This clinical e-newsletter from The North American Menopause Society (NAMS) presents questions and cases commonly seen in a menopause specialist’s practice. Recognized experts in the field provide their opinions and practical advice. Nancy Ann Roberson Jasper, MD, NCMP, the Editor of Menopause e-Consult, encourages your suggestions for future topics. The opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or by Dr. Jasper.

**Question**

A 41-year-old woman has menstrual-related migraine that is significantly affecting her quality of life. She has tried nonsteroidal anti-inflammatory drugs without significant relief. She has heard that oral contraceptives might be helpful for management and asks your opinion. How would you advise her?

**Commentary by**

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Menstrual-related migraine (MRM) is arguably the most common disabling condition encountered in women’s health. These migraines are more severe, longer lasting, and more resistant to treatment than those occurring elsewhere in the cycle.\(^1,2\)

And although headache medicine specialists are adept at diagnosing migraine and prescribing a host of antiepileptic drugs and other migraine preventives, most are not comfortable with manipulating the hormonal underpinnings of these “super migraines.”

The trigger appears to be estrogen withdrawal in susceptible women—either in the natural menstrual cycle or as a result of cycling onto placebo pills in a combined hormone contraceptive (CHC).

A population study found that 39% of menstruating women experience headaches with menses, and almost a third of these headaches meet established criteria for MRM.\(^2\)

**Diagnosis**

Migraine is formally diagnosed by meeting at least two of four signature characteristics: 1) moderate to severe pain, 2) throbbing, 3) unilateral location, and 4) intensification of headache with activity. Any two will suffice, much to the astonishment of patients who mistakenly believe that migraine must be severe or must be one sided.

Additionally, attacks must have at least one of two associated symptoms: either nausea or both photophobia and phonophobia, the latter usually diagnosed by the simple preference to avoid bright light or loud noises during an attack.

Untreated, migraines usually last from 4 to 72 hours. A practical, clinical approach to the diagnosis is simply “episodic disabling headaches.”

A stable history of attacks with predictable menstrual association offers further con-
Eliminating these headaches is relatively easy for the experienced women’s healthcare provider but quite difficult for most neurologists whose training is usually completely inadequate in hormone management. The goal is either to eliminate the cyclic drop in estrogen or minimize it to the equivalent of 10 µg estrogen or less.

**Specific preventive strategies for MRM**

1. Extended-cycle CHC regimens can afford lengthy reprieves from MRM. Breakthrough bleeding is the most common adverse effect but tends to decrease over time. It is preferable to dose CHC agents at bedtime to avoid estrogen nadirs during rapid eye movement sleep stages, which may be associated with migraine generation. It is also prudent to avoid concomitant drugs that might increase the rate of hepatic metabolism of estrogen (eg, high doses of topiramate), resulting in more rapid declines in estrogen concentration.

2. When using extended-cycle regimens that allow for periodic withdrawal bleeds, estrogen supplementation is needed during the withdrawal week to limit the drop to 10 µg ethinyl estradiol (EE) or less. For example, a 20 µg EE extended-cycle product with 10 µg EE in the thirteenth week would be adequate as packaged.

3. Traditional 21/7 or 24/4 hormone contraceptives can be used with supplemental estrogen during the placebo week. In a small open-label study, women took a CHC containing 20 µg EE on days 1 to 21, followed by 0.9 mg conjugated equine estrogens on days 22 to 28. All patients recorded at least a 50% reduction in migraine frequency, with a mean reduction of 78%.

4. Parenteral options can be created using a transdermal 20 µg EE/norelgestromin patch or a 15-µg EE/etonogestrel vaginal ring. With the former approach, I recommend the addition of a 0.1-mg EE patch in the withdrawal week to prevent MRM; with the latter, a 0.075 mg EE patch may be used in the week after ring removal.

5. Menstrually targeted estrogen supplements: With contraindications to the use of CHCs, some women may yet be candidates for targeted strategies such as perimenstrual administration of estradiol patches or gels. One study found that a 0.1-mg estrogen patch (applied just before the expected onset of menses and worn for 7 days) was effective, but lower doses were not. Other studies report that doses of 0.075 mg to 0.1 mg patch, cream, or gel beginning 5 to 7 days before expected menses and continuing through the first or second day of menses are helpful as well.

With successful elimination of MRM, there is typically a substantial reduction in headache burden, headache disability, and medication-overuse headache. The goal is then that random, episodic migraines can be quickly eliminated in the mild pain stage with a single fast-acting triptan.
References

Disclosures: Dr. Calhoun has no relevant financial relationships.

Case
A healthy 52-year-old postmenopausal (4 y) woman with a family history of breast cancer presents for her annual wellness exam. She notes ongoing dyspareunia despite regular use of over-the-counter moisturizers and lubricants. She has been unwilling to use local vaginal estrogen therapy (ET) in the past but understands that FDA has recently approved vaginal dehydroepiandrosterone (DHEA). She would like to understand the difference between DHEA and estrogen and whether this is an appropriate option for her.

