

Research Submission

Diagnosis and Treatment of the Menstrual Migraine Patient

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Women presenting with recurrent disabling headache frequently have migraine; but physicians need to rule out other headache disorders before they reach a diagnosis of migraine with or without aura. Many women who experience migraine in close association to their menstrual cycle may meet the diagnostic criteria for either menstrually related migraine (MRM), or pure menstrual migraine (PMM). Once an accurate diagnosis is made, treatment may be established to best suit the individual needs of that patient. Most women will find that migraine associated with hormone fluctuations respond well to standard treatment approaches including pharmacological and nonpharmacological treatments. Pharmacological approaches include acute, preventive, and short-term prophylaxis. Herein we review the difference between non-menstrual migraine, PMM, and MRM and identify effective treatment strategies for appropriate management of migraine associated with hormonal fluctuations.

Key words: menstrual migraine, triptans, short-term prophylaxis, migraine, prevention, headache

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Women presenting with recurrent disabling headache frequently have migraine; but physicians need to rule out other headache disorders before they reach a diagnosis of migraine with or without aura. For women who meet classification criteria for migraine (International classification criteria, 2004), assessment of the influence of hormones (eg, menses) on these recurrent disabling headaches is warranted.¹ Many women meet the criteria for menstrually related migraine (MRM), or pure menstrual migraine (PMM). Herein we review the difference between non-menstrual migraine, PMM, and MRM in order to

achieve a better understanding of the in-role sex hormones have on triggering headache.

DIAGNOSTIC CRITERIA FOR MENSTRUAL MIGRAINE

Over the years, migraine that is associated with the menstrual cycle has varied in definition and terminology.² Given the evidence that migraine is frequently associated with menses, clinical practice and

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Table 1.—IHS Diagnostic Criteria for Migraine without Aura¹

International Headache Society Classification of Migraine without Aura¹

A. At least 5 attacks fulfilling Criteria B-D (below)

B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)

C. Headache has at least 2 of the following characteristics

1. unilateral location
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)

D. During headache at least 1 of the following:

1. nausea and/or vomiting
2. photophobia and phonophobia

E. Not attributed to another disorder

research requires a systematic approach to the classification of menstrual migraine. Current classifications for diagnosing menstrual migraine as a disorder falls into two separate diagnoses based on the characteristics of the attack and its relation to migraine without aura (Table 1). The International Classification Criteria Appendix defines these as follows:¹

Pure menstrual migraine without aura—meet diagnostic criteria for migraine without aura (Table 1) and 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—meet diagnostic criteria for migraine without aura (Table 1) and 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 month

Diagnosing menstrual migraine is critical to provide optimal treatment strategies and medications for women. Treatment approaches and medication choices will vary. Some women only need acute treatment; others need focused migraine prevention during a time when migraine is predictable. Menstruation is often preceded or associated with symptoms of premenstrual dysphoric disorder (PMDD) including

moodiness, depression, and backache. Menstruation itself is often associated with dysmenorrhea. Educating women on how differentiate signs and symptoms of PMDD from migraine will help them manage their migraine attacks.

HORMONALLY RELATED MIGRAINE AND THE FEMALE LIFE SPAN

During the woman's life cycle, the time periods when women have a change in their headache susceptibility is correlated to their changing hormonal milieu. Changes in the body's hormonal environment occur at 4 separate times (Fig. 1).³⁻⁵ These are also times of changing migraine status. For example, young women beginning their menstrual cycle may be when their migraine starts. For most women, the time of childbearing years is also a time of high migraine risk. Pregnancy may be associated with a decrease in headache frequency because of sustained estrogen levels, but this may not be true for all women during all 3 trimesters.⁶ Perimenopause is a time when the levels of circulating sex hormones fluctuate irregularly and this is often associated with a change in headache patterns. Standard management strategies may not be consistently effective in this environment of hormonal fluctuation. After physiological menopause, when sex hormone levels stabilize, migraine improves in most women.^{7,8}

Neri and colleagues studied the prevalence of primary headaches in 556 postmenopausal women.⁹ Headache was present in 13.7% of participants and most of them (82%) had headaches prior to the onset of menopause. Sixty-two percent reported having migraine without aura and the remainder had tension-type headaches. None of the participants had migraine with aura or cluster headache. Two-thirds of women with prior migraine improved with physiologic menopause; but in contrast, two-thirds of women who had surgical menopause had a worsening of migraine. Collectively, these studies show that migraine frequency and severity changes during the course of the female life cycle, and this may be largely due to the continuous changing hormonal environment.

