

W O M E N ' S I S S U E S I N M I G R A I N E



A CONTINUING MEDICAL EDUCATION PROGRAM

PRESENTED BY THE NATIONAL HEADACHE FOUNDATION

*Supported by an unrestricted educational grant from  
UCB Pharma, Inc. and Elan Biopharmaceuticals*

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## NEEDS ASSESSMENT

There are approximately 20 million American females with migraine. Compared with males, females have more frequent, more severe, and more disabling migraines. Treatment of migraine in women is complicated by hormone-related events, such as the menstrual cycle, pregnancy, and menopause. Unfortunately, because of risk to the fetus or newborn, many of the most effective drugs used to treat migraine cannot be used in pregnant or lactating migraineurs. For these reasons, there is a need to update practicing physicians on the general principles of treating migraine in women, the available treatment options, and the issues, such as pregnancy and breast-feeding, that may complicate therapy.

## INTENDED AUDIENCE

This activity is intended for primary care and other physicians who treat patients with migraine headache.

## METHOD OF PARTICIPATION

The information is presented in a monograph and an audio CD. The reader's knowledge is tested by the CME quiz. It is anticipated to take 1 hour to complete the activity.

## EDUCATIONAL OBJECTIVES

After listening to the audio CD and reading this monograph, participants should be better able to:

- Describe differences in headache epidemiology by sex
- Describe the role of female hormones in the pathophysiology of migraine
- Identify the comorbidities of migraine
- Describe the advantages of stratified care vs step care of headache
- Decide when to initiate migraine prophylaxis
- Treat migraine in the pregnant or lactating migraineur

## EVALUATION

An evaluation form will provide the participants with the opportunity to review the activity content and method of delivery, and to help identify future educational needs and any possible bias in the monograph.

## FACULTY DISCLOSURE

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Speaker, consultant, and/or research support from  
GlaxoSmithKline, UCB Pharma, Merck, Ortho-McNeil

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GlaxoSmithKline, Merck, AstraZeneca, Pfizer, Ortho-McNeil,  
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## PROFESSIONAL CREDIT

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Finch University of Health Sciences/The Chicago Medical School and the National Headache Foundation. Finch University of Health Sciences/The Chicago Medical School is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

Finch University of Health Sciences/The Chicago Medical School certifies that this continuing medical education activity meets the requirements for 1.0 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association.

Finch University of Health Sciences/The Chicago Medical School is solely responsible for the content of this continuing medical education activity. This educational activity was planned and produced in accordance with the ACCME essentials and standards. This activity expires on January 31, 2005.

## EDUCATIONAL GRANT

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## NATIONAL HEADACHE FOUNDATION

The National Headache Foundation (NHF) is a non-profit organization established in 1970 to provide services to headache sufferers, their families and the healthcare professionals who treat them. Physician membership in the NHF provides the following benefits: *Standards of Care for the Diagnosis and Treatment of Headache*, the *Therapeutic Guide for the Treatment of Headache*, copies of *NHF Head Lines*, our award-winning bimonthly newsletter, patient education information, inclusion on the NHF physician membership list (if desired), listing in the NHF professional membership directory, opportunities to speak at public education seminars in your area, details on grants available through NHF, discounts on audio and videotapes, toll-free access to the NHF office, information via our web site, assistance in organizing local support groups, and more. Take advantage of all these great membership benefits for only \$100 a year. To join as a professional member or learn more about the services we offer call 888-NHF-5552 or visit our web site at [www.headaches.org](http://www.headaches.org).



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## Epidemiology and impact of migraine in women

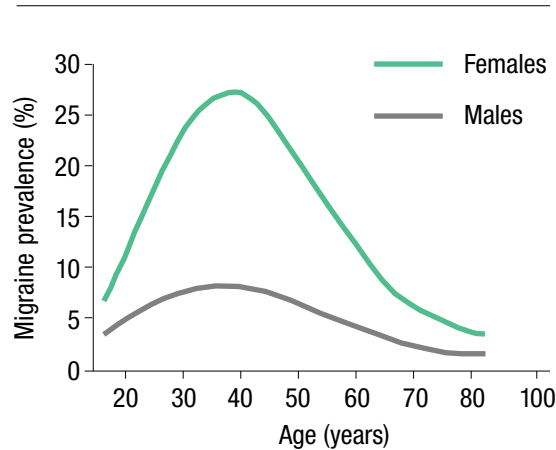
**M**igraine often begins in childhood. Between 4% and 10% of school-age children have migraines, and one in five adults with migraine report that their headaches began before age 10. Before puberty the prevalence of migraine is higher in boys than in girls. By their early 20s, however, women have an incidence of migraine three times higher than that in men.<sup>1</sup> The American Migraine Study II sent questionnaires to 20,000 American households.<sup>2</sup> Responses indicated a migraine prevalence of 18.2% for women and 6.5% for men. Women are also more likely than men to suffer severe functional disability from migraine.<sup>3</sup> Of the estimated 28 million migraineurs in the U.S., approximately 20 million are female.

