Migraine in Women

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ABSTRACT

Purpose of Review: This article discusses hormonal milestones and the influence that hormonal fluctuations make in the frequency and severity of migraine in women and includes information on acute, short-term, and preventive strategies for hormonally influenced migraine and the situations in which hormonal therapies may be offered.

Recent Findings: Genomic patterns in adolescent girls differentiate between menstrually related migraine and non–menstrually related migraine. The age at initiation of estrogen replacement therapy appears to be significant with respect to stroke. No increase in stroke occurred in women on low-dose (50 μg or less) transdermal estrogen replacement compared to women not using estrogen replacement. Childhood maltreatment is more common in women with migraine and depression than in women with migraine alone.

Summary: Management of hormonally influenced migraine involves a clear identification of the relationship between migraine and hormone change. A thorough history and detailed diary are critical in identifying this relationship and in predicting response or following response to hormonal therapies. The evolution of migraine in an individual may be strongly driven by hormonal shifts. Although limited, clinical evidence suggests that oral contraceptive use in young women with episodic migraine may transform their pattern into chronic migraine. Thus, particular attention to changes in migraine patterns following either endogenous or exogenous hormonal changes is crucial. Providing reassurance and education that migraine is a biological disorder and providing an understanding of the role of estrogen in the frequency and severity of migraine can guide treatment choices. Pharmacologic treatments include acute therapy, with short-term and standard prevention offered where appropriate. Hormonal therapies are not first-line therapies but may be important choices for a woman with migraine whose estrogen fluctuation is continually exacerbating migraine attacks. Given the many hormonal stages during the life of a woman with migraine, therapies may vary according to hormonal stage and status. Overall wellness should also be emphasized; regular exercise, balanced diet, smoking cessation, weight control, and sleep hygiene are important in the management of migraine.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Brandes discusses the unlabeled use of medications for hormonal management and nonhormonal management of migraine in women, none of which are specifically US Food and Drug Administration approved for migraine.

INTRODUCTION

In 1984, one of the first reviews of the role of estrogen in migraine noted that ''the femaleness of the migraine condition is inescapable.''[1] Considerable evidence has since accumulated that links the female ovarian steroid hormones estrogen and progesterone to migraine. Migraine is more common in women (18%) than in men (6%).[2] The female preponderance of migraine seems to be related to hormonal milestones and epochs of time throughout the reproductive life cycle: menarche, pregnancy, the postpartum state and breast-feeding, perimenopause, menopause, and the use of oral contraceptive pills (OCPs) and hormone replacement therapy (HRT) (**Table 7-1**). During any of these stages, or therapy related to

KEY POINTS

- Migraine diaries or calendars are essential for diagnosis of hormonally influenced migraine.
- Take the hormonal history to determine possible influence on migraine.
- Ask specifically about hormonal therapies because many women forget to include oral contraceptives, patches, injections, pellets, intrauterine devices, and creams when listing their medications.

TABLE 7-1 Milestones Likely to Impact Migraine Frequency, Severity, and Pattern

- Menarche
- Pregnancy
- Perimenopause
- Menopause
- Late-life migraine accompaniments

them, both the prevalence and severity of migraine may change. Therapeutic intervention may become necessary during puberty as menstrual cycles begin, throughout reproductive years, and again at perimenopause and postmenopause. Establishing the historical features of hormonally triggered migraine[3] is critical in designing effective treatment strategies.

Diagnosis and management of hormonally influenced migraine is virtually impossible without a migraine diary or calendar. Many women, who often minimize the role of menses or OCPs when initially asked about a temporal relationship, simply have never kept track of their headaches or hormonal influences. The initial interview for women presenting with headache should include the history of her hormonal events. Start by asking the age at which she first recalls any headaches. Ask about age at onset of menses and whether any headaches were noticed around the time of menses. Determine past use of OCPs, including when OCPs were begun, any headaches occurring within months of OCP therapy, and any change in headaches. Did a first migraine aura occur while on OCPs? What type of OCP was taken? Was it dosed continuously or cyclically? Be clear about why OCPs were taken, eg, for endometriosis, for cycle regulation, for contraception.

Next, ask about the impact of pregnancies and/or fetal losses on headache. Ask about specific trimesters of pregnancy, eg, did the headache worsen during the entire pregnancy or just during the first trimester? If migraine began during pregnancy, was it accompanied by aura? If so, was a complete evaluation conducted to determine underlying stroke risk factors? Ask about the frequency of headaches during breast-feeding. If they reduced in frequency or severity, did the headache pattern resume or worsen once lactation ended? Ask about any other hormonal manipulation that a woman may have experienced. Was there treatment for infertility? For irregular cycles? For recurrent fetal loss? How did the headaches respond to the hormonal change?

For women who have undergone partial hysterectomy (uterus removal only), total hysterectomy (uterus removal and bilateral oophorectomy and salpingotomy), or endometrial ablation, ask about the change in headache frequency and severity, when and if hormone therapy was begun, and how the headache responded. Obtain the specifics of the formulation and dosages of the hormone therapy. Was hormone replacement discontinued because of fear of complications or because headache worsened?

Answers to these questions, along with a careful headache diary of at least several months' duration, allow the clinician to predict likely responses to hormonal therapies and their influences on hormonally driven migraine. When exogenous hormonal therapies worsen migraine attacks, offering more hormonal treatments is unlikely to yield improvement in frequency or severity. For women whose pattern improves with stabilization of estrogen levels, hormonal therapies may be included as first-line therapy, unless contraindications are present.

