

# Menopause and Migraine

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Migraine is an extremely common disorder in primary care clinics, and a major source of medical morbidity in the productive years of adulthood. Headaches are carefully defined in the International Headache Society's (IHS) *International Classification of Headache Disorders (ICHD-II, 2004)*.<sup>1</sup> Migraine is a particular type of headache, as defined by established criteria of the IHS. The criteria for "migraine without aura," the most common headache for which patients seek medical care, are shown in the Table.

Although these criteria were developed initially for research purposes, they can be used clinically. Application of these criteria has undoubtedly helped increase the recognition of migraine over the last two decades. Clearly, the majority of headaches that are sufficiently troublesome to come to clinical attention are migraine.

More detailed diagnostic categorization may not make a great deal of practical difference in the typical clinic setting. Many headache specialists subscribe to the "spectrum hypothesis" of migraine,<sup>2</sup> believing that migraine and tension-type headaches merely represent the two ends of a continuous spectrum of headache disorders. Furthermore,

the significant majority of self-diagnosed "sinus headaches" are actually migraines.<sup>3</sup> These diagnostic points have significant implications, meaning that we may be somewhat inclusive of other headache disorders when we talk about hormonal influences. In the clinic, the spectrum hypothesis means that even when a headache is not a "perfect" migraine,

our therapeutic options can encompass usual migraine treatments.

## Migraine, Gender and Age

The prevalence of migraine in adulthood by age and gender is shown in the Figure. The prevalence of migraine in childhood is roughly equal for boys and girls, but right around the time of menarche the prevalence in females increases rapidly and never again drops to par with the male curve. The highest prevalence in both males and females occurs during the thirties and forties, and the female-to-male gender prevalence ratio is roughly 3:1.<sup>4</sup>

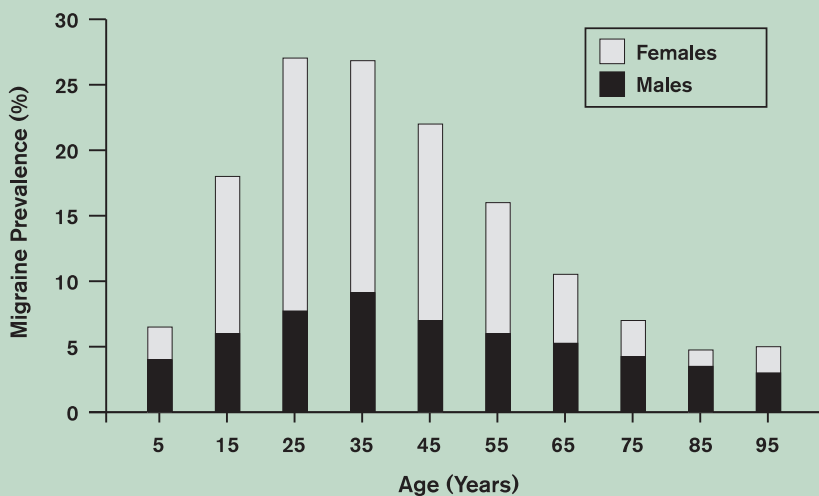
It is tempting to ascribe the increased prevalence of migraine in women to hormonal influences, with the drop in migraines after age 40 due to a decrease in hormonal triggers. However, if female hormones were solely responsible for the gender differential, one would expect a more precipitous drop during the postmenopausal age range, and a decrease in the gender ratio. Also, although male prevalence is lower throughout adulthood, the pattern varies with age in much the same way as female prevalence. Clearly, there is also an age effect on migraine in both sexes, independent of hormones.

### Table. International Classification of Headache Disorders (ICHD) Criteria for the Diagnosis of Migraine Without Aura<sup>1</sup>

#### Diagnostic criteria

- A. At least 5 attacks fulfilling criteria B-D
- B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
- C. Headache has at least two of the following characteristics:
  - a. Unilateral location
  - b. Pulsating quality
  - c. Moderate or severe pain intensity
  - d. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
- D. During headache at least one of the following:
  - a. Nausea and/or vomiting
  - b. Photophobia and phonophobia
- E. Not attributed to another disorder

Source: International Headache Society



**Figure.** Adjusted age-specific prevalence of migraine by sex, 1999.<sup>4</sup>

Adapted from Lipton RB, Diamond S, Reed M, et al. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache* 2001;41:646-57.

which implicated a drop in estrogen levels as the major trigger for menstrual migraine. More recent work and clinical observations have verified this.<sup>7-10</sup> Clinical experience also suggests that almost any hormonal fluctuation can be linked to migraine in certain individuals, although statistical support is less compelling.

