

MANAGING MENSTRUAL MIGRAINE

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MANAGING MENSTRUAL MIGRAINE

OVERVIEW

ACTIVITY OVERVIEW

As many as 60% of women with migraine report increased attacks at the time of menses, while a smaller percentage experiences migraine exclusively during menstruation. There is strong evidence linking migraine with estrogen, and both the timing and frequency of migraine attacks are influenced by hormone-related events. This compelling new CD-ROM program from the National Headache Foundation and Primary Care Network provides a comprehensive review of the literature on menstrually associated migraine, a review of treatment options, and a practical, hands-on video case study of a young woman with menstrually associated migraine. The monograph is in the form of PDFs, which may be printed from your computer to provide an enduring resource.

LEARNING OBJECTIVES

After viewing the video and reading the monograph, participating physicians should be better able to:

- Identify migraine in women with menstrually associated headaches.
- Recognize the role of estrogen in migraine and its potential implications for treatment.
- Implement effective treatment strategies for patients with menstrual migraine.
- Identify the patient at risk for medication overuse, or rebound, headache.

ACCREDITATION STATEMENT

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FACULTY DISCLOSURE

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SEX DIFFERENCES IN MIGRAINE EPIDEMIOLOGY

In prepubertal children, there is no difference between the sexes in the prevalence of migraine, which occurs in approximately 4% of both boys and girls.¹ After puberty, however, the prevalence of migraine increases markedly in women, affecting 18.2%, while only 6.5% of men are affected.² The prevalence of migraine increases in both males and females until approximately age 40, after which it declines in both sexes (Figure 1).³

Of the 28 million Americans with migraine, approximately 20 million are female.² The highest prevalence of migraine in women occurs between the ages of 25 and 55 — a woman's most productive years.⁴ Furthermore, women in their thirties tend to have an increase in the frequency and severity of their attacks.⁵ Women with migraine are also more likely than men to suffer severe functional disability and impairment in quality of life.⁶ As a result of its prevalence and impact, migraine is one of the most important issues in women's health.

MIGRAINE AND SEX HORMONES

Throughout their lives, women experience significant changes in their headache patterns that are directly related to changes in their reproductive cycles. Menarche, menstruation, oral contraceptives, pregnancy, and menopause affect migraine through changing levels of sex hormones. As many as 60% of women with migraine report increased attacks at the time of menses, while a smaller percentage experiences migraine exclusively during menstruation.^{7,8} There is strong evidence linking migraine with estrogen, and both the timing and frequency of migraine attacks are influenced by hormone-related events. It has long been recognized that migraine can be triggered by estrogen withdrawal.⁹ After several days of exposure to high levels of estrogen during menses, a migraine is triggered by the sudden decline in estrogen levels. A similar pattern is seen with users of oral contraceptives, up to 70% of whom experience headaches during the placebo week.¹⁰ In addition,

estrogen modulates serotonergic tone, has both direct and indirect effects on the vasculature, and influences the concentrations of endogenous, pain-relieving β -endorphins.¹¹⁻¹³ Some researchers and reviewers have suggested that progesterone may also play a role but, as early as 1971, *Somerville* showed that migraines were *not* triggered in subjects when progesterone concentrations declined, but *were* triggered when their estrogen levels fell.^{9,14}

TOWARD A DEFINITION OF MENSTRUAL MIGRAINE

In a population study, *Stewart et al* examined 98-day headache diaries of 81 menstruating women with clinically diagnosed migraine.¹⁵ The daily diary was used to record the occurrence of menses, headache days, and headache features (pain quality and intensity, and degree of disability at work and home). A significantly elevated risk of headache on days 0 and 1 (OR: 2.04; 95% CI; 1.49-2.81) and also in the two days before onset of menses (OR: 1.80; 95% CI; 0.27-0.72) was observed for migraine without aura but not migraine with aura (day 0 = first day of menses).

