Migraine in Women

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KEYWORDS

• Women • Migraine • Menstrual migraine • Hormonal
• Management

As noted, after puberty there is an emerging female predominance in migraineurs, and thus adolescence can be a time of troublesome headaches, with an overall estimate of 5% to 10% of children being afflicted with migraine. Many practitioners miss the diagnosis of migraine at this stage in a young woman's life. As women grow older, and headache patterns become more established, migraine may be more identifiable and more accurately diagnosed, but yet still not treated adequately. Changes in the hormonal milieu can impact migraine in women, and these hormonal changes occur not only monthly, triggering menstrual migraine, but there are also numerous other times in a woman's life when endogenous or exogenous changes in estrogen will impact her migraines. These changes in estrogen may be more predictable as in pregnancy or quite unpredictable as in the chaotic changes in estrogen levels occurring in puberty or in the years leading to menopause. Because gender is a risk factor for chronification of headache, with women more commonly affected with chronic daily headache than men, educational efforts, accurate diagnosis, and appropriate intervention are critical.

MENSTRUAL MIGRAINE

As early as 1666, menstrual migraine (MM) was described by Johannis Van der Linden,[1] who wrote about a one-sided headache associated with nausea and vomiting, occurring monthly during the menstrual flow of the Marchioness of Brandenburg. In modern times, close to 60% of women migraneurs experience menstrually related migraines.[2] MM develops most frequently in the second decade of life, around the onset of menarche, and prevalence peaks around age forty; as menopause approaches prevalence declines.[3] Migraine attacks may occur before, during, or after menstruation, but attacks associated with menstruation are often more severe, of longer duration, and less responsive to both acute and prophylactic treatment than migraines occurring at other times of the cycle.[4–6]

Pure menstrual migraine (PPM) affects 10% to 14% of women with migraine and refers to attacks occurring exclusively on days 1 $\pm$ 2 (ie, days -2 to +3 of menstruation)

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in at least two out of three cycles and at no other time of the month.[7–9] Menstrually related migraine (MRM) affects over 50% of women who have migraine and by definition migraines occur not only in the perimenstrual period as described, but also at other times of the month. By definition, menstrual migraine (both PMM and MRM) is migraine without aura, although a patient who have MRM may experience aura during migraine attacks outside the menstrual period.[7,8] Both MRM and PMM typically occur from 2 days before, through the first 3 days of the cycle, with an increased severity and prevalence of nausea and vomiting. The highest risk of migraine is during the first three days of the cycle.[4] It is important to distinguish premenstrual headache from MM. Premenstrual headache occurs earlier in the cycle, typically 2 to 7 days before the onset of menses and may be part of premenstrual syndrome (PMS). Whereas MM begins around the onset of menses, headache associated with PMS usually resolves with the onset of menstruation.[10]

Pathophysiology of Menstrual Migraine

Throughout a woman's life, from puberty through menopause, there is a constant cycling of ovarian function under the influence of hypothalamic-secreted gonadotropin-releasing hormone (GnRH), pituitary-secreted luteinizing hormone (LH), and follicle- stimulating hormone (FSH), leading to the ovarian secretion of estrogen and progesterone. The luteal phase is key in triggering migraine, when, in the event of a lack of fertilization and implantation, there is an abrupt drop in both estrogen and progesterone levels, heralding menstruation. This drop in estrogen is felt to be an important trigger in MM.[11,12] This fall in estrogen may in some yet-to-be described fashion prime blood vessels to be more susceptible to other factors. One of these factors may be the prostaglandins (PGs), which are fatty acid derivatives of arachidonic acid believed to promote neurogenic inflammation and inhibit norepinepherine release. PGs may play a role in MM, given that there is a threefold increase in prostaglandin levels by the luteal phase, with a further increase during menstruation.[8] Additionally, PG inhibitors, such as the nonsteroidal anti-inflammatory drugs (NSAIDs), have been found to be effective in treating and preventing MM in some women.

Treatment of Menstrual Migraine

Treatment of MM is often challenging, because acute treatments may suffice for some women, while others may require prophylactic therapy, either hormonal or nonhormonal. Effective treatment of MM, however, can lead to a reduction in headache burden.[13] A critical first step in the management process is to have the patient keep a headache diary for 3 months to determine whether there is indeed a link between her headaches and her period. Both nonpharmacologic methods (including avoidance of known triggers, regular exercise, sleep hygiene, good hydration, and biofeedback) and pharmacologic approaches should be explored, and most women will require both approaches. It can be frustrating for women to determine triggers, because certain triggers may be critically important during a MM attack, and yet be insufficient to trigger a migraine at another time of the month. Other than the migraine-specific triptans that have shown clear benefit, pharmacologic agents are chosen based upon comorbid conditions, previous successes or failures, and the adverse effect profiles of the various medications. Patients must be advised to use adequate birth control methods, because many of the drugs used in the treatment of migraine are contraindicated in pregnancy and should be avoided in a woman who is attempting to conceive.