MENSTRUAL MIGRAINE

Among women with migraine, 11% have onset of migraine at menarche and are more likely to experience menstrual migraine.[4] Only 14% of women with migraine have migraine only in association with their menstrual periods. Approximately 60% have migraine with menses and at other times during the menstrual cycle. Although no formal International Headache Society classification exists, a common definition of menstrual migraine is an attack (mostly without aura) occurring in two out of three menstrual cycles. However, a variety of definitions are used in clinical studies and therapeutic trial studies, eg, in triptan short-term prevention trials, the definition includes migraine experienced 2 days before the onset of menses to 3 days after the start of menstruation. Not surprisingly, differences in the prevalence of menstrual migraine are observed depending on the definition, and these prevalence estimates range from as low as 4% to as high as 73%. To lessen confusion in definitions of menstrually related migraine, the International Classification of Headache Disorders, Second Edition (ICHD-II) includes suggested definitions in its appendix to encourage validation by research (**Table 7-2**).[3,5]

The trigger for migraine onset is timelocked with the drop in estrogen occurring during the luteal phase of the menstrual cycle and is an important guide to therapy. In seminal work that has subsequently been replicated, Somerville noted the association between migraine and a prolonged high level of estrogen before the fall in estrogen levels, and was able to delay the onset of migraine by artificially but briefly maintaining high estrogen levels.[6] Clinical experience attests to the occasional link between migraine attacks and ovulation, but this has never been confirmed epidemiologically. The presumed mechanism of attack is an abnormally high level of estrogen preceding a hypoestrogenic postovulatory phase long enough to trigger an attack.[7]

Changes in multiple neurotransmitter systems occur with decreases in estrogen and are purported to be relevant to migraine attacks. Much regarding these mechanisms is speculative because of sparse clinical research. Hypotheses include prostaglandin release, changes in opioid tonus, increased sensitivity of dopamine receptors and serotonergic transmission, altered reactivity of cerebrovasculature to serotonin, and impaired nocturnal melatonin increase.[8]

Genomic patterns in adolescent girls have recently been shown to differentiate between menstrually related migraine and non–menstrually related migraine attacks. If the underlying biological pathway unique to menstrual attacks can be identified by biomarkers, then perhaps cell signaling can be manipulated to prevent or abort attacks.[9]

The lack of patient awareness of the link between menstrual cycles and headache is an obstacle to the diagnosis of menstrual migraine. Patients may not describe prodromal depression, food cravings, yawning, and irritability, considering these symptoms to be psychiatric or simply part of the premenstrual syndrome. Many patients do not report symptoms because they believe no effective treatment is available or they have used ineffective remedies in the past. Women often mistakenly attribute the headache to a monthly sinus headache, and physicians do not recognize the headache as being migraine or menstrually related. Symptoms can also be masked by habitual use of nonsteroidal anti-inflammatory drugs (NSAIDs) for other menstrual-related symptoms.

A cornerstone in management of menstrual migraine is clearly identifying the relationship between the menstrual cycle and migraine. Accordingly, thorough

KEY POINTS

- The presumed triggering mechanism for a menstrual migraine attack is a high estrogen level followed by a drop in estrogen.
- Genomic patterns in adolescent girls can differentiate between menstrual and nonmenstrual migraine attacks.

KEY POINTS

- Identify ''stackable'' triggers of menstrual migraine such as sleep deprivation, alcohol, or attitudinal changes. Determine which are ''unstackable'' and can reduce severity, or even risk, of a migraine attack if avoided.
- Menstrual migraine attacks seen in clinical practice are longer in duration and more severe.

TABLE 7-2 Diagnostic Criteria and Characteristics of Menstrual Migraine[a,b]

▶ **Pure Menstrual Migraine**
Migraine without aura that occurs exclusively on day 1±2 (ie, days -2 to +3) of menstruation in at least two of three menstrual cycles.
The first day of menstruation is day 1, and the preceding day is day -1; there is no day 0.
No migraine occurs at other times of the cycle.

▶ **Menstrually Related Migraine**
Migraine without aura that occurs on day 1±2 of the menstrual cycle in at least two of three consecutive menstrual cycles.
Additional attacks of migraine with or without aura occur at other times of the cycle.

▶ **Menstrual Migraine Characteristics**
Migraines are usually more resistant to treatment, are generally not associated with aura or longer duration, and are associated with more functional disability than attacks at other times of the month.

[a] Data from Headache Classification Subcommittee of the International Headache Society, Cephalalgia.[5] *cep.sagepub.com/content/24/1_suppl/9.long.*
[b] Reprinted with permission from Brandes JL, JAMA.[3] © 2006, American Medical Association. All rights reserved. *jama.jamanetwork.com/article.aspx?doi=10.1001/jama.295.15.1824.*

histories and patient diaries are essential. In their diaries, patients should circle the days of their menstrual cycle and ovulation, if determinable, and mark headache days. Headache months should be compared serially at office visits. Patients should be provided with the knowledge that migraine is a biological disorder related to the hormonal changes of either ovulation or menstruation. Assisting patients in recognizing and avoiding triggers is equally important. Triggers are often ''stackable,'' so patients with other known triggers should avoid them around the likely time of menses onset. Good sleep hygiene may also be helpful during menses (**Table 7-3**).