The highest incidence of migraine in women occurs between the ages of 25 and 55 — the most productive years of their lives. Furthermore, women in their 30s tend to have an increase in the severity as well as the frequency of attacks.<sup>4</sup> After approximately age 40, the prevalence of migraine tends to decline (Figure 1).<sup>5</sup> The female/male migraine prevalence ratio also varies with age. Cyclical hormone changes account for some but not all of the difference between the sexes, since migraine prevalence remains much higher in women even well past the age of 70 (Figure 2).

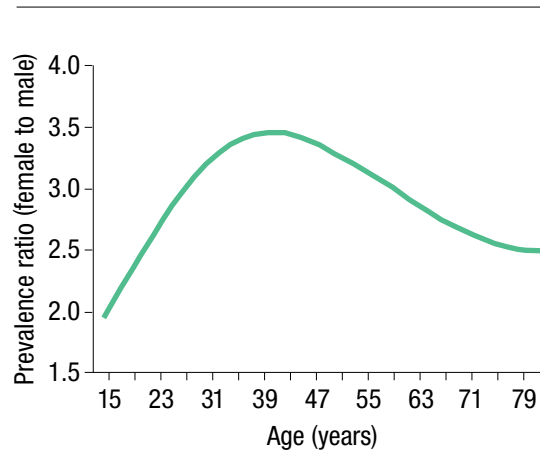
### Hormones and migraine

The timing and frequency of migraine attacks in women are influenced by hormone-related events, such as pregnancy, menopause, and the menstrual cycle. As many as 70% of women with migraine report increased attacks at the time of menses. Others experience migraines as part of a premenstrual syndrome (PMS), which is a part of the diagnostic criteria for late luteal phase dysphoric disorder (LLPDD). The latter is a menstrually related mood disorder that may include backache, breast swelling and tenderness, and nausea.<sup>6</sup>

**Figure 1.** Migraine prevalence in women and men (from Silberstein et al)<sup>5</sup>



**Figure 2.** Sex ratio for migraine (from Silberstein et al)<sup>5</sup>



Menstrual migraine tends to occur at the time of greatest fluctuation in estrogen levels, typically at the same time every month.<sup>5</sup> The menstrual cycle is governed by an elaborate sequence of interactions among the hypothalamus, pituitary, ovary, and endometrium. These events are modulated by the sex hormones, which have potent effects on neurotransmitters and their receptors. Silberstein postulated that menstrual migraine results from a mismatch



*This Continuing Medical Education monograph is a companion piece to an audio CD of a roundtable discussion held October 18, 2002 in Chicago, Illinois*



between the ovarian cycles of the sex hormones and the inherent rhythm of estrogen-sensitive neurons, including those of the serotonergic pain-modulating system.<sup>6</sup> Menstrual migraine thus appears to be an estrogen-withdrawal phenomenon that occurs in susceptible women. After several days of exposure to high levels of estrogen during menses, a migraine is triggered by the simultaneous fall of estrogen and progesterone levels.<sup>5,7</sup> There have been several attempts to detect differences in hormone levels between women with and those without menstrual migraine, but results have been inconsistent.<sup>8</sup>

The older combined oral contraceptives (OC) may change the frequency and severity of migraines. Some patients improve, some worsen, and others experience their first migraines on OCs. OCs usually trigger first attacks in women with a family history of migraine.<sup>6</sup> The newer OCs appear to be associated with a lower incidence of headache. Over three dosing cycles, a new oral contraceptive containing a third-generation progestin was associated with a low incidence of headache.<sup>5</sup>