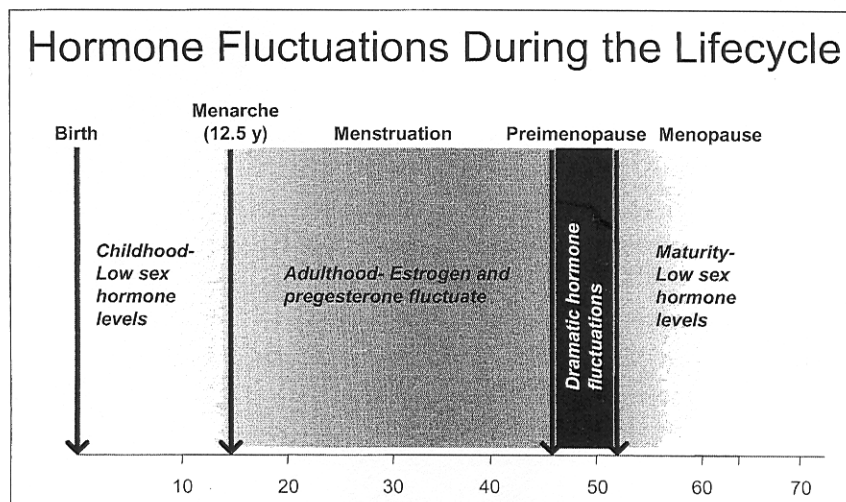


Fig 1.—This figure depicts 4 separate transitions of significant hormonal changes that occur in women during the life cycle. This initially is seen with increases in headache frequency following onset of menses. In older women, the greater fluctuations in hormones during perimenopause can help explain exacerbations of headaches in this population of women. Two-thirds of menopausal women experience an improvement in their migraines if they go through menopause spontaneously.

PHARMACOLOGICAL MANAGEMENT OF MENSTRUAL MIGRAINE

Migraine associated with hormonal fluctuations may respond well to standard migraine treatment approaches including pharmacological and nonpharmacological considerations. Before medications are prescribed and a treatment plan in place, several general principles of care may apply:

- Reassure the patient that what they are experiencing is real, biologically based, and treatable
- Identify and remove potential triggers (eg, caffeine, analgesic overuse, alcohol, etc.)
- Identify headache patterns in relation to hormonal fluctuations and other lifestyle factors
- Consider evidence-based migraine medications first and assess potential contraindications or intolerance limitations
- Encourage lifestyle modifications that may improve headache hygiene (eg, exercise, routine sleeping and eating habits, hydration, trigger avoidance, among others)

Pharmacological approaches to management of menstrual migraine include acute, preventive, rescue, hormonal, and nonpharmacological treatments.

Acute pharmacotherapy for migraine is given to stop pain and treat nonpain symptoms (eg, photophobia, nausea, vomiting, phonophobia) of an immediate attack. Acute treatments may be divided into nonspecific treatments that are used for general pain management, and migraine-specific treatments.¹⁰ Nonspecific treatments include aspirin, acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), opiates, and combination analgesics; migraine-specific treatments include ergotamine, dihydroergotamine, and the triptans.¹¹ Although the majority of patients with menstrual migraine will respond well to acute therapy only, a subset of patients will require preventive treatment. Acute and preventive treatments proven effective in menstrual migraine are listed in Table 2.

Acute Treatment of Menstrual Migraine.—Prospective randomized, double-blind trials for the acute management of menstrual migraine have been done and both prospective and retrospective studies show most triptans are effective in reducing the pain associated with MRM. Positive clinical evidence exists for: almotriptan,¹² frovatriptan,¹³ naratriptan,¹⁴ rizatriptan,¹⁵ sumatriptan, sc, po,^{16,17} and zolmitriptan.¹⁸ Non-inflammatories and combination analgesics have also been proven effective for the acute treatment of migraine^{6,19}. Dihydroergotamine is a