As for migraine in general, nonpharmacologic treatment may include cognitive or behavioral therapy and biofeedback; however, no data suggest that these alone are useful. Although not universally accepted, menstrual migraine attacks are generally considered to last longer, to be more severe, and to be more resistant to therapy than other attacks. Women seen in tertiary headache settings for menstrual migraine tend to have more resistant attacks. Recognizing the degree of disability associated with menstrual headache is important in determining treatment. Many women cease activities around the time of their menstrual period, and specific questioning or the use of disability surveys may determine the need for more aggressive therapy. Patients usually receive acute treatment for menstrual migraine. If acute therapy is not effective, prophylactic therapy may be indicated for very severe attacks (**Table 7-4**).[10]

Acute Treatment

The principles of acute therapy are to reduce pain and restore function (**Figure 7-1**). The goals should be relief of pain within 1 to 2 hours, control of nausea and vomiting, improvement in functional disability, and elimination of headache recurrence. Acute treatment

TABLE 7-3 Summary of Approaches to Management of Hormonally Influenced Migraine

- Identification of relationship between migraine and hormonal change through patient history and a detailed diary
- Reassurance and education
- Pharmacologic measures to abort and prevent migraine
- Trigger avoidance
- Overall wellness including exercise, balanced diet, smoking cessation, and sleep hygiene

KEY POINT

- Triptans are effective first-line acute therapy for menstrual migraine.

can involve multiple choices. Migraine-specific therapy with triptans is a first-line approach. Other drugs used include dihydroergotamine preparation, NSAIDs, antiemetics, cyclooxygenase 2 inhibitors, combination analgesics, hormonal therapy, steroids, and opioids or related analgesics.[11]

The triptans offer impressive efficacy in all end points, including pain relief, pain-free status, control of nausea and vomiting, and relief of functional disability. Several studies show that sumatriptan, both subcutaneous and oral, is as effective for the treatment of menstrual migraine as it is for nonmenstrual migraine. In one study, 67% of participants experienced headache relief 4 hours after receiving oral sumatriptan 100 mg compared with 33% for placebo. Rates of relief are even higher with subcutaneous sumatriptan (80% experience headache relief at 1 hour).[12] The efficacy of rizatriptan 10 mg was compared in patients with menstrual migraine and those with nonmenstrual migraine; responder rates at 2 hours were similar and in some cases higher in the patients who had menstrual-associated migraine. Approximately 70% of women achieve pain relief after 2 hours (compared with 44% of women on placebo), and 42% are pain free after 2 hours.[13] Zolmitriptan shows similar efficacy when patients choose to treat mild versus moderate to severe attacks. With zolmitriptan, 72% of patients achieve a 2-hour headache response.[14]

Prophylaxis

Cyclic or mini-prophylaxis, now termed short-term prophylaxis, involves using

TABLE 7-4 Types of Therapy for Hormonally Influenced Migraine

- **Acute (Abortive) Therapy**
  Aborts pain and migraine-associated symptoms after headache begins
- **Short-Term Prevention**
  Prevents recurring migraine attacks by using medication during the menstrual window of vulnerability
- **Long-Term Continuous Prevention**
  Aims to prevent the onset of pain
  Ongoing daily prevention may be used for patients who experience migraine throughout their cycle or for those with concomitant medical conditions
- **Education/Behavior Modification**

KEY POINTS

- Short-term prevention of menstrual migraine works best in women with predictable menstrual cycles.
- Menstrually related migraine refers to the pattern of having migraine in association with the menstrual cycle plus additional attacks outside the menstrual window. Pure menstrual migraine refers to attacks exclusively associated with the menstrual cycle.

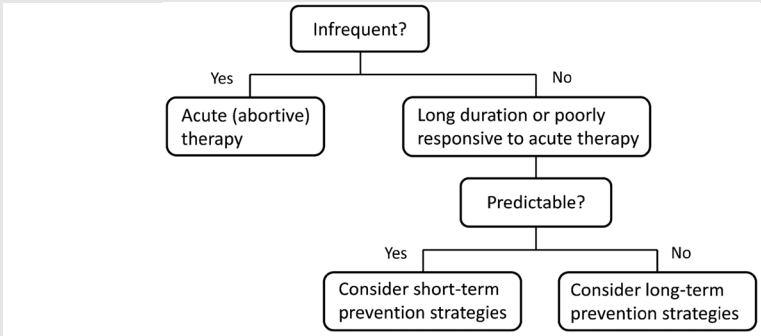

FIGURE 7-1 Menstrual migraine pharmacologic treatment decision tree.

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conventional abortive medications (such as NSAIDs or triptans) continually 2 or 3 days before menses up to 2 weeks after onset of menses. Short-term prevention may be useful for patients who have predictable onset of menstrual headache and who struggle with recurrence and lack of pain freedom with acute therapy. An adequate trial should include treatment through two menstrual cycles at a dose determined to be effective; patients may benefit from two to three menstrual cycles on similar management with adequate rescue provided. Patients using 1 mg naratriptan twice a day 2 days before and through 3 days of menstruation experience a reduction in number of attacks.[15] Frovatriptan shows efficacy in reducing severity and number of days with headache in women with difficult-to-treat menstrual migraine. After a loading dose on the first day of the regimen, frovatriptan should be taken 2 days before and through 3 days of menstruation at a dose of 2.5 mg either once or twice daily. A dose-response curve is seen, with higher efficacy in the patients treated twice a day.[16] Mini-prophylaxis has also been studied with naproxen sodium. In one small study, 33% of patients receiving naproxen 3 times a day were free of menstrual headache versus 0% with placebo.[17] In addition, naproxen reduces headache intensity, duration, and number of headache days.

