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Menstrual migraines: Which options and when?

Would your patient benefit from abortive therapy or prophylactic treatment? And which regimen is likely to provide the best—and safest—relief? Read on.

PRACTICE RECOMMENDATIONS

› *Consider recommending that patients with menstrual migraines try using prophylactic triptans 2 days before the onset of menses.* (B)

› *Advise against estrogen-containing contraception for women who have menstrual migraines with aura, who smoke, or are over 35, due to the increased risk of stroke (absolute contraindication).* (A)

› *Consider estrogen-containing contraception if the benefits outweigh the risks for women with migraines who are under 35 and do not have aura (relative contraindication).* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE ▶ Mary, a 34-year-old woman, is a new patient to your practice after moving to the area for a job. She has a history of migraine headaches triggered by her menstrual periods. She has been taking combined oral contraceptives (COCs) since she was 17, with a few years off when she had 2 children. Her migraines improved when she was pregnant, but worsened postpartum with each of her daughters to a point where she had to stop breastfeeding at 4 months to go back on the pills.

On the COCs, she gets one or 2 mild-to-moderate headaches a month. She uses sumatriptan for abortive treatment with good relief. She has not missed work in the past 4 years because of her migraines. During the 6 months she was off COCs when trying to get pregnant, she routinely missed 2 to 3 workdays per month due to migraines. She knows when she is going to get a headache because she sees flashing lights in her left visual field. She has no other neurologic symptoms with the headaches, and the character of the headaches has not changed. She is a non-smoker, has normal blood pressure and lipid levels, and no other vascular risk factors.

You review her history and talk to her about the risk of stroke with migraines and with COCs. She is almost 35 years of age and you recommend stopping the COCs due to the risk. She feels strongly that she wants to continue taking the COCs, saying her quality of life is poor when she is off the pills. What should you do?

Migraine headaches are 2 to 3 times more prevalent in women than in men,[1] with a lifetime risk of 43% vs 18%, respectively.[2] Women account for about 80% of the $1 billion spent each year in the United States in medical expenses and lost work productivity related to migraines.[1,2]

Clinical patterns suggestive of menstrual migraine. About half of women affected by migraine have menstrually-

TABLE 1

Diagnostic criteria for migraine without aura[3]

At least 5 total episodes of headache* that last 4-72 hours each	
With at least 2 of these characteristics:	**AND with at least 2 of these symptoms:**
Unilateral location	Nausea
Pulsating quality	Vomiting
Moderate-to-severe pain	Photophobia
Aggravation with movement	Phonophobia
Causes avoidance of routine activities	Osmophobia

*Headache episodes cannot be attributed to another disorder.

related migraines (MRM); 3% to 12% have pure menstrual migraines (PMM).[3] MRM and PMM are both characterized by the presence of symptoms in at least 2 to 3 consecutive cycles, with symptoms occurring from between 2 days before to 3 days after the onset of menstruation. However, in PMM, symptoms do not occur at any other time of the menstrual cycle; in MRM, symptoms can occur at other times of the cycle. PMM is more likely to respond to hormone therapy than is MRM.

Multiple studies in the United States, Europe, and Asia have noted that migraines related to menses typically last longer, are more severe, less likely to be associated with aura, and more likely to be recurrent and recalcitrant to treatment than non-menstrual migraines.[1] **TABLE 1**[3] describes diagnostic criteria for migraine without aura.