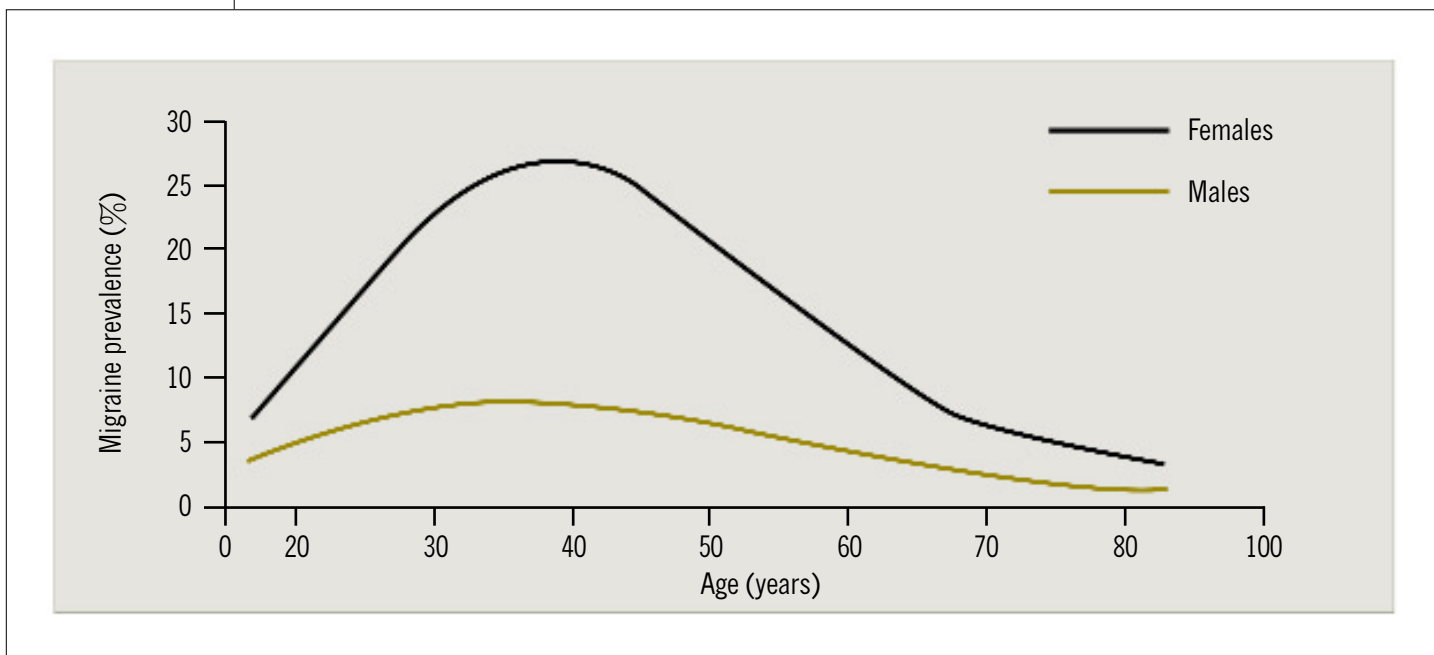
There is no universal agreement on the definition of menstrual migraine. In 1988 the International Headache Society did not establish criteria for menstrual migraine. However, they suggested that 90 percent of attacks should occur between two days before menses and the last day of menses.¹⁶

The latest IHS classification uses an Appendix to present research criteria for headache entities that have not been sufficiently validated by research studies. In this Appendix, migraine without aura is subdivided into several categories, including pure menstrual migraine, menstrually related migraine and nonmenstrual migraine (Table 1).¹⁷ The clinical trials to date, however, have used a variety of definitions, making it difficult to compare results.

