gt;14 hot flashes/wk</td>
<td>Reduction in vasomotor symptoms (frequency, composite scores): 28%–55%</td>
</tr>
<tr>
<td>SNRIs** (venlafaxine, desvenlafaxine)</td>
<td>Duration, 12–52 wk; RPL trials with all agents; N = 20–65 in VEN; N = 120–200 in DVS; Entry criteria &gt;14 hot flashes/wk for VEN; &gt;50/wk for DVS</td>
<td>Reduction in VMS (frequency, composite scores): 35%–58% for VEN, 55%–68% for DVS</td>
</tr>
<tr>
<td>Gabapentin**</td>
<td>Duration: 4–12 wk; RPL trials; N = 20–100; entry criteria for most trials: &gt;14–50 hot flashes/wk</td>
<td>Reduction in vasomotor symptoms (frequency, composite scores): 50%–70%</td>
</tr>
</tbody>
</table>

*All studies of menopausal, nondepressed women.

**Treatment is off label.


Can your patient restart HT?
If so, should HT be offered vaginally or systemically?
Non-HT may be enough for vaginal dryness. Benefit has been shown with the use of vaginal moisturizers twice weekly and

Do you have a menopause management dilemma? See page 41
lubricants as needed for sexual activity. Therefore, the local application of daily lubricants, such as olive oil, along with the use of moisturizers with regular sexual intercourse may be enough to maintain vaginal health and function.

In randomized trials, phytoestrogens lack benefit data for vaginal atrophy. Small pilot studies of the effect of oral/vaginal phytoestrogens on vaginal atrophy do not show any benefit on vaginal pH or vaginal maturation index and mixed improvement in vaginal dryness. In addition, no clear effect of these agents has been seen compared with placebo, except that there may be less progression of vaginal atrophy over time with phytoestrogens. It is possible that the benefits of phytoestrogens may take longer to take effect than the 12 weeks required to see an effect with HT.

Vaginal estrogen: limited safety data. No published clinical trials have assessed the impact of topical vaginal estrogen on risk of recurrence in breast cancer survivors, and concern exists because detectable estradiol levels have been reported in women who take aromatase inhibitors and have very atrophic vaginal mucosa. NAMS recommends that the discussion about vaginal estrogen be individualized between the patient, her provider, and her oncologist.

Vaginal estrogen creams and tablets (Vagifem 10 µg per tablet) are often started daily for 2 weeks for a “priming dose” then dosed twice per week. To minimize systemic absorption, creams may be used externally or with smaller doses vaginally. The higher the dose or more frequent the use, the greater the risk of significant systemic absorption, particularly when the vagina is atrophic. Another option is the vaginal estradiol ring, which delivers a low dose (7.5 µg per day) for 90 days.

**DR. SIMON** When you want the lowest dose of vaginal estradiol, consider Vagifem; the total dose of estrogen is lower over 90 days than with the vaginal ring.
Progestogen therapy is generally not needed when low-dose estrogen is administered locally to treat vaginal atrophy. Progestogen therapy is generally not needed when low-dose estrogen is administered locally to treat vaginal atrophy.12

A new oral option. A new oral option. In February 2013, ospemifene, a selective estrogen receptor modulator (SERM), was approved for pain with intercourse and vaginal dryness. (See “New treatment option for vulvar and vaginal atrophy,” by Andrew M. Kaunitz, MD, at obgmanagement.com.)

There is concern with systemic estrogen use. If her hot flashes remain persistent and bothersome, low-dose estrogen could be considered. However, data from the Breast Cancer Surveillance Consortium9 showed that as postmenopausal HT use decreased (from 35% to 11% between 1999 and 2005), rates of ADH decreased from a peak of 5.5 per 10,000 mammograms in 1999 to 2.4 per 10,000 mammograms in 2005. Similarly, rates of invasive cancer with ADH decreased from a peak of 4.3 per 10,000 mammograms in 2003 to 3.3 per 10,000 mammograms in 2005. This finding—that rates of ADH and invasive breast cancer were significantly linked to postmenopausal use of HT—raises concern about using HT in women with prior ADH. Of note, the cancers linked with ADH were of lower grade and stage and more estrogen receptor–positive than cancers not linked with ADH.17

How do you manage your patient’s increased risk of breast cancer? In examining the answer to this management point, we need to first ask and answer, “How does ADH develop?” and “What is her risk of developing breast cancer?”

The development of invasive breast cancer is believed to involve a complex, multistep process. Initially, there is disruption of normal cell development and growth, with overproduction of normal-looking cells (hyperplasia). These excess cells stack up...
Counsel your patients to use layered clothing, avoid overheating, try alternative therapies, and consider low-dose antidepressants or gabapentin used off label for troublesome hot flashes.

and/or become abnormal. Then, there is continued change in appearance and multiplication, becoming ductal carcinoma in situ (noninvasive). If left untreated, the cells may develop into invasive cancer. See Table 2 for the relative risk of a patient with ADH developing breast cancer.

