Migraine Throughout the Female Reproductive Life Cycle

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CME Activity

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Learning Objectives: On completion of this article, you should be able to (1) describe the epidemiology of migraine in women, (2) describe the reproductive factors that influence the course of migraine in women, and (3) effectively treat migraine in women, including menstrual-related migraine, migraine during pregnancy and lactation, and migraine that worsens in the menopausal transition.

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Dr Faubion is a consultant for Mithra Pharmaceuticals and Procter & Gamble Co. Dr Calhoun is a consultant for Amgen, Depomed, and electroCore; is on the speaker's bureaus for Avanir, Depomed, Promius Pharma, Supernus and Teva and has received research support from Allergan, Autonomic Technologies, Capnia, and Scion NeuroStim.

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Abstract

By the end of their reproductive life cycle, roughly 40% of women have experienced migraine. Women have certain times of vulnerability for migraine that relate to abrupt declines in estrogen levels. Specifically, the prevalence of migraine is higher after menarche, during menstruation, during the postpartum period, and during perimenopause, but it is commonly lower during the second and third trimesters of pregnancy and the postmenopausal years. Therapeutic strategies for migraine management include hormonal manipulation aimed at eliminating or minimizing the decreases in estrogen that trigger the especially severe menstrual-related attacks. This article reviews special considerations for triptan use in pregnant and lactating women and in women with high risk for cardiovascular disease. Health care professionals caring for women throughout their life span should be aware of these important sex-based differences in migraine and migraine management.

By the end of their reproductive life cycle, roughly 40% of women have experienced migraine. Migraine is 3 times more common in women than in men, and worldwide, roughly one-fourth of reproductive-aged women have migraine. Of those who seek headache treatment from their health care professional (HCP), more than 90% meet diagnostic criteria for migraine,[1] yet the majority do not receive a correct diagnosis. In one review, 46% of persons with migraine in the United States thought they had a sinus headache, and 32% thought they had a tension headache.[2] When patients with chronic migraine consult an HCP who is not a headache specialist, only 16% receive a correct diagnosis.[3] The International Classification of Headache Disorders criteria for diagnosis of migraine are summarized in Table 1.[4]

The prevalence of migraine steadily increases through childhood, and the male to female ratio shifts with puberty, when migraine becomes markedly more prevalent in females and remains so throughout the rest of their lives. Most headache centers report that roughly 85% of their patients with migraine are women, and up to 70% of female migraineurs report a menstrual association with their attacks and changes in headaches related to hormonal contraception, pregnancy, and menopause. Thus, patients with menstrual-related migraine (MRM) account for about half of all migraineurs.

Which HCP a woman selects can greatly influence her course of treatment. Traditionally, neurologists are not trained in the hormonal management of MRM or catamenial epilepsy, and most training in gynecology, family medicine, and internal medicine does not delve into the hormonal management of neurologic disorders. A serious need exists to educate HCPs about sex-based differences in migraine and strategies for management of hormonally related headaches.

TABLE 1. International Classification of Headache Disorders Criteria for Migraine

Migraine is an episodic, recurring headache that lasts 4 to 72 hours and meets the following criteria:

1. Any 2 of these 4 pain qualities:
   - Moderate to severe intensity
   - Pulsatile[a]
   - Unilateral[b]
   - Exacerbated by or causing avoidance of routine physical activity
2. Either or both of these associated symptoms:
   - Nausea or vomiting (or both)[c]
   - Photophobia and phonophobia

[a]But 50% are steady.
[b]But 59% are bilateral.
[c]But almost 70% are not associated with vomiting.
Data from *Cephalalgia*.[4]

MENSTRUAL-RELATED MIGRAINE

Menstruation is a potent migraine trigger. By the end of their reproductive years, 40.9% of women have had migraine,[5] and menstrual attacks are up to 4 times more likely to be severe, to be associated with nausea and vomiting,[6] or to be resistant to abortive treatments.[7]

Although a review of conventional strategies for management of migraine is beyond the scope of this concise review, prophylactic strategies often include antihypertensives, anticonvulsants, and antidepressants.[8] Hormonal prophylaxis may be helpful for hormonally triggered migraines that do not respond to these treatments and can be used in conjunction with them. Targeted strategies can often be used in which a hormonal agent is prescribed for only a few days in each cycle. A prospective, randomized clinical trial confirmed the efficacy of 1.5 mg of transdermal estradiol gel applied for 7 days, beginning 10 days after ovulation and continued through the second day of menstrual bleeding.[9] In a similar study, 1.5 mg of estradiol gel was effective, whereas lower doses were ineffective.[10] This therapy provides serum estradiol levels of approximately 75 pg/mL (to convert to pmol/L, multiply by 3.671), but efficacy requires correct timing of the intervention.

Some women have noncontraceptive indications that support the use of combined hormonal contraception (CHC), including irregular menstrual cycles, dysmenorrhea, heavy menstrual bleeding, acne, hirsutism, and endometriosis, all of which are commonly managed with CHC. This therapy can be judiciously tailored to prevent the sudden declines in estrogen that trigger MRM.[11]

One approach is the use of extended-cycle CHC (for ≥12 weeks).[12] Oral CHC at doses of 20 to 35 μg of ethinyl estradiol (EE) can be used with continuous dosing of the active

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