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FIGURE 1. Migraine prevalence (from Silberstein et al)³



MacGregor *et al* prospectively followed 55 women who were being treated at a headache clinic to determine the proportion of patients who experienced increased attacks during menstruation and those whose attacks occurred *only* during menstruation (true menstrual migraine, or TMM).¹⁸ TMM was defined as attacks that occur on or between days -2 to +3 of the menstrual cycle and at no other time. Results showed that 34.5% had an increased frequency of attacks during menstruation, while 32.7% did not. Of the patients studied, only 7.2% had TMM. If the definition of TMM is changed to attacks that occur on or between days -4 to +4, the percentage increased to 10.9%.

There is also debate whether migraine that occurs during menstruation is more severe than nonmenstrual migraine and/or more refractory to treatment.¹⁹⁻²² A Dutch study assessed the prevalence of menstrual migraine and its restriction on daily activities in 1181 women, aged 18-55 years. In this population, the prevalence of menstrual migraine was only 3% (lower than that reported in the literature), but attacks of menstrual migraine were more severe, of longer duration, and more resistant to treatment than migraine attacks at other times of the month.²⁰

However, the study by Stewart *et al* does not support this observation.¹⁵ In their diary study, migraines that occurred during the first two days of menses were more painful than those occurring at other times, but the differences were small. A recent review by Calhoun suggests that the “intractable” nature of menstrual migraine may be the result of our trial-and-error approach to its treatment, and that the response of these headaches to exogenous or endogenous estrogen is actually very predictable.²³ The differences in opinion may reflect differences in populations studied: women who consult for migraine care, regardless of its association with menses, may have more refractory cases than non-consulting women in the general population.

MIGRAINE, ORAL CONTRACEPTIVES, AND THE RISK OF STROKE

Women with migraine have an increased risk of ischemic stroke (OR 2 to 3) compared with women without migraine. The risk of stroke approximately doubles in young women who have migraine with aura (OR 3.8 to 6.2).²⁴ Because of this increased risk, the use of oral contraceptives (OCs) in women

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TABLE 1.

IHS definitions of pure menstrual migraine and menstrually related migraine¹⁷

Pure menstrual migraine without aura

Diagnostic criteria:

- A. Attacks, in a menstruating woman, fulfilling criteria for *migraine without aura*
- B. Attacks occur exclusively on day 1 ± 2 (ie, days -2 to +3) of menstruation in at least two out of three menstrual cycles and at no other times of the cycle*

Menstrually related migraine without aura

Diagnostic criteria:

- A. Attacks, in a menstruating woman, fulfilling criteria for *migraine without aura*
- B. Attacks occur on day 1 ± 2 (ie, days -2 to +3) of menstruation in at least two out of three menstrual cycles and additionally at other times of the cycle*

* Notes:

1. The first day of menstruation is day 1 and the preceding day is day -1; there is no day 0.
2. For the purposes of this classification, menstruation is considered to be endometrial bleeding resulting from either the normal menstrual cycle or from the withdrawal of exogenous progestogens, as in the case of combined oral contraceptives and cyclical hormone replacement therapy.

with migraine has been controversial. Much of this controversy stems from the time when high-dose estrogen OCs were common; risks are lower with low-dose estrogen and progesterone only OCs.²⁵⁻²⁷ However, if a woman with migraine smokes or has high blood pressure, the use of OCs substantially increases the risk of stroke.^{28,29} The general consensus is that low-dose OCs are safe for use in women with migraine.³⁰

How do OCs affect headache patterns? In most women, headache patterns do not change, but there are important exceptions. OC use may trigger a first migraine, increase the incidence and severity of attacks, or alleviate migraine. When OC use exacerbates migraine, headaches typically occur on days off the OC. Stopping the OC may or may not relieve the headaches immediately; there may be delayed or no relief.³¹ Keeping a headache diary is important to monitor any changes related to OC use.