This is most understandable if we consider that the primary trigger for migraine is probably *change* itself. This is not limited to hormonal changes. Change in weather, stress, sleep, eating patterns and much more can trigger migraine. However, the unpredictable hormonal changes of perimenopause and menopause can be related to noticeable difficulties with regard to headache frequency, severity and predictability.

Studies that have looked at the patterns of migraine during perimenopause have suggested that some women are indeed more prone to migraine at this time.<sup>11</sup> There is considerable individual variation, and there is some suggestion that “hormonally sensitive” women are more likely to have difficulty with migraine at this stage. No formal definition of “hormonally sensitive” has been put forth, but the term generally refers to women who have experienced migraine changes in conjunction with previous hormonal events such as menstruation, pregnancy and use of oral contraceptives (OCs). On the other hand, the link between menopausal complaints and migraine is weak at best,<sup>12</sup> and this is consistent with a similarly poor correlation between migraine and premenstrual symptoms in younger women. A few cautions are

### Hormones and Migraine at Menopause

For the woman with migraine, the hormonal irregularities of perimenopause and menopause are

particularly troublesome. The traditional theory of menstrual migraine is an estrogen-withdrawal theory, based on the work of Somerville in the early 1970s,<sup>5,6</sup>

also in order. Women may over- or underestimate the hormonal connections to migraine, and headache diary data can be imperfect.

As for menopause itself, it is important to distinguish between natural and surgical menopause. In natural menopause, the likelihood that the pattern of preexisting migraine will improve has been reported as high as 50%-60%,<sup>13,14</sup> although there is much variability between studies. Some women do worsen, many experience no change in their migraines, and some even develop new-onset migraine around the time of menopause. There is a logical suggestion that women with menstrual migraine would be most likely to improve after menopause, but supporting data for this notion are limited.

Surgically induced menopause (that is, oophorectomy with or without hysterectomy) appears to be associated with worsening of migraine in a substantial percentage of women;<sup>13</sup> again, however, the numbers vary widely in studies. This worsening occurs even with retention of the ovaries or postsurgical estrogen therapy.<sup>15</sup> The fraction of women who worsen is definitely sufficiently high (often cited informally as two-thirds) for surgical menopause not to be considered a treatment for migraine at this time, no matter how hormonally sensitive the woman appears to be. The reason for this worsening is unclear, but it may be related to the abrupt, large change in hormones and/or the use of supplementary estrogen following surgery. Chemical oophorectomy with estrogen add-back therapy has been at-

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tempted in the prevention of refractory migraine,<sup>16</sup> and this has been suggested as a way of selecting women for surgical menopause. However, this remains very much unproven and unreliable. Migraine is *not* an indication for total hysterectomy. It is not a contraindication if oophorectomy with or without hysterectomy needs to be done for another compelling medical reason, but it is important to make sure the patient knows that the surgery is unlikely to benefit migraine and may, in fact, make it worse.

#### **Migraine and the Risk of Stroke**

The risk of stroke is of increasing concern as women age through menopause. It is an area that has been controversial for years, but some patterns and recommendations have emerged from studies.<sup>17-19</sup> Migraine with aura does seem to carry a roughly 3-fold increase in the risk of stroke in young women

(under the age of 45). On the other hand, migraine without aura has not clearly been associated with increased stroke risk. There is also little hard evidence for a correlation between stroke and migraine over the age of 50, except perhaps for a small increase among women with migraine with aura. Smoking appears to compound the stroke risk in migraine with aura, as does the use of estrogen-containing OCs. Currently, the World Health Organization (WHO), the American College of Obstetricians and Gynecologists (ACOG) and the IHS all recommend that women who have migraine with aura not use combination OCs. Concurrent smoking or history of thrombosis, such as deep vein thrombosis, are also WHO and ACOG contraindications to OC use. Since OCs are often used to control menstrual problems in the perimenopausal years, women who have migraine with aura should be warned against using estrogen-containing OCs for any indication.