Migraine may either improve or worsen at menopause, and hormone replacement therapy may exacerbate headaches. However, estrogen alone or combined with testosterone may relieve postmenopausal migraine.<sup>6</sup>

The increase in estrogen levels that occurs in early pregnancy has a protective effect against headache in many women.<sup>9</sup> Approximately 60-70% of migraineurs will improve during pregnancy. In a minority of women migraine may worsen; in 10-15%, it will appear for the first time, usually during the first trimester. Migraine that begins during pregnancy is predominantly migraine with aura,<sup>8</sup> while migraine that disappears during pregnancy often recurs postpartum. Bousser et al interviewed 703 women shortly after delivery to study the relationship between migraine and pregnancy.<sup>10</sup> Of the women interviewed, 116 met IHS diagnostic criteria for migraine. Migraine improved or disappeared in 69%, was variable in 5%, was unchanged in 8%, wor-

sened in 7%, and appeared for the first time in 11%. Disappearance or improvement did not differ significantly in migraine with or without aura, but worsening occurred more frequently in migraine with aura. Menstrual migraine was more likely to improve during pregnancy than non-menstrual migraine. In a retrospective study of 1300 women, Granella et al found that migraine improved during pregnancy in 67% of women with a history of prior migraine and was unchanged or worsened in 33%.<sup>11</sup> Among women with no history of migraine, migraine occurred for the first time during pregnancy in 1.3% and for the first time postpartum in 4.5%.

Frequent prepregnancy headache has been found to be a strong predictor of ill-being in pregnant women. Aromaa et al conducted a stratified, randomized cluster sampling of 1443 women expecting their first child to examine whether prepregnancy headache predicts problems in the well-being of pregnant women and newborn babies.<sup>12</sup> They found that impairment of health during the first and third trimesters was more often reported by women with frequent prepregnancy headache. Women with prepregnancy headache also had a poorer mental health status, more fatigue and depression, more anxiety and stress, and worsened relationships with their spouses. The investigators did not find significant differences between the groups in the well-being of newborns.

Postnatal headaches are very common. In a series of 71 women followed prospectively by Stein, postnatal headache (PNH) occurred in 27 (39%) and was most frequent three to six days postpartum.<sup>13</sup> In this study, 58% of women with a history of migraine developed PNH, but their attacks tended to be less severe than their typical migraines.

Fortunately, migraines do not appear to adversely affect pregnancy outcomes. In a retrospective review of 777 women, Wainscott found that the incidence of miscarriage, toxemia, congenital abnormalities, or stillbirth was not increased among migraine sufferers compared to controls or national averages.<sup>14</sup>

## Migraine and comorbidities

The term ‘comorbidity’ refers to the greater-than-coincidental association of two or more conditions in the same person. It is a cliché in neurology that “if you find one thing wrong in the brain, you’ll find more than one.” Migraine is indeed associated with several neurological and psychiatric disorders, including epilepsy, stroke, depression, bipolar disorder, and anxiety disorders. Migraine also appears to be associated with irritable bowel syndrome, mitral valve prolapse, and asthma.<sup>5</sup> Patients with migraine without aura have also been shown to score significantly higher than controls on indices of aggression-hostility.<sup>15</sup> Migraine may also be associated with impaired cognitive function. Waldie et al conducted a longitudinal birth cohort study to investigate the association between migraine and cognitive ability.<sup>16</sup> They found that enrolled subjects with migraine showed subtle but significant impairment on tests of verbal ability (especially language reception), compared with subjects who were headache-free or had tension-type headaches. Peres et al found that women with chronic migraine scored significantly higher on the fatigue severity scale (FSS) than men, and that the fatigue was strongly associated with fibromyalgia.<sup>17</sup>

Physicians-in-training are often taught to be suspicious of patients who present with ‘too many’ disorders. However, the presence of migraine should increase the level of suspicion for epilepsy, depression, and anxiety disorders.<sup>5</sup> Comorbidities have implications for both the diagnosis and treatment of migraine. There is considerable symptomatic overlap with several of the conditions comorbid with migraine, so careful differential diagnosis is necessary. For example, both migraine and epilepsy are associated with altered consciousness. Silberstein et al note that comorbidities impose both limitations on, and opportunities for, therapy.<sup>5</sup> When migraine and depression occur together, an antidepressant may treat both conditions; when migraine and epilepsy occur together, an anticonvulsant may treat both conditions.