TREATMENT OPTIONS

Treatment for women who have migraine associated with menses should include a complete headache evaluation. The patient needs to be reassured that her headaches are benign and educated about the nature of her headaches so she can play an active role in her care. The headache diary is particularly useful in identifying a perimenstrual pattern of headache as well as nonmenstrual precipitating factors. Pharmacological management of menstrually associated migraine should start with acute treatment of migraine attacks. If acute therapy does not provide consistent, complete pain relief in a timely manner or there is continuing disability due to migraine, prophylactic strategies can be employed. Table 2 presents a brief treatment algorithm for menstrually associated migraine.

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TABLE 2. Acute, hormonal, and prophylactic management of menstrually associated migraine (from Mannix)³²

Acute therapy: *

- Oral triptans
- Nonoral triptans
- Rescue therapy, when needed

If acute therapy does not provide consistent, complete pain relief in a timely manner or there is continuing disability due to migraine, add one or both of the following:

Hormonal manipulation

- Oral contraceptive (OC)
- OC + estrogen during week of menses
- Long-cycle OC

Short-term prophylaxis

- NSAIDs
- Magnesium
- Triptans[†]

* All women will require acute therapy for migraine attacks

† Observe total daily dose limits (acute plus prophylaxis dose)

TRIPTANS

The acute treatment of migraine was revolutionized by the development of the triptans, a class of highly selective serotonin-receptor agonists. Stimulation of the 5-HT_{1B/1D} serotonin receptors inhibits the neurogenic inflammation and the abnormal dilation of intracranial blood vessels characteristic of migraine attacks. Triptans have also been shown to be effective in relieving the nausea, photophobia, and phonophobia associated with migraine. These agents are available in a variety of dosage forms, including oral tablets (including a new rapid-release sumatriptan tablet), intranasal sprays (sumatriptan and zolmitriptan), orally disintegrating wafers (rizatriptan and zolmitriptan), and subcutaneous injection (sumatriptan). Selection of a particular dosage form can take into account the patient's headache characteristics, as well as her personal preference. For example, if the patient has a very rapid time to peak pain, subcuta-

neous sumatriptan may be a good choice because it has the most rapid and consistent efficacy. However, some patients are reluctant to self-administer injections; for them an intranasal spray or a rapid-acting oral tablet (e.g., rizatriptan) may be appropriate. Similarly, the half-lives of triptan tablets vary from 2.5 hours (sumatriptan) to 26 hours (frovatriptan). A patient with prolonged migraine attacks may benefit from a long-half-life triptan.

The triptans have been found to be effective in the acute treatment of menstrually associated migraine attacks. These reports come mostly from retrospective analysis of randomized controlled trials or open-label studies of acute migraine in which treatment within or outside of a specified "menstrual window" is reported.³³⁻³⁶ Recently, two large prospective placebo-controlled trials of acute treatment of menstrual migraine have been reported.

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A randomized, double-blind, placebo-controlled, single-attack study assessed the efficacy of 50 mg and 100 mg sumatriptan administered during the mild pain phase of menstrually associated migraine, defined as any migraine starting on or between 2 days before to day 4 after the onset of menses.³⁷ In this trial, attacks were to be treated within 1 hour of onset of pain, if the pain was mild. The results showed that sumatriptan was more effective than placebo in the 349 women with menstrually associated migraine. A total of 61% and 51% of patients who used sumatriptan 100 mg and 50 mg, respectively, were pain-free 2 hours after treatment compared with 29% of patients who used placebo ($p < 0.001$). At 2 hours after treatment, 51% and 45% of women in the sumatriptan 100 mg and 50 mg groups were free of pain and associated symptoms (photophobia, phonophobia, nausea, vomiting), respectively, in contrast to 25% of subjects in the placebo group ($p < 0.001$ for both comparisons). It was concluded that both doses of sumatriptan were generally well tolerated and effective in providing pain-free relief and relief of the associated symptoms of menstrually associated migraine when administered in the mild pain phase.