When patients have frequent migraines outside of the menstrual window, continuous prophylaxis may be considered, with the option of increasing dosages of prophylactic medications around the time of menstrual vulnerability. Conventional prophylactic agents for menstrual migraine may include beta-blockers, calcium channel blockers, anticonvulsants, tricyclic antidepressants, and magnesium (dosed at 400 mg 2 times a day with dosage reduction in patients with any renal risk). As with any patient with migraine, the presence of comorbid disorders must be considered when selecting prophylactic therapy, because sometimes it is possible to choose a prophylactic agent that can control both conditions. For example, patients with depressed mood during their premenstrual and menstrual states may benefit from an escalation in an established tricyclic antidepressant regimen. Rarely, catamenial epilepsy and menstrual migraine may occur in the same patient, and boosting the antiepileptic therapy used as prophylaxis for both seizures and migraine may be appropriate. Specific

consideration for anticonvulsant therapy used for menstrual migraine prophylaxis relates to changes in the efficacy of OCPs. Gabapentin, topiramate (at US Food and Drug Administration [FDA]–recommended migraine prophylactic doses), divalproex, and levetiracetam do not interfere with OCP efficacy. For women of childbearing age it is also important to note that the use of divalproex has been associated with neural tube defects and the development of polycystic-appearing ovaries.[18] For all women of childbearing potential, whether on antiepileptic drugs (AEDs) or not, the US Department of Health and Human Services Office of Women's Health recommends a minimum of 400 mcg to 800 mcg (0.4 mg to 0.8 mg) of folic acid daily,[21] and in women with migraine the typical recommended dosage is 1 mg/d (**Table 7-5**).

Hormonal Prophylaxis

Manipulation of hormonal levels, especially estrogen, is an alternative approach to prevention of attacks that is usually reserved for patients unresponsive to the management options already discussed, unless previous experience has shown responsiveness, eg, as a byproduct of OCP use for contraception. Transdermal estradiol gel was studied in two double-blind placebo-controlled trials and reduced migraine frequency, duration, and severity.[22,23] It can be given daily for 7 days in 1.5-mg doses starting 2 days before the anticipated menses, maintaining mean estradiol plasma levels around 80 pg/mL, which seems to be the critical level to achieve effectiveness. Transcutaneous estradiol patches have also been studied using three separate doses: TTS-25, delivering 25 μg; TTS-50, delivering 50 μg; and TTS-100, delivering 100 μg of estradiol per 24 hours. With these regimens, serum estradiol levels approximate 23 pg/mL, 39 pg/mL, and 74 pg/mL, respectively. Not surprisingly, TTS-100 is superior and lower doses are ineffective.[24,25]

Although no randomized controlled clinical trials show benefit, resulting in lack of consensus on their utility, OCPs have been used for the prophylaxis of menstrual migraine. OCPs have a variable impact on migraine and can decrease migraine frequency, induce migraine, or produce no change in existing headache patterns.[26] Detailed diary

KEY POINTS

- Standard prevention should be offered to women with high-frequency menstrually related migraine attacks.
- When choosing a preventive agent, it is important to consider any comorbid disorders and the impact of the drug on those comorbid conditions, including potential impact on contraceptive efficacy.
- Women of childbearing potential should take 0.4 mg to 0.8 mg of folic acid per day, whether or not they are on antiepileptic drugs.
- Dosage of transdermal estrogen appears important in reducing severity, duration, and frequency of migraine attacks.
- Oral contraceptive pills can have a variable impact on migraine, either inducing attacks, improving attack frequency, or producing no change in attacks.

TABLE 7-5 Preventive Management Strategies in Menstrual Migraine

Patient Profile	Treatment Recommendation
Predictable occurrence of headaches, inadequate response to abortive therapy	Short-term prevention with nonsteroidal anti-inflammatory drug or triptan starting 2 to 3 days before menses for up to 1 week
Menstrual migraine during placebo week of oral contraceptive	Omit placebo week between packs of oral contraceptives
Already taking preventive medication	Increase dose near time of menses[19]
Presence of comorbid disorders	Consider comorbid disease when selecting therapy (eg, beta-blockers or antiepileptic drugs)[20]

information should establish the pattern for the patient. OCPs can induce the first migraine attack, most often reported in women with a family history of migraine. Existing migraine may increase in frequency and severity, including new onset of aura, and headaches may occur on placebo days of OCPs (**Case 7-1**).

Effective therapeutic options include shortening placebo days or continuous use, typically three consecutive packs of active pill followed by a pill-free interval.[27] During pill-free intervals patients can be placed on mini-prophylaxis, often with both an NSAID and a triptan. Irregular bleeding can be a complication of this management, and patients often have a consistent pattern of bleeding onset at a shorter interval than the typical 9 weeks. That interval can then be used as the marker for continuous pill use to that time. OCPs may benefit conditions often comorbid with migraine, including menorrhagia, dysmenorrhea, premenstrual syndrome, and irregular menstruation. Patients who have a history of thrombosis, ischemic

Case 7-1

A 24-year-old woman was sent for headache evaluation for difficult-to-treat migraine attacks. She had migraine without aura and experienced headache 2 to 3 days per week. Her headache would usually respond to an oral triptan within 2 to 3 hours, but about every 2 weeks she needed bed rest and attacks were less likely to completely resolve with triptans. Her history revealed onset of menarche at age 10, and her first headaches occurred at age 11. Through her preteen years and adolescence, she had mild headaches, often with menses, that were easily relieved by over-the-counter analgesics. During her freshman year in college she began taking oral contraceptive pills (OCPs) for birth control. By her senior year of college, she noted that she had more severe attacks, always accompanied by nausea, and was given a triptan for therapy. She also noticed that her migraine was most severe during the placebo week of her OCPs; thus her gynecologist recommended that she begin a continuous regimen of OCPs, eliminating the placebo week.

Two years later, she presented with 9 to 11 headache days per month, but every other week she had attacks with nausea lasting 2 to 4 days, which interfered with activities and work.