Lipton offered the following possible explanations for the association of migraine with higher than normal incidences of epilepsy, depression, anxiety, and stroke:<sup>18</sup>

1. **One condition may cause the other.** For example, a prolonged migraine aura may result in a cerebral infarction.
2. **There may be a common mechanism underlying both conditions.** For example, alterations in serotonin are thought to play an important role in both migraine and depression.
3. **Genetic factors may cause a susceptibility to two or more neurologic disorders.**
4. **Environmental factors could alter brain function in a way that increases the likelihood of two neurological disorders occurring.** Head injuries, for example, may lead to both chronic headaches and epilepsy.

## Migraine and stroke

Both migraine and stroke are associated with altered cerebral blood flow, focal neurological deficits, and headache. In 1975, the Collaborative Group for the Study of Stroke in Young Women suggested that migraine may be a risk factor for stroke.<sup>19</sup> In that case-control study, the risk for stroke was doubled in women with migraine compared to community controls. In a subsequent case-control study, Tzouzio et al found a 400% increase in the risk of stroke in women with migraine under age 45.<sup>20</sup> Smoking and overuse of ergotamine may further increase the risk.<sup>21</sup> The annual rate of cerebral migrainous infarction has been estimated at 3.36 cases per 100,000.

Stroke appears to be most strongly associated with migraine with aura.<sup>22</sup> The causal relationship between migraine and stroke is complex and not fully understood. Migraine may coexist with stroke,





stroke may occur with the clinical features of migraine, or stroke may be induced by migraine. In the last case, a prolonged migraine aura may cause a condition called 'true migrainous infarction.'<sup>5,23</sup> The deficits caused by migraine-related stroke may improve or resolve completely with treatment; in other cases the deficits are permanent.

### **Migraine and epilepsy**

An association between migraine and epilepsy has long been recognized. In a large study by Lipton et al, it was found that patients with epilepsy were 2.4 times more likely to experience migraines than their relatives without epilepsy.<sup>24</sup> The prevalence of migraine was 24% among those with epilepsy and 15% among their relatives without epilepsy (similar to the prevalence in the general population). Conversely, Andermann has shown that patients with migraine have a 5.9% prevalence of epilepsy; this compares with a 0.5% prevalence of epilepsy in the general population.<sup>25</sup>

Differential diagnosis between migraine and epilepsy may be difficult, especially between migraine with aura and a complex partial seizure, which have common features.<sup>26</sup> The fact that both migraine and epilepsy can often be treated with anticonvulsants, such as valproate and topiramate, suggests a common mechanism for the disorders. Lipton et al propose that an increase in neuronal excitability, caused by genetic or environmental factors, underlies both conditions.<sup>24</sup> While anticonvulsant drugs may benefit both conditions, antimigraine drugs that lower the seizure threshold should generally be avoided. These include tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and neuroleptics.

### **Migraine and affective disorders**

Epidemiologic studies by Merikangas et al<sup>27</sup> and by Breslau and Davis<sup>28</sup> have shown that the occurrence over a lifetime of depression, anxiety disorders, and bipolar disorder are significantly higher in migraine sufferers than in the general population. Merikangas et al found odds ratios of 2.2 for depression, 2.9 for

bipolar disorder, 2.7 for generalized anxiety disorder, 3.3 for panic disorder, 2.4 for simple phobia, and 3.4 for social phobia.<sup>27</sup> They also found that, in migraineurs with major depression and anxiety disorders, the onset of anxiety usually preceded the onset of migraine, while the onset of major depression usually followed the onset of migraine. After adjusting for sex, Breslau and Davis found odds ratios of 4.5 for major depression, 6.0 for a manic episode, 3.2 for any anxiety disorder, and 6.6 for panic disorder.<sup>28</sup> In their study, migraine with aura was more strongly associated with neuropsychiatric disorders than migraine without aura.

The coexistence of migraine and depression creates both treatment problems and opportunities. Beta blockers are commonly used for migraine prophylaxis, but they would probably not be appropriate in a migraine patient prone to depression. On the other hand, amitriptyline might be successful in preventing migraine and depression in a patient who has both of these disorders.