In a multicenter, double-blind, randomized, parallel-group, placebo-controlled, multiple-attack study of zolmitriptan, menstrually associated migraine was defined as migraine that consistently occurred from 3 days before to 5 days after onset of menses in at least 2 of the 3 preceding months.³⁸ Women included in the study could have migraine attacks both inside and outside the menstrual window. Subjects were randomized to treat one attack per menstrual cycle for 3 months with either zolmitriptan or placebo. Medication dose was then determined by baseline attack intensity: mild migraine attacks were treated with zolmitriptan 1.25 mg, moderate attacks with zolmitriptan 2.5 mg, and severe attacks with zolmitriptan 5 mg, or matching placebo. Headache response in this trial was defined as a reduction in headache intensity from moderate to severe to mild or no pain, and from mild pain to no pain. Among the 579 women enrolled in the study, a total of 1232 attacks were treated.

At 2 hours, a headache response was achieved in 48% of attacks treated with zolmitriptan compared with 27% of attacks in patients in the placebo group ($p < 0.0001$). Zolmitriptan was superior to placebo in

achieving a headache response as early as 30 minutes (18% versus 14%, $p = 0.03$) and at 1 hour (33% versus 23%, $p < 0.001$). Zolmitriptan was shown to be superior compared to placebo for other measures, including meaningful migraine relief, the overall percentage of attacks with improvement in migraine-associated symptoms of nausea, photophobia, and phonophobia at 2 hours. These results demonstrate that orally administered zolmitriptan was effective and well tolerated in the treatment of menstrually associated migraine.

Since menstrually associated migraine typically occurs at the same time every month, it is often possible to employ the timed use of medications (cyclic prophylaxis) to prevent menstrual migraine attacks. In a randomized, double-blind, placebo-controlled, parallel-group trial *Newman et al* studied the efficacy of oral naratriptan 1 mg and 2.5 mg in the prophylaxis of menstrually associated migraine (MAM).³⁹ Naratriptan was selected because of its good tolerability profile and long half-life (approximately 6 hours). Menstrually associated migraine was defined as migraines occurring on day -2 to +4 relative to onset of menses. Naratriptan 1 mg, 2.5 mg, or matching placebo tablets (1:1:1) were administered twice daily for five days, starting two days before the predicted onset of MAM, during four perimenstrual periods. A total of 206 women were randomized and treated during at least one evaluable perimenstrual period (1 mg $n = 70$, 2.5 mg $n = 70$, placebo $n = 66$). Naratriptan 1 mg significantly reduced the number of MAMs and MAM days compared with placebo (2.0 MAMs vs. 4.0 MAMs, $p = 0.011$; 4.0 days vs. 7.0 days, $p = 0.001$). More women treated with naratriptan 2.5 mg had a reduced number of MAMs and MAM days, but the difference did not reach statistical significance. The incidence and severity of adverse events in the active treatment groups and the placebo group were similar. The authors concluded that naratriptan 1 mg is effective and well tolerated as short-term prophylaxis for menstrually associated migraine.

Two additional randomized, double-blind, placebo-controlled, parallel group studies ($n = 346$ and $n = 287$) have evaluated the use of naratriptan for prophylaxis of menstrually associated migraine.^{40,41} Naratriptan 1 mg or placebo was administered twice daily starting

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3 days before expected onset of MAM and continuing for a total of 6 days for 4 menstrual cycles. Patients could treat breakthrough migraine attacks with 2.5 mg naratriptan. The results show that the mean percentage of perimenstrual periods (PMP) without MAM per patient was 38% to 40% among naratriptan-treated patients treating at least 1 PMP compared with 27% to 29% among placebo-treated patients ($p < 0.05$ naratriptan versus placebo for both studies). The percentage of patients with no MAM in at least 50% of treated PMPs and the median number of MAM days across 4 PMPs were statistically significantly ($p < 0.05$) reduced by naratriptan compared with placebo. Furthermore, this naratriptan treatment strategy was found to be safe, well-tolerated, and effective in the long-term prospective, multicenter, uncontrolled, open-label study up to 12 months.⁴²