Imaging studies have suggested an increased number of clinically silent white matter lesions, sometimes interpreted as ischemic events, specifically localized to the posterior circulation in migraineurs.<sup>20,21</sup> The relationship of age and hormonal status to these lesions is unclear, although in general, small white matter hyperintensities visible on magnetic resonance imaging increase with age. At this point, there is no indication for systemic antithrombotic treatment in migraineurs, even in patients with such cerebellar lesions.

It does appear from the Women's  
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Health Initiative (WHI) reports that hormone therapy (HT) increases the risk of stroke.<sup>22,23</sup> However, there are no specific data suggesting that migraine and HT interact; thus, migraine without aura in itself is not currently a contraindication to the use of HT in menopausal women.

### Treatment and Prevention of Migraine in the Menopausal Years

First-line treatment of hormonally triggered migraine does not involve hormonal manipulation. Rather, it involves the same abortive and preventive agents used to treat any other migraine. For some time now, specialists have debated whether menstrual migraines (the prototype for hormonally triggered migraines) are truly different, more intractable and harder to treat than other migraines. Still, several standard medications, such as triptans, have been shown to be quite successful in menstrual migraine, whereas hormone manipulation is less predictable and may actually worsen migraine in a significant percentage of patients. Also, hormone changes are likely best viewed as potent migraine *triggers*—akin to red wine and monosodium glutamate—rather than as fundamental causes of migraine (integral parts of a universal pathophysiology).

*Abortive therapy.* For significant (moderate to severe) migraines, the current first-line abortive agents are the triptans. Triptans are the most effective abortives for migraine, and there is no reason to think that they should be less effective at or after

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menopause than in earlier years. Safety is not a large concern, although menopause can serve as a signal to review cardiac and cerebrovascular risk factors. A 10-year retrospective assessment of sumatriptan (Imitrex) in clinical use failed to show an increase in myocardial infarction or stroke, although it was acknowledged that sumatriptan has generally not been given to patients with significant risk factors.<sup>24</sup> A different statistical examination of the question of triptan safety asked whether a cardiac workup should be considered before prescribing triptans; the conclusion was that potential triptan use did not add to the need for a cardiac workup.<sup>25</sup> In other words, a cardiac workup should be undertaken if there are cardiac concerns, but should not be done solely because a triptan is being prescribed. Current contraindications for triptan use remain known cardiovascular disease, uncontrolled hypertension and basilar or hemiplegic migraine (migraine with auras in-

volving multiple brainstem signs and symptoms, or motor weakness).

Nonsteroidal anti-inflammatory drugs in prescription doses have been successful in some women for hormonally related migraines. Other abortives are also acceptable, or at least as acceptable at menopause as at other ages and life stages. Overuse and rebound headaches can occur at any age, and potentially habit-forming medications—particularly barbiturates and narcotics—should be used extremely sparingly, if at all.

*Preventive therapy.* The usual rules for preventive therapy hold during the perimenopausal and menopausal years as well. Indications for preventive treatment include (but are not limited to) overly frequent migraine, incompletely effective abortive therapy and cardiovascular or other contraindications to effective abortive therapy. The term “overly frequent migraine” has a range of possible interpretations, but any time the migraine frequency averages twice per week or more, the potential for rebound becomes significant and prevention should be seriously considered. Standard preventives, including beta blockers, tricyclic antidepressants and some of the antiepileptic drugs, are all useful in this age range, and should be prescribed based on the patient’s individual profile.

### Menopause and Medication Overuse

Rebound (medication-overuse) headache is an important clinical problem in this age group. It is critical to remember that medication overuse actively prolongs chronic headaches, sometimes for years. There is, as previously noted, a tendency for

migraine to improve with age, and some women do improve with menopause. If a patient is in rebound, however, any natural tendency to improve with age or hormonal status may well be masked. In other words, menopause will not “cure” rebound headaches, and medication overuse must be treated aggressively at any age. This author has treated many women in their 60s, 70s and even 80s who have medication-overuse headaches and who have been taking abortive medications (often butalbital or codeine) daily for 40 years or more. Some of these women, if successfully weaned from their abortives, become virtually migraine-free, making one wonder how many years ago they would have naturally improved had they not continued to overuse medications. Hope for a “miraculous menopause” should not delay appropriate treatment. Generally, overuse is defined as regular use of abortive therapy on more than about 2 days per week on average.