### **Importance of the headache diary**

The present faculty were in universal agreement about the importance of a headache diary to provide detailed and accurate information about individual headaches. Many patients have surprisingly inaccurate ideas about the frequency of their own headaches and the amount of medication they use to treat their headaches. An accurate headache diary enables the physician to design an appropriate treatment plan, to stratify the care to the headache type and determine whether acute treatment is adequate or if prophylaxis is required. For example, a patient may report having only two headache days in the previous month, but the diary reveals that she took 50 butalbital during that period. What actually occurred was a pattern of daily headaches aborted by medication, with two days of breakthrough headaches. This patient is clearly a candidate for migraine prophylaxis. Another useful tool is the Migraine Attack Profile (MAP), which helps physicians determine the characteristics of a patient's migraines, such as symptoms, duration,

and what makes an attack improve or worsen. Although individual attacks may differ, a pattern emerges over time and physicians can use this information to select the most appropriate treatment.

### **Treatment strategies: step care vs stratified care**

There are two major approaches to the acute treatment of migraine: traditional step care and stratified care. In the step-care approach, patients are started at the bottom of a therapeutic pyramid and, if treatments fail, therapy is escalated. If the patient is satisfied with first-line treatment (usually simple analgesics), that treatment is continued. If the patient is not satisfied, a second-line drug is prescribed, usually a combination analgesic. If the second-line treatment fails, the patient is switched to more effective, more specific medications; typically a triptan. The fundamental, but erroneous, assumption of step care is that all patients have the same needs. The disadvantages of step care are (1) successful treatments may be delayed, (2) resources may be wasted on follow-up visits and failed prescriptions, (3) patients may become discouraged and lapse from care, and (4) overuse of ineffective medications may lead to chronic daily headache or analgesic rebound headache. As one faculty member (JB) noted, most patients who see physicians for headache have already been through the step care approach, on their own or with other physicians.

Stratified care is a more logical approach to migraine treatment. In this method, the physician stratifies the attacks and the patients according to specific therapeutic needs. Patients with severe, disabling headaches would be prescribed highly effective, migraine-specific medications early in therapy. Mild attacks may require only simple analgesics or NSAIDs, while moderate attacks may require an oral triptan. Severe attacks may require a rapidly acting treatment, such as subcutaneous sumatriptan. Extremely severe migraine, where the patient presents in a hospital emergency department, may require intravenous dihydroergotamine (DHE) plus metoclopramide.

Migraine attacks can also be stratified according to time-to-peak pain and headache duration. Attacks with a very rapid time-to-peak pain would need a sumatriptan injection, nasal spray, or a rapid-acting alternative, such as a DHE injection. Patients with moderate to severe headaches that peak in a few hours may be controlled on a rapid-acting oral triptan, such as rizatriptan, which can have a significant effect within one hour. Patients with prolonged migraine may respond better to a triptan with a longer duration of action, such as frovatriptan, which has a 26-hour half-life. Patients prone to headache recurrence might also benefit from a long-acting agent. Thus, there are several ways to stratify migraine attacks and the clinician should attempt to prescribe the appropriate medication for the patient's specific needs.

### **When to choose migraine prophylaxis**

The pharmacologic treatment of migraine can be either acute (abortive) or prophylactic. Patients with frequent severe headaches may require both approaches.<sup>5</sup> The decision to initiate prophylaxis should be based on a number of criteria; these are summarized in Table 1. Patient preference should also be considered. In general, prophylaxis should be considered if attacks occur more frequently than twice per week, if the severity or duration of attacks justifies prophylaxis, or if there is a need to enhance the efficacy of symptomatic medications.<sup>29</sup> Patients on daily prophylaxis should also be provided with a supply of abortive medication to treat breakthrough headaches. The supply should be limited, to reduce the possibility of drug-induced daily rebound headache. Certain abortive and prophylactic medications should not be used together, or should be used together with caution. DHE and a triptan, for example, may have enhanced vasospastic properties when used with methysergide. Medications for migraine prophylaxis fall into the following major medication groups: beta blockers, antidepressants, calcium channel blockers, serotonin antagonists, anticonvulsants, and NSAIDs. Drugs currently





**Table 1.** Criteria for considering migraine prophylaxis

- Headache frequency (>2 days per week)
- Degree and frequency of migraine-related disability
- Amount of prescription and OTC medications used by patient
- Presence of concomitant disorders (e.g., depression)
- Willingness and ability of patient to comply with daily medication regimen
- Success or failure of nondrug prophylactic therapies
- Special circumstances, such as hemiplegic migraine or headaches that risk permanent neurologic injury
- Patient preference

approved by the FDA for migraine prophylaxis include propranolol, timolol, methysergide, and divalproex sodium.