Commentary by

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Genitourinary syndrome of menopause (GSM) is an area of unmet medical need for many women. Genitourinary syndrome of menopause affects 50% of postmenopausal women and becomes more severe with time since menopause. It will progress if not treated. Current estimates are that 32 million US women suffer from GSM, but only 7% of women are treated.¹

Genitourinary syndrome of menopause develops as a result of a fall in estrogen at menopause and declining androgen levels. These hormone changes result in an increase in vaginal pH, an increase in vaginal parabasal cells, and a reduction in superficial cells.

A higher vaginal pH results in an altered vaginal microbiome; lactobacilli disappear, and the vagina becomes colonized with pathogenic bacteria. The changes in the epithelial lining result in decreased lubrication and tissue friability.

Symptoms of GSM include vaginal dryness, irritation, pain with intercourse, and recurrent urinary tract infections. It is well established that GSM and associated vaginal discomfort negatively affects a woman’s sexual health, intimacy, partner relationships, and quality of life.²

Over-the-counter nonhormone moisturizers and lubricants are first-line therapies for GSM and can be helpful for symptoms, but they are often inadequate because they do not correct the underlying physiologic changes.

Estrogen therapy, either systemic or local, effectively treats GSM and the associated symptoms by restoring vaginal pH and healthy vaginal microbiome, thickening the vaginal epithelium, and increasing lubrication.
Systemic ET, although effective for treating GSM, results in sustained increases in serum estradiol levels and is contraindicated in women with a history of breast cancer and other medical conditions.

Low-dose vaginal estrogen products (creams, ring, and tablets) all effectively treat GSM and deliver a cumulative annual exposure of estradiol magnitudes lower than systemic products. Low-dose vaginal products are believed to exert their effects locally, without systemic effects. Vaginal estrogen products do not cause sustained increases in serum estradiol levels above the postmenopause range, although in some women there may be a short transient increase in estradiol levels with initial use.

Even with the differences in dosing and systemic levels, both systemic and vaginal estrogen products have the same package labeling and carry the same black-box warning. All estrogen-containing products, including low-dose vaginal products, cite an increase in breast cancer, cardiovascular disease, and dementia with use, despite the lack of data supporting this association with vaginal products.

This package labeling of vaginal estrogen products creates fear in women and is one of the factors that contributes to women with GSM remaining untreated. NAMS supports a modified labeling for vaginal estrogen products. In November 2015, after receiving a NAMS-sponsored petition requesting another look at the label, FDA held a scientific workshop to review data and consider a label change. A final decision on a label change from FDA is expected in 2017.

Use of vaginal ET in survivors of breast cancer remains controversial. Despite a recent American Congress of Obstetricians and Gynecologists 2016 position statement supporting the use of vaginal ET as an option for patients with breast cancer, citing the lack of data showing an increase in breast cancer recurrence in users of vaginal ET, many women will not be offered or will be unwilling to use this treatment option. This unmet medical need has led to interest in and research directed at finding safe and effective alternative nonestrogen therapies.

In 2013, ospemiphene, an oral selective estrogen receptor antagonist, was approved to treat dyspareunia associated with GSM. Although animal models and changes in breast density suggest a reduction in breast cancer risk with ospemiphene, the package labeling indicates because it has not been studied in women with a personal history of breast cancer, it should not be used in women with this history.

In November 2016, FDA approved vaginal DHEA, the newest option to treat moderate to severe dyspareunia associated with menopause. In the efficacy trials that led to approval, once-daily vaginal ovules of DHEA 6.5 mg inserted at bedtime were associated with improvement at the four coprimary endpoints: improvement in dyspareunia, increase in superficial cells, reduction in parabasal cells, and a reduction in vaginal pH.

Vaginal DHEA was found to be effective in trials lasting up to 12 months. The most common adverse event (AE), vaginal discharge, noted in 6% of women, was related to melting of the vehicle at body temperature. No serious treatment-emergent AEs were noted. Intravaginal DHEA given for up to 52 weeks has no stimulatory effect on the endometrium.

Dehydroepiandrosterone is a prohormone produced in the adrenal glands that is not itself biologically active. In postmenopausal
women, all estrogens and androgens come from conversion of DHEA intracellularly in peripheral tissues. The conversion requires aromatase. Vaginal administration of DHEA is effective because vaginal cells contain aromatase. This administration results in intracrine conversion of DHEA to estrogen and testosterone and produces local benefit, including improvement in vaginal pH and epithelial cell changes that result in improvement in dyspareunia. The conversion of DHEA is followed by local inactivation; therefore, circulating levels of androgens are within normal postmenopausal values after administration of vaginal DHEA.

Undiagnosed abnormal genital bleeding is a contraindication to vaginal DHEA. A history of breast cancer is not necessarily a contraindication, although the package insert states that it has not been studied in this population, and there is a warning regarding estrogen-sensitive breast cancer and in women aged younger than 40 years. Vaginal DHEA is expected to be available in pharmacies later in 2017.

Vaginal DHEA should be considered an effective and well-tolerated alternative option to vaginal ET for women aged older than 40 years with dyspareunia associated with GSM. Vaginal DHEA also may be a more acceptable option for those women with dyspareunia and GSM who are fearful of estrogen use.

References

Disclosures: Dr. Larkin has no relevant financial relationships.

What do you think about FDA’s approval of vaginal DHEA for GSM? Do you think that you will find many women asking for it as an alternative to vaginal estrogen? Will you be recommending it? Visit our Member Forum to discuss the January Menopause e-Consult.