Comment. Ironically, the introduction of a continuous OCP regimen only further promoted the progression in severity and frequency of this patient's migraine. She originally noted easily treated menstrual migraine, and her first exacerbation occurred after OCPs were introduced. The attempt to help the more severe migraine during her placebo week only worsened her attacks. Management choices included stopping the OCP and offering prophylaxis with acute polytherapy. She elected to stop her OCPs altogether; use nortriptyline 10 mg (escalating to 75 mg over several weeks); and use an oral triptan/naproxen/ondansetron combination for acute attacks. Migraine severity decreased within a few weeks, and by the third month she had only attacks associated with ovulation and menses, easily relieved by acute therapy. It is important to establish the response of migraine to hormonal changes in terms of both frequency and severity. The initial pattern in this case was gradually and subtly worsened by OCP therapy, which had been continued without examination of the underlying effect.

heart disease, stroke, or valvular disease, or who are smokers, should not be considered candidates for any combined OCP use in migraine prevention.[28,29] In women for whom combined OCPs are contraindicated, the progestogen-only pill has been shown to reduce duration of aura symptoms and frequency of migraine attacks.[30]

PREGNANCY

Improvement or relief of migraine during pregnancy is noted in 55% to 90% of patients, but migraines may remain unchanged in 5% to 30% of cases.[31] Sometimes, improvement is limited to migraine without aura primarily in the second and third trimesters. The increase in estrogen levels during the first trimester with subsequent stabilization of estrogen may explain this benefit. Patients with more severe migraines may not fare as well and may even worsen during pregnancy. In general, the beneficial effect of pregnancy on migraine is observed more frequently in women who have menstrual migraine and/or women whose migraines began at menarche.[32]

For women with migraine wishing to become pregnant, clinicians should be cautious about prescribing acute medication around the potential time of conception. Prepregnancy planning allows greater options for avoidance of medications during the early weeks of pregnancy. Nonpharmacologic preventive therapies should be emphasized during preovulatory days. Continuous prophylaxis should cease if possible or, if not, should be changed to medication acceptable for continuation during pregnancy. Although limited data show efficacy, magnesium 400 mg twice a day, along with riboflavin 400 mg/d, remains one of the safest prophylactic options. When a patient is uncertain whether she is pregnant or is postovulation, analgesics, opioids, antiemetics, and corticosteroids are safer acute migraine therapy choices.

Because migraine generally improves during pregnancy, nonpharmacologic management can be encouraged. Biofeedback, relaxation, massage, avoidance of triggers, regular exercise, and adequate sleep may all minimize attack frequency and severity. For acute therapy, NSAIDs before 32 weeks, acetaminophen, and opioids may be used. While hydrocodone carries an FDA risk of B, codeine has recently been implicated in midline defects. Dihydroergotamine and ergotamine should be avoided during pregnancy. Triptans are FDA category C, meaning risk to humans has not been ruled out (**Table 7-6**).[33] As of October 3, 2011, the Sumatriptan/Naratriptan/Treximet Pregnancy Registry, the largest of the triptan registries, had a total 666 pregnancy exposures to sumatriptan, naratriptan, and/or a fixed-dose combination of sumatriptan–naproxen sodium (Treximet). Review of more than 500 prospectively enrolled first-trimester sumatriptan exposures does not indicate major teratogenicity. While this is reassuring, the total number in all the triptan registries remains small, and no large-scale sample populations are available for evaluation.[34] For more severe acute attacks, triptans may be considered and combined with caffeine (category B) and with the antiemetic ondansetron (category B). Rescue therapy with steroids and IV hydration may be necessary in extreme circumstances.[35]

Although no adequate well-controlled studies in pregnant women are available, patients who continue to have severe and frequent attacks may need preventive therapy. Beta-blockers may be used but must be tapered 4 weeks prior to delivery. Oral clefts associated with topiramate use during pregnancy have prompted a change in its FDA category from C to D.[36] Nortriptyline

KEY POINTS

- Women with a history of thrombosis, ischemic heart disease, stroke, or smoking should not be offered combined oral contraceptives.
- Improvement of migraine during pregnancy occurs in more than 55% of women, but migraines may be unchanged in 5% to 30%.
- Triptans are designated FDA category C for use during pregnancy but are approved for use during breast-feeding.
- Oral clefts associated with topiramate use during pregnancy have prompted a change in its FDA category from C to D.

TABLE 7-6 US Food and Drug Administration Pregnancy Categories for Drug Use[a,b]

Category	Description
A	Adequate and well-controlled studies have failed to demonstrate a risk to fetus in first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to fetus and there are no adequate and well-controlled studies in pregnant women.
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug despite potential risks.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

[a] Reprinted from University of Washington.[33] *depts.washington.edu/druginfo/Formulary/Pregnancy.pdf.*
[b] Categories are determined by the reliability of data and the risk to benefit ratio.

and amitriptyline are other acceptable choices and may be continued during breast-feeding. During breast-feeding, acetaminophen and ibuprofen may be used acutely to treat migraine, although caution is required with aspirin. Sumatriptan is rated as safe to use during breast-feeding by the American Academy of Pediatrics. Moderate caffeine use is also acceptable. The American Academy of Pediatrics guidelines also report no adverse effect on breast-feeding infants whose mothers are on amitriptyline, nortriptyline, labetalol, nadolol, propranolol, timolol, and verapamil. Bromocriptine, ergotamine, and lithium should be avoided.[37,38]