Acute therapy of MM employs migraine-specific agents often in conjunction with gastrokinetic antiemetics such as metoclopramide or prochloperazine, or NSAIDs

may be required. Choice of the seven available triptans is made on patient's prior success or failure, speed of onset, associated nausea/vomiting, and personal preference. Preventative therapy should be considered for women experiencing three to four or more debilitating headaches per month, or in whom MM is unresponsive to abortive medications. The goal of prevention is to reduce the frequency, duration, and intensity of the migraine headaches. Unfortunately, as previously noted, MM can be very difficult to treat, and even with preventative therapy, a woman may continue to experience MM, despite relief of headache at all other times of the month. Daily preventatives are used for those experiencing MRM and frequent migraine at other times, and miniprophylaxis is used for the patient who has PMM or MRM and few other migraine attacks. Miniprophylactic therapy requires that the timing of the migraine can be predicted either by a regular menstrual cycle or by associated features heralding its occurrence.

In miniprophylaxis, both hormonal and nonhormonal prophylactic options are available. In nonhormonal prophylaxis, standard migraine prophylactic agents and some abortive medications are used perimenstrually. One class of abortive agents is the NSAIDs. Naproxen sodium (550 mg twice daily) or mefenamic acid (500 mg TID) may be used effectively 2-4 days before the MM and continued through day 3 of menstrual flow.[14,15] As response is variable, it is important to try different classes of NSAIDs, because a lack of response to one type of NSAID does not rule out a response to an alternate NSAID.

Triptans have been studied as preventative agents for MM, and sumatriptan (25 mg three times daily), naratriptan (1 mg twice daily), frovatriptan (2.5 mg twice daily), and zolmitriptan (2.5 mg two or three times daily) have been found to be effective.[16–19] Dosing of the triptan begins 2 days before the onset of the MM and is continued for a total of 5 to 6 days. Ergotamine derivatives may be used for short-term prophylaxis without risk of developing ergot dependence provided they are used only during the vulnerable period.[20] Effective regimens include ergotamine tartrate one tablet twice daily or 0.5 suppository taken every night over the vulnerable perimenstrual time period. Dihydroergotamine (DHE) has shown effectiveness in its various forms and in a double-blind cross-over trial, DHE nasal spray given every 8 hours for a 6 days was effective,[20] as was intermittent prophylaxis with a timed-release formulation of DHE.[21] Triptans and ergot preparations must be avoided in women who have uncontrolled hypertension, or other risk factors for vascular disease.

Standard migraine prophylactic medications, including anticonvulsants, β-blockers, calcium channel blockers, and antidepressants may be used for 5 to 7 days before the onset of menses and continued through to the end of menses or vulnerable time for migraine. For women who are taking preventative agents, transiently increasing the dose during the perimenstrual period may reduce or eliminate the MM.

Hormonal prophylaxis attempts to counteract or prevent the luteal phase drop in estrogen and may be considered for refractory MM provided there are no contraindications to estrogen therapy, including a history of migraine with aura, blood clotting disorders, and risk factors for arterial disease such as diabetes, hypertension and tobacco use. Any patient who develops an aura while on hormones, or in whom there is a change from simple aura, should discontinue its use. Hormonal intervention has variable effect on migraine (headaches may improve, worsen, or remain unchanged), and this should be communicated to patients.[22]

The lowest effective dose should be used when attempting to stabilize estrogen levels and percutaneous and transdermal methods are preferred to oral supplementation; the latter has more variable absorption and can lead to unstable plasma levels, resulting in reduced efficacy. Most women, however, prefer oral contraceptives. If

there are no contraindications, the patient could be switched to periodic noncycling of the oral contraceptive pill to eliminate three of every four cycles and therefore in theory, three of every four MRM attacks.

Using 1.5 mg percutaneous estradiol daily for the 3 days before menses and continued for 6 days has shown efficacy in two studies.[23,24] When using transdermal estradiol, a 100 μg patch is placed 3 days before menses, then replaced 1 day before menses and replaced again on day 2 after menses begins. In either case, when using an estrogen supplement, it is advisable to check progesterone levels to ensure that there is adequate endometrial protection.

