NAMS Practice Pearl

Evaluation and Management of Migraine in Midlife Women

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Migraine is highly prevalent in women and, in addition to the pain component, can be associated with significant disability and loss of productivity. Migraine is often connected to fluctuations in hormones (primarily estrogen), commonly arising in puberty, worsening in perimenopause, and quiescing in late menopause. This* Practice Pearl *discusses the various types of migraine with respect to hormone fluctuations and details acute as well as preventive treatment.

At least three times more prevalent in women than in men, migraine is a chronic disorder, with episodic attacks manifested by headaches of long duration characterized by moderate to severe pain and associated symptoms such as photophobia, phonophobia, nausea, and vomiting. Although the annual prevalence of migraine in women of all ages is 17%, the peak prevalence of migraine occurs in premenopausal women in their late 30s at approximately 30%.[1]

Few studies address epidemiology or treatment of migraines in midlife women. Clinical observations, supported by epidemiologic studies, suggest that migraine generally worsens during the menopause transition and improves postmenopause.[2,3] Perimenopause-related increases in comorbid conditions (anxiety, depression, sleep disturbances) also may contribute to worsening of migraine. The association between perimenopause and migraine exacerbations appears most pronounced in women with a history of menstrual migraine and declines after menopause, with stabilization and lowering of endogenous estrogen levels.[2,3] In contrast with spontaneous menopause, induced menopause, including surgical menopause, appears to be associated with increase in frequency or intensity of migraines.[3]

Most women with migraine describe specific triggers for their migraine attacks.[4] The recognition of a 5-day window of migraine occurrence around the start of menses is predominantly based on women's frequent reports that menstruation triggers their migraines. A recent study using data from the Study of Women Across the Nation showed faster decline in urinary estradiol in the 2-day postluteal peak in women with migraine compared with controls, independent of headache occurrence in the cycle, suggesting that faster estrogen decline is an inherent trait of women with migraine.[5]

The International Classification of Headache Disorders criteria define three subtypes of migraine in relation to perimenstrual attacks.[6] This nomenclature varies from common gynecologic nomenclature for menses, with the onset of menses referred to as day 1 and the period of perimenstrual migraine referred to as day −2 to +3 (± 2 days from the first day of bleeding).

Migraines that occur only perimenstrually are categorized as pure menstrual migraine (PMM), a condition that affects 7% of premenopausal women with migraines. In contrast with PMM, most women with migraine experience migraine headaches perimenstrually and at other times of their cycles. This condition is defined as menstrually related migraine (MRM) and is estimated to affect approximately 70% of premenopausal women who report migraine. When migraines do not appear to be related to menstruation, they are classified as nonmenstrual migraine.

The diagnosis of the subtypes of menstrual migraine requires diary confirmation, with perimenstrual attacks occurring in at least two out of three cycles.[6] Accordingly, encouraging women to maintain headache diaries is a key component of effective diagnosis and treatment of migraine. The predictability of perimenstrual attacks in women of reproductive age allows for effective short-term treatment in days at risk for menstrual migraine while minimizing exposure to medication, the so-called "miniprophylaxis."[7,8]

Treatment of migraine in all stages of life may be acute or preventive, with practitioners often prescribing both treatments concomitantly.[7-9] In terms of a woman's lifespan, migraine treatment has been conceptualized around the reproductive cycle, with miniprophylaxis often recommended for PMM and MRM[7,8] and specific recommendations available for treatment of migraine in pregnancy and lactation.[9] No specific recommendations regarding migraine treatment exist for the menopause transition and menopause.

In deciding treatment approaches for midlife women, the clinician should consider the characteristics and frequency of the woman's headaches, relationship of headache to the menstrual cycle, stage of menopause, exogenous hormone use, other comorbidities and medications, smoking history, and a woman's preferences. The increased age of the postmenopausal population carries with it higher rates of disease, particularly cardiovascular disease (CVD), and because of this potential, vasoconstricting drugs such as triptans and ergots are often avoided in this setting.[10] An integrated approach should be advocated, potentially encompassing exogenous hormone treatment, preventive and acute headache medication, and nonpharmacologic treatments such as behavioral changes (trigger recognition and management) and behavior therapy (such as relaxation, cognitive behavioral therapy, biofeedback).[7-9] It is often helpful to combine relaxation and biofeedback training with medication therapy.[9]

In terms of acute treatment, nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstay, followed by triptans, which can also be used as the first line of acute treatment in perimenopausal and postmenopausal women in the absence of cardiovascular risk factors or a history of CVD.[7,8] Miniprophylaxis starting 2 to 5 days before the onset of menses is recommended for menstrual migraine in those with regular cycles treating with NSAIDS or triptans. Additionally, transdermal estradiol (eg, a 0.1-mg patch) applied for a week starting about 5 to 7 days premenstrually and continuing through the second day of bleeding has been shown to decrease migraine occurrence and is particularly effective in those in whom perimenstrual attacks do not respond to nonhormone strategies.[7,8] These short-term prevention strategies are not feasible in women with irregular cycles, necessitating prevention with daily migraine medication rather than focused only on days around menses. Most migraine preventive agents, including beta-blockers, topiramate, tricyclic antidepressants, and additional second-line agents (selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, magnesium) can be used safely in midlife women.

In addition to acute and preventive medications commonly used in premenopausal and postmenopausal women, exogenous estrogen formulations have been used in the treatment of migraine during perimenopause to mitigate fluctuating estrogen levels.[2,3] In premenopausal women who suffer from migraine with aura (MA), a transient sensory disturbance typically manifesting with visual symptoms before headache pain, use of combination (estrogen-progestin) hormone contraceptives (CHC) increases risk of stroke.[10] Although exogenous estrogen has been observed to trigger aura de novo and worsen the severity and frequency of preexisting attacks in women with MA,[10] these appear to be primarily because of high doses of estrogen and are less likely to occur with newer CHC formulations containing lower doses of estrogen.[11] Furthermore, use of hormone therapy (HT) is not contraindicated in migraine with or without aura.[3]

A recent Women's Health Initiative study evaluating the risk of CVD in postmenopausal women did not detect significant risk associated with history of migraine if HT was used.[12] Accordingly, some experts recommend that when HT is used in perimenopausal women with migraine and an intact uterus, doses of oral estrogen lower than those used in traditional low-dose oral contraceptives should be combined with progestin doses sufficient to prevent ovulation. Two examples of such formulations (both labeled for the treatment of vasomotor symptoms) are ethinyl estradiol 5 µg combined with norethindrone acetate (NA) 1 mg, and estradiol 1 mg combined with 0.5 mg NA (both formulations available as generics). If transdermal estradiol is used in this setting, it can be combined with one-quarter or one-half of a 5 mg NA tablet daily.

Perimenopause often provides challenges in the treatment of migraine because of loss of predictability of hormone-related attacks and frequent worsening of symptoms. Women should be instructed to keep a headache diary, and both preventive and acute treatment options should be considered on the basis of headache frequency and burden. Treatment of other comorbidities will guide the choice of agents used. In addition to medication options, behavioral treatment modalities may be helpful in symptom control and management. Finally, midlife women with migraines will benefit from collaborative care provided by headache specialists (https://americanmigrainefoundation.org/find-a-doctortreatment) and clinicians with special expertise in menopause.

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Disclosures

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