Menstrual Migraine: The Role of Hormonal Management

Susan Hutchinson, MD

CONTINUING MEDICAL EDUCATION

GOAL

To discuss the pathophysiology, diagnosis, and treatment of hormonally associated migraine throughout a woman's reproductive cycle.

OBJECTIVES

1. To differentiate between pure menstrual migraine and menstrually related migraine in women.
2. To describe the various forms of hormonal therapy available to treat menstrual migraine in women.
3. To project the course and management of menstrual migraine in postmenopausal women.

ACCREDITATION

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This activity has been peer reviewed and approved by Brian Cohen, MD, professor of clinical OB/GYN, Albert Einstein College of Medicine. Review date: February 2007. It is designed for OB/GYNs, primary care physicians, and nurse practitioners.

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Dr Hutchinson reports that she has received grant/research support from GlaxoSmithKline; is consultant to Allergan Pharmaceuticals Inc; Endo Pharmaceuticals; Forest Pharmaceuticals, Inc; GlaxoSmithKline; and Ortho-McNeil, Inc; and is on the speakers' bureaus of Endo Pharmaceuticals; Forest Pharmaceuticals, Inc; GlaxoSmithKline; Merck & Co, Inc; Pfizer Inc; and Ortho-McNeil, Inc. All disclosures reported by the author present no conflict of interest to this article. Dr Hutchinson reports that this article discusses the unlabeled use of hormonal preparations, including contraceptives, for prevention of menstrual migraine. Dr Cohen reports no conflict of interest.

Menstrual migraine management often includes hormonal strategies. But what is the basis for this approach, and do hormonal therapies actually reduce the occurrence and/or symptoms of migraine?

The annual prevalence of migraine in the US female population older than age 12 years is 18%, rising to 26% to 27% in women aged 30 to 49 years (Figure 1). Among female migraineurs, 60% report worsening of headaches around the time of menses[1]; a study of 21 women with chronic migraine found that frequency, severity, and disability were all greater in the first 6 days after the onset of menses.[2] In addition, a greater degree of disability is associated with menstrually related migraine.[3] A trial involving more than 1,000 women showed that those with menstrual migraine had significant disability involving social activity (84%), household chores (81%), and work (45%).[4]

PATHOPHYSIOLOGY

According to criteria from the International Headache Society, there are two types of menstrual migraine.[5] "Pure" menstrual migraine is defined as migraine without aura occurring in at least 66% of menstrual cycles and exclusively

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during the 5-day perimenstrual period from day -2 through day +3 (day 1 = the first day of flow). This type of headache—previously termed "true" menstrual migraine—occurs in 14% of female migraineurs.[6] More common is the menstrually related migraine, a migraine without aura occurring both perimenstrually in 66% of cycles, but also at other times of the month; this was previously termed "menstrually associated migraine." Menstrually related migraine accounts for 46% of female migraineurs.[6]

A landmark study of the hormonal connection in menstrual migraine compared the effects of estradiol versus progesterone given late in the luteal phase.[7] Progesterone delayed the onset of bleeding but not migraine, whereas estradiol delayed the onset of migraine but not bleeding (Figure 2). It was therefore hypothesized that the perimenstrual drop in estrogen was the trigger for menstrual migraine.

Decreased levels of estradiol, occurring from the end of the luteal phase through menses, are associated with a reduction in peripheral serotonin levels.[8] This in turn initiates a cascade of events involving activation of the dorsal raphe nucleus and locus ceruleus, dilation of intracranial extracerebral blood vessels, and activation of the trigeminal nucleus caudalis.[8] In addition, decreased levels of estradiol are associated with an increase in monoamine oxidase levels in the brain, making the cerebral blood vessels more susceptible to neurochemicals associated with migraine—eg, calcitonin gene-related peptide, substance P, prolactin, norepinephrine, and serotonin. Finally, falling estrogen levels reduce endogenous endorphin activity, raising sensitivity to pain.[9] This migraine cascade appears to occur only when serum estradiol levels fall below 45 to 50 pg/mL.[10]

Some women report midcycle migraines, but this has not been confirmed in any epidemiologic studies. One theory is that because the estrogen peak at ovulation is brief, the immediate postovulatory decrease is not sufficient to precipitate a full migraine attack[11]; this would explain why midcycle migraines are less frequent than perimenstrual migraines.