A similar study compared frovatriptan 2.5 mg qd, 2.5 mg twice daily, and placebo in over 500 menstrual migraine sufferers at 36 U.S. clinics.⁴³ At 26 hours, frovatriptan has the longest half-life of available triptans. Patients were evaluated over three menstrual cycles, during which each patient received all three dose regimens in randomized order. During each cycle, subjects took a loading dose on the first day of treatment and continued their treatments for a total of six days, starting 2 days before the onset of menses. Of patients completing the study, 52% were headache-free during the 5.0 mg treatment period, 41% were headache-free during the 2.5 mg treatment period, and 26% were headache-free during the placebo treatment period ($p < 0.0001$). There were also statistically significant reductions in the severity and duration of headache, and a concomitant reduction in subjects' functional impairment. The incidence of adverse events was similar for all treatment groups.

While the results of these trials are promising, *Loder* has cautioned that further study of the triptans in the prophylaxis of menstrual migraine is needed. She noted the lack of consensus on a definition of menstrual migraine, as well as the need for better evidence of the efficacy, safety, and cost-effectiveness of this strategy.⁴⁴ In clinical practice, this strategy can be individualized and possibly used for shorter duration. When treating breakthrough attacks with triptans, it must be with the same triptan being used prophylactically and daily limits must be observed.

NSAIDs

NSAIDs may also be effective in the short-term prophylaxis of menstrually associated migraine. Naproxen sodium 550 mg bid or rofecoxib 25-50 mg qd may be initiated two to three days before the predicted onset of headache and continued throughout the period of vulnerability.^{45,46} An open-label pilot trial of rofecoxib was conducted by *von Seggern et al* in 14 patients with perimenstrual migraine.⁴⁶ Enrolled patients experienced at least one migraine monthly during the perimenstrual period. Patients who completed a baseline diary for the first month were randomized to receive either rofecoxib 25 mg or 50 mg daily for 10 days, beginning five days before onset of menses. Headaches experienced during the 10-day period were recorded in the patients' diaries. Patients continued rofecoxib for two consecutive menstrual cycles. The mean migraine frequency decreased from 5.6 to 2.6 migraines per menstrual cycle ($p = 0.005$). Eight of the 14 patients (57%) had a $\geq 50\%$ reduction in headache frequency. No significant differences were seen in headache intensity, duration, or functional impairment.

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Al-Waili studied the effects of mefenamic acid, a prostaglandin-synthesis inhibitor, in 24 women with menstrual migraine without aura.⁴⁷ The patients were treated for two consecutive menstrual cycles, one with 500 mg mefenamic acid and one with placebo. Patients took a dose of mefenamic acid 500 mg or placebo at the onset of pain and repeated the dose every eight hours during the menstrual period. Medication use was double-blind. Pain intensity was rated on a four-point scale, while functional disability was rated from 0 to 3. The mean pain score for attacks treated with mefenamic acid decreased significantly from 2.46 (± 0.5) to 0.62 (± 1.0) at two hours post-dose. Results showed that 79.6% showed significant pain relief with mefenamic acid compared with 16.6% with placebo, while 83.3% of patients were able to function with mefenamic acid compared with 12.4% with placebo.

Use of short-term NSAIDs for prevention of menstrual migraine allows for acute treatment of breakthrough headaches with triptans. NSAIDs may also benefit any dysmenorrhea. GI side effects may be associated with NSAIDs.

