Women's Issues and Migraine

BY SUSAN HUTCHINSON, MD

How common is menstrual migraine? Approximately 60% of female migraineurs have perimenstrual exacerbation of their migraine headaches.

Introduction

WOMEN SUFFER FROM MIGRAINE HEADACHE AT A 3:1 RATIO TO MEN. This ratio is established at puberty (before puberty, boys have a slightly higher prevalence) and continues until menopause (1). The major change occurring in women at puberty is the beginning of ovarian cycling of both estrogen and progesterone. At menopause, women lose this cyclical endogenous hormonal fluctuation. Therefore, it makes sense to look at the changing hormonal milieu in women migraine patients and see how such changes can affect migraine. By establishing patterns of headache with hormonal changes, we as health care providers can be in a much better position to help our women patients with migraine.

There is an often-quoted annual prevalence of 28 million migraine sufferers in the U.S. for men and women combined. The 3:1 female-to-male ratio translates to 21 million women and 7 million men. This would equate to 18% annual prevalence for women and 6% for men (2). However, the prevalence in women is not consistent in all age groups. Women between the ages of 30 and 49 have the highest prevalence. Specifically, population-based studies reflect a 27% migraine prevalence in women ages 30-39 and a 26% migraine prevalence in women ages 40-49 (2). A study looking at the prevalence and characteristics of migraine in a population-based cohort reported that migraine has affected up to 40.9% of women by the conclusion of the reproductive years (3).This article will explore some of the issues specific to the female migraine patient. Specific migraine headache treatment will be discussed, taking into account issues such as hormonal changes. It is hoped that readers of this article will be better prepared to manage women patients who suffer with migraine.

Physiology of the Menstrual Cycle

THE NORMAL MENSTRUAL CYCLE IS DEFINED as beginning on the first day of menses; this is considered "Day 1" of the cycle. The cycle ends the day before the next onset of menses and traditionally lasts about 28 days. The cycle can be divided into two phases: the follicular and the luteal phase. During the follicular phase, there is an increasing level of estradiol in preparation for ovulation, which coincides with follicular maturation. At ovulation (mid-cycle), serum estradiol reaches a peak and then slightly decreases during the early luteal phase, the second phase of the menstrual cycle. As the luteal phase

(opposite)
Title: Yellow Migraine (No Escape)
Artist: Mighty Eee
Migraine Masterpieces art used with permission of the National Headache Foundation.
For more information on headache causes and treatments visit www.headaches.org

continues, the estradiol level steadily rises and then drops precipitously at the time of menses. This drop in estradiol at the end of the luteal phase is associated with a time of increased migraine in many women migraineurs.

Serum progesterone levels are low until early in the luteal phase, peak during the mid-luteal phase, and then drop at the time of menses. The drop in both estradiol and progesterone late in the luteal phase initiates the menses, unless pregnancy has occurred. Estrogen and progesterone are only part of the physiology of the menstrual cycle. This regulation involves the hypothalamus and pituitary along with a host of neurohormonal agents such as LH (luteinizing hormone), FSH (follicle-stimulating hormone), GnRH (gonadotropin-releasing hormone), prostaglandin, norepinephrine, and serotonin. An in-depth discussion of the relationship of ovarian hormones with various neurotransmitter systems is beyond the scope of this article. For those wanting more information, there is an excellent review article in Headache (2006) on this subject (4).

Hormones and Migraine

A LANDMARK STUDY BY SOMMERVILLE IN 1972 offered support for a specific hormonal influence on migraine (5). He compared the effect on migraine of giving estradiol vs. progesterone late in the luteal phase of women migraine patients who had a menstrual association with their migraines. When progesterone was given, it delayed the onset of bleeding but not migraine; when estrogen was given, it delayed the onset of migraine but not bleeding. In these women, the estrogen injection did not prevent the menstrual migraine completely—it simply delayed the onset until the estradiol level from the injection dropped to a low enough level to trigger the migraine. Sommerville postulated that it was the drop in estrogen and not progesterone that triggered, in part, the menstrual migraine. Follow-up research studies have shown this same pattern of dropping estradiol levels causing a susceptibility to migraine. Therefore, treatment strategies for women who suffer menstrual migraine now often include hormonal therapies which prevent or lessen drops in estradiol.