Possible mechanisms of MRM and PMM. The etiology of migraine is not well understood and is likely multifactorial.[4] Incidence of menstrual migraines is related to cyclic changes in female hormones—specifically, the decreasing levels of estrogen that typically happen the week before onset of menses.[1] The mechanism is not yet clear, though it is thought that a decline in estrogen levels triggers a decline in serotonin levels, which may lead to cranial vasodilation and sensitization of the trigeminal nerve.[5,6] Estrogen decline has also been linked to increased cranial nociception as well as decreased endogenous opioid activity. A study using positron emission tomography found increased activity of serotonergic neurons in migraineurs.[7] The evidence that triptans and serotonin receptor agonists are effective in the treatment of migraine also supports the theory that serotonin neurohormonal signaling pathways play a critical role in the pathogenesis of migraines.[7]

Prevalence patterns point to the role of estrogen. The prevalence of migraines in women increases around puberty, peaks between ages 30 and 40, and decreases after natural menopause.[6] Migraine prevalence increases during the first week postpartum, when levels of estrogen and progesterone decrease suddenly and significantly.[1] Migraine frequency and intensity decrease in the second and third trimesters of pregnancy and after menopause, when estrogen levels fluctuate significantly less.[1] In the Women's Health Initiative study, women who used hormone replacement therapy (HRT) had a 42% increased risk of migraines compared with women in the study who had never used HRT.[8]

The association of migraine with female hormones was further supported by a Dutch study of male-to-female transgender patients on estrogen therapy, who had a 26% incidence of migraine, equivalent to the 25% prevalence in natal female controls in this study, compared with just 7.5% in male controls.[9] The association between migraine and estrogen withdrawal was investigated in studies performed more than 40 years ago, when women experiencing migraines around the time of menses were given intramuscular estradiol and experienced a delay in symptom onset.[10]

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Migraines related to menses typically last longer, are more severe, less likely to be associated with aura, and more likely to be recalcitrant to treatment than non-menstrual migraines.

Triptans are contraindicated for women with a history of cardiac disease or uncontrolled hypertension.

Abortive and prophylactic treatments: Factors that guide selection

In considering probable menstrual migraine, take a detailed history, review headache diaries if available to determine association of headaches with menses, and perform a thorough neurologic examination. If a diagnosis of menstrual migraine is established, discuss the benefits of different treatment options, both abortive and prophylactic.

For the patient with MRM, take into account frequency of symptoms, predictability of menstruation, medication costs, and comorbidities. Both triptans and nonsteroidal anti-inflammatory drugs (NSAIDs) can be effective treatments for MRM.[11] Abortive therapy may be appropriate if a patient prefers to take medication intermittently, if her menses are unpredictable, or if she does not get migraine headaches with every menses. Mefenamic acid, sumatriptan, and rizatriptan have category B recommendations for abortive treatment for menstrual migraines (**TABLE 2**[11-16]). (For the patient who has regular MRM but unpredictable menses, ovulation predictor kits can be used to help predict the onset of menses, although this would involve additional cost.)

For the patient who has predictable menses and regularly occurring menstrual migraine, some data show that a short-term prophylactic regimen with triptans started 2 to 3 days before the onset of menses and continued for 5 to 7 days total can reduce the incidence of menstrual migraine (**TABLE 2**[11-16]). At least one high-quality randomized controlled trial (RCT) showed a significant reduction in the incidence of MRM when women were treated prophylactically with frovatriptan, a long-acting triptan with a half-life of approximately 26 hours. Participants received frovatriptan 2.5 mg once a day or twice a day or placebo in the perimenstrual period (day -2 to +3). The incidence of MRM was 52%, 41%, and 67%, respectively (P<.0001).[11,17]

Another RCT of fair quality examined the effect of naratriptan (half-life 6-8 hours) on the median number of menstrual migraines over 4 menstrual cycles. Women who received 1 mg of naratriptan BID for 2 to 3 days before menses had 2 MRM episodes over the 4 cycles compared with 4 MRM episodes in women who received placebo over the same time period (P<.05).[11,18] A third RCT, also of fair quality, compared 2 different regimens of zolmitriptan (half-life 3 hours) with placebo and found that women who received 2.5 mg of zolmitriptan either BID or TID 2 to 3 days prior to menses had a reduction both in frequency of menstrual migraines and in the mean number of breakthrough headaches per menstrual cycle, as well as a reduction in the need for rescue medications.[12,19] Triptans are contraindicated in women with a history of cardiac disease or uncontrolled hypertension. Also, triptans can be expensive, precluding their use for some patients.

