

Target Audience

Primary care physicians, internists, and other health care professionals who treat patients with menstrual migraine.

Educational Objectives

After reading this supplement, the participant should be able to:

- Describe the clinical significance of differentiating menstrual migraine (MM) versus other types of migraine
- Describe the pathophysiology of MM, including the hormonal mechanisms involved and the relationship of hormonal fluctuations to MM
- Review the impact of MM on patient quality of life and functionality
- Discuss the optimal pharmacotherapeutic management of MM using an evidenced-based approach
- Distinguish between the approaches of acute therapy, short-term prevention, and long-term prevention of MM
- List challenges in and strategies to identify, assess, and manage patients with MM

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STRATEGIES FOR

Optimizing Management of Menstrual Migraine

Vincent Martin, MD

Professor of Medicine
 University of Cincinnati
 College of Medicine
 Cincinnati, Ohio

Jan Lewis Brandes, MD

Clinical Instructor
 Vanderbilt University School of Medicine
 Neurologist
 Nashville Neuroscience Group, PC
 Nashville, Tennessee

The 2004 International Classification of Headache Disorders gave new attention to the link between menstruation and migraine, differentiating between pure menstrual migraine and menstrual-related migraine.¹

Declines in estrogen and progesterone during the late luteal phase of the menstrual cycle result in the predictable occurrence of perimenstrual migraine headache in as many as 35% to 68% of reproductive age female migraineurs.²⁻⁷ Migraine is classified as being with or without aura; migraine with aura is less common. *Pure menstrual migraine* is classified as migraine without aura that occurs exclusively during the perimenstrual window, from 2 days before the onset of menstruation (day -2) to 3 days afterward (day +3), during at least 2 of 3 menstrual cycles.⁷ Approximately 7% to 19% of women with migraine have pure menstrual migraine.^{2-4,7,8}

Menstrual-related migraine is migraine without aura that occurs primarily between days -2 to +3 of the menstrual cycle, but also at other times of the month, during at least 2 of 3 menstrual cycles.¹ Approximately 35% to 51% of women with migraine have menstrual-related

Practice Recommendations

- Determine whether a patient is experiencing menstrual migraine through a 3-month diary recording headache and migraine patterns that indicate increased incidence of migraine during perimenstrual period and increased risk for functional and social disability with headache (SOR: A)
- Eliminate known triggers of menstrual migraine (SOR: A)
- Administer nonpharmacologic therapy (SOR: B)
- Administer acute therapy early in the course of the migraine attack (within 15 minutes) (SOR: A)
- Administer short-term preventive therapy with triptans (SOR: A) or other therapeutic agents (SOR: B) 1 to 2 days prior to the expected onset of menstruation to prevent the development of menstrual migraine
- Administer long-term preventive therapy if the patient has recurrent migraine that does not respond to acute or short-term preventive therapy, has frequent nonmenstrual migraine, or has a concomitant medical condition that would benefit from the therapy (SOR: B)

SOR = STRENGTH OF RECOMMENDATION

migraine.⁸ The term *menstrual migraine* encompasses both pure menstrual migraine and menstrual-related migraine.

PATHOPHYSIOLOGY

The precise mechanisms that cause menstrual migraine are unknown. Both estrogen and progesterone levels decline sharply during the late luteal phase; estrogen decline appears to trigger migraines.

Estrogen exerts wide-ranging effects, including direct effects on the central nervous system, vascular effects, and modulation of serum magnesium concentrations.^{8,9} The decline in estrogen levels may trigger migraine through any or all of these pathways. At the same time, serum prostaglandin levels increase during menstrual migraine, suggesting that these potent mediators of hyperalgesia may contribute to the pathogenesis of migraine as well.¹⁰