In addition to the late luteal drop in estradiol, there are other situations in which a woman's estradiol level drops. These situations would include post-partum, surgical menopause, and the "placebo" week of cyclical contraception. It is prudent to consider all these times of hormonal change as times of vulnerability for increased migraine in women.

How common is menstrual migraine? Approximately 60% of female migraineurs have perimenstrual exacerbation of their migraine headaches; of those, the majority experience migraines at other times of the month, as well, from other triggers (6). This group of women would be considered to have menstrual-related migraine. A smaller group, about 7-14% of the total female migraine population, have pure menstrual migraine, ie, migraine experienced only with menses (6). Menstrual migraine is defined by the International Headache Society as migraine without aura that occurs between days -2 through +3 of the menstrual cycle in at least 2 out of 3 cycles.

Clinical Presentation of Menstrual Migraine

MANY WOMEN REPORT THEIR MENSTRUAL MIGRAINE as more severe, more prolonged, and less responsive to treatment than their other migraines. Studies indicate that menstrually associated migraines respond as well as non-menstrually associated migraines to triptan therapy (7). However, in clinical practice, many women disagree with this based on their own experience. An observational study of 155 women with menstrually related migraine indicated that menstrual migraines were more likely to be severe (8). Another study showed a longer duration of migraine during the perimenstrual period than other migraines and resulted in more work-related disability. Significantly, this same study showed a lower 2-hour response rate after treatment (13.5% pain free) for menstrual migraine compared to non-menstrual migraine treatment (32.9% pain free) (9). A higher rate of headache recurrence after sumatriptan has been observed in menstrual migraine compared to non-menstrual migraine treatment (10). The continued drop in estrogen that is occurring could help explain the more prolonged duration of menstrual migraine — ie, the triptan may help relieve the acute headache, supporting studies that show good initial response. However, because the trigger (the low estradiol) is still present, there is a high rate of recurrence. Therefore, trying to maintain an even estradiol level may be an important treatment strategy. Calhoun reported improved migraine management when using various strategies to maintain even estradiol levels (11).

Treatment of Migraine in Women

HORMONAL AND NONHORMONAL STRATEGIES will be discussed in this section. Hormonal strategies can be useful in women with migraines that occur in conjunction with times of hormonal change such as menses, post-partum, the placebo week of the pill, and surgical menopause. Such strategies will be discussed in this first part of the treatment section.

In younger and middle-age women with menstrual migraine, continuous contraception can be a useful preventive treatment strategy. This is best done with a "low-dose" monophasic oral contraceptive pill or the vaginal contraceptive ring. In this treatment approach, the patient has the estrogen/progesterone contraceptive dose delivered every day into her blood system, thereby maintaining a more even estradiol level. It is now wellaccepted in the OB-GYN community that women do not have to cycle off and have a withdrawal bleed every 4 weeks. In fact, there is an extended-release oral contraceptive that has been FDA-approved and widely used—the name brand is Seasonale®*, a 35-mcg estrogen-containing contraceptive. With this formulation, the pill pack has 12 weeks of active contraception and then a placebo week for week 13. Therefore, the woman only cycles off every 3 months. Such

an approach can be applied to any monophasic form of contraception, meaning that the estrogen and progesterone amounts are the same in all the active pills. For the vaginal contraceptive ring, it is simply left in for 4 weeks instead of 3; then a new one is inserted at the end of 4 weeks. This treatment approach is generally safe for the majority of women with menstrual migraine. By definition, menstrual migraine is migraine without aura.