Prophylactic medication is usually given daily for periods of months to years. It can also be given episodically; this is called cyclic prophylaxis or mini-prophylaxis. Cyclic prophylaxis is used when patients are exposed to a known headache trigger for a limited period. Women with menstrual migraine represent a special category of candidates for cyclic prophylaxis, since they can often predict when headaches are likely to occur. Either abortive or prophylactic medications can be prescribed for a specific, limited number of days per month to prevent perimenstrual migraine attacks.<sup>21,30</sup>

Migraine associated with menstruation is often refractory to treatment.<sup>5,21</sup> DHE, given once or twice daily for five to ten days perimenstrually, has been shown to be effective in many cases.<sup>30</sup> Two recent studies, one of acute treatment and one of cyclic prophylaxis, have shown the triptans to be effective in menstrual migraine. A retrospective analysis was conducted in 95 women, who used rizatriptan 10 mg

to treat a total of 1839 menstrual migraine attacks. Depending on the definition of menstrual migraine used, the investigators found that rizatriptan relieved 78-79% of attacks at two hours.<sup>31</sup>

The second study was a double-blind, placebo-controlled, crossover trial of frovatriptan as cyclic prophylaxis in over 500 menstrual migraine sufferers.<sup>32</sup> Each patient received frovatriptan 2.5 mg, 5 mg, or placebo in randomized order for six days over three menstrual cycles. Both doses proved to be highly effective in reducing the incidence, severity, and duration of menstrually associated migraines. During the six-day period when they took the 5-mg dose, 52% of the women were headache-free; on the 2.5-mg dose, 41% were headache-free; on placebo, only 26% were headache-free. The differences were highly significant ( $p < 0.0001$ ). Frovatriptan also significantly reduced the severity and duration of attacks and the degree of functional impairment.

**Triptans and safety issues in women**

All of the triptans are contraindicated in patients with known ischemic heart disease, because of their small but significant potential for inducing coronary vasospasm. This class of drugs must also be used with caution in patients with risk factors for coronary disease. The assessment of coronary risk in women requires some special considerations, since chest pain may not have the same significance in women as in men. Douglas and Ginsburg note that all forms of chest pain, including typical angina, are associated with a lower incidence of angiographically verified coronary artery disease in women than in men.<sup>33</sup> They add that the differentiation between typical and atypical chest pain is particularly important in women. There is a higher incidence of less common causes of ischemia, such as vasospastic and microvascular angina, as well as syndromes of nonischemic chest pain, such as that associated with mitral valve prolapse (a migraine comorbidity). It is also possible that the higher incidence of vasospastic angina in women makes them more sensitive than men to the vasoconstrictive effects of the triptans, although this must remain speculative.

## Treating migraine during pregnancy and lactation

The primary considerations in the management of migraine during pregnancy are the potential for adverse effects of medications and of migraine itself on the developing fetus. Although migraine usually improves after the first trimester, some women continue to have severe, disabling headaches. If these are associated with nausea, vomiting, and dehydration, they may pose a risk to the fetus.

Because of the risk of injury to the fetus, medication use should be severely limited during pregnancy.<sup>30</sup> Nonpharmacological therapies should be tried first in pregnant migraineurs; these may include relaxation, regular sleep, massage, ice packs, or biofeedback. Migraine triggers, such as chocolate or tyramine-containing foods, should be avoided.

Studies by Marcus et al evaluated the effectiveness of different nondrug approaches. In the first study, a combined nonpharmacological treatment consisting of relaxation, skin-warming biofeedback, and physical therapy was evaluated in pregnant women with chronic headaches.<sup>34</sup> Symptoms improved in 79% of subjects, with an overall 72.9% reduction in headaches. In a second study, the above combined nonpharmacological treatment was compared with an attention control that included headache education and skin-cooling biofeedback. Both groups improved with treatment; however, 72.9% of the combined nonpharmacological treatment group experienced significant relief, compared with 28.6% of the attention control group ( $p < 0.03$ ). Significant improvement was maintained at a six-month follow-up for over 50% of patients.