HORMONAL MANIPULATION

Another approach to the prophylaxis of menstrually associated migraine is hormonal manipulation. Since migraine can be triggered by falling estrogen levels, stabilization of estrogen throughout the menstrual cycle can often prevent attacks. *Magos et al* treated 24 patients with menstrual migraine with estradiol implants for up to five years.⁴⁸ Regular menstrual periods were induced with cyclic oral progestogens. The implants were not associated with any adverse events, and 23 of 24 patients improved with treatment, while 20 patients (83%) became headache-free or nearly headache-free. Percutaneously applied estradiol gel used during menses has also been shown in controlled trials to be effective in the prevention of MAM.⁴⁹

Oral contraceptives may also be effective; if the patient is already on an OC, the dose should be reduced to the lowest effective dose to reduce the drop in estrogen from active tablet to placebo. If headaches are not controlled during the placebo week, a 0.1 mg estradiol patch can be applied

two days before the onset of menstruation to further reduce the estrogen drop. Combined OCs with a formulation that is monophasic in both estrogen and progestin can be given continuously for three months, followed by seven days of 0.1 mg transdermal estradiol to lessen the likelihood of precipitating a menstrually associated migraine.⁵⁰

For severe and intractable MAM, a gonadotropin-releasing hormone (GnRH) agonist with add-back estrogen therapy has been found to be effective. *Murray and Muse* treated five women whose severe migraines were limited to the perimenstrual period.⁵¹ After two months of baseline evaluation, they received GnRH-a (leuprolide acetate depot formulation) 3.75 mg IM monthly for 10 months. Beginning at Month 5, transdermal E2, 0.1 mg daily was added to the regimen. Each day, patients rated headache severity from 0 (absent) to 3 (severe) and combined daily scores to obtain a monthly cumulative score. The mean headache scores for the GnRH-a and add-back treatment months (3.1 ± 0.7) were each significantly lower than those of the control months (15.3 ± 2.4). The treatments were well tolerated.

CONCLUSIONS

Today, women's health issues occupy a prominent place in the national consciousness. Because of the significant burden it imposes on a woman's quality of life, migraine is one of the most important of these issues. Menstrually associated migraine poses a unique set of challenges for the clinician, but there are a variety of effective modalities and strategies available, from acute treatment with a triptan to short-term prophylaxis with NSAIDs or triptans to hormonal manipulation. By individualizing therapy according to the patient's headache patterns, response to treatment, and personal preference, menstrually associated migraine can be managed effectively.

▶ *References on pages 8 and 9*

▶▶ *Post-test on page 10*

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MANAGING MENSTRUAL MIGRAINE

POST~TEST

Eight correct answers are required for credit.

1. What is the prevalence of migraine in the U.S. in males and females, respectively?
 A. 4.3% and 12.8%
 B. 5.0% and 20.2%
 C. 6.5% and 18.2%
2. Which of the following can affect the frequency and/or severity of migraine in women?
 A. Menarche
 B. Menstruation
 C. Oral contraceptives
 D. Pregnancy
 E. Menopause
 F. All of the above
 G. A, B, and E above
3. Approximately what percentage of women report increased migraine attacks at the time of menses?
 A. 25%
 B. 45%
 C. 60%
4. Falling levels of progesterone have been shown to trigger migraine attacks.
 A. True B. False
5. What is the estimated increased risk for stroke in women who have migraine with aura?
 A. The risk is approximately doubled.
 B. The risk is increased by 50%.
 C. The risk is increased by 75%.
6. Triptans act to abort migraine attacks by selectively stimulating 5-HT_{1B/1D} serotonin receptors.
 A. True B. False
7. Cyclic prophylaxis involves the timed, limited use of medications to prevent menstrually associated migraine that typically occurs at the same time every month.
 A. True B. False
8. NSAIDs are generally not appropriate agents for short-term, or cyclic, prophylaxis.
 A. True B. False
9. A GnRH agonist with add-back estrogen therapy may be effective in reducing severe, intractable menstrually associated migraine.
 A. True B. False
10. Which of the following best describes how oral contraceptives (OCs) affect migraine patterns?
 A. OCs may trigger a first migraine.
 B. OCs may increase the frequency and severity of migraine attacks.
 C. OCs may alleviate migraine.
 D. All of the above

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