For refractory cases, it is best to discuss this with the patient's gynecologist. Both the synthetic androgen, danazol acting as an estrogen antagonist, and the antiestrogen tamoxifen have shown efficacy in miniprophylaxis.[25,26] The dopamine receptor agonist bromocriptine, an inhibitor of prolactin release, given three times daily during the luteal phase, has also showed moderate effect.[27] GnRH analogs, which induce a medical menopause, also have been effective; however, they generally are limited to short (6 month) courses.[28,29] None of these methods have been subjected to clinical trials and therefore are not recommended universally for therapy of MM. Additionally, these drugs often cause unpleasant or intolerable adverse effects.

No long-term or controlled studies have been undertaken evaluating hysterectomy or oophorectomy for treating MM. In one study, two thirds of patients undergoing surgical menopause reported a worsening of their headaches.[30] Anecdotal reports of success are complicated by the postoperative use of daily estrogen replacement, which may account for the positive results.[31] As such, there is no role for hysterectomy or oophorectomy for managing MM.

ORAL CONTRACEPTIVE USE

For millions of women, oral contraceptive pills (OC) are the birth control method of choice; however, their use in migraineurs requires careful thought, as their effect is unpredictable. Because most women who have migraine are afflicted during their childbearing and peak productive years, the question of birth control invariably will arise whether in the adolescent girl or in the young through older-aged premenopausal woman. Thus, one must be aware of the risks and benefits of the use of the birth control pill to accurately council patients who have migraine. When a woman who has migraine begins OC therapy, the migraine may improve, worsen, remain stable, or occur for the first time.[32] In women who experience a worsening of their migraines, it is typically during the placebo week. Generally speaking, OC use is considered safe in women who experience migraine without aura or migraine with simple aura and in whom there is an absence of vascular risk factors.[33] If after beginning an OC the aura pattern changes or develops for the first time, the OC should be discontinued because of increased stroke risk.[34] As estrogen levels tend to fluctuate more with oral dosing, a patch or vaginal insert contraceptive may provide more steady-state levels and be less likely to impact migraine. Because the patch provides very high levels of estrogen, however, it may be relatively contraindicated due to potential stroke risks.

When choosing an OC. it is best to choose a low-dose, monophasic pill, rather than a mid- or high-dose pill. Biphasic and triphasic pills, while commonly prescribed, are not generally the best choice in migraineurs because of the fluctuating levels of estrogen. As previously noted, in women who have MRM, adding on estrogen during the placebo week can be helpful, as can noncycling of an OC, as it reduces the number of menstrual cycles and thus the number of MRMs.

PREGNANCY AND THE POSTPARTUM PERIOD

As previously noted, most migraine patients are women in their childbearing years; thus there is inevitably potential for the unintentional administration of acute migraine therapy in early pregnancy.[35] Given this, and the fact that perhaps more than 50% of pregnancies are unplanned, it is advisable to discuss migraine treatment and pregnancy issues with all female patients. In retrospective studies, 60% to 70% of pregnant migraineurs reportedly improve and in a more recent prospective study, up to 87% improved.[36] This improvement in or alleviation of migraine typically occurs during the second and third trimesters, although migraine often persists during the first trimester.[37,38] Improvement in pregnancy is more likely in women who have migraine without aura and in women who previously experienced MRM.[36] Migraine beginning for the first time in pregnancy is more often migraine with aura.[39] In addition to the hormonal changes of pregnancy, disrupted sleep, nausea, dehydration, and stress likely contribute to headache.

In pregnant women who have a prior history of migraine and an uneventful pregnancy, the challenge faced by the clinician is not usually diagnostic, but rather therapeutic. Given the unpredictable nature of migraine symptoms, however, management during pregnancy should begin by ruling out underlying pathology with new-onset headaches and then selecting a treatment to maximize benefit to the woman while minimizing risk to the fetus. The greatest concern regarding treatment of migraine during pregnancy of course relates to the potential teratogenicity of drug therapy. Reassurance, rest, ice packs, acupuncture, biofeedback, and avoidance of known triggers are often beneficial and may help the pregnant patient get through the first trimester, after which migraine may improve. No increased risk of major or minor abnormalities in infants born to women with migraine has been found.[40,41]

