

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



THIS SLIDE KIT WITH LECTURE NOTES IS BASED
ON A CONTINUING MEDICAL EDUCATION PROGRAM
PRESENTED BY THE NATIONAL HEADACHE FOUNDATION
AND SUPPORTED BY AN EDUCATIONAL GRANT FROM
UCB PHARMA, INC. AND ELAN BIOPHARMACEUTICALS

*Merle Diamond, MD, Associate Director, Diamond Headache Clinic,
Chicago, Illinois, served as faculty chairperson for this program.*

Contents



I. Epidemiology and impact of migraine in women

II. Hormones and migraine

III. Migraine comorbidities

A. Migraine and stroke

B. Migraine and epilepsy

C. Migraine and affective disorders

IV. The headache diary

V. Treatment strategies

A. Step care

B. Stratified care

C. Migraine prophylaxis

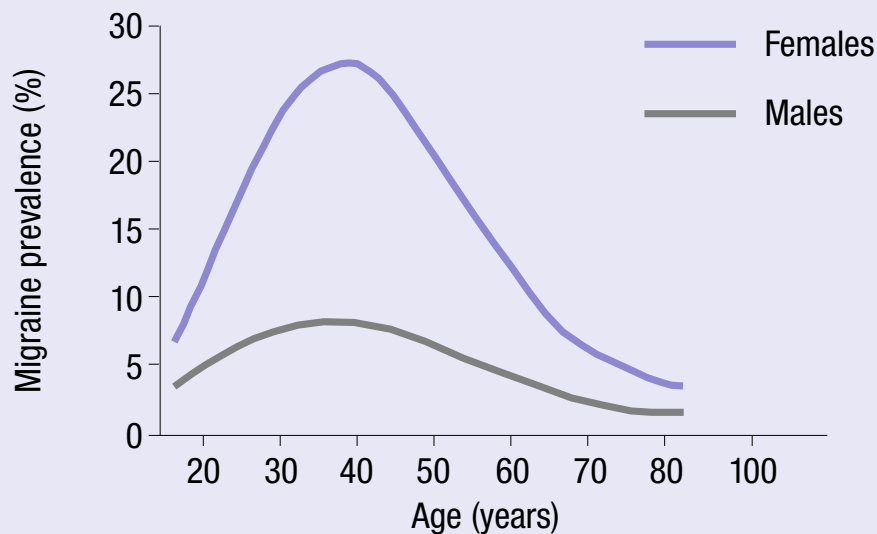
VI. Triptans and safety issues in women

VII. Treating migraine during pregnancy and lactation

VIII. Conclusion



Migraine Prevalence in Women and Men



Migraine 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.¹ The American Migraine Study II sent questionnaires to 20,000 American households.² 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.³ 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. After approximately age 40, the prevalence of migraine tends to decline.⁴ The female/male migraine prevalence ratio also varies with age. Cyclical hormone changes account for some but not all of the differences between the sexes, since migraine prevalence remains much higher in women even well past the age of 70.

1. Winner PK. Headaches in children. When is a complete diagnostic workup indicated? *Postgrad Med.* 1997;101(5):81-90.

2. Lipton RB, Stewart WF, Diamond S, et al. Prevalence and burden of migraine headache in the United States: data from the American Migraine Study II. *Headache.* 2001;41(7):646-657.

3. Kumar KL, Mathew NT, Silberstein SD. Migraine: the road to relief. *Patient Care.* 1995;(Sept 15):90-110.

4. Silberstein SD, Lipton RB, Goadsby PJ. *Headache in Clinical Practice.* Oxford: Isis Medical Media Ltd, 1998.



Hormones and Migraine

- Up to 70% of women with migraine report attacks at the time of menses
- Some migraines are associated with PMS and LLPDD
- Menstrual migraine triggered by fall in estrogen and progesterone
- Hormone differences between women with and without menstrual migraine are not consistent

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.¹ Menstrual migraine tends to occur at the time of greatest fluctuation in estrogen levels, typically at the same time every month.² Silberstein postulated that menstrual migraine results from a mismatch between the ovarian cycles of the sex hormones and the inherent rhythm of estrogen-sensitive neurons, including those of the serotonergic pain-modulating system.¹ 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.^{2,3} There have been several attempts to detect differences in hormone levels between women with and those without menstrual migraine, but results have been inconsistent.⁴

1. Silberstein SD, Merriam GR. Sex hormones and headache. *J Pain Symptom Manage.* 1993;8(2):98-114.

2. Silberstein SD, Lipton RB, Goadsby PJ. *Headache in Clinical Practice.* Oxford: Isis Medical Media Ltd, 1998.

3. Somerville BW. The role of estradiol withdrawal in the etiology of menstrual migraine. *Neurology.* 1972;22:355-365.

4. Uknis A, Silberstein SD. Review article: migraine and pregnancy. *Headache.* 1991;31(6):372-374.

Migraine and Pregnancy



- 60-70% of migraineurs improve during pregnancy
- Among 116 pregnant migraineurs (Bousser et al):
 - Migraine improved or disappeared in 69%
 - Was variable in 5%
 - Was unchanged in 8%
 - Worsened in 7%
 - Appeared for the first time in 11%

The increase in estrogen levels that occurs in early pregnancy has a protective effect against headache in many women.¹ 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,² 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.³ 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%, worsened 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.