Evidence is insufficient to recommend for or against the use of NSAIDs as prophylaxis for MRM.[11] NSAIDs may be contraindicated in women with a history of peptic ulcer disease or gastrointestinal bleeding. That said, if NSAIDs are not contraindicated, a trial may be reasonable given their low cost.

Data are sparse on the use of vitamins and supplements in treating and preventing PMM or MRM. In one very small double-blind, placebo-controlled study in 1991 (N=24, with efficacy data for 20), participants received a 2-week course of oral magnesium premenstrually. There was a statistically significant reduction in the number of days with headache per month (from 4.7±3.1 days to 2.4±2.2 days; P<.01) and in the total pain index (P<.03).[20] A number of studies have demonstrated a correlation between hypomagnesemia and migraine headaches.[5,21] The exact mechanism for this relationship is unclear.

Some recent evidence-based reviews have examined the efficacy of nutraceuticals such as magnesium, feverfew, butterbur, coenzyme Q10, and riboflavin on typical migraine, but it is not clear if these results are translatable to the treatment and prophylaxis of menstrual migraine.[11,22] A multicenter, single-blind, RCT is underway to examine the efficacy of acupuncture as prophylaxis for MRM.[23]

TABLE 2

Abortive and prophylactic treatment of pure menstrual migraine and menstrual-related migraine[11-16]

Treatment	Dose	Contraindication	Caution	LOE*
Abortive				
NSAID				
Mefenamic acid	500 mg TID	Active PUD	History of GI bleed or CV disease	B
Triptans	**(single dose)**			
Naratriptan	2.5 mg	Cardiac disease, uncontrolled HTN, concomitant ergotamine/ MAOI use		I
Rizatriptan	10 mg			B
Sumatriptan	50 mg, 100 mg			B
Zolmitriptan	1.25 mg, 2.5 mg, 5 mg			C
Prophylactic				
NSAID				
Naproxen	500 mg BID	Active PUD	History of GI bleed or CV disease, renal impairment	I
Triptans†				
Frovatriptan	2.5 mg BID	Cardiac disease, uncontrolled HTN, concomitant ergotamine/ MAOI use		B
Naratriptan	1 mg BID			B
Zolmitriptan	2.5 mg TID			B‡
Magnesium citrate	600 mg/d§			I
Phytoestrogens	Soy isoflavones, 60 mg/d Dong quai, 100 mg/d Black cohosh, 50 mg/d	Pregnancy Anticoagulant/antiplatelet medication Pregnancy	**Isoflavones:** Multiple interactions with medications **Dong quai:** Hormone-sensitive conditions; recent surgery **Black cohosh:** Statin use; cytochrome P450 substrates; hepatotoxic medication use	I
Ethinyl estradiol		See **TABLE 3**		B‖
Topical gel	1.5 mg/d, Days -2 to 5			
Transdermal patch	100 µg/d, Days -7 to 7			
COCs with 3rd-generation progestin	20-35 µg with continuous cycling			
COCs with estrogen supplementation	20 µg during the hormone-free week			
Progestin only				
Desogestrel	75 µg/d	Thromboembolic disorders, vascular disease		B‖

COC, combined oral contraceptives; CV, cardiovascular; GI, gastrointestinal; HTN, hypertension; LOE, level of evidence; MAOI, monoamine oxidase inhibitor; NSAID, nonsteroidal anti-inflammatory drug; PUD, peptic ulcer disease.

*The levels of evidence given here are based on the grading system used by the US Preventive Services Task Force, as applied by the authors. **A**: There is high certainty that the net benefit is substantial; **B**: There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial; **C**: There is at least moderate certainty that the net benefit is small; **D**: There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits; **I**: Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

†Studies vary in use of a total of 5-7 days of treatment, starting 2-3 days prior to the onset of menses.