**Seasonale is a registered trademark of Barr Laboratories, Inc.*

Estrogen-containing contraception is contraindicated in women who experience migraine with aura, according to WHO (the World Health Organization) and ACOG (the American College of Obstetricians and Gynecologists). This is due to the higher risk of stroke in women who experience aura as part of their migraine, and the estrogen would further increase that risk. Fortunately, the majority of migraines are migraine without aura; therefore, for most women, estrogen-containing contraception is safe and can be a very useful treatment option in preventing menstrual migraine.

For women who don't need or want contraception, then supplementation with an estradiol patch during the perimenstrual time can be a useful preventive approach. Studies indicate greater efficacy if the 0.1 mg estradiol patch is used rather than lower dosages such as 0.05 or 0.025 mg estradiol-containing patches (12). The estradiol patch can also be used when cycling off contraceptive to help prevent the drop in estradiol; the woman will still bleed since there is no progesterone in the patch. The goal is to prevent menstrual migraine by lessening the drop in estrogen, whether that drop is endogenous (from a woman's own ovaries) or exogenous (from hormonal supplementation such as oral contraceptives). In my clinical experience, I find it helpful to try hormonal strategies in my women patients with migraine for two cycles. I have them track the effect in their headache diaries, and then follow up with an office visit for a careful assessment of whether hormonal strategies are helping.

Nonhormonal strategies in female migraine patients include traditional migraine treatments such as the triptans and the NSAIDs (nonsteroidal anti-inflammatory drugs) for acute treatment of migraine. Often, the combination of a triptan with an NSAID can be helpful and may offer advantages over either agent alone. The severity, duration, and associated symptoms of the migraine attack help dictate which triptan and which formulation may be best for that patient. Women who experience slowlyevolving menstrual migraine may benefit from the longer-acting triptans, such as frovatriptan and naratriptan. Those who wake up with a severe migraine, accompanied by nausea and/or vomiting, may benefit from one of the non-oral

formulations such as the sumatriptan injection or the nasal formulations of sumatriptan and zolmitriptan. Often a woman can experience different manifestations of migraine and may need more than one treatment approach.

In treating women with migraine, the clinician needs to be aware of specific populations that require a different approach than what has been discussed thus far. Specifically, women who are pregnant or breast-feeding have more limited treatment options. These two groups of migraine patients will be discussed in this final section. Lastly, the needs of the mature aging menopausal woman will be addressed in regards to treatment of her migraines and hormonal needs.

Pregnancy and Migraine

PREGNANCY IS CHARACTERIZED BY STEADILY RISING LEVELS of estradiol in the first trimester followed by sustained high levels during the second and third trimesters. The majority of women patients with migraine experience a cessation or marked improvement in their migraine headaches during pregnancy. The improvement is considered attributable to the sustained, more "even" levels of estradiol. This improvement in migraine pattern during pregnancy, despite high levels of estradiol, supports the well-accepted belief that estrogen itself is not the trigger for migraine, but, rather, changes or drop in estrogen levels.

Treatment of migraine headache during pregnancy often involves nonpharmacologic treatment such as biofeedback, acupuncture, physical therapy, hot/cold packs, massage therapy, relaxation exercises, and good health habits. When medication is needed, Category B drugs such as acetaminophen and metoclopramide may be used. There is debate over the use of NSAIDs during pregnancy. Most OB-GYNs choose not to prescribe them at all, and some will prescribe them only up to 32 weeks of pregnancy (to avoid premature closure of the patent ductus arteriosus). All seven triptan drugs are Category C for pregnancy, meaning that the risk needs to be weighed against the benefit of using the drug. All the triptan manufacturers have Pregnancy Registries and, so far, all the data is reassuring. Sumatriptan is the largest pregnancy registry and has 651 cases as of April 2006. There does not appear to be any increased risk of teratogenicity or of increased spontaneous miscarriage; however, the numbers are too low to draw definitive conclusions (13).