If a migraine does not respond to a nondrug approach, a symptomatic drug is indicated. Acetaminophen, alone or with codeine can be safely used during pregnancy. Aspirin and ibuprofen are not associated with significant teratogenic risks, although they should be avoided during the last trimester. Prochlorperazine, chlorpromazine, trimethobenzamide, and promethazine can be used to

treat severe, migraine-related nausea in pregnant patients.<sup>5,35</sup> Metoclopramide can be used to alleviate gastric atony and enhance absorption of migraine medications. DHE, and ergotamine tartrate are contraindicated in pregnant women.<sup>35</sup> Animal studies of the triptans have shown possible adverse effects on fetuses at doses many times greater than the equivalent human doses. Triptans should be used in pregnancy only if the potential benefit justifies the potential risk. Migraine prophylactic medications should generally be avoided during pregnancy. Silberstein et al recommend that prophylaxis be considered only as a last resort, if migraine attacks are incapacitating, unresponsive to abortive therapy, or result in dehydration and fetal distress.<sup>5</sup> Women with epilepsy who take anticonvulsants during pregnancy have double the general population risk of fetal malformations.<sup>36</sup> Pfaffenrath and Rehm state that the only prophylactic agents that can be safely given during pregnancy are the beta blockers propranolol and metoprolol.<sup>35</sup>

Many drugs can be detected in breast milk, usually at 1-2% of the maternal dose; in most cases this is not significant.<sup>36</sup> Table 2 lists the American Academy of Pediatrics' guidelines for prescribing drugs for lactating women.<sup>37</sup>



**Table 2.** AAP guidelines for prescribing drugs for lactating women<sup>37</sup>

- Is the drug necessary? If so:
- Use the safest drug (e.g., acetaminophen instead of aspirin)
- If there is a possibility that a drug may present a risk to the infant (e.g., with phenytoin or phenobarbital), consider measuring the blood level in the nursing infant.
- Drug exposure to the nursing infant may be minimized by having the mother take the medication just after completing a breast-feeding.



**Table 3.** Migraine drugs compatible with breast-feeding<sup>35</sup>

■ **Simple analgesics**

Aspirin (with caution)  
Acetaminophen  
Caffeine

■ **Narcotics**

Butorphanol  
Codeine  
Hydromorphone  
Meperidine  
Methadone  
Morphine  
Propoxyphene

■ **Migraine-specific agents**

Triptans (with caution)

The breast-feeding migraineur should avoid bromocriptine, ergotamine, and lithium. The triptans, benzodiazepines, antidepressants, and neuroleptics should be used cautiously. Aspirin should also be used with caution; it may produce metabolic acidosis or abnormal platelet function. Acetaminophen is excreted into breast milk in low concentrations, but adverse effects in breast-feeding infants are very rare. Moderate caffeine use is compatible with breast-feeding, but excessive use can cause accumulation in nursing infants. The American Academy of Pediatrics does not consider sumatriptan to be contraindicated in breast-feeding mothers. Although sumatriptan is excreted in breast milk, the amount reaching the systemic circulation of a breast-feeding infant is probably negligible.<sup>38</sup> The amount could be further reduced by discarding the milk for eight hours after a dose. While narcotic use is compatible with breast-feeding, phenobarbital has been found to cause sedation in nursing infants.<sup>5</sup> Codeine also passes into breast milk, but in amounts that are probably insignificant.<sup>38</sup> Butorphanol, a narcotic agonist-antagonist, is also considered by the American Academy of Pediatrics to be acceptable for use in breast-feeding mothers.<sup>38</sup> Table 3 lists drugs frequently used to treat migraine that are generally compatible with breast-feeding.

## Conclusion

With the exception of cluster headache, all types of headache are more common in women than in men. Headaches in women are more frequent, more severe, and associated with more disability. Fortunately, this is an age when women's health issues are in the forefront. It's also an age when the biological basis of migraine is beginning to be understood and when migraine-specific medications are widely available. Numerous medications and strategies are available for the prevention and treatment of menstrual migraine, but pregnant migraineurs present a therapeutic challenge. The most effective migraine medications cannot generally be used in this population, and nondrug therapies, while helpful and safe, may be less than optimally efficacious. Treatment of the pregnant migraineur must remain conservative, with physician and patient buoyed by the knowledge that the condition generally improves during pregnancy.