‡Based on one study with limited information on randomization.

§No clear recommendations for magnesium dosing. This dose is recommended by the Canadian Headache Society; https://www.guideline.gov/summaries/summary/38455/canadian-headache-society-guideline-for-migraine-prophylaxis.

‖Based on very small studies.

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TABLE 3

US Medical Eligibility Criteria for COC use in women with migraines[36]

	Migraine with aura	Migraine without aura
Age <35 years		
Non-smoker	Unacceptable health risk	Advantages generally outweigh theoretical and proven risks
Smoker		Theoretical or proven risks usually outweigh the advantages*
Vascular risk factors†		Unacceptable health risk
Age ≥35 years		
Non-smoker	Unacceptable health risk	Theoretical or proven risks usually outweigh the advantages
Smoker		Unacceptable health risk
Vascular risk factors†		Unacceptable health risk

COC, combined oral contraceptives.

*An odds ratio for risk of stroke of 34.4 is based on one study[37] and 13.9 is based on another.[38]

†Includes poorly and uncontrolled hypertension, diabetes, and known vascular or cardiac disease.

Estrogen: Prescribing criteria are strict

The association between MRM and hormonal variation makes exogenous hormone therapy a tempting prophylactic treatment. A study by Somerville showed that using exogenous estrogen to mitigate the decrease in estrogen through the menstrual cycle can raise the headache threshold and thereby decrease the frequency and severity of MRM.[10] Progesterone levels also vary throughout the menstrual cycle; however, this variation has not been shown to correlate with MRM. Some investigators have speculated that continuous exogenous progesterone may decrease the frequency of MRM through the blunting of estrogen cycles.[5,10,24]

Most studies examining the role of exogenous estrogen in reducing menstrual migraines have used topical estrogen (either in patch or gel formulations) in the perimenstrual window (**TABLE 2**[11-16]). The topical estrogen route has been examined, in particular, as it is presumed to confer less risk of hypercoagulability by avoiding first-pass metabolism. However, there is conflicting evidence on this issue, in particular regarding premenopausal women.[13,25] Additionally, many of the studies of estrogen supplementation show a trend toward increased headache once estrogen is discontinued, presumably due to estrogen withdrawal.[10,24]

That said, one study by MacGregor, et al demonstrates that the use of estradiol gel in the perimenstrual window leads to a 22% reduction in migraine days as well as less severe migrainous symptoms.[26] This trend has been demonstrated in other studies examining estrogen supplementation. Of note, the estrogen studies generally are small, older, and of fair to poor quality.[11] These studies have used higher doses of estrogen than are commonly used for contraception today because lower doses of estrogen seem not to have the same impact on migraine.[5,24]

As for COCs, with either normal or extended cycling, data are more mixed than for estrogen supplementation alone; equivalent numbers of women experience improvement, no change, or worsening of their headache pattern. Many women have continuing or worsening migraines in the hormone-free week, and thus most studies have examined the use of extended cycling COCs.[5] Sulak, et al demonstrated a statistically significant reduction in headache frequency using extended-cycling COCs, though they did not examine MRM in partic-

ular.[27] The efficacy of extended-cycling COCs for reduction of MRM was confirmed by Coffee and colleagues with a small but statistically significant decrease in daily headache scores.[28]

Adverse effects. All estrogen therapies pose the risk of adverse effects (deep vein thrombosis, hypertension, breast tenderness, nausea, etc). Additionally, estrogen supplementation may actually trigger migraines in some women if, when it is discontinued, the blood estrogen level does not remain above a threshold concentration.[5,10,24] Estrogen may also trigger migraine in previously headache-free women and may convert migraine without aura into migraine with aura. In either case, therapy should be stopped.[5,24]

There is promising evidence from 2 small RCTs and one observational trial that progestin-only contraceptive pills (POP) may reduce the frequency and severity of menstrual migraines (**TABLE 2**[11-16]). More prospective data are needed to confirm this reduction, as there have not been specific studies examining other progesterone-only preparations to prevent menstrual migraines.