Table 2.—Pharmacologic Treatments for Menstrual Migraine

Acute	Short-term preventive	Long-term preventive
Strong clinical evidence supporting efficacy* in menstrual migraine		
Ergotamine derivatives	NSAIDs	
DHE nasal spray, IM ^{6,20}	Naproxen sodium ^{21,22}	
NSAIDs	Ergotamine derivatives	
AAC ¹⁹	Ergotamine ± belladonna + phenobarbital ⁶	
Triptans	DHE nasal spray ²³	
Almotriptan ¹²	Minerals and supplements	
Frovatriptan ¹³	Magnesium ²⁷	
Naratriptan ¹⁴	Triptans	
Rizatriptan ¹⁵	Frovatriptan ²⁶	
Sumatriptan ^{16,17}	Naratriptan ^{24,25}	
Zolmitriptan ¹⁸	Sumatriptan ¹³	
Limited clinical evidence or supporting clinical experience suggesting potential efficacy in menstrual migraine		
Eletriptan	DHE	Aspirin
NSAIDs	Ergotamine	AAC
	Flurbiprofen	Ergotamine
	Ketoprofen	Divalproex sodium
	Magnesium	Propranolol
	Mefenamic acid	Timolol
	Meclofenamate	Topiramate
	Methysergide	

*one or more randomized, double-blind, placebo-controlled trials.

AAC = acetaminophen + aspirin + caffeine.

nonselective 5-HT₁ agonist and also has been suggested as effective for the treatment of menstrual migraine when given as a nasal spray or injection.^{6,20}

Short-Term Prevention of Menstrual Migraine.

—Preventive treatment is categorized as short-term preventive (miniprophylaxis) therapy and long-term continuous therapy. Patients on preventive therapies also need acute treatment and most will also need rescue medications for breakthrough attacks and difficult-to-treat attacks respectively. The goal of short-term preventive therapy is to prevent menstrual migraine headaches before they occur. Short-term preventive treatment is administered only during the period of time that the patient is at risk for menstrual migraine. Many women may find this a preferred treatment because it limits the use of daily medication use to the time of highest vulnerability. This reduces the risk of side effects that may be associated with long-term preventive treatment. Drugs that have

been tried as short-term prophylaxis include NSAIDs, ergotamine, DHE, methysergide, methylergonovine, triptans, and magnesium (Table 2).

Naproxen sodium has been shown to be effective for short-term prevention of migraine^{21,22} and a number of other non-steroidal anti-inflammatory agents have suggested as being effective when studied smaller clinical trials (mefenamic acid, flurbiprofen, ketoprofen, and meclufenamate).^{6,23} Dihydroergotamine mesylate (DHE-45) administered as a nasal spray for 6 days starting 2 days before the expected onset of headache in 40 women with menstrual migraine was shown to reduce the severity of MRM.²⁴ Prospective controlled studies show short-term prevention to be an effective treatment approach with naratriptan,^{25,26} frovatriptan,¹³ and oral sumatriptan²⁷ (Fig. 2). In a large-randomized, double-blind, placebo-controlled trial patients received frovatriptan 2.5 mg QD or frovatriptan 2.5 mg bid or placebo to treat menstrual migraine. Treatment was initiated 2

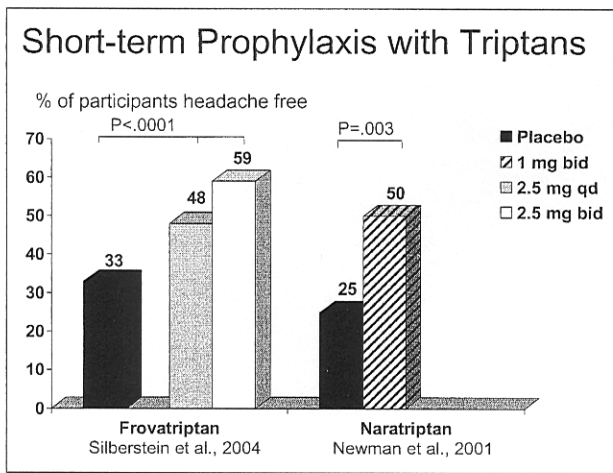


Fig 2.—Naratriptan and frovatriptan have been studied in prospective, randomized, placebo-controlled trials and both were proven effective for short-term prophylaxis of migraine. Naratriptan 2.5 mg BID was also tested and not found to be effective in reducing the number of menstrually related migraine attacks.

days prior to the expected onset of headache and continued for 6 days. More than 50% of women receiving frovatriptan 2.5 mg bid were menstrual-migraine free for all 3 cycles.¹³ In this study, a loading dose of frovatriptan 5 mg followed 2.5 mg twice daily was more effective than placebo for short-term prophylaxis of menstrual migraine.