PERIMENOPAUSE/MENOPAUSE

The average age of a woman entering menopause in the United States is 51.5 years, with menopause occurring an average of 2 years earlier in smokers. For many women who remain on OCPs during perimenopause, however, the onset of menopause may not be clear. Perimenopause is defined as the time period 2 to 8 years prior to menopause, with onset of menopause at the end of 12 months with no menstrual cycles.[39,40] No difference is apparent between women with migraine or without migraine in age at onset of menopause. Vulnerability to migraine during perimenopause and menopause may be seen in women who have mild menstrual migraine, unrecognized as such until the dramatic fluctuations in estrogen begin during perimenopause. Women who have a history of menstrual migraine may be more vulnerable to exacerbations of migraine during these years of hormonal instability, as

might women with a history of hormonally influenced headache secondary to OCP use, pregnancy, or postpartum. The prevalence of migraine is known to decrease with age in both sexes, although the female preponderance persists even after menopause. Migraine tends to worsen during perimenopause or early menopause and thereafter improve. However, no change or worsening has been observed in as many as 50% of patients. Neri and colleagues reported an improvement after spontaneous menopause in two-thirds of women. In contrast, a worsening occurred in two-thirds of women with migraine after surgical menopause.[41]

Perimenopause is characterized by fluctuating estrogen levels, ultimately resulting in falling estrogen levels and the loss of the orderly pattern of estrogen and progesterone secretion. Menopausal symptoms begin for many women during waning ovarian function.[42] Estrogen deficiency during menopause can be characterized by multiple signs and symptoms, including hot flashes, night sweats, joint and muscle pain, skin dryness, vaginal dryness, dyspareunia, fatigue, irritability, depression, anxiety, memory loss, decreased libido, fear of loss of attractiveness, and fear of HRT, particularly in light of the Women's Health Initiative findings on use of Premarin and Provera.[43] These symptoms usually respond to HRT, but the course of migraine can improve, worsen, or be unchanged. Findings show that thermal pain perception is lower in women on HRT compared to women not on HRT and men, so careful observation of the headache frequency and severity following the initiation of HRT, if offered, is important. Menstrual cycle irregularities may lag behind any exacerbation in migraine during perimenopause[44] (**Case 7-2**).

HRT with estrogens alone or in combination with progestins (in patients with an intact uterus) can be useful in preventing menopausal symptoms and osteoporosis. Various types of estrogens are used: pure estrones, estradiols, and synthetic ethinyl-estradiol. Estrogens are available orally and parenterally in the form of injections, percutaneous gels, transdermal patches, and vaginal creams.[45] Unopposed estrogens and combined regimens in the past were given sequentially for 25 days per month but often exacerbate migraine in women who have a history of menstrual migraine. Since oral estrogens are associated with wide fluctuations daily, which can trigger migraine, transdermal preparations are preferred as they yield more stable estrogen levels. Preferred synthetic estrogens may include oral estradiol (Estrace) 0.5 mg twice a day and transdermal 50 μg/d with estradiol transdermal (Climara) weekly, estradiol transdermal (Estraderm), and estradiol transdermal (Vivelle) every 3 days. Micronized progesterone at 100 mg/d is preferred over medroxyprogesterone and is available in combination with estrogen as estradiol/levonorgestrel transdermal system (Climara Pro). On the basis of currently available data, the safest regimen appears to be low-dose transdermal HRT (**Case 7-3**).

Small studies have investigated a potential role for pharmacologic menopause as a means of treating menstrual migraine. To date, no clear benefit has been shown after use of a gonadotropin-releasing hormone agonist and transdermal estrogen in perimenopausal women.[46]

Isoflavone (soy), soy isolate, dong quai, vitamin E, bioflavonoids, black cohosh, garden sage, and motherwort are all used for symptoms of menopause, but none has been adequately studied in clinical trials for influence on migraine during perimenopause.[47]

Again, headache diaries in perimenopausal and menopausal patients with migraine are critical to establish headache

KEY POINTS

- Improvement in migraine has been noted in two-thirds of women after spontaneous menopause. In contrast, worsening is reported in two-thirds of women after surgical menopause.
- Hormone replacement therapy can worsen, improve, or leave unchanged the course of migraine.
- Pharmacologic menopause has shown no clear benefit as a treatment for menstrual migraine.

Case 7-2

A 44-year-old woman presented with a history of mild to moderate, easily treated migraine since age 11. At the time of menarche at age 15, she developed menstrually related migraine. She was treated with oral contraceptive pills (OCPs) at age 18 with no change in migraine severity or frequency. Her first severe, debilitating migraine occurred at age 24, and she had two to three severe attacks annually. During her first pregnancy at age 26, she had no migraine attacks after her first trimester and no attacks during breast-feeding. She resumed OCPs between pregnancies, having only one moderate, easily treated attack during her placebo week. Her second pregnancy, at age 29, was also notable for the lack of migraine attacks after the first trimester. At age 40, a diagnosis of migraine was made when menstrual migraine attacks became more severe and longer in duration. Her gynecologist prescribed a continuous OCP regimen for treatment, after which she continued to have ''menstrual migraine'' attacks every 4 weeks, despite no breakthrough or withdrawal bleeding. These attacks were treated with short-term prophylaxis (ibuprofen 600 mg 3 times a day), which provided pain relief in 2 hours, and no attacks were associated with missed work or activities. At age 43, she began to have an increase in migraine frequency, noting at least one attack per week. Within 6 months, she began having spells of vertigo lasting up to 3 days, accompanied by nausea, photophobia, and phonophobia. She was initially treated with a diuretic and the vertigo attacks shortened in duration. Two months later, she awakened with an excruciating migraine headache and vertigo, for the first time occurring during the same attack.

Neuro-otologic evaluation was normal. Ménière disease was excluded as a diagnosis, and she was referred for neurologic consultation. At the time of presentation, she was having weekly attacks of vertigo lasting from 15 minutes to 2 hours followed by posterior throbbing headache of moderate to severe intensity accompanied by nausea, occasional vomiting, photophobia, and phonophobia. The attacks lasted 48 to 72 hours, during which time she had to lie down. Combination acetaminophen/caffeine/aspirin was minimally effective. Other weekly attacks were identical, except for the absence of headache, and lasted up to 4 hours. She could not drive or continue activities during these attacks, and they persisted despite daily diuretic therapy.