HORMONAL THERAPIES

Given this research, increasing the estradiol level during the late luteal and menstrual period would seem to be a reasonable approach to preventing menstrual migraine. The most common strategy is to maintain a steady estradiol level throughout the cycle. This can be accomplished using a continuous-dose regimen of oral contraceptives (OCs)—eg, a monophasic pill containing ≤ 0.035 mg of estrogen[12,13]; the incidence of headache complaints has been reported at 9.7% in women using extended-regimen OCs versus 17.3% in those using standard-regimen OCs.[14] The current trend is to continue active OC use until significant bleeding, cramping, or bloating occurs. Another option is a continuous regimen using the transdermal contraceptive patch, eliminating the patch-free week. However, caution is advised because patch users may be exposed to 60% more estrogen than women using a 0.035-mg OC[15]; in addition, the level of estradiol provided by the patch may not remain steady, and the peak value may be 25% lower than that experienced with OCs.[15] The contraceptive vaginal ring can also be used continuously, replacing the ring every 4 weeks.

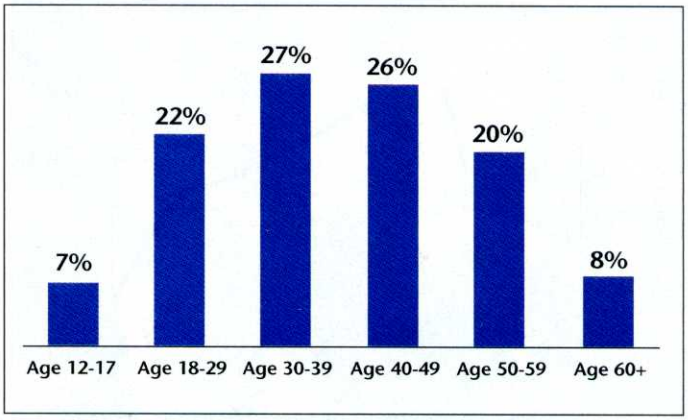


FIGURE 1. Migraine prevalence peaks among reproductive-aged women.[3]

Reprinted with permission from Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: Data from the American Migraine Study II. *Headache.* 2001;41(7):646–657.

. . . falling estrogen levels reduce endogenous endorphin activity, raising sensitivity to pain.

The most common side effect of continuous, estrogen-based contraception is breakthrough bleeding during the first 3 months. During the infrequent pill-free breaks from OCs, a 0.1-mg estradiol patch may help prevent migraine.

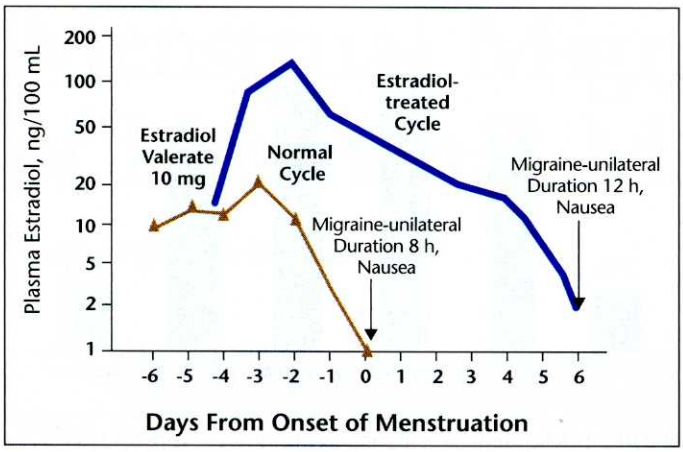


FIGURE 2. Effect of estradiol therapy on menstrual migraine.[7]

Reprinted with permission from Somerville BW. The role of estradiol withdrawal in the etiology of menstrual migraine. *Neurology.* 1972;22:355-362.