Newman and colleagues assessed the efficacy of naratriptan 1 mg and 2.5 mg form short-term prevention and found naratriptan 1 mg bid also was effective in reducing the number of menstrually associated migraines and migraine days (Fig. 2).²⁵

One study also evaluated the effects of oral magnesium pyrrolidone carboxylic acid in 20 patients with menstrual migraine.²⁸ Magnesium 360 mg/day or placebo were given on the 15th day of the cycle and continued till the next menses, for 2 months. Oral magnesium was then supplemented in an open design for the next 2 months. At the end of the double-blind phase (2nd month), the pain total index score was decreased in both groups, but subjects receiving magnesium showed the lower pain scores and the number of days with headache was significantly lower in the patients on magnesium. Mg treatment also improved premenstrual complaints. Additional studies are warranted that evaluate the potential role of mineral and

vitamin supplementation as a further means for menstrual migraine prophylaxis.

Long-Term Migraine Prevention.—Long-term continuous therapy is given daily throughout the menstrual cycle and aims to prevent both menstrual and non-menstrual migraine.²⁹ In women who need preventive medication, there are limited prospective, randomized, controlled trials.³⁰ Randomized, prospective, placebo-controlled trials, assessing the efficacy of standard long-term migraine preventive therapies specifically for treatment of menstrual migraine, are clearly needed. However, in the absence of these trials, it may prove helpful, especially if short-term prevention has proven insufficient, to try medications already established as effective for migraine prevention. Effective migraine preventive therapies include topiramate, divalproex sodium, propranolol, and timolol.³¹ One strategy for using long-term prevention is to slightly increase the dose of the migraine preventive treatment perimenstrually—a higher migraine vulnerability for breakthrough attacks.⁶

Hormonal Therapy for Migraine Prevention.—To date, no single hormone treatment or combination of hormone therapies has United States Food and Drug Administration approval for treatment of migraine or other headache indication. Most importantly, because of a suggested increased risk of ischemic stroke, treatment guidelines recommend against the use of estrogen-containing contraceptives in many women with migraine with aura.³²⁻³⁶ Results of the Women's Health Initiative Study recommend against the routine use of estrogen replacement therapy in most women.^{37,38} Despite this recommendation, there are several reports that for some women, this approach may be useful, either as short-term or long-term preventive therapy for menstrual migraine especially in women who have contraindications or intolerability to standard acute and preventive migraine therapies. Several agents have been studied in small trials and are used tested in selected women for migraine prevention (Table 3).

Percutaneous Gel Formulation of Estradiol.—Percutaneous administration of estrogen gel has been studied in 3 studies. In one study, treatment with 1.5 mg of estradiol in 2.5 g of gel from day -2 to day +5 reduced the frequency, duration, and severity of

Table 3.—Hormonal Treatment for Migraine Prevention⁶

List of hormones studied being evaluated for prevention of menstrual migraine

- Estrogens (with or without androgens or progestin)
 - Combine oral contraceptives
 - Synthetic androgens (danazol)
 - Antiestrogens
 - Medical oophorectomy (GnRH analogs) with or without add-back androgens
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migraines compared with placebo gel alone.³⁹ In a second study, which involved 22 women treated for 7 days encompassing onset of menses, occurrence of moderate to severe migraine was significantly reduced.⁴⁰ Women (n = 35) with regular menstrual cycles were enrolled in a 6-cycle crossover study using estradiol gel (1.5 mg) or placebo to prevent menstrual attacks of migraine. Gel was first applied on the 10th day following the first day of peak fertility and continued daily until, and including, the second full day of menstruation. Percutaneous estradiol 1.5 mg was associated with a 22% reduction in migraine days and attacks were less severe and less likely to be associated with nausea. However, in those in the estradiol gel group, there was a 40% increase in migraine in the 5 days following estradiol discontinuation. All 3 of these studies were small and did not control for actual estrogen levels and days with each woman's individual cycle.⁴¹

Patch Administration of Estradiol.—Administering estrogen with a transdermal patch also has been evaluated for prevention of menstrual migraine in 2 small trials. In one study of 20 patients with PMM, treatment with either 17-beta estradiol 50 µg or placebo was evaluated over 3 successive menstrual cycles.⁴² No difference was observed in the number, duration, or severity of migraine attacks during estrogen-treated cycles vs the placebo-treated cycles.⁴² The second trial was an open-label study in which 24 women with menstrual migraine were treated with 25 µg or 100 µg using a transdermal patch from day -4 to day +4 for 2 cycles.⁴³ A nonsignificant reduction in the frequency of menstrual migraine and a *statistically* significant reduction in the use of rescue medication was observed with the 100 µg dose compared with untreated

cycles during the observation phase of the trial. No significant benefit was attained with the lower estrogen dose.

