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A Cyclic Pain: The Pathophysiology and Treatment of Menstrual Migraine

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Catamenial migraine is a headache disorder occurring in reproductive-aged women relevant to menstrual cycles. Catamenial migraine is defined as attacks of migraine that occurs regularly in at least 2 of 3 consecutive menstrual cycles and occurs exclusively on day 1 to 2 of menstruation, but may range from 2 days before (defined as −2) to 3 days after (defined as +3 with the first day of menstruation as day +1). There are 2 subtypes: the pure menstrual migraine and menstrually related migraine. In pure menstrual migraine, there are no aura and no migraine occurring during any other time of the menstrual cycle. In contrast, menstrually related migraine also occurs in 2 of 3 consecutive menstrual cycles, mostly on days 1 and 2 of menstruation, but it may occur outside the menstrual cycle. Catamenial migraine significantly interferes with the quality of life and causes functional disability in most sufferers. The fluctuation of estrogen levels is believed to play a role in the pathogenesis of catamenial migraine. In this review, we discuss estrogen and its direct and indirect pathophysiologic roles in menstrual-related migraine headaches and the available treatment for women.

Target Audience: Obstetricians and gynecologists, family physicians

Learning Objectives: After completing this CME activity, physicians should be better able to discuss the pathophysiology of catamenial migraine, identify the risk factors for catamenial migraine among women, and list the prophylactic and abortive treatments for migraines.

Headache is one of the most common chief complaints in any neurology practice. Headache can be divided into 2 categories, either primary or secondary headache. Primary headaches are headaches that cannot be attributed to an underlying disorder, whereas secondary headaches may have an organic cause. A primary headache diagnosis is a diagnosis of exclusion. As such, a primary headache diagnosis should be made only after completing a thorough history, physical and comprehensive neurological examination, and relevant diagnostic testing. Primary headaches include migraine, tension-type headache, cluster headache, and a variety of other headache syndromes. A secondary headache manifests as a symptom of an underlying medical condition. Table 1 lists some examples of secondary headaches.

Although tension-type headache is the most common primary headache disorder with a lifetime prevalence of 88% in women and 68% in men in the United States, patients are more likely to seek professional medical attention for migraine headaches. This is due primarily to the generally low to moderate intensity of tension-type headache, versus the severe and disabling intensity of migraines.[2,3] Migraine has a higher prevalence in women, and for many women, there is often an association between their migraines and their menstrual

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TABLE 1
Causes of Secondary Headache[1]

Cause	Examples
Cerebrovascular diseases	Carotid or vertebral artery dissections, cerebral venous sinus thrombosis, arteriovenous malformations, subdural hematoma, giant cell arteritis
Intracranial pressure dysfunction	Altered CSF dynamics, idiopathic intracranial hypertension, hydrocephalus, spontaneous CSF leak
Intracranial space-occupying lesion	Neoplasm, abscess
Infection	Meningitis, encephalitis, abscess, sinusitis
Trauma	
Musculoskeletal disorders	Cervical spine disorders, temporomandibular joint
Medications	Medication-overuse headache

CSF indicates cerebrospinal fluid.

cycle. In this article, the roles of estrogen in the pathophysiology of migraine are discussed. In addition, therapeutic options focusing on menstrual-associated migraine are reviewed.

DIAGNOSIS

The diagnosis of migraine can be established only after secondary causes of headache have been ruled out. Migraine can be divided into 2 categories based on the presence or absence of aura. The *International Classification of Headache Disorders, Second Edition* diagnostic criteria for migraine with aura and migraine without aura are listed in Table 2.

Migraines can be further subdivided by the frequency and if there is a menstrual association with changes in attack frequency and severity. If the migraine frequency is less than 15 days per month, the diagnosis is episodic migraine. If the frequency is greater than 15 days per month, the diagnosis is chronic migraine. If the migraines have a temporal association with menses, they are often referred to as catamenial migraines and can be classified as either pure menstrual migraine or menstrually related migraine. Pure menstrual migraine is defined as attacks of migraine without aura that occur exclusively during the menstrual cycle during at least 2 of 3 consecutive menstrual cycles and occurs exclusively on day 1 ± 2 of menstruation, where days range from -2 to +3 with the first day of menstruation as day +1 and no day 0. Menstrually related migraine is similar to pure menstrual migraine, but also involves headaches outside the menstrual cycle.