Risk of ischemic stroke. Unfortunately, there are population data showing that second-generation and, to a smaller degree, third-generation progestins, which include the desogestrel used in the above studies, may increase the risk of ischemic stroke. This is a particular concern in women who experience migraine.[29] Second-generation progestins include levonorgestrel, which is in the levonorgestrel IUD; however, there is no direct evidence for increased ischemic stroke in this particular preparation, and the circulating plasma levels are low. Etonorgestrel, the active ingredient in the contraceptive implant, is a third-generation progestin, though there is no direct evidence of increased ischemic stroke with use of the etonorgestrel implant.

There is a 2- to 4-fold increased risk of ischemic stroke in women who experience migraine.[1,5,30] As stated above, this risk may be further increased by some progesterone formulations. But there is also a demonstrable increase in ischemic stroke risk with the use of estrogen, particularly at the higher concentrations that have been shown to prevent MRM.[31,32] The overall incidence of ischemic stroke in menstrual-age women is low, which has limited the number of studies with enough power to quantify the absolute increased risk of stroke in conjunction with estrogen use. Nevertheless, exogenous estrogen is thought to increase the risk of ischemic stroke an additional 2- to 4-fold.[1,5,29,30,32-34]

Women who experience aura. MRM, as it is defined, typically excludes women who experience aura; however, the number of women who experience aura with migraine either in proximity to their menses or throughout the month has not been well documented. The risk of ischemic stroke is higher for women who experience migraine with aura than those with migraine alone, possibly because aura is associated with reduced regional vascular flow leading to hypoperfusion, which sets the stage for a possible ischemic event.[4,5,35] The risk of ischemic stroke is amplified further for women who are over 35, who smoke, or who have additional vascular risk factors (eg, uncontrolled hypertension, diabetes, or known vascular or cardiac disease).[1,5,34] This array of evidence serves as the basis for the US Medical Eligibility Criteria (USMEC) recommendations[36] for hormonal contraceptive use, in particular the absolute contraindication for estrogen use in women who experience migraine with aura (**TABLE 3**[36-38]).

The risk of stroke is also thought to be heightened possibly during the first 4 years following onset of migraine, especially if associated with aura, with migraines occurring more than 12 times a year, or with a history of migraine spanning more than 12 years.[32,34] These factors need further study. Ischemic stroke can be a devastating event, especially in young, otherwise healthy women. Therefore, administration of estrogen to reduce MRM should only be considered in low-risk women who do not experience aura, are under 35, and do not smoke.

CASE ▶ Given Mary's experience of aura with migraine, you talk with her at length about the risk of ischemic stroke and the USMEC recommendation that she absolutely should

Evidence is insufficient to recommend for or against the use of NSAIDs as prophylaxis for menstrually-related migraines.

not be taking COCs. You suggest a progestin-only method of contraception such as depot medroxyprogesterone acetate, a progestin intrauterine device, or a hormonal implant, which may suppress ovulation and decrease her headaches. You discuss that while some women may have headaches with these progestin-only methods, stroke risk is significantly reduced. You also suggest a trial of prophylactic triptans as another possible option.

She says she understands the increased risk of stroke but is still unwilling to try anything else right now due to worries about her quality of life. You decide jointly to refill COCs for 3 months, and you document the shared decision process in the chart. After advising the patient that you will not continue to prescribe COCs for an extended period of time, you also schedule a follow-up appointment to further discuss risks and benefits of migraine treatment and means of reducing other risk factors for stroke. JFP

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A number of studies have demonstrated a correlation between hypomagnesemia and migraine headaches. The exact mechanism for this relationship is unclear.

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