Progesterone.—Progesterone has not been proven effective and part of the reason for this may be that the most commonly tested progesterone therapies are not natural progesterone (also known as neurosteroids).⁴⁴ Studies remain to prove if natural progesterone offers benefit for migraine prevention.

Hormonal Contraception.—Hormonal contraception includes estrogen or progesterone or a combination of these agents. Many women find they have increased frequency of headache during the placebo week, although there are few randomized controlled studies, and findings are inconsistent.⁶ For years, women have taken continuous hormonal contraception by not taking the placebo week of treatment. Now, these women may take one of the newer agents that provide 3 months of continuous estrogen in an effort to avoid the biological responses associated with estrogen withdrawal (eg, bleeding and headache, among others). Women who find a relationship between their headache and the placebo week of oral contraception cycle may find these newer agents helpful in reducing migraine frequency with attacks limited to the placebo week, which would be once every 3 months.

Ten years ago, the concept hormone replacement therapy (HRT) was to be given to women during menopause in order to protect them from impending cardiovascular disease. However, randomized double-blind trials demonstrated that HRT was not protective against cardiovascular disease in postmenopausal women.⁴⁵ Newer studies show that estrogen may have dual and opposing activity in women. Estrogen may retard early atherosclerosis via endothelial function and reduction of blood lipids. However, estrogen also triggers acute events due to procoagulant activity and inflammatory mechanisms.⁴⁵

In another study, Nappi and colleagues obtained 7 months of diary information in 54 subjects seeking evaluation of menopause who also had migraine.⁴⁶ Data were collected on headache frequency, intensity, and climacteric symptoms. Subjects were divided into those with migraine and those with episodic tension-

type headache. After a 1 month run-in period, subjects received transdermal estrogen for 28 days along with medroxyprogesterone acetate administered for the last 14 days or 0.625 mg of conjugated equine estrogens along with medroxyprogesterone acetate for the last 14 days. Attack frequency, days with headache and analgesic intake statistically significantly increased in the group receiving conjugated equine estrogens, although headache severity was unchanged. The group receiving transdermal estrogen experienced worsening of headache, but it was less pronounced than in the group receiving oral estrogens. The explanation for this may be that the transdermal delivery bypasses first-pass hepatic metabolism thereby providing more consistent levels of estradiol available systemically.

Collectively, the available evidence supporting or negating the effectiveness of hormone therapy for migraine is limited with results inconsistent. Additional studies are needed with standardized protocols that will help determine how hormonal supplementation can safely be used as a migraine preventive strategy. Clinical judgment is needed to determine the individual benefits and risks for each patient. Until additional evidence becomes available, no recommendations can be made on the use of these agents for treating migraine in women.

CONCLUSIONS

Estrogen decline is associated with exacerbation in migraine in susceptible women. These women often have a diagnosis of MRM or PMM, and they may also have other nonheadache symptoms that are due to variations in circulating hormone levels (eg, anxiety, depression, dysphoria, among others). Differential diagnosis is an important part of successfully identifying the type of headache so treatments may be prescribed accordingly. Assessment of nonpain symptoms will also influence treatment decisions and therefore, frequency, severity, nonpain symptoms and disability all need to be fully assessed in relation to hormonal influences.

For many women with MRM, monotherapy can be successful in treating all their attacks, whether associated with menstruation or not. However, such an approach may not be sufficient for all women, and

some may need short or long-term prevention in addition to acute treatment and rescue medications. Polytherapy may also extend to treat coexisting conditions or symptoms (eg, PMDD, depression, anxiety, among others). Although migraine associated with changes in circulating estrogen levels is now a well-accepted clinical phenomenon, treatment aimed at modifying plasma estrogen levels is still under investigation. Randomized, double-blind, long-term controlled trials are warranted to further assess the optimal strategy and effective treatments for hormonal treatment of migraine associated with estrogen fluctuations.

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