Her attacks met the proposed criteria for definite migrainous vertigo. Her OCP was changed to a continuous daily dosage of levonorgestrel/ethinyl estradiol with no placebo days. Topiramate was begun for prevention, using fixed-dose sumatriptan/naproxen and ondansetron for acute treatment of all attacks. Five months after this course of combined hormonal and traditional therapy she was completely free of all attacks.

Comment. This woman was diagnosed quite late with both migraine without aura and migrainous vertigo. The epidemiologic association between migraine and vertigo suggests that migrainous vertigo affects a significant proportion of patients presenting with headache and dizziness. Hormonal precipitants leading to the development of migrainous vertigo are not well described, are often underrecognized, and may lead to delayed diagnosis of this entity. Migrainous vertigo presenting during perimenopause triggered by the onset of perimenopausal fluctuations in estrogen should be considered when vertigo, migraine, or both present or change during the perimenopausal life stage. Hormonal and traditional therapies can be offered simultaneously.

frequency, duration, intensity, and associated disability and to elicit the potential links between menopausal symptoms and migraine. Nonhormonal triggers should be evaluated and the efficacy of acute therapy should be particularly scrutinized (**Table 7-7**). The old cyclic HRT of using estrogen on days 1 through 25 and progesterone on days 15 through 25 is rapidly falling out of favor. Continuous HRT of estrogen with or without progesterone in patients with an intact uterus is becoming more standard. Once HRT is initiated in women who clearly have an exacerbation of migraine, the choices may be to reduce the dose of estrogen, change the form of estrogen, or convert from

Case 7-3

A 47-year-old academic researcher had had migraines since childhood. She recalled episodic headache from age 6, occurring as severe attacks 2 to 3 times per year. At the time of her menarche at age 13, she began to experience migraines of moderate to severe intensity, occurring during her menstrual cycle but not during every cycle. This pattern continued throughout college. In graduate school, she married and oral contraceptive pill (OCP) therapy was begun with marked improvement in her migraines. She experienced only mild migraine during her placebo week on OCPs, and she had disabling attacks of migraine only 2 to 3 times per year. At age 40, her OCPs were discontinued because of her age, and her migraines remained stable for several years. At age 44, after 1 year of heavy, lengthy menstrual cycles, she was offered endometrial ablation. After ablation, her menstrual cycles did not resume. By age 45, she began to have severe 3- to 5-day migraine attacks every 2 weeks that did not respond to over-the-counter medications, higher-dose nonsteroidal anti-inflammatory drugs (NSAIDs), or oral triptans. Her she also began to experience fatigue, irritability, anxiety, and depression and became concerned about subtle cognitive changes. Her sleep was increasingly fragmented, and she felt that her symptoms were related to increasing responsibilities for her academic appointment. She had greater difficulty at work because of migraine severity. At consultation she reported daily headache of mild to moderate severity in addition to severe attacks.

Comment. The patient's pattern of migraine without aura is consistent with episodic menstrually related migraine. Having had a strong menstrual association with migraine, she no longer had her traditional marker or trigger for migraine once she underwent endometrial ablation. At age 47, while not having hot flashes or night sweats, her history is strongly suggestive of entry into perimenopause with migraine worsening in response to her changes in estrogen-level variability. Her neurologic examination was normal, hypercoagulation status was normal, and follicle-stimulating hormone level was elevated. With no family history of malignancy, she was offered hormone replacement therapy with transdermal estrogen/progesterone (Climara Pro), and valproate was started with a target dose of 1000 mg. Her daily analgesics were stopped, and within 7 to 8 weeks her daily headache had resolved. Her pattern reverted to episodic, but with increasing infrequency, and she was able to abort acute attacks with a triptan and high-dose NSAID taken simultaneously. Sleep, cognition, and mood were also markedly improved, and within 4 months, she was having only one to two migraine attacks per month, achieving pain freedom within 30 minutes after acute therapy.

interrupted to continuous administration. In women who clearly worsen on HRT or who have contraindications, including a history of thromboembolism, cancer, or hypercoagulable states, HRT must be stopped.

If migraine continues during the initial years of menopause and beyond, standard migraine prevention with AEDs to reduce brain excitability may be indicated. In such cases, AED-induced bone disease, a form of osteomalacia, might compound high-turnover osteoporosis. In patients on non–enzyme-inducing AEDs, bone changes do not occur. For all women in perimenopause and

KEY POINT

- If estrogen replacement therapy exacerbates migraine, the choices include reducing the estrogen dose, changing the form of estrogen, or stopping the dose. Cyclic estrogen therapy should be avoided as fluctuation in estrogen often underlies exacerbation.