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.⁴

-
1. Marcus DA. Pregnancy and chronic headache. *Expert Opin Pharmacother*. 2002;3(4):389-393.
 2. Uknis A, Silberstein SD. Review article: migraine and pregnancy. *Headache*. 1991;31(6):372-374.
 3. Bousser MG, Ratinahirana H, Darbois X. Migraine and pregnancy: a prospective study in 703 women after delivery. *Abstr Neurology*. 1990;40(Suppl 1):437.
 4. Wainscott G, Volans GN. The outcome of pregnancy in women suffering from migraine. *Postgrad Med J*. 1978;54:98-102.



Migraine Comorbidities

■ Neurological/psychiatric:

Epilepsy	Stroke
Depression	Bipolar disorder
Anxiety disorders	Impaired cognition

■ Other:

Irritable bowel syndrome	Mitral valve prolapse
Asthma	

The term 'comorbidity' refers to the greater-than-coincidental association of two or more conditions in the same person. Migraine is 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.¹ Patients with migraine without aura have also been shown to score significantly higher than controls on indices of aggression-hostility.² Migraine may also be associated with impaired cognitive function (especially language reception).³ 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.⁴ 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.¹ When migraine and depression occur together, an antidepressant may treat both conditions; when migraine and epilepsy occur together, an anticonvulsant may treat both conditions.

1. Silberstein SD, Lipton RB, Goadsby PJ. *Headache in Clinical Practice*. Oxford: Isis Medical Media Ltd, 1998.

2. Cao M, Zhang S, Wang K, et al. Personality traits in migraine and tension-type headaches: a five-factor model study. *Psychopathology*. 2002;35(4):254-258.

3. Waldie KE, Hausman M, Milne BJ, et al. Migraine and cognitive function: a life-course study. *Neurology*. 2002;59(6):904-908.

4. Peres MF, Zukerman E, Young WB, et al. Fatigue in chronic migraine patients. *Cephalalgia*. 2002;22(9):720-724.

Migraine and Stroke



- Migraine is a risk factor for stroke
- Stroke is associated with migraine with aura
- Causal relationship complex:
 - Migraine may coexist with stroke
 - Stroke may occur with clinical features of migraine
 - Stroke may be induced by migraine (true migrainous infarction)

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.¹ 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, Tzourio et al found a 400% increase in the risk of stroke in women with migraine under age 45.² Smoking and overuse of ergotamine may further increase the risk.³ 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.⁴ 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'.^{5,6} The deficits caused by migraine-related stroke may improve or resolve completely with treatment; in other cases the deficits are permanent.

1. Collaborative Group for the Study of Stroke in Young Women. Oral contraceptives and stroke in young women. *JAMA*. 1975;231:718-722.

2. Tzourio C, Tehindrazanarivelo A, Iglesias S, et al. Case-control study of migraine and risk of ischemic stroke in young women. *Br Med J*. 1995;310:830-833.

3. American Council for Headache Education. *Migraine: A Complete Guide*. New York: Dell Publishing, 1994.

4. Rothrock J, North J, Madden K, et al. Migraine and migrainous stroke: risk factors and prognosis. *Neurology*. 1993;43:2473-2476.

5. Welch KMA. Relationship of stroke and migraine. *Neurology*. 1994;44(Suppl 7):33-36.

6. Silberstein SD, Lipton RB, Goadsby PJ. *Headache in Clinical Practice*. Oxford: Isis Medical Media Ltd, 1998.



Migraine and Epilepsy

- Patients with epilepsy are 2.4 more times likely to have migraine than their relatives without epilepsy
- 24% prevalence of migraine among people with epilepsy (Lipton et al)
- 5.9% prevalence of epilepsy among those with migraine (vs. 0.5% in general population) (Andermann)

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.¹ The prevalence of migraine was 24% among those with epilepsy and 15% among their relatives without epilepsy. 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.²

Differential diagnosis between migraine and epilepsy may be difficult, especially between migraine with aura and a complex partial seizure, which have common features.³ 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.¹ 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.

1. Lipton RB, Ohman R, Ehrentesy B, et al. Comorbidity of migraine: the connection between migraine and epilepsy. *Neurology*. 1994;44(Suppl 7):528-532.