In a pioneering study by Somerville,¹¹ 6 women with menstrual migraine received estradiol injections shortly before onset of menstruation. None of the women experienced migraine while the levels of estradiol remained high (>20 ng/100 mL). Once the levels declined, headache developed, indicating that withdrawal of estrogen is associated with precipitation of menstrual migraine. Similar manipulation of proges-

terone levels did not affect onset of menstrual migraine.¹²

Further evidence of the link between estrogen withdrawal and migraine was provided by a study of postmenopausal women.¹³ All participants were given depo-estradiol cyprionate, 5 mg IM. The women who had a history of menstrual migraine developed a severe migraine with estrogen decline; migraine occurred at an average of 18.5 days postinjection. None of the women in the control group, who did not have a history of menstrual migraine, developed a migraine. The difference was significant ($P \leq .05$). The authors concluded that hormonal migraine can be precipitated by a drop in serum estrogen levels.

IMPACT OF MENSTRUAL MIGRAINE DISABILITY, SEVERITY, AND DURATION

The extent of disability from migraine parallels the intensity of symptoms, which range from mild to severe and may vary from episode to episode.¹⁴ Patients with severe symptoms may report reduced ability to participate in activities of daily living and may require bed rest.¹⁵

Several studies indicate that menstrual migraine is more severe and of greater duration than nonmenstrual migraine and thus may result in substantial disability.^{4,16-19} Dowson et al¹⁸ surveyed 1434 female patients who visited general practitioners in the United Kingdom. Patients responded to questionnaires about headache prevalence, association with menstrual cycle, depression, and degree of disability. Women reported more than 50% reduction in productivity with migraine headaches that occurred during the menstrual period than with those that occurred at other times during the menstrual cycle ($P = .01$). Investigators found no such reports of disability with nonmigraine headaches that occurred during the menstrual period.

A study of 1181 women in the Netherlands¹⁶ showed that menstrual migraine was more severe, of longer duration, and less responsive to treatment than migraine that occurred outside the menses. Disability associated with menstrual migraine included restrictions in: social activities (84% of patients); household chores (81%); family activities (58%); sports (55%); and work (45%). Disability levels for menstrual migraine were higher than for other types of headache (FIGURE).

Granella et al⁴ also found that migraine headaches during the perimenstrual period were significantly longer (premenstrual vs nonmenstrual migraine, $P < .0001$), were less responsive to treatment, and

resulted in significantly more work-related disability than other migraine (premenstrual vs nonmenstrual, 51% vs 27.3%, $P = .006$). In this study, menstrual-related headaches were more likely to recur (odds ratio=1.96 [95% confidence interval (CI), 1.46-2.63] and 2.15 [95% CI 1.67-2.78] for premenstrual and menstrual headache, respectively). Of the patients who reported menstrual migraine, only 13.5% were pain free 2 hours after taking the first symptomatic drug (mostly nonsteroidal anti-inflammatory drugs [NSAIDs]) compared with 32.9% of those with nonmenstrual migraine.⁴

A study of 155 women with menstrual-related migraine revealed that for individual women, headaches that occurred from day -2 were 2.1 times more likely to be severe than headaches that occurred at other times during the cycle. Headaches in the first 3 days of menstruation were 3.4 times more likely to be severe. The probability of headache occurrence also was greater during the perimenstrual period.²⁰

Another recent study examined the relation between the menstrual cycle and migraine characteristics. Migraine headache was reported to be significantly more severe, disabling, and frequent during the menstrual intervals of the reproductive cycle than during the midluteal or midcycle intervals.¹⁹