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P O S T - T E S T A N S W E R S  
& A C T I V I T Y E V A L U A T I O N

To earn one (1) hour of Category 1 CME credit after reading this monograph and listening to the audio CD, please send the completed post-test answers, activity evaluation, and personal information questionnaire to Finch University of Health Sciences/The Chicago Medical School in the enclosed envelope.



*Separate this form along the perforation, fold, and mail in the enclosed envelope.*



## POST-TEST ANSWERS

*Circle the appropriate letter for each question.*

- |          |              |               |
|----------|--------------|---------------|
| 1. A B C | 6. A B       | 11. A B       |
| 2. A B C | 7. A B C     | 12. A B C D E |
| 3. A B C | 8. A B C     | 13. A B       |
| 4. A B   | 9. A B C D E | 14. A B C D E |
| 5. A B C | 10. A B      |               |

## ACTIVITY EVALUATION

Strongly Agree

Strongly Disagree

**1**                      **2**                      **3**                      **4**                      **5**

1. This activity helped to increase my knowledge base.

**1**                      **2**                      **3**                      **4**                      **5**

2. This activity gave me new information that will influence how I practice.

**1**                      **2**                      **3**                      **4**                      **5**

3. The technical quality of the activity was good.

**1**                      **2**                      **3**                      **4**                      **5**

4. The activity met its objectives.

**1**                      **2**                      **3**                      **4**                      **5**

5. I would recommend this activity to my peers.

**1**                      **2**                      **3**                      **4**                      **5**

6. There was no significant commercial bias in the activity.

**1**                      **2**                      **3**                      **4**                      **5**

Comments \_\_\_\_\_

## PERSONAL INFORMATION

Name/degree (please print) \_\_\_\_\_

Address

City \_\_\_\_\_ State \_\_\_\_\_ Zip \_\_\_\_\_

Telephone \_\_\_\_\_

Social Security number \_\_\_\_\_

Medical Education (ME) number \_\_\_\_\_

I have read the monograph, listened to the audio CD, and completed the post-test and activity evaluation.

Signature \_\_\_\_\_

Date \_\_\_\_\_



11 correct answers are required for credit

1. According to the results of the American Migraine Study II, what is the prevalence of migraine in American women?
  - A. 6.5%
  - B. 12.4%
  - C. 18.2%
2. Approximately what percent of women with migraine report increased frequency of attacks at the time of menses?
  - A. 25%
  - B. 70%
  - C. 85%
3. At menopause, migraine. . .
  - A. generally improves
  - B. generally worsens
  - C. may improve or worsen
4. There are distinctive and consistent differences in circulating hormone levels between women with and those without menstrual migraine.
  - A. True
  - B. False
5. Approximately what percentage of migraineurs will improve during pregnancy?
  - A. 25-30%
  - B. 60-70%
  - C. 85-90%
6. A retrospective review found that the presence of migraine significantly increased the incidence of miscarriage and stillbirth in pregnant women.
  - A. True
  - B. False
7. What was the approximate increase in the risk for stroke among women with migraine in the 1975 Study of Stroke in Young Women?
  - A. 100%
  - B. 150%
  - C. 200%
8. What is the prevalence of epilepsy among patients with migraine?
  - A. 0.5%
  - B. 5.9%
  - C. 9.5%
9. Which of the following are disadvantages of the step-care approach to migraine therapy?
  - A. Successful treatment may be delayed
  - B. Overuse of ineffective medications may lead to chronic daily headache
  - C. Resources may be wasted on follow-up visits and failed prescriptions
  - D. All of the above
  - E. A and C above
10. In general, migraine prophylaxis should be considered if migraines occur more often than twice per week.
  - A. True
  - B. False
11. Long half-life triptans may prove beneficial in patients with prolonged migraine or migraine prone to recurrence.
  - A. True
  - B. False
12. Which of the following is the drug of choice to safely treat nausea during pregnancy?
  - A. Prochlorperazine
  - B. Chlorpromazine
  - C. Promethazine
  - D. Trimethobenzamide
  - E. All of the above
13. DHE and ergotamine are contraindicated in pregnant women.
  - A. True
  - B. False
14. Which of the following drugs can be safely used by the breast-feeding migraineur?
  - A. Bromocriptine
  - B. Ergotamine
  - C. Lithium
  - D. All of the above
  - E. None of the above