2. Andermann E, Andermann F. Migraine-epilepsy relationships: epidemiological and genetic aspects. In: Andermann F, Logaresi E (eds). *Migraine and Epilepsy*. Boston: Butterworths, 1987:281-291.

3. Marks DA, Ehrenberg BL. Migraine-related seizures in adults with epilepsy, with EEG correlation. *Neurology*. 1993;43:2476-2483.

Migraine and Affective Disorders



- Odds ratios for patients with migraine (Merikangas et al):
 - 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
 - 3.4 for social phobia

Epidemiologic studies by Merikangas et al¹ and by Breslau and Davis² 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.¹ 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.² 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.

1. Merikangas KR, Angst J, Isler H. Migraine and psychopathology: results of the Gurich Cohort Study of Young Adults. *Arch Gen Psychiatry*. 1990;47:849-853.

2. Breslau N, Davis GC. Migraine, major depression and panic disorder. A prospective epidemiologic study of young adults. *Headache*. 1994;34(7):387-393.



Importance of the Headache Diary

“ A 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. ”

An accurate headache diary is an essential diagnostic and therapeutic tool. Many patients have surprisingly inaccurate ideas about the frequency of their own headaches and the amount of medication they use to treat their headaches. A 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



- Patients start at the bottom of a therapeutic pyramid and if treatments fail, therapy is escalated
- Disadvantages:
 - Successful treatment may be delayed
 - Resources may be wasted on follow-up and failed prescriptions
 - Patients may lapse from care
 - Overuse of medications may lead to chronic daily headache

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. In fact, most patients who see physicians for headache have already been through the step-care approach, on their own or with other physicians.



Treatment Strategies: Stratified Care

- Physician stratifies the attacks and the patients according to specific therapeutic needs
- Examples:
 - Patients with severe migraines are prescribed effective, migraine-specific medications early in therapy
 - Patients with rapid time-to-peak pain may be given sumatriptan injection, nasal spray, or DHE injection
 - Patients with prolonged migraine may be given a triptan with a long duration of action; e.g., frovatriptan, which has a 26-hour half-life

Stratified care is a more logical approach to migraine treatment than step care. 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. 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.

Treatment Strategies: When to Choose 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



The pharmacologic treatment of migraine can be either acute (abortive) or prophylactic. Patients with frequent severe headaches may require both approaches.¹ The decision to initiate prophylaxis should be based on a number of criteria; these are summarized in this slide. 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.² 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 approved by the FDA for migraine prophylaxis include propranolol, timolol, methysergide, and divalproex sodium.

1. Silberstein SD, Lipton RB, Goadsby PJ. *Headache in Clinical Practice*. Oxford: Isis Medical Media Ltd, 1998.

2. Mathew NT. Abortive vs prophylactic treatment of migraine: a reappraisal. *Headache*. 1990;30:238-239.



Cyclic, or “Mini” Prophylaxis

- Women with menstrual migraine represent a special category of candidates for cyclic prophylaxis
- Abortive or prophylactic medications can be prescribed for a specific, limited number of days per month
- Shown to be effective in menstrual migraine:
 - DHE (cyclic prophylaxis)
 - Rizatriptan (acute treatment)
 - Frovatriptan (cyclic prophylaxis)

Prophylactic medication may be given episodically; this is called cyclic prophylaxis or “mini” prophylaxis. Women with menstrual migraine represent a special category of candidates for cyclic prophylaxis, since they can 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.^{1,2} DHE, given once or twice daily for five to ten days perimenstrually, has been shown to be effective as cyclic prophylaxis.² A retrospective analysis was conducted in 95 women who used rizatriptan 10 mg for acute treatment of a total of 1839 menstrual migraine attacks. In this analysis, rizatriptan relieved 78-79% of attacks at two hours.³

A double-blind, placebo-controlled, crossover trial of frovatriptan as cyclic prophylaxis was recently conducted in over 500 menstrual migraine sufferers.⁴ 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. On 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 ($p < 0.0001$).

1. American Council for Headache Education. *Migraine: A Complete Guide*. New York: Dell Publishing, 1994.

2. Raskin NH. *Headache*. (2nd ed). New York: Churchill Livingstone, 1988.

3. Silberstein SD, Massiou H, McCarroll KA, et al. Further evaluation of rizatriptan in menstrual migraine: retrospective analysis of long-term data. *Headache*. 2002;42(9):917-923.

4. Data on file, UCB Pharma.

Triptans and Safety Issues in Women



- Triptans contraindicated in patients with known or suspected CAD
- Use with caution in patients with CAD risk factors
- Chest pain in women associated with lower incidence of confirmed CAD
- Women have higher incidence of vasospastic and microvascular angina

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.¹ 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.