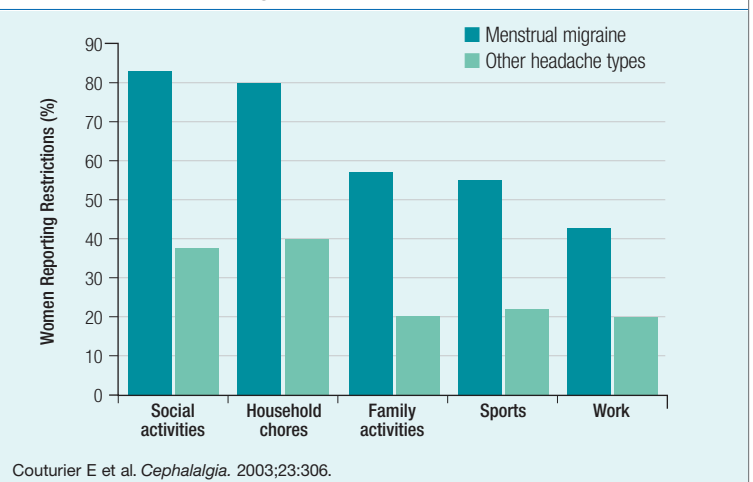
Menstrual migraine appears to recur more often than nonmenstrual migraine. In a study of 366 migraine patients being treated with a triptan, headache recurrence was found to be higher for menstrual migraine.¹⁷ *Headache recurrence* was defined as headache that recurred in at least 80% of treated episodes. Following oral or subcutaneous therapy with sumatriptan, 54% to 63% of women with menstrual migraine experienced headache recurrence.¹⁷ Of the women whose migraines were not associated with menstruation, the percentage with headache recurrence was 4% to 5%.

DIAGNOSIS OF MENSTRUAL MIGRAINE

Women who are suspected to have menstrual migraine should keep a 3-month headache diary. The diary should track: (1) onset and duration of menstruation; (2) date and duration of each headache episode (indicating severity on a scale of 1 to 10); and (3) modifiable triggers such as altered sleeping patterns, trigger foods, medications, and illnesses.⁵ Physicians also should ask

FIGURE

Headache-related restrictions in daily activities for menstrual migraine vs other headache types



patients about the impact of symptoms on their quality of life to develop an individualized treatment plan.

TREATMENT

The US Headache Consortium—a group of 7 professional organizations with an interest in improving migraine care—defines the goals of migraine treatment as: (1) reduce the frequency and severity of attacks; (2) reduce migraine-related disability; (3) improve quality of life; (4) prevent headache; (5) avoid escalation of the use of headache medication; and (6) educate and enable patients to manage their disease.²¹ Treatment options for menstrual migraine include both nonpharmacologic and pharmacologic approaches. Many of the acute pharmacologic approaches are used for both menstrual and nonmenstrual migraine. However, the periodicity of menstrual migraine suggests that short-term preventive therapies should be considered in addition to the acute therapies used for nonmenstrual migraine, especially when severe or disabling attacks do not respond to abortive medications or last more than 2 days.⁸

Nonpharmacologic Approaches

Lifestyle changes to minimize or eliminate known triggers of menstrual migraine—many of the same triggers associated with nonmenstrual migraine—are essential.⁵ These include certain foods, alcohol, exercise, anxiety, stress, bright lights, loud noise, altitude change, oral contraceptives, and lack of sleep. Patients also should maintain regular routines for eating, sleeping, and exercise, including aerobic exercise.

Pharmacologic Approaches

Pharmacologic approaches to menstrual migraine include acute therapy, short-term preventive therapy, and long-term continuous preventive therapy. *Acute therapy* is used to abort migraine attacks once they arise. *Short-term preventive therapy* aims to prevent migraine headaches before they occur and is administered only during the period in which the patient is at risk for menstrual migraine (ie, generally beginning 2 days before onset of menstrual migraine and ending 4-7 days later). *Long-term continuous preventive therapy* is given daily throughout the menstrual cycle to prevent attacks of both menstrual and nonmenstrual migraine.

Acute therapy

Acute therapy can abort or shorten a migraine episode once symptoms occur, thus reducing disability.⁶ Agents used for acute treatment of menstrual migraine are the same as those for nonmenstrual migraine and include NSAIDs, cyclooxygenase-2 (COX-2) inhibitors, triptans, ergot derivatives, analgesics, and antiemetics. These agents have been discussed in detail elsewhere,^{11,21-29} and as these treatments do not differ between menstrual and nonmenstrual migraine, will not be discussed further.