The diagnosis of catamenial migraine can be confirmed by using headache diary recordings over at least 3 months to determine if there is a temporal association between the headaches and the menstrual cycle. In the setting of chronic migraine, this association may not be clear to the patient initially, and headache diaries can be helpful in establishing a diagnosis, as well as timing appropriate treatment.

EPIDEMIOLOGY

Migraine headache is the second most common type of primary headache. It has a worldwide prevalence of 10%, with a 14% female prevalence and a 6% male prevalence. The estimated total economic burden of migraine is more than $13 billion annually, and the majority of this burden is due to lost productivity and work absenteeism. In North America, there is a prevalence of 13% in the general population, with an 18% female prevalence and a 6% male prevalence. This

TABLE 2
ICHD-II Migraine Diagnostic Criteria[4,5]

Migraine without aura
A. At least 5 attacks fulfilling criteria B-D
B. Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
C. Headache has at least 2 of the following characteristics:
Unilateral location
Pulsating quality
Moderate or severe pain intensity
Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
D. During headache at least 1 of the following:
Nausea and/or vomiting
Photophobia and phonophobia
E. Not attributed to another disorder
Migraine with aura
A. At least 2 attacks fulfilling criteria B-D
B. Aura consisting of at least 1 of the following, but no motor weakness:
Fully reversible visual symptoms including positive features (eg, flickering lights, spots or lines) and/or negative features (ie, loss of vision)
Fully reversible sensory symptoms including positive features (ie, pins and needles) and/or negative features (ie, numbness)
Fully reversible dysphasic speech disturbance
C. At least 2 of the following:
Homonymous visual symptoms and/or unilateral sensory symptoms
At least 1 aura symptom develops gradually over >5 min, and/or different aura symptoms occur in succession over >5 min
Each symptom lasts >5 and <60 min
D. Headache fulfilling criteria B-D for migraine without aura begins during the aura or follows aura within 60 min
E. Not attributed to another disorder

ICHD-II indicates *The International Classification of Headache Disorders: Second Edition*.

greater prevalence of females with migraine to males with migraine is in contrast to the greater male-to-female ratio of cluster headache, which is approximately 3:1 to 6:1. Cluster headache, however, has a much lower prevalence, which is estimated to be 0.1%.[6] Before the onset of puberty, boys and girls have a nearly equal prevalence of migraine at approximately 4%.[7] Although the onset of migraine can occur in childhood, 80% of women have an onset between the ages 10 to 39 years with 5% to 10% of adolescent girls suffering from migraines, 20% to 25% of menstruating women aged 30 to 50 years suffering from migraines, and less than 10% of postmenopausal women experiencing migraines.[8–11] Among female migraineurs, pure menstrual migraine has a prevalence of 3.5% to 12%, and menstrually related migraine has a prevalence of about 50%.[12]

PATHOPHYSIOLOGY

The underlying pathophysiology of migraine is thought to be primarily due to neurovascular dysfunction, which occurs as a result of a phenomenon known as cortical spreading depression (CSD).[13] Cortical spreading depression is a propagating wave of neuronal and glial depolarization that is evoked in the cortex, cerebellum, basal ganglia, thalamus, and hippocampus. Cortical spreading depression occurs in response to increases in extracellular potassium ion and glutamate concentrations, which can lead to the release of neuroinflammatory mediators such as calcitonin gene-related peptide, substance P, and neurokinin A. These molecules induce vasodilation and plasma extravasation from meningeal vessels, as well as neurogenic inflammation involving macrophages and mast cells.[13–21] The meningeal blood vessels are innervated by the first division of the trigeminal ganglion, and pain signals from these neurons project onto the second-order sensory neurons in the trigeminal nucleus caudalis.[22,23] Projections to these second-order neurons are thought to account for central sensitization, causing cutaneous allodynia and poor response to abortive treatments for migraine. Cortical spreading depression susceptibility is thought to be modulated by genetic and environmental factors.[18] Sleep dysfunction, certain foods, and stress may play a role in CSD generation.[19] There is also some evidence to suggest that transient hypoxic events, such as the microemboli generated secondary to a patent foramen ovale, can serve as a trigger for CSD.[20]