It has been found that a 0.1-mg transdermal estradiol patch applied perimenstrually can be effective in preventing menstrual migraine, whereas a 0.05-mg patch was ineffective.[16] Although this study did not include OC users, the data suggest that it may be necessary to maintain a serum estradiol level > 45 pg/mL to prevent menstrual migraine, as the 0.1-mg patch produces serum estradiol levels of 45 to 75 pg/mL.[10] Alternatively, oral estrogen can be given during the OC- or patch-free week; 0.9 mg/d of conjugated equine estrogens (CEEs) during this interval was shown to yield a 77% reduction in the number of headache days per cycle.[17]

Some women with menstrual migraine cannot use estrogen, either because it aggravates their migraines or it is contraindicated due to factors such as migraine with aura, cigarette smoking, or certain medical conditions. In these cases, contraceptive choices include progestin-only OCs, depot medroxyprogesterone acetate, intrauterine devices, and leuprolide (ie, medical oophorectomy).

Leuprolide use has been shown to alleviate menstrual migraine, producing a > 50% improvement in 17 out of 29 severely affected women.[18] In addition, five women with pure menstrual migraine experienced a 74% decrease in the headache index compared with baseline.[19] These results suggest a beneficial effect from hormonal therapies that minimize fluctuations in ovarian hormones.

Female migraineurs who do not desire contraception can also utilize hormonal therapies in the perimenstrual period, including transdermal estradiol (0.1-mg patch)[16] or oral estrogen (0.9 mg/d of CEEs).[17] In women not using contraception, 0.025-mg and 0.05-mg estradiol patches did not prevent menstrual migraine when used perimenstrually.[16] Given the available research, the transdermal patch would seem preferable in this setting, as there are no data on perimenstrual oral estrogen in women not using OCs.[16]

MENOPAUSE

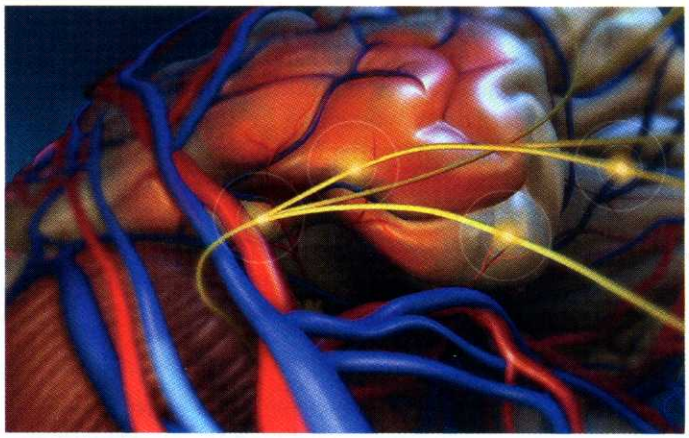
Female migraineurs who experience natural menopause have a 66% chance of improving with regard to headaches, whereas 66% of those undergoing surgical menopause report an exacerbation of migraines.[20] The effect of postmenopausal hormone therapy (HT) on migraine is unpredictable, as it can cause headaches to improve, worsen, or remain unchanged.[21] The dosage and route of administration of estrogen may be a factor. For example, headaches have been shown to worsen in women receiving oral CEEs plus medroxyprogesterone acetate, but no such exacerbation occurred in those using a 0.05-mg transdermal estradiol patch and medroxyprogesterone acetate.[22] There was a modest preventive benefit for migraine headache in 21 women who used a 0.1-mg transdermal estradiol patch following medical menopause induced by gonadotropin-releasing hormone agonists[23]; a subsequent study randomized the same patients to either 0.05- or 0.1-mg transdermal estradiol treatment, but only the 0.1-mg patch prevented migraine—suggesting that a critical range of estradiol is needed for migraine prophylaxis.[24]

CONTRAINDICATIONS

The World Health Organization considers estrogen-containing contraception to be contraindicated in women who have migraine with aura, as the overall risk of ischemic stroke is increased in migraine with aura in all age groups (increased 2.3; confidence interval = 1.6-3.2). The absolute risk for stroke is 8 per 100,000 nonmigraine population, 17 per 100,000 any-migraine individual, and 52 per 100,000 in individuals with migraine with aura.[25,26] Additionally, women who smoke or have a clotting disorder, a history of deep vein thrombosis (DVT), or risk factors for DVT/

stroke are not considered good candidates for estrogen-containing contraception.