1. Douglas PS, Ginsburg GS. Current concepts: the evaluation of chest pain in women. *N Engl J Med.* 1996;334(20):1311-1315.



Treating Migraine During Pregnancy

- Both migraine and migraine medications may pose a risk to the fetus
- Try nonpharmacological approaches first; e.g.,
 - Relaxation techniques
 - Regular sleep
 - Massage
 - Ice packs
 - Biofeedback

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.¹ Nonpharmacological therapies should be tried first; these may include relaxation, regular sleep, massage, ice packs, or biofeedback. 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.² 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 ($p < 0.03$).

1. Raskin NH. *Headache*. (2nd ed). New York: Churchill Livingstone, 1988.

2. Marcus DA, Scharff L, Turk DC. Nonpharmacological management of headaches during pregnancy. *Psychosom Med*. 1995;57(6):527-535.

Drug Treatment of the Pregnant Migraineur



- May be used:
 - Acetaminophen (alone or with codeine)
 - Aspirin (avoid during last trimester)
 - Ibuprofen (avoid during last trimester)
 - Prochlorperazine, chlorpromazine, trimethobenzamide, promethazine (for nausea)
 - Metoclopramide (to alleviate gastric atony)
 - Triptans (with caution)
- Contraindicated:
 - DHE and ergotamine tartrate

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, or promethazine can be used to treat severe, migraine-related nausea in pregnant patients.^{1,2} Metoclopramide can be used to alleviate gastric atony and enhance absorption of migraine medications. DHE and ergotamine tartrate are contraindicated in pregnant women.² The triptans should be used only if the potential benefit outweighs the potential risk to the fetus. 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.¹ Women with epilepsy who take anticonvulsants during pregnancy have double the general population risk of fetal malformations.³ Pfaffenrath and Rehm state that the only prophylactic agents that can be safely given during pregnancy are the beta blockers propranolol and metoprolol.²

1. Silberstein SD, Lipton RB, Goadsby PJ. *Headache in Clinical Practice*. Oxford: Isis Medical Media Ltd, 1998.

2. Pfaffenrath V, Rehm M. Migraine in pregnancy: what are the safest treatment options? *Drug Saf*. 1998;19(5):383-388.

3. Silberstein SD. Headache and women: treatment of the pregnant and lactating migraineur. *Headache*. 1990;33(10):533-540.



Migraine Drugs Compatible with Breast-Feeding

- **Simple analgesics**
 - Aspirin (with caution; may produce metabolic acidosis or abnormal platelet function)
 - Acetaminophen
 - Caffeine
- **Migraine-specific agents**
 - Triptans (with caution)
- **Narcotics**
 - Butorphanol
 - Codeine
 - Hydromorphone
 - Meperidone
 - Methadone
 - Morphine
 - Propoxyphene

Many drugs can be detected in breast milk, usually at 1-2% of the maternal dose; in most cases this is not significant.¹ Nevertheless, the American Academy of Pediatrics has recommended the following guidelines when prescribing drugs to lactating women.²

- 1. Is the drug necessary? If so: ■ 2. Use the safest drug (e.g., acetaminophen instead of aspirin)
- 3. 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. ■ 4. Drug exposure to the nursing infant may be minimized by having the mother take the medication just after completing a breast-feeding.

The breast-feeding migraineur should avoid bromocriptine, ergotamine, and lithium. The triptans, benzodiazepines, antidepressants, and neuroleptics should be used cautiously. 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.³ The amount could be further reduced by discarding the milk for eight hours after a dose. Moderate caffeine use is compatible with breast-feeding, but excessive use can cause accumulation in nursing infants. While narcotic use is compatible with breast-feeding, phenobarbital has been found to cause sedation in nursing infants.⁴ This slide lists drugs used to treat migraine that are generally compatible with breast-feeding.

1. Silberstein SD. Headache and women: treatment of the pregnant and lactating migraineur. *Headache*. 1990;33(10):533-540.

2. American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. *Pediatrics*. 1989;84:924-936.

3. Briggs GG, Freeman RK, Yaffe SJ. *Drugs in pregnancy and lactation, 6th ed*. Philadelphia: Lippincott Williams & Wilkins, 2002.

4. Silberstein SD, Lipton RB, Goadsby PJ. *Headache in Clinical Practice*. Oxford: Isis Medical Media Ltd, 1998.

Summary

- Except for cluster headache, all types of headache are more common in women
- Headaches in women are more frequent, more severe, and cause more disability
- Menstrual migraine can generally be controlled
- Pregnant migraineurs with continuing headaches remain a therapeutic challenge



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 remain 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.

Patients and healthcare providers can obtain additional information on headache causes and treatments from the National Headache Foundation. Please visit our web site at www.headaches.org or call toll-free at (888) NHF-5552.