Observations from clinical studies disclosed a strong association between the role of estrogen and the development of migraines in women. Abrupt drops in estrogen occurring just before menses have commonly been observed to trigger migraines.[23,24] Notably, premenstrual administration of estrogen delayed the onset of migraines but not menses,[23,24] whereas premenstrual progesterone administration delayed menses but not migraines.[22–25] Administration of long-acting estrogen implants that deliver uneven amounts of estrogen can cause fluctuating estrogen levels with irregular uterine bleeding and can trigger migraines.[26] Laboratory experiments have demonstrated that an abrupt drop in estrogen level or chronically sustained high estrogen levels influenced trigeminal activity in cell culture.[27] However, there is no significant hormonal difference between premenstrual syndrome patients and control subjects during the menstrual cycle, but rather they have an abnormal response to the hormonal changes.[27] A study of 98 women with migraine undergoing in vitro fertilization were given gonadotropin-releasing hormone analog to decrease estrogen levels before ovarian hyperstimulation. There was a correlation between declining levels of 17β estradiol and an increase in the number of debilitating migraines.[28] A prospective study including 16 postmenopausal women with a history of migraines on sole estrogen supplementation demonstrated that all of these women had estrogen withdrawal–triggered migraines upon stopping the estrogen supplementation.[29] In addition, 12 menopausal women who previously had no migraine history developed migraines upon withdrawing from estrogen. These multiple clinical observations suggest an association between the abrupt withdrawal of estrogen and the onset of migraines. A history of menstrually related migraine often leads to retained sensitivity to estrogen withdrawal, and larger doses of estrogen may produce more severe estrogen-withdrawal migraines.[29]

Prostaglandins, 20-carbon fatty acid derivatives of arachidonic acid,[30] may also play a direct and indirect role in triggering menstrually related migraines. The physiologic functions of prostaglandin include inhibiting adrenergic transmission by blocking norepinephrine release in the central nervous system (CNS) and regulating gonadotropin-releasing hormone release.[30–32] Prostaglandins cause antidromic sensory nerve stimulation, which in turn causes vasodilation and leakage of plasma proteins, such as substance P, calcitonin gene-related peptide, and neurokinin A.[30,32] These proteins are thought to cause peripheral nociceptor sensitization[33] and promote neurogenic inflammation.[32,33] Local administration of prostaglandins have been shown to decrease the pain threshold.[32] Administration of alprostadil, a prostaglandin E_1 used in the treatment of erectile dysfunction through vasodilation, can

incidentally trigger migraine-like headaches and abdominal cramping.[34,35] Furthermore, infusion of prostacyclin commonly causes a dull, throbbing headache.[36,37] Estrogen and progesterone influence the local prostaglandin (especially prostaglandin E_2 and F_2) production in the uterus, which in turn causes uterine contractions. In fact, the endometrium of dysmenorrheic women was found to have higher prostaglandin levels[38–40] and elevated plasma levels of prostaglandin F_2 during migraine episodes.[34,35] Beyond the reproductive system, estrogen is able to regulate prostaglandin synthesis and has an indirect role in the pathophysiology of migraines.[36,37] However, the precise role of prostaglandins in the pathogenesis of migraine remains unclear.