Migraine is not a contraindication for postmenopausal HT. Migraine does not appear to be a risk factor for stroke in women older than age 45 years.[27] The Women's Health Initiative reported that oral CEEs administered daily with a progestin increase the risk of stroke (hazard ratio [HR] = 1.41) compared with estrogen alone (HR = 1.39).[28] Contraindications for HT include breast cancer or other estrogen-dependent cancer, undiagnosed vaginal bleeding, thrombophlebitis, or risk factors for thromboembolism.



RECOMMENDATIONS

A practical approach to the female migraineur should:

- Establish whether there is a hormonal relationship to headache; this is best established using a headache diary
- Review the patient's history regarding hormonal medications and headache, including current hormonal treatments and if hormone use aggravates headache
- Identify any contraindications to estrogen treatment—eg, smoking, cardiac risk, migraine with aura
- Design a strategy to maintain a steady serum estradiol level, preferably > 45 pg/mL, to prevent menstrual migraine

Coding for Menstrual Migraine

Philip N. Eskew, Jr, MD

In the *International Classification of Diseases, Ninth Revision, Clinical Modification*, the code for the classical, common, and other variants/forms of migraine is **346**. However, as described in this article, when the patient's history suggests a hormonal connection, the code **625.4** is applied:

- **625**—Pain and other symptoms associated with female genital organs
- **625.4**—Premenstrual tension syndromes; menstrual, migraine

This is the only code that applies when migraine is related to either the perimenstrual period or to the menstrual cycle.

Evaluation and management services codes are used to document the activities involved in diagnosing this condition. With appropriate documentation, the patient should undergo comprehensive history-taking and physical examination, comprising a medical decision-making process of moderate-to-high complexity. This is described by one of the following categories:

- **99204** or **99205**—New patient
- **99214** or **99215**—Established patient
- **99244** or **99245**—Outpatient consultation
- **99254** or **99255**—Inpatient consultation

If the patient mentions her migraine symptoms during an annual preventive visit, she should be advised to keep a detailed diary during her next menstrual cycle and return for another office visit to discuss and diagnose the condition. For this follow-up visit, time is the determining factor in choosing the appropriate code for evaluation and management services for an established patient:

- **99212**—10 min
- **99213**—15 min
- **99214**—25 min
- **99215**—40 min

Times are averages, and any discussion during this visit must be documented.

Philip N. Eskew, Jr, MD, is past member, *Current Procedural Terminology (CPT)* Editorial Panel; past member, *CPT* Advisory Committee; past chair, American College of Obstetricians and Gynecologists Coding and Nomenclature Committee; and instructor, *CPT* coding and documentation courses and seminars.

- Give the patient realistic expectations, explaining that hormonal therapy does not always reduce migraines and that she should report any worsening in headache pattern
- Provide the patient with a prescription medication (eg, triptan) for breakthrough menstrual migraine
- Include a return visit in 1 to 3 months to review the patient's headache diary for exacerbation or onset of aura.

CONCLUSION

There are still insufficient data to form definitive conclusions regarding hormonal treatment of migraine. However, attempting to maintain a steady estradiol level in the female migraineur with documented menstrually related migraine is a reasonable treatment option. Clearly, more research remains to be done.

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AMA/CME TEST 280

Menstrual Migraine: The Role of Hormonal Management

This activity has been planned and produced in accordance with ACCME Essentials. The estimated time to complete this activity is 1 hour.

Instructions: Read the article beginning on page 54 and select the best answer for each of the following questions. Test form and mailing instructions are on the next page.

1. **Approximately what percentage of female migraineurs note some association between migraine and menses?**
   a. 25%
   b. 40%
   c. 60%
   d. 80%

2. **Approximately 14% of female migraineurs experience:**
   a. migraine with aura.
   b. pure menstrual migraine.
   c. menstrually related migraine.
   d. both pure and menstrually related migraine.

3. **Menstrually related migraine occurs:**
   a. in almost 50% of female migraineurs.
   b. either just before or just after menses.
   c. only in women younger than age 40 years.
   d. primarily in nulliparous women.

4. **Menstrual migraine has been associated with decreased levels of all of the following except:**
   a. progesterone.
   b. estradiol.
   c. serotonin.
   d. endorphins.

5. **The preferred therapy for menstrual migraine is ≤ 0.035 mg/d of estrogen in the form of:**
   a. standard-regimen oral contraceptives (OCs).
   b. continuous-regimen OCs.
   c. an estrogen-containing vaginal ring for 3 wk/mo.
   d. a transdermal contraceptive patch.