TABLE 7-7 Initial Treatment Strategies

▶ **Keep a 3-Month Diary**
Establish headache frequency, duration, intensity, and associated disability
Elicit a possible link between menopausal symptoms and migraine
Identify nonhormonal triggers
Assess the efficacy of acute therapy

KEY POINTS

- Migraine is an independent risk factor for stroke and carries twice the risk seen in patients without migraine.
- Women with migraine should not smoke, especially if using oral contraceptives.
- Early perimenopause may represent a critical time window during which estrogen replacement provides beneficial effects on cognition and neuroprotection.
- High-dose transdermal and oral high- and low-dose estrogen have been shown to increase stroke risk compared to women who do not use hormone replacement therapy (HRT). If offering HRT, use a low-dose transdermal formulation and consider evaluation for hypercoagulable states before initiating therapy.
- The increased ischemic stroke risk in women with any type of migraine occurs only in women younger than age 45.

menopause, unless another contraindication exists, the current recommendations to prevent bone disease are 1500 mg to 2000 mg of calcium and vitamin D 400 units/d, adequate sunshine, and weight-bearing exercise. Body weight changes may also be important in menopausal women with migraine. Cognitive effects from AED therapy may pose particular challenges.[48]

ORAL CONTRACEPTIVES, HORMONE REPLACEMENT THERAPY, MIGRAINE, AND STROKE RISK

The effect of oral contraceptives on migraine is particularly relevant because migraine reaches its peak during childbearing years. The second- or third-generation low-dose formulations of combined OCPs are known to be safe and highly effective for contraception, yet their effects on migraine are variable. As might be predicted from the known influence of estrogen in menstrual migraine, use of the original very high estrogen pill forced attacks into the placebo days of the withdrawal bleed in women previously experiencing attacks throughout their cycle.

Of clear concern is the relationship between migraine, OCPs, and stroke.[49] Migraine carries an independent risk factor for ischemic stroke of around twice that of the person without migraine.[50] In migraine, and particularly in patients with aura, OCP use increases stroke risk around 10- to 13-fold. While the absolute risk of ischemic stroke is low, women with migraine should be carefully evaluated for hypercoagulable states and other stroke risk factors before OCPs are used. The European community tends to be restrictive in using OCPs in women with migraine. The International Headache Society task force on combined OCPs and HRT recommends that clinicians individually assess and evaluate risk for ischemic stroke in women with migraine.[51] It is critical to diagnose the migraine type, with particular attention to aura, and to identify all other stroke risk factors.[52] Women with migraine should not smoke if using OCPs.

The controversy related to oral postmenopausal HRT is largely based on the Women's Health Initiative findings of an increased risk for nonfatal stroke, coronary heart disease, and breast cancer.[43] With respect to stroke, a woman's age at initiation of HRT appears to be significant. Early perimenopause may represent a critical time window during which estrogen replacement provides beneficial effects on cognition and neuroprotection.[53] With an average participant age of 63, the Women's Health Initiative findings of increased nonfatal stroke risk may reflect an increased sensitivity to ischemic insult after a period of hypo-estrogenicity, having missed estrogen replacement at early perimenopause.[54]

An observational case-control cohort study in the United Kingdom reveals no increase in stroke in women on low-dose (50 μg or less) transdermal HRT compared to women not on HRT. In contrast, women receiving high-dose (greater than 50 μg estrogen) transdermal HRT show an increase in stroke risk.[55] Because data are insufficient to support an increased risk of ischemic stroke in women over age 45 with any type of migraine and no direct study of the relationships between migraine, HRT, and stroke has been done, the usual indications and contraindications for HRT should be applied. The benefits of HRT must also be taken into account, including prevention of osteoporotic fractures and colorectal cancer, based on patient risk factors.[56]

ABUSE

Discreet questioning for a history of past or current maltreatment and the

age at onset should be part of the evaluation of patients with migraine with depression and frequent headache. While migraine prevalence has long been established as higher in women, abuse and posttraumatic stress disorder are also reported to have higher prevalence in women.[57] The lifetime prevalence of abuse in the general population is reported to be about 25%. A recent study found similar lifetime prevalence in a headache clinic population.[58] Childhood maltreatment is recognized as playing a role in the subsequent development of chronic disorders, including migraine. Prevalence of abuse (physical, sexual, and emotional) ranges from 13% to 27% in childhood, and a host of population-based studies show an association between abuse and headache.

In a headache clinic population of 1032 women, 92% had migraine, 38% reported physical or sexual abuse, and approximately 12% reported both physical and sexual abuse in the past. Overlap among maltreatment types was also noted. In women with a history of childhood onset of sexual maltreatment, 36% experienced physical abuse, 29% described fear for life, 52% witnessed abusive behaviors between adults as a child, and 45% reported drug or alcohol abuse by adults in their childhood home. Approximately one-fifth of patients (n=180) reported childhood onset of sexual abuse, physical abuse, or fear for life. Interestingly, no differences in maltreatment types were found by age or race among patients with migraine, but women with a history of maltreatment had a lower household income and lower education compared to women without any history of maltreatment. A higher proportion of women who report physical abuse, sexual abuse, or fear for life related to abuse have chronic headache. Headache disability, depression, and somatic symptoms are also more prevalent in patients reporting a history of maltreatment. History of maltreatment is significantly associated with severity of depression. The study findings conclude that childhood maltreatment is more common in women with migraine and depression than in women with migraine alone. The study further demonstrates that sexual abuse in childhood amplifies the association with migraine and depression when the abuse occurred both before and after age 12. These results are supportive of the hypothesis that stressful events, such as childhood maltreatment, may lead to a variety of conditions putatively linked to serotonin dysfunction, including migraine, depression, and anxiety.

KEY POINTS

- Eliciting a history of past or current abuse should be a standard element of the migraine history.
- Childhood maltreatment is more common in women with migraine and depression than in women with migraine alone.

CONCLUSION

Ovarian steroid hormones, especially estrogen, play a major role in migraine but often in an unpredictable way. Nevertheless, responses to fluctuating estrogen levels have etiologic implications and therapeutic potential for better understanding mechanisms of hormonally influenced migraine. Women with migraine and their treating clinicians should view migraine as part of a chronic biological disorder with frequency and severity that waxes and wanes as women with migraine move through their hormonal milestones. Standard therapy to abort acute attacks of migraine and preventive therapies should take into account hormonal milestones and factors that at times may require hormonal manipulation.

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