Accumulated evidence suggests that estrogens have effects on modulating endogenous opiate pathways in the CNS that may alter headache pathophysiology. β-Endorphins are endogenous substances that produce analgesic effects. They function as a local neuromodulator for pain both in the peripheral nervous system and the CNS. The pituitary gland and hypothalamus make most of the plasma β-endorphin in the body, especially during exercise,[41] excitement, pain, consumption of spicy food, sexual intercourse, and orgasm.[38–40] Premenstrually compromised responses of plasma β-endorphins and cortisol are evident in women with migraine. A decreased opioid sensitivity is correlated with an increased migraine frequency.[42,43] Production of β-endorphins may be modulated by estrogen.[44] A decreased cerebrospinal fluid level of β-endorphin was found to be inversely proportional to increased estrogen levels and correlated well with the decreased naloxone responsiveness, as well as worsening frequency and intensity of headaches.[45] These observations suggest that the production of endogenous opioids may be modified by the fluctuation of estrogen levels, which play a role in the pathogenesis of migraine. On the other hand, opioid peptides act on μ receptors of hypothalamic arcuate nucleus, which inhibits gonadotropin-releasing hormone, and subsequently diminish the pituitary secretion of luteinizing hormone (LH).[46] This action is reversibly blocked by naloxone, an opioid receptor antagonist, and causes a rise in LH during the early luteal phase.[42,43] The effects of the naloxone-promoted LH response is diminished during the early luteal phase in women with severe and/or chronic headaches,[45,47] the late luteal phase with menstrual migraine,[48–54] premenstrual syndrome,[42] and postmenopause. These observations further suggest that estrogen may trigger or exacerbate migraines by modulating certain opiate pathways.[55]

The estrogen receptor α, when stimulated, promotes endothelial nitric oxide (NO) synthase activity[56,57] by activating protein phosphatidylinositol 3-OH kinase in a nonnucleated or membrane-associated compartment.[48–54] Nitric oxide synthase catalyzes the production of NO from L-arginine. Nitric oxide is a critical cellular signaling molecule, which plays an important role in many biological processes including the vascular changes that occur during migraines. Sarchielli et al[58] studied the relationship between NO production and estrogen levels in the platelet arginine/NO pathway during the ovarian cycle in 60 women with menstrual migraine, nonmenstrual migraine, and nonmigraine. Their findings demonstrated that the women with menstrual migraine had increased NO production and increased L-arginine pathway activity, especially around the luteal phase.[58] Interestingly, decreased serotonin levels were observed during the luteal phase.[56,57]

MENSTRUAL MIGRAINE GENETICS

Several polymorphisms have been noted to be risk factors for migraine.[59–61] The polymorphism of estrogen receptor 1 gene G594A substitution in exon 8 has been associated with increased migraine incidence.[62] It is speculated that this receptor may affect NO production and alter vascular tone.[49] PROGINS, polymorphisms of progesterone receptor, have shown effects of negatively impacting progesterone expression. In a cross-sectional association analysis of 1150 men and women, Colson et al[50] found that this polymorphism positively correlated with a 1.8-fold increase in migraine attacks. In another study of 5360 twins, including 1013 monozygotic and 1667 same-sex dizygotic twin pairs from the population-based Danish Twin Registry, Gervil et al[63] demonstrated an additive risk of estrogen receptor 1 gene G594A substitution in progesterone alleles, leading to 3.2-fold increased migraine attacks. Those findings provided evidence that genetic factors play a role in the etiology of migraine.[63]

On the other hand, estrogen influences the expression of multiple genes relevant to pain. Puri et al[26] studied the effects of estrogen on various genes expressed in adult rat trigeminal ganglial sensory neuronal cultures. Up-regulation of synapsin 2, endothelin receptor type B activity, neurotransmitter-induced early gene 7 (ania-7), phosphoserine aminotransferase, MHC-1b, and ERK-1 were noted. Down-regulation of IL-R1, bradykinin B2 receptor, CCL20, GABA transporter protein, fetal intestinal lactase-phlorizin hydrolase, carcinoembryonic antigen–related protein, zinc finger protein 36, epsin 1, and cysteine string protein were also noted.[26] Activation of ERK, which has been linked to inflammatory pain, was evident in neurons by

immunocytochemistry.[26] Corresponding changes with estrogen in the levels of neuropeptide Y, which regulates inflammation and central nociception, have been demonstrated.[64] This fluctuation can also lead to more functional disability. These changes may occur through a mechanism of galanin-modulating gonadotropin-releasing hormone and LH.[64,65] Thus, these gene products may be potential therapeutic targets for the treatment of the menstrual-related pain syndromes such as migraine.