6. **During the first 3 months of continuous-regimen OC use, the most common side effect is:**
   a. nonmigrainous headache.
   b. weight gain.
   c. acne.
   d. breakthrough bleeding.

7. **In women who cannot or do not wish to use estrogen, a > 50% improvement in menstrual migraine has been reported for:**
   a. progestin-only OCs.
   b. the progestin-releasing intrauterine device.
   c. leuprolide.
   d. depot medroxyprogesterone acetate.

8. **Improvement in menstrual migraine is likely in 66% of female migraineurs who:**
   a. experience natural menopause.
   b. experience surgical menopause.
   c. experience premature ovarian failure.
   d. use postmenopausal hormone therapy.

9. **Estrogen-containing OCs are contraindicated in female migraineurs who:**
   a. have nonmenstrual migraine.
   b. have migraine with aura.
   c. are older than age 40 years.
   d. have more than one migraine per week.

10. **Women with menstrual migraine who are using estrogen therapy:**
    a. also require a prescription for rescue medication.
    b. do not require a prescription for rescue medication.
    c. should also use triptans for migraine prophylaxis.
    d. should not receive estrogen supplementation during the pill-free interval.

Menstrual Migraine: The Role of Hormonal Management

Susan Hutchinson, MD

(Termination date: March 31, 2008. No credit will be given after that date.)

Record your answers here by circling the appropriate letter:

1. a b c d
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The Female Patient®

PATIENT HANDOUT

What You Should Know About Migraines

Calling a migraine "just a headache" is like calling a hurricane "just a sprinkle." Severe head pain is only one symptom of migraine, and the misery of migraine can take you out of action for hours or even days.

Fortunately, migraine management is improving, and while there is still no cure, now more can be done to reduce migraine frequency and severity, and sometimes even prevent them before they start.

How to Tell if Your Headache Is a Migraine

If you have migraines or think you might, you are certainly not alone. More than 29 million Americans suffer from migraine, and about three of every four of them are women. Recurring, severe headache is the central symptom of migraine, but migraine often has other symptoms and characteristics that distinguish the condition from other kinds of headaches. Some of the signs and symptoms of migraine include:

- Intense pulsing or throbbing pain, usually on just one side of the head
- Attacks that last between 4 hours to 3 days, and sometimes longer
- Attacks that are worsened by physical activity
- Nausea or vomiting
- Severe sensitivity to light, noise, or odors
- Changes in vision, including blurring and blind spots
- Stuffed-up nose
- Tender scalp
- Stiff or tender neck
- Lightheadedness
- Feeling cold or sweaty.

In addition, about one of every five people with migraine also experience auras—warning symptoms that occur about 20 minutes to an hour before the start of the migraine itself.

Aura signs and symptoms can include:

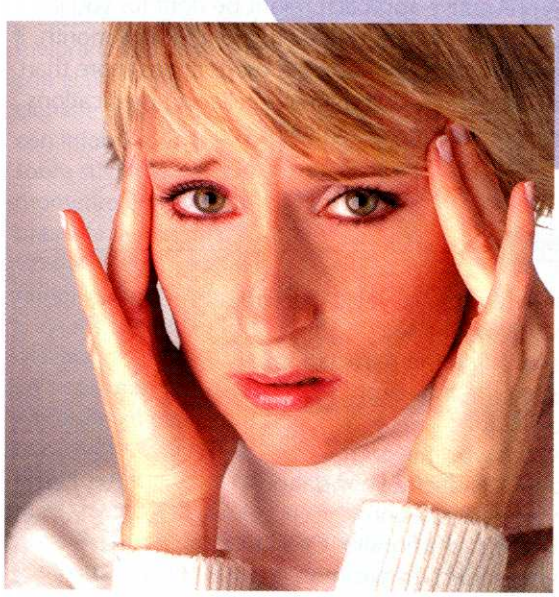
- Seeing flashing lights or zigzag or wavy lines
- Feeling tingling, prickly, or "pins-and-needles" sensations in one arm or leg
- Having difficulty speaking or a feeling of weakness.