With acute therapy, migraine should be treated as early in the progression of the attack as possible for best effectiveness. In a study by Burstein, patients treated before development of allodynia (a marker for central sensitization of second order neurons of the trigeminal nerve) were significantly more likely to be pain free after treatment with a triptan.³⁰ Allodynia is pain resulting from a stimulus (eg, a light touch of the skin) that would not normally provoke pain. When triptan therapy was delayed and central sensitization was allowed to develop, subsequent administration of triptan therapy did not block the development of migraine.

Step care vs stratified care

Physicians also must decide whether to use a step care or a stratified care approach with acute therapy.³¹ In *step care*, treatment is initiated with a nonspecific or inexpensive agent (such as an NSAID or an analgesic), and the patient is switched to a more migraine-specific therapy (such as a triptan or ergot derivative) only if the initial treatment fails. In *stratified care*, treatment is matched to the needs of the patient, from a less potent agent if the migraine is less disabling to a more potent migraine-specific therapy if the headache is more disabling. In a recent study, a greater headache response at 2 hours posttreatment was seen in the stratified-care

group (52.7%) vs the step-care group (36.4%; $P < .001$).³¹

Short-term preventive therapy

The goals of short-term preventive therapy are to prevent migraine from occurring and to reduce the severity of symptoms and their associated disability. Short-term preventive strategies become practical with menstrual migraine because of the periodicity of the menstrual cycle. Short-term preventive therapy is generally considered when acute therapies have not provided an adequate response. Medications commonly used for short-term preventive therapy include many of the same agents used for acute therapy: NSAIDs, ergot derivatives, and triptans. In addition, hormonal treatments, such as transdermal estradiol patches, can be effective for short-term prophylaxis. It is important to note that ergots and triptans should not be used within 24 hours of each other. All fertile women taking ergots or triptans should be sure to use an appropriate birth control method. One should note that none of the therapies described herein are approved by the US Food and Drug Administration for short-term prevention of menstrual migraine.

NSAIDs

Nonsteroidal anti-inflammatory drugs have been effective in short-term prevention of menstrual migraine. In a study by Sances et al,³² naproxen sodium, 550 mg twice daily, the most commonly used NSAID for migraine pain, effectively prevented menstrual migraine when initiated on day -7 and continued through day +6. This therapy reduced headache intensity and duration, as well as the number of days with headache.

Ergots

No randomized controlled studies of ergots for short-term preventive therapy of menstrual migraine have been published; however, in a case series report ($N = 20$),²⁴ a time-released formulation of dihydroergotamine reduced headache index score, analgesic use, and headache duration by the fifth month of treatment. In another case series report ($N = 40$),³³ ergonovine (0.2 mg 4 times daily, from day -1 to day +1 for 3 months) reduced the severity of attacks in 60% of participants, lessened the number of attacks in 15%, and had no effect in 35%.