CLINICAL FEATURES OF MIGRAINE INVOLVING HORMONAL CHANGES

The Menstruating Women

Migraines that occur during the menstrual cycle have significant clinical implications that differ from those occurring off cycle. Menstrual migraines tend to be more resistant to treatment,[66] last longer,[12] typically lack aura,[9,67] and lead to more functional disability.[66] The severity of the menstrual migraine headaches vary individually, but invariably worsen during the perimenstrual period.[66] A study of the menstrual and nonmenstrual migraines in 64 women revealed that headaches were worse on days 1 to 7 of the menstrual cycle than at other times.[68] By analyzing diary data from 155 women, the prevalence of migraine was 1.7 times more likely to occur during the 2 days before menstruation and 2.1 times more likely to be severe when compared with all other times of the cycle.[9,67] The symptoms of premenstrual syndrome worsened during the late luteal and early follicular phases of the menstrual cycle, and the severity was moderately correlated with headache outcome measures during natural menstrual cycles and after medical oophorectomy in 21 female migraineurs.[69] However, not all the migraines were more severe during the perimenstrual period compared with other times in the cycle.[66,67] Migraines that occur before menstruation may be accompanied with depression, anxiety, crying spells, difficulty thinking, lethargy, nausea, backache, breast tenderness, and cramps.[68,70] Comorbidities of depression, panic disorder, and phobias are 1.9 to 3.4 times more common in female migraineurs.[71] The association between these comorbidities and menstrual migraines warrants further investigation.

The Pregnant Women

During pregnancy, estrogen levels progressively increase and then drop after delivery. During pregnancy, migraines may worsen initially, although most women experience improvement of their headaches during their second and third trimesters, which is likely due to a relatively stable and sustained estrogen levels. Approximately 25% of women have no change in their migraines.[22,72,73] Sances et al[74] studied the course of migraine during pregnancy and postpartum in 47 women with migraines without aura. They observed that 80% of women had no headaches during the third trimester.[74] De novo migraine during pregnancy occurs in less than 3% of women, typically during the first trimester.[22,70] For women who experience improvement of their migraines during pregnancy, 94% report return of their migraines after delivery.[71] Among the women who experienced a return of their migraines in the postpartum period, bottle feeding and maternal age younger than 30 years were risk factors correlated with accelerated return of migraine.[22,72,73] Indeed, women who breast-feed had a lower incidence of migraine in the postpartum period.[74,75] These findings suggest that earlier resumption of the menstrual cycle may promote the recurrence of migraine, which is again related to fluctuating estrogen levels.

The Postmenopausal Women

It is commonly recognized that migraines tend to decrease in frequency and intensity during menopause, which correlates with both a decrease in and stabilization of estrogen levels. A study of 556 menopausal women showed that 82% had headaches before menopause, and 62% of the women with premenopausal headaches had abatement of their headaches after menopause.[76] The Women's Health Study was a self-reporting cohort that involved 17,107 postmenopausal women. Of these women, 11% continued to have migraines after menopause. Apparently, estrogen replacement therapy increased the risk of migraines to 13%, compared with 9% among women with no hormone supplementation.[77] Risk factors for women who have postmenopausal migraines include younger age at onset of menopause, surgical menopause, daily alcohol consumption, current smoking, prior oral contraceptive use, and current hormone replacement therapy, especially with depot estrogen preparations.[74]

In Obese Women

Production of estrogen in women primarily occurs in the ovaries, except during pregnancy when the placenta becomes the main source. In addition, estrogen can also be produced in many different tissues including adipose tissue, liver, adrenal glands, breasts, and glial cells in the brain.[75,78] Adipose tissue can contribute significantly to the circulating estrogen level. The enzyme aromatase is found in adipocytes

and catalyzes the conversion of steroid precursors into estrogen in peripheral tissue. Increased body fat increases the capacity of estrogen production.[79] However, whether obese women produce higher estrogen levels relevant to migraines remains to be proven.