Now, we can address, “How do you manage this patient’s increased risk of breast cancer?”

More frequent breast screening!

- Clinical breast exams twice per year
- Screening mammograms annually
- Screening tomosynthesis (These are additional digital screening views which provide almost a 3D view.)
- Screening breast ultrasound
- Screening breast MRI — if she has a 20% lifetime risk of breast cancer (family history or genetic predisposition) (Table 3).

Careful consideration of medications

Since it is possible that estrogen may fuel the growth of some breast cancers, avoiding systemic menopausal HT may be safest.

Counsel her about strategies to reduce breast cancer risk

These include:

- **Lifestyle changes**, including weight loss, exercise, and avoiding excess alcohol intake.
- **Preventive medications**. Tamoxifen or raloxifene (Evista) can be used for 5 years. These medications block estrogen from binding to the breast estrogen receptors. Another option is an aromatase inhibitor, which decreases estrogen production.

**Dr. Kaunitz**

It is important to note that both of the SERMs just mentioned (tamoxifen and raloxifene), as well as aromatase inhibitors, may cause women to experience vasomotor symptoms. SERMs also increase the risk of venous thromboembolism.

- Risk-reducing (prophylactic) mastectomy.

Management approach for this patient

This patient has had her ADH surgically excised. She will remain at higher risk for breast cancer and should consider strategies to decrease her risk, including lifestyle changes and the possible initiation of medications such as tamoxifen or raloxifene. New screening modalities, such as tomosynthesis or breast ultrasound, may be used to screen for breast cancer, and she may be a candidate for alternating mammograms and MRIs at 6-month intervals.

For her vaginal dryness, over-the-counter lubricants and moisturizers may be helpful. If not, topical or vaginal estrogen is available (as creams, tablets, or a ring) and provides primarily local benefit with limited systemic absorption.

For her bothersome hot flashes, if lifestyle changes don’t work, nonhormonal

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**TABLE 2** Relative risk of developing breast cancer

<table>
<thead>
<tr>
<th>Risk</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical ductal hyperplasia</td>
<td>4-5</td>
</tr>
<tr>
<td>Atypical ductal hyperplasia and positive family history</td>
<td>6-8</td>
</tr>
</tbody>
</table>

**TABLE 3** ACS guidelines for screening breast MRI

<table>
<thead>
<tr>
<th>Risk</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15% lifetime risk</td>
<td>MRI not recommended</td>
</tr>
<tr>
<td>15% to 20% lifetime risk</td>
<td>Talk about benefits and limitations of MRI screening</td>
</tr>
<tr>
<td>&gt;20% lifetime risk</td>
<td>Annual mammogram and annual MRI alternating every 6 months</td>
</tr>
</tbody>
</table>
therapies can be offered off label, such as effexor, desvenlafaxine, gabapentin, or any of the SSRIs—including those tested in large, randomized, controlled trials, such as escitalopram and low-dose paroxetine salt, at low doses.

**DR. KAUNITZ** Sertraline seems to be more likely to cause sweating than other SSRIs. For this reason, I don't prescribe sertraline off label to treat vasomotor symptoms.

If she is taking tamoxifen, however, SSRIs such as paroxetine should be avoided due to P450 interaction.

If her hot flashes remain persistent and bothersome, low-dose estrogen could be considered, with education about the potential risks, as she is already at higher risk for breast cancer. 

**Acknowledgment**

The author would like to thank Andrew M. Kaunitz, MD, for his forward thinking in helping to establish this new series on menopause.

**Disclosures**

Dr. Kaunitz reports that his institution receives grant or research support from Agene, Bayer, Endoceutics, Teva, Medical Diagnostic Laboratories, and Noven, and that he is a consultant to Bayer, Merck, and Teva.

Dr. Pinkerton reports that her institution receives consulting fees from Pfizer, DepoMed, Shionogi, and Noven and multicenter research fees from DepoMed, Endoceutics, and Bionova.

Dr. Simon reports being a consultant to or on the advisory boards of Abbott Laboratories, Agile Therapeutics, Amgen, Ascend Therapeutics, BioSante, Depomed, Lelo, MD Therapeutics, Meda Pharmaceuticals, Merck, Noven, Novo Nordisk, Novogyne, Pfizer, Shionogi, Shippan Point Advisors LLC, Slate Pharmaceuticals, Sprout Pharmaceuticals, Teva, Warner Chilcott, and Watson. He also reports receiving (current or in the past year) grant/research support from BioSante, EndoCeutics, Novo Nordisk, Novogyne, Palatin Technologies, Teva, and Warner Chilcott. He reports serving on the speakers bureaus of Amgen, Merck, Novartis, Noven, Novo Nordisk, Novogyne, Teva, and Warner Chilcott. Dr. Simon is currently the Chief Medical Officer for Sprout Pharmaceuticals.

**References**


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