### **Hormonal Manipulation and Migraine at Menopause**

Just a few years ago, a large percentage of menopausal women were using HT at menopause. Since the release of the WHI reports, however, many more women are going through menopause without HT, although some have returned to HT because of unacceptable menopausal symptoms.

Low-dose OCs, most typically containing 20-30 mcg of ethinyl estradiol, are frequently given to women in perimenopause. Women who are prone to migraine may experience what is essentially a menstrual migraine during the placebo

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week of the pills, when estrogen levels fall. Continuous administration regimens of OCs are available, and may theoretically decrease the number of estrogen-withdrawal headaches. In practice, however, migraine-prone women often report irregular headache occurrence regardless. The low estrogen content of these pills may not fully override natural hormone fluctuations in some perimenopausal women.<sup>26</sup> If a woman who has migraine with aura asks about use of low-dose OCs at menopause, it would be wise to advise against the OCs because of the stroke risk. If she does not have auras, another consideration is whether she has ever had trouble tolerating OCs in the past. If so, it is probably best to avoid them now.

The effect of HT on migraine is likely highly individualized, but it appears that current users are more likely to report migraine than are nonusers.<sup>27-29</sup> Case reports also indicate that HT can trigger migraine aura, particularly at higher doses.<sup>30</sup> Given the concern about the correla-

tion of migraine with aura and stroke, new-onset aura may be considered a contraindication to the continued use of HT. HT that is given cyclically may trigger estrogen-withdrawal migraines, much like OCs.

Oral HT formulations are associated with wide variations in blood levels of estrogen, and studies suggest that non-oral estrogen delivery is associated with better outcomes in migraine sufferers.<sup>27</sup> Theoretically, transdermal patches probably provide the smoothest release form of HT. If HT is being used solely for relief of hot flashes and other vasomotor symptoms, dosing should be started as low as possible and increased only as necessary in order to prevent aggravating migraine. High doses of HT, even given transdermally, have been associated with development of auras as well as increased migraine severity. If this happens, reduction or withdrawal of estrogens is recommended.

Many women now are using over-the-counter preparations to treat menopausal symptoms such as hot flashes. Most typically, these preparations contain soy and/or black cohosh, sometimes in fairly complex herbal combinations. They may have some estrogenic activity, although they probably offer little symptom relief.<sup>31</sup> Since these preparations are not regulated as drugs, the amount of potentially active components may vary significantly. This means that hormonally sensitive women may find that these treatments actually trigger migraines. Migraine patients should be encouraged to always report all medications they are taking, including any herbal and vitamin supplements, and they

should be aware that “natural” is not a synonym for “safe.”

For the woman with migraine, caution and individualization of treatment is the bottom line when it comes to use of HT in any form. For most female migraineurs, going through menopause without additional hormones is likely to be the most beneficial course for their headaches. If they need HT for other reasons, the above recommendations may be considered. It's worth keeping in mind, though, that standard nonhormonal preventives for migraine help a significant percentage of patients, and only rarely worsen headaches. Hormones, on the other hand, may make some women better, but worsen significant numbers as well. The odds favor the standard preventives, and when HT worsens migraines but is otherwise deemed necessary, adding a preventive may be the most rational route to take.

## Summary and Conclusions

Hormonal changes in the perimenopausal and menopausal years can be potent triggers for migraine. There are wide individual differences, but migraine tends to improve into old age. How much of this is related to hormone change is debatable. With increasing age comes increasing concern about stroke risk and the safety of hormone use, but little is known about how migraine factors into this equation.

In the menopausal woman, treatment of migraine should initially proceed along standard migraine abortive and preventive protocols. Most medications used in younger patients, including the triptans, con-

tinued to be useful in healthy women in this age group. HT may cause increased difficulty with migraines in the hormonally sensitive woman, and should be used cautiously. Control of migraine via hormonal manipulation is difficult at best, and there is no role for oophorectomy with or without hysterectomy for migraine treatment. ■

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*Dr. Geweke reports no potential conflicts related to the content of this article.*

*This article includes discussion of off-label use of medication.*

*Submitted: August 1, 2006. Accepted: April 15, 2007.*

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