Obesity is comorbid with a number of chronic pain syndromes, including headache. An estimated 64% of US adults are either overweight or obese.[80,81] Body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) is commonly used to define the obesity. A BMI of 20 to 25 kg/m^2 is accepted as normal weight, 25.0 to 29.9 kg/m^2 is considered overweight, 30.0 to 34.9 kg/m^2 is class I obesity, 35.0 to 35.9 kg/m^2 is class II obesity, and BMI greater than 40.0 kg/m^2 is class III obesity. Most of the studies that determined a correlation between obesity and migraine were carried out on women with a BMI of 30 kg/m^2 or greater, although the highest risk was seen for class II obese women of reproductive age. In a study of 18,968 individuals with migraine, very frequent headaches (10-14 d/mo) were observed in 7.4% of the overweight ($P = 0.10$), 8.2% of the class I obese ($P < 0.001$), and 10.4% of the class II/III obese ($P < 0.0001$) subjects, compared with 6.5% of normal weight individuals.[82] In a study of 30,215 migraineurs, 4.4% had 10 to 15 headache days per month in the normal-weight group, increasing to 5.8% in the overweight (odds ratio [OR], 1.3), 13.6% in class I obese (OR, 2.9), and 20.7% in the class II (OR, 5.7).[83,84] Expectedly, weight loss after bariatric surgery decreased the frequency of migraine headaches in obese migraineurs.[85,86]

TREATMENT

Making an accurate diagnosis is essential in formulating a treatment plan for any primary headache disorder. Pharmacologic treatment falls into 2 major categories, prophylactic or abortive.

Prophylactic Treatment

Prophylactic treatments are typically initiated when headaches are high in frequency or significantly interfere with activities of daily living or in situations where acute treatments are contraindicated or not effective. In selecting a prophylactic treatment, the medication with the best efficacy, fewest adverse effects, and capacity of treating a coexisting condition is the optimal choice. An initial low starting dose, slow titration, and adequate trial duration are all important considerations once a drug is selected. Some common classes of drugs that have demonstrated efficacy in migraine treatment include antiepileptic drugs (topiramate, carbamazepine, valproate, gabapentin, and pregabalin), calcium-channel blockers (verapamil), β-blockers (propanolol, atenolol, nadolol, timolol, metoprolol), and tricyclic antidepressants (amitriptyline, nortriptyline).[87] These medications have varying degrees of efficacy for migraine prophylaxis.

Oral Contraceptives

Theoretically, stabilizing estrogen levels may serve as a therapeutic strategy in preventing menstrual migraines because fluctuation, especially sudden drops, in estrogen levels after prolonged elevation can precipitate migraines.[88] However, administration of estrogen has demonstrated mixed results. A study of hormone supplemental therapy by administration of 20 μg daily of ethinyl estradiol on days 1 to 21 of the cycle followed by 900 μg of conjugated equine estrogens on days 22 to 28 in 20 female migraineurs showed there was a 76% reduction in headache days per month, suggesting a beneficial effect of supplemental estrogen.[89,90] However, studies on the effects of the 50-μg estrogen patch versus placebo in pure menstrual migraine failed to show therapeutic benefits.[89,90] Notably, a study of 16 women receiving either serotonin agonist or transdermal estrogen versus placebo for 1 week demonstrated that the placebo group tended to have a poorer neuroendocrine response with decreased release of cortisol and prolactin. This neuroendocrine response improved in the group receiving either the serotonin agonist or the transdermal estrogen and was accompanied by improvements in the duration and severity of their migraines.[91]