In the early stages of pregnancy, small doses of caffeine and acetaminophen are considered safe. Several NSAIDs are category B in pregnancy and include diclofenac, flurbiprofen, ibuprofen, ketoprofen, naproxen, piroxicam, and indomethacin; however, they are all category D in the third trimester. Some narcotics, meperidine and morphine, are category B, except in the third trimester when their use is cautioned. Codeine, while often used in pregnancy, has been associated with cardiac, respiratory, and cleft defects, but the relationships may not be causal. After the first trimester, category B antiemetics include dimenhydrinate, diphenhydramine, pyridoxine, and Emetrol. In suppository form, prochlorperazine, metoclopramide, and promethazine are generally considered safe. If steroids are required, prednisone often is preferred to dexamethasone, because the latter crosses the placenta more easily. Clearly more data are needed to guide clinicians in the safe use of therapeutic options in the pregnant migraineur.[42]

Triptans, ergots, and aspirin should be avoided. Pregnancy registries have been established for several of the triptans to monitor women (and their pregnancy outcomes) who inadvertently took these medications while pregnant. No evidence for any specific effect of sumatriptan on pregnancy outcome has been found.[43,44] Proof of absence of any risk is never absolute, however, and as such, it is not recommended to prescribe a triptan to a pregnant migraineur without clear indication.

For pregnant women who have severe, intractable migraine (often accompanied by nausea, vomiting and dehydration), medical therapy may be indicated, because this could pose a risk to the developing fetus greater than the risk of medication. For severe attacks, intravenous fluids and an intravenous antiemetic often are indicated. When migraine is frequent and disabling (three to four prolonged, severe migraines per month), preventative therapy may be required but should be undertaken with

the full consent of both the patient and her partner, because most preventatives are category C or higher. Commonly employed agents include labetolol, propranolol, and occasionally amitriptyline or fluoxetine. Migraine often recurs in the postpartum period, presumably related to the rapid fall in estrogen levels.

PERIMENOPAUSE AND MENOPAUSE

Migraine tends to improve with age, and in women who have a history of menstrually related migraine, there may be improvement following menopause. On average, menopause is reached around age 50 years, with most women completing menopause by age 55 years. However, in the years preceding menopause, the perimenopause, many women notice a worsening of their migraines, and unfortunately, this stage in a woman's hormonal life may last several years. This is a transitional phase, which may begin in the mid- to late thirties and may last 10 years or more. During this time, episodic fluctuations in hormone levels occur, along with an overall decline in absolute levels, culminating in the symptoms of perimenopause, which may include fatigue, insomnia, irritability, irregular periods, night sweats, hot flashes, forgetfulness, a drop in libido, and difficulty concentrating.

In a woman who has migraine, worsening headaches may herald the onset of perimenopause. The chaotic, often unpredictable hormonal fluctuations of this time may even contribute to the new onset or return of previously abated migraines. In women who have MRM, a worsening in both the severity and frequency of migraines may occur, and monthly menstruation can become an important and predictable trigger for migraine. When irregular cycles set in and make migraine attacks unpredictable, treatment is more challenging. The other symptoms of perimenopause such as poor sleep from hot flashes and insomnia also contribute to worsening headaches. Although hormone levels can be measured, their absolute results are unlikely to sway the diagnosis and treatment plan significantly. In some women, the symptoms of perimenopause are managed with hormone replacement therapy (HRT).

Depending on the route of administration, type of estrogen, and cyclical versus continuous use, HRT has varying effects on a woman's migraines.[45–48] For women experiencing the ill effects of the fluctuating hormones of perimenopause, HRT on a short-term basis to stabilize estrogen levels may prove beneficial. For others, HRT may worsen migraine and consequently, strategies will need to be considered. In women migraineurs, the type of estrogen used and its method of delivery can impact migraine significantly.

To cope with worsening migraine, numerous strategies may be employed including reducing the dose of HRT, using a noncycling method, switching from conjugated estrogens to pure estradiol or from synthetic to bioidentical estrogen.[46] Switching from oral to transdermal is also beneficial, because with oral estrogen replacement, serum levels rise rapidly and thereafter decline until the next dose. The amount of estrogen absorbed also can vary with each dose. These fluctuations may be a trigger for migraine, especially because a woman's own endogenous estrogen levels also are fluctuating.[47,49] Transdermal estrogens, in contrast, provide more stable physiologic estrogen levels. If adjustments in the estrogenic component of the HRT are unsatisfactory with respect to improving migraine, then manipulation of the progesterone component can be considered.

SUMMARY

Migraine affects women from the preadolescent through the postmenopausal years. As such, clinicians involved in managing migraine need to be aware of the particular

issues facing women migraineurs. The effect of hormonal fluctuations, whether endogenously or exogenously induced, is often unpredictable, and thus careful thought must be given to the various treatment options. Additionally, the potential for pregnancy always must be considered. With perseverance, effective migraine control usually is achieved in most patients.

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