Triptan therapy

Triptans are effective for both acute and short-term

TABLE 1

**Early acute and short-term
preventive therapy with oral triptans***

Study Drug†	Study Design	Patients No.	Dosage	Results
Early Acute Therapy				
Sumatriptan (Salonen, 1999)	Randomized, placebo-controlled	115	100 mg	Headache relief at 4 hours: placebo, 35%; sumatriptan 100 mg, 67%
Sumatriptan (Nett, 2003)	Randomized, double-blind, placebo-controlled, single-attack	349	50 mg, 100 mg, administered in mild-pain phase	2-Hour pain-free rate: placebo, 29%; sumatriptan 50 mg, 51%; sumatriptan 100 mg, 61%; 2-hour pain-free period with no migraine-associated symptoms (eg, photophobia, phonophobia, nausea, vomiting): placebo, 25%, sumatriptan 50 mg, 45%; sumatriptan 100 mg, 51%
Frovatriptan (Macgregor 2000)	Open-label	151	2.5 mg	Nearly half of menstrual-related attacks successfully treated with 1 dose of frovatriptan 2.5 mg
Rizatriptan (Silberstein, 2002)	Retrospective	95	10-mg wafers	Rizatriptan 10 mg equally effective for menstrual and nonmenstrual migraine over a 6-month period, regardless of migraine definition or stringency of outcome criteria
Zolmitriptan (Loder, 2004)	Randomized, double-blind, placebo-controlled, parallel-group	579	Starting dose based on intensity of baseline migraine Mild: zolmitriptan 1.25 mg Moderate: zolmitriptan 2.5 mg Severe: zolmitriptan 5 mg or matching placebo	Overall 2-hour pain relief (headache response): placebo, 27%; zolmitriptan, 48% ($P < .0001$) 30-Minute headache response: placebo, 14%; zolmitriptan, 18% ($P = .03$) 1-hour headache response: placebo, 23%; zolmitriptan, 33% ($P < .001$)
Short-term Preventive Therapy				
Frovatriptan (Silberstein, 2004)	Randomized, double-blind, placebo-controlled, 3-way crossover	443	Loading dose (10 mg) followed by 2.5 mg twice daily starting 2 days before (-2) through 4 days after (+4) onset of menstruation, for 3 cycles	Incidence of menstrual migraine: placebo, 67%; frovatriptan, 41% ($P < .0001$)
Naratriptan (Newman, 2001)	Randomized, double-blind, placebo-controlled, 3-arm, parallel-group	206	1 mg twice daily, 2.5 mg twice daily, starting day -2 for 5 days for 4 cycles	Incidence of menstrual migraine: placebo, 75%; naratriptan, 50% ($P = .003$)
Naratriptan (Moschiano, 2005)	Open, noncomparative pilot	59	1 mg twice daily starting day -2 for 6 days, for 3 cycles	Number of menstrual migraine attacks during a 3-month treatment period reduced from 3.5 to 1.6.
Sumatriptan (Newman, 1998)	Open-label pilot	20	25 mg 3 times daily starting day -2 to -3 for 5 days, for 6 cycles	Incidence of menstrual migraine: sumatriptan, 48%; (no placebo group)

*None of the triptans are approved for short-term prevention of migraine.
†All of the studies in this table were sponsored by pharmaceutical companies.

therapeutic approaches (TABLE 1). Frovatriptan, naratriptan, and sumatriptan have all been found to be effective in short-term prevention of menstrual migraine. In a study by Silberstein et al,³⁴ patients ($N = 546$) received frovatriptan, a triptan with a half-life of 26 hours, or placebo, from day -2 through day +4, for each of 3 menstrual cycles. After treatment, the incidence of menstrual migraine was 52% for frovatriptan, 2.5 mg once daily, 41% for frovatriptan, 2.5 mg twice daily, and 67% for the placebo group. Both frovatriptan regimens were significantly superior to placebo ($P < .0001$), and the twice-daily regimen was superior to the once-daily regimen ($P < .001$). Frovatriptan therapy also reduced migraine severity ($P < .0001$), duration ($P < .0001$), and use of rescue medication (twice daily, $P < .0001$; once daily, $P < .01$).

In a similar study, Newman et al³⁵ administered naratriptan, or an identical-looking placebo, from day -2 through day +3 for 4 menstrual periods ($N = 171$).

Significantly more patients taking naratriptan, 1 mg, were headache-free compared with those taking placebo (50% vs 25%; $P = .003$). In a study by Moschiano et al,³⁶ short-term naratriptan prophylaxis in 61 patients during a 3-month treatment period reduced the mean number of migraine attacks from 3.5 to 1.6.

Sumatriptan also has been evaluated for the short-term treatment of menstrual migraine. In a small, open-label pilot study, sumatriptan, 25 mg 3 times a day, was administered from days -2 to -3 for a total of 5 days for a mean of 6 menstrual cycles.³⁷ Patients were pain free in 52% of treated attacks and severity was reduced by 50% in 42% of attacks.