The use of estrogen-containing hormone supplements is traditionally thought to increase the risk of stroke in women with migraine, particularly migraine with aura.[92–94] Among menopausal women with migraines, the use of estrogen supplementation may increase the frequency of headaches. The Women's Health Study evaluated the effects of different doses of hormone therapy on migraine headache in 17,107 postmenopausal women.[88,95,96] An intermediate dose of 0.625 mg/d of estrogen had an OR of 1.28 for migraine; higher doses had an OR of 1.72, whereas lower doses had an OR of 2.00. Thus, estrogen supplementation therapy may worsen migraines and is therefore not recommended as first-line treatment of postmenopausal women with migraines.[92–94] As such, a decision to use estrogen-containing hormone supplemental therapy should cautiously be made in certain patients after failure of conservative treatments and after careful evaluation of risks versus benefits with regard to the small increased risk of stroke. Ongoing research is reassessing the use of newer-generation combined

hormonal contraceptives in the prevention of menstrual migraine because of their safer adverse effect profiles and the underwhelming evidence that combined hormonal contraceptives significantly alter the stroke risk.[88,95,96]

Abortive Treatment

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the oldest class of drugs used for the abortive treatment of migraines. Nonsteroidal anti-inflammatory drugs are effective in symptomatic management via several mechanisms including blocking prostaglandin synthesis by inhibiting the enzyme cyclooxygenase,[32] enhancing adrenergic transmission by increasing norepinephrine release,[97,98] and suppressing inflammation, which subsequently plays a role in preventing central sensitization.[99] In addition to these actions, certain drugs in this class have additional activity. For example, meclofenamates are prostaglandin receptor antagonists, and ketoprofen inhibits 5-lipooxygenase, which forms inflammatory leukotrienes.[32] As different members of the NSAID class, they have slightly different pharmacology. Failure of one drug to effectively terminate a migraine does not necessarily imply failure of all drugs in the class. In other words, certain NSAIDs may be efficacious, whereas others may not.

Triptans

Triptans are another class of abortive treatment that works via their agonist effects on the 5-HT1B and 5-HT1D receptors. Those receptors in turn cause vascular smooth muscle vasoconstriction and inhibit vasoactive peptide release. A robust body of evidence regarding the efficacy in administering triptans for menstrual migraine has been obtained in both retrospective[100,101] and prospective clinical studies.[102–104] Although their efficacy as abortive drugs has been demonstrated, triptans may provide sustained relief for only 20% to 30% of patients.[105,106] Importantly, each drug in the triptan class has slightly different pharmacology, and, like NSAIDs, failure of one drug to effectively terminate a migraine does not necessarily imply failure of all.

Dihydroergotamine

Dihydroergotamine is a nonselective 5-HT1 agonist that has proven to be effective for menstrually related migraines,[107,108] by preventing neurogenic inflammation and central sensitization by blocking neuropeptide release.[109] Dihydroergotamine in doses as low as 1-mg intramuscular injection has proven to be effective for treating menstrual and nonmenstrual migraines.