Whether or not they experience aura, some people have other symptoms that let them know a migraine might be coming on. These "prodrome" symptoms, which generally occur several hours or a day before the migraine, can include:

- Feeling thirstier than usual
- Feeling drowsy
- A desire for sweet foods
- Feeling "up" or very energetic
- Feeling depressed or irritable.

Doctors can often diagnose migraine based on these symptom patterns alone. That is why it's so important for women who think that they might have migraines to keep careful track of their symptoms over time. It can help to keep a migraine diary (a record of when your migraines occur and what you were doing at the time, where

...about one of every five people with migraine also experience auras—warning symptoms that occur about 20 minutes to an hour before the start of the migraine itself.



in your menstrual cycle you were, and what seemed to make them better or worse) so that you can be very clear with your doctor about what's happening and when. A migraine diary can also help you keep track of what might be triggering your migraines. Sometimes doctors will order tests, such as brain scans or blood tests, to make sure that there is no other cause for the symptoms. If none is found and the symptom patterns fit, then the picture points to migraine. (No test is currently available to confirm a migraine diagnosis.)

What Makes Migraine Happen

The causes of migraine are not yet completely understood. Research suggests, though, that they are related to changes in levels of brain chemical messengers, including serotonin. When serotonin levels are too low, blood vessels on the brain's surface widen. These expanded blood vessels can press on nearby nerves, which causes pain. Just why these changes happen is not clear. But they do appear to be linked to genetics, since as many as eight of 10 migraine sufferers have a family history of the condition.

Managing Migraine

There are two main ways to approach migraine management: Treat attacks once they start (acute management), or try to prevent them from happening in the first place (preventive management). Some people combine both strategies. The choice of which approach is best for you depends on how frequent, severe, and disabling your migraines are. A preventive approach might be right for you if you suffer at least two disabling attacks a month, if you use migraine-relieving medications more than twice a week, or if migraine-relieving medications do not work consistently for you.

Acute Management.—Several medications are available that can help to relieve migraines once they start. Nonsteroidal anti-inflammatory drugs such as aspirin or ibuprofen may help relieve milder migraines, but they generally are not effective for more severe attacks. Ergots, like ergotamine (Ergostat) or dihydroergotamine (injection [DHE-45] or nasal spray [Migranal]) are available by prescription and may be helpful for more severe migraines. Triptans, including eletriptan (Relpax), sumatriptan (Imitrex), and zolmitriptan (Zomig), among others, were the first medications developed specifically to treat migraine. These drugs act like serotonin and cause the blood vessels to narrow. All of the acute medications are most effective when taken at the very first signs of an attack.

Preventive Management.—A number of medications can be taken on an ongoing basis for migraine prevention. Examples include amitriptyline (Elavil), propranolol (Inderal), and topiramate (Topamax). These medications usually will not get rid of migraine completely, but they may reduce the frequency and duration of attacks.

You can also help prevent migraines by keeping track of what seems to trigger them or set them off. Everyone has different triggers, but some common ones include:

- Changes in weather or altitude
- Changes in your sleep times and patterns
- Getting your period, or taking oral contraceptives or other hormones
- Skipping meals
- Exerting yourself during physical activity, including sexual activity
- Loud noises, bright lights (including sun glare), or strong odors (including smoke)
- Certain foods or beverages, including processed meats, aged cheeses, caffeine, nuts and peanut butter, and alcohol (especially red wine).

General healthy lifestyle habits can also help with migraine prevention. Try to eat well-balanced meals, get some physical activity every day, get enough sleep, and if you smoke, stop. Taking care of yourself can help you take care of your migraines.

Resources

- The National Women's Health Information Center
  http://www.WomensHealth.gov
- The National Migraine Association
  http://www.migraines.org
- The Mayo Clinic
  http://www.mayoclinic.com
- The National Headache Foundation
  http://www.headaches.org
- National Menstrual Migraine Coalition
  http://www.headachesinwomen.org

This Patient Handout was prepared by Nancy Morgan Andreola, RN, using materials from Hutchinson S. Menstrual migraine: The role of hormonal management. The Female Patient. *2007;32(3):54-58; the National Women's Health Information Center Web site; the National Institute of Neurological Disorders and Stroke Web site; the Mayo Clinic Web site; the American Academy of Family Physicians Web site; and the National Headache Foundation Web site.*