Hormonal therapy

As discussed earlier, the decline in estrogen that occurs during the luteal phase of the menstrual cycle is associated with the onset of menstrual migraine, making the use of hormonal therapy an option as both short- and

TABLE 2

Hormonal therapy with efficacy for menstrual migraine*

Therapy	Dosage/Agent	Administration
Estradiol gel	Estradiol, 1.5 mg	Between day -2 and day +5
Transdermal patch	Ethinyl estradiol, 100 µg	7 Days prior to onset of menstruation
Combined OCs plus Estrogen supplementation	Ethinyl estradiol, 20 µg Estrogen	From week 1 through week 3 During week 4
Combined OCs	Ethinyl estradiol, 20 µg	Continuous 11 weeks [†]

*None of these therapies are approved by the US Food and Drug Administration for the treatment of menstrual migraine.
[†]Continuous administration for 11 weeks limits ovulation and menses to 4 times per year.
 Allais G et al, *Neural Sci.* 2005;26:S125-S129; Loder E, *Neural Sci.* 2005;26:S121-S124; Mannix LK, Calhoun AH, *Curr Treat Options Neurol.* 2004;6:489-498; Martin VT, *Options Neurol.* 2004;8:229-237.

long-term prevention (TABLE 2). The goal of hormonal therapy is to reduce the extent of the decline in estrogen. Estrogen gel and estrogen patches have been used successfully in the treatment of menstrual migraine.³⁸ Preventive therapy with estradiol gel, 1.5 mg, between day -2 and day +5 has demonstrated efficacy for patients with menstrual migraine.³⁹ Efficacy with the transdermal estrogen patch has been shown with the 100-µg formulation.⁴⁰ The patch can be administered several days prior to the onset of menstruation and maintained for up to 1 week. The disadvantage of preventive therapy with the transdermal patch is that it can delay development of follicles in the next menstrual cycle, delay ovulation, and make subsequent menstrual periods irregular in some women. This irregularity interferes with the predictability of menstrual migraine.

Long-term continuous preventive therapy

Long-term continuous preventive therapy may be recommended for patients who experience frequent migraine headache (>3-5 days per month) both during and outside of the perimenstrual period and who are refractory to short-term prophylaxis.⁸ Medications for long-term prevention include those typically given for other conditions (eg, beta-blockers, calcium blockers, anticonvulsants, tricyclic antidepressants). This approach may be useful in patients who have concomitant medical conditions (eg, depression, angina, hypertension, epilepsy, anxiety disorder, or bipolar disorder),^{8,23} allowing the therapy to serve a dual purpose.⁴¹

Hormonal therapy

Hormonal therapies also may be used as long-term preventive therapy. Among women taking oral con-

traceptives (OCs), menstrual migraine generally occurs during the pill-free week of therapy. Continuous use of OCs (for 42, 63, or 84 days), therefore, would suppress ovulation and the menses for a longer duration and, consequently, reduce the number of menstrual migraine episodes.^{8,22} Alternatively, a combined OC with ethinyl estradiol, 20-35 µg, can be administered during weeks 1 through 3 of the menstrual cycle, followed by estrogen supplementation during week 4.

This regimen limits the decline in estrogen to an equivalent of 10 µg, a level that is suggested to prevent menstrual migraine.⁵ Neither of these treatment strategies affect menstruation or reduce the efficacy of OCs as a method of birth control.

Use of OCs for long-term prevention of menstrual migraine has had varying results, improving symptoms in some patients and causing them to worsen in others.⁴² Additionally, OCs tend to cause increased weight gain and bloating. The primary drawback to OC use, however, is an increased risk for stroke, especially among patients who smoke.⁴³ Migraine independently increases the risk for stroke among young women 4-fold.⁴² When women with migraine take OCs, the risk of stroke is increased 8-fold.⁴⁴