Spot Menstrual Prophylaxis Using NSAIDs or Triptans

In addition to the abortive therapeutic effects, short-term prophylactic administration of NSAIDs and triptans during and around the time of menses may have a preventive role in the treatment of menstrual migraine. In a double-blind and placebo-controlled study, Sances et al[110] studied the administration of naproxen at 550 mg given twice per day versus placebo 7 days before and into day 6 of the menstrual cycle in 40 women. Naproxen reduced intensity, duration, and analgesic use. Notably, 33% of the naproxen group had no migraine attacks. Newman et al[111] studied the effects of sumatriptan at 25 mg 3 times per day for 5 days versus placebo in 20 women 2 to 3 days before menses. In the sumatriptan treatment group, 50% of the women had no headaches during the medication administration period, and those who had headaches had a reduction in severity. In addition, Newman et al[112] studied the effects of naratriptan, which is a longer-acting triptan, in 206 women taking either 1 or 2.5 mg twice per day for 5 days versus placebo starting 2 days before menses for 4 cycles. The naratriptan group demonstrated a 50% headache-free rate during the time of medication administration versus 25% in the placebo group.[112] Similarly, Moschiano et al[113] observed the therapeutic effects in 59 women taking naratriptan 1 mg twice per day 2 days before menses for 6 days versus placebo for pure menstrual migraine. In the naratriptan group, migraine attacks decreased by nearly 2-fold over 3 months. Frovatriptan is a long-acting triptan, which has been used for spot menstrual headache prophylaxis. Silberstein et al[114] noticed a dose-dependent response in reduction of menstrual migraine headaches treated with frovatriptan 2.5 mg on either daily or twice-per-day dosing versus placebo in 579 women. Frovatriptan was started on days 2 to 5 after a loading dose of 5 mg on day 1. There was a reduced incidence of migraine over 3 cycles. Frovatriptan was superior to placebo ($P < 0.0001$) and the twice-per-day regimen was superior to the daily regimen ($P < 0.001$). The twice-per-day regimen effectively improved menstrual migraine by diminishing severity, shortening duration, decreasing menstrually related symptoms, and minimizing the need for rescue medications.[114]

Bariatric Surgery

In a prospective observational study by Bond et al,[85] 24 migraineurs, who were mostly female (88%), middle-aged (mean age, 39.3 years), and severely obese (mean BMI, 46.6 kg/m^2) at baseline, were assessed before and 6 months after bariatric surgery.

The number of headache days per month was reduced from 11.1 preoperatively to 6.7 postoperatively ($P < 0.05$), after a mean percent excess weight loss of 49.4%. The odds of experiencing a less than 50% reduction in headache days were related to greater percent excess weight loss, which was independent of surgery type ($P < 0.05$). Reductions in severity were also observed ($P < 0.05$), and the number of patients reporting moderate to severe disability due to migraine decreased from 12 (50.0%) before surgery to 3 (12.5%) after surgery ($P < 0.01$). The severely obese migraineurs experienced marked improvement of headaches after significant weight reduction from bariatric surgery.[85,86] This observation was supported by another similar clinical study.[115] In a 6-month post–bariatric surgery follow-up study, Novack et al[115] reported the effects of surgical weight loss on migraine in 29 premenopausal obese migraineurs demonstrating a significantly reduced frequency ($P < 0.001$) and duration ($P = 0.02$) of migraine attacks, lower medication use ($P = 0.005$), less or nonmigraine pain ($P = 0.05$), and diminished headache-related disability.[115] In addition, in a report presented at the eighth Annual Meeting of the American Society for Metabolic & Bariatric Surgery in June 2011,[86] Gunay et al[86] demonstrated that bariatric surgery can lead to total or partial alleviation of migraines in nearly 90% of morbidly obese migraineurs. In this study with an average follow-up of 3 years after gastric bypass surgery, 70% of patients never had another migraine, and 18% had partial resolution with migraine attacks dropping from 5 to 2 per month. Those patients also experienced less severe migraines and took less abortive medication.[86,115] Interestingly, in addition to diminish migraines, bariatric surgery also improved cognitive function.[116]

CONCLUSIONS

Catamenial migraine is a primary headache disorder in women associated with menstrual cycles, which can cause significant disability for many sufferers. The fluctuation of estrogen levels is believed to play a central role in the pathophysiology of catamenial migraine. However, the intracellular and molecular roles of estrogen in the pathogenesis of catamenial migraine have yet to be fully elucidated. A thorough history with detailed attention to headache characteristics is essential in establishing an accurate diagnosis and treatment plan. Hormone supplementation therapy may have mixed results in terms of headache prophylaxis and should be used with caution based an appropriate risk to benefit evaluation with a focus on stroke risk factors. In addition to conventional medication regimens for the symptomatic management, prophylaxis around the time of menses with agents such as NSAIDs or triptans, alone or in combination, may be effective for the treatment of catamenial migraine.

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