CONCLUSIONS

Menstrual migraine is triggered by hormonal fluctuations and neurochemical changes at the onset of the menstrual cycle; therefore, it is predictable and can be treated effectively with acute or short- and long-term preventive therapies. Acute therapy is used to abort or shorten a migraine episode once symptoms occur, thus reducing disability. It is most effective when used at the onset of migraine, during the mild-pain phase. The aim of short-term prophylaxis is to prevent migraine from occurring and to reduce the severity of symptoms and their associated disability when acute therapy has not been successful. By targeting therapy for the period during which women are most likely to experience migraine—2 days prior to the onset of menstruation through 3 days afterward—short-term prophylaxis can reduce the incidence and severity of menstrual migraine. Long-term continuous preventive therapy should be considered for patients in whom short-term preventive therapies are refractive, and also may be useful in patients who have concomitant medical conditions (eg, depression, angina, hypertension, epilepsy,

anxiety disorder, or bipolar disorder), allowing the therapy to serve a dual purpose.

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CME Posttest

For each of the following questions, please circle the best response.

- Declines in estrogen and progesterone encountered during the late luteal phase of the menstrual cycle result in the predictable occurrence of migraine headache during the perimenstrual time period in as many as _____.**
 - 80%-90% of female migraineurs of reproductive age
 - 35%-75% of female migraineurs of reproductive age
 - 40%-80% of female migraineurs of reproductive age
 - 20%-35% of female migraineurs of reproductive age
- The 2004 International Classification of Headache Disorders defines menstrual-related migraine as _____.**
 - migraine without aura occurring primarily during days -2 to +3 of the menstrual cycle, and at other times of the month, during ≥ 2 of 3 menstrual cycles
 - migraine with aura occurring primarily during days -2 to +3 of the menstrual cycle, and at other times of the month, during ≥ 2 of 3 menstrual cycles
 - migraine without aura occurring primarily during days -3 to +5 of the menstrual cycle, and at other times of the month, during ≥ 2 of 3 menstrual cycle
 - migraine with aura occurring primarily during days -3 to +5 of the menstrual cycle, and at other times of the month, during ≥ 2 of 3 menstrual cycles
- Couturier et al found that, compared with nonmenstrual migraine, menstrual migraine is associated with impaired quality of life and increased disability, with episodes that are _____.**
 - more severe
 - of longer duration
 - less responsive to treatment
 - all of the above
- The primary endogenous trigger for menstrual migraine is _____.**
 - increased estrogen levels during the luteal phase of the menstrual cycle
 - decreased estrogen levels during the luteal phase of the menstrual cycle
 - increased estrogen levels during the follicular phase of the menstrual cycle
 - decreased estrogen levels during the follicular phase of the menstrual cycle
- Appropriate approach(es) to the treatment of menstrual migraine include(s):**
 - Acute therapy with triptans, nonsteroidal anti-inflammatory drugs (NSAIDs), ergot derivatives, or analgesics
 - Short-term preventive therapy with triptans, NSAIDs, ergot derivatives, or analgesics
 - Long-term preventive therapy with hormonal agents or drugs that treat concomitant medical conditions
 - All of the above
- The stratified approach to management of menstrual migraine is _____.**
 - more cost-effective than step care
 - appropriate only after step care has been attempted
 - inappropriate for the management of menstrual migraine
 - none of the above
- Early treatment of menstrual migraine with triptans _____.**
 - prevents central sensitization
 - reduces functional disability
 - increases pain-free status
 - all of the above
- The advantage(s) of NSAID therapy in menstrual migraine is/are:**
 - Lack of serious side effects
 - Efficacy for long-term prophylaxis
 - Low cost
 - All of the above
- The goal of hormonal therapy in menstrual migraine is:**
 - To address the decline in estrogen typically associated with the onset of menstruation
 - To address the decline in progesterone typically associated with the onset of menstruation
 - To make the menstrual cycle more regular
 - None of the above
- When women with migraine take oral contraceptives, the risk of stroke is increased _____.**
 - 2-fold
 - 4-fold
 - 8-fold
 - 10-fold

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Please circle the letter that best reflects your agreement with the statements below, using the following scale:

A. Strongly disagree B. Disagree C. Agree D. Strongly agree E. Does not apply

- | | | | | | |
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