It is important to report pregnancy exposures to the respective registries. The phone numbers are as follows:

1. Astra-Zeneca (zolmitiptan)	302-886-1652
2. Endo (frovatriptan)	800-462-3636
3. GlaxoSmithKline (sumatriptan/naratriptan)	800-336-2176
4. Merck (rizatriptan)	800-986-8999
5. OrthoMcNeil (almotriptan)	800-682-6532
6. Pfizer (eletriptan)	800-438-1985

Breast-feeding and Migraine

WHEN A PREGNANT WOMAN DELIVERS, her estrogen level falls precipitously at the time of delivery. For the migraine post-partum patient, this sudden change in estrogen can hallmark a return of her migraines from which she may have had a reprieve during pregnancy. Anticipating the post-partum return of migraines and having a treatment plan that will allow the patient to breast-feed is advised. Fortunately, the breast-feeding migraine patient has more options than she did during pregnancy. Most OB-GYNs are comfortable with both prescription and OTC NSAIDs as well as acetaminophen during breast-feeding. The triptan drugs are all in a "use with caution" category as established by AAP (American Academy of Pediatrics) with the exception of sumatriptan, which is now considered "compatible with breast-feeding" by the AAP (16). Therefore, it is no longer considered necessary to pump and discard the breast milk after use of sumatriptan. With the other triptans, the common practice is to pump and discard the breast milk for 6-8 hours after the triptan is taken.

For more severe migraines or when rescue is needed, the following drugs are considered compatible with breast-feeding:

1. Butorphanol
2. Codeine
3. Meperidine.

Menopause and Migraine

MENOPAUSE IS COMMONLY DEFINED AS NO MENSES for one year or an elevated FSH coupled with a low estradiol that fits in the menopause ranges for that particular laboratory. This stage in a woman's life reflects the cessation of ovarian cycling of estrogen and progesterone and for many women, their migraines go away or markedly improve. About two thirds of women who go through spontaneous menopause will experience marked improvement of their migraines. Only about one third of women who go through surgical menopause will notice improvement in their migraines (17). Therefore, women with migraine fare better with allowing a gradual lessening of ovarian function. The dramatic drop in hormone levels with surgical menopause (ovaries removed) can aggravate the migraine control.

Perimenopause is characterized as a time of great change and fluctuations in hormonal levels and as such, can represent a very vulnerable time for women and their headache control. Typically, this lasts over a 4-year period preceding menopause and begins around the age of 47 for many women. In addition to increased migraines, vasomotor symptoms such as hot flashes, night sweats, and insomnia are often present. Mood swings can be pronounced and this group of women can be very challenging for the practicing clinician. Preventive strategies can be very important and can vary from the typical migraine preventives to hormonal therapy.

Can female migraine patients safely take hormones for vasomotor symptoms? In most cases, hormones can safely be taken

by the majority of women migraineurs. Patients and clinicians may be concerned that HT (hormone therapy) will aggravate their migraines. Evidence is now accumulating that the transdermal estradiol patch and topical estrogen may be less likely to aggravate migraines than oral formulations (18). If an oral formulation is desired, then starting low and titrating up to a therapeutic response is recommended. Sometimes changing from a conjugated estrogen to a pure estradiol, to synthetic ethinyl estradiol, or to a pure estrone can lessen hormone-related headache (19).

Summary

HORMONES PLAY A SIGNIFICANT ROLE IN 60% TO70% of women migraineurs who report exacerbation of migraine headaches perimenstrually. Other times of hormonal change include pregnancy, post-partum, perimenopause, and menopause. These times of hormonal change can markedly affect migraine headaches, and attention to a woman's hormonal milieu can help in the management of her migraine symptoms. Contraception and hormonal therapy are not contraindicated in the majority of women with migraine and, in fact, trying to maintain an even estradiol level can often be an important treatment strategy. Understanding that hormones can greatly influence migraine headaches can help both the healthcare provider and the patient achieve optimal headache management.

REFERENCES

1. Stewart WF, Lipton RB, Celanto DD, et al. Prevalence of migraine headache in the United States, relation to age, income, race, and other sociodemographic factors. JAMA. 1992;267:64-69.
2. Lipton RB, Stewart WF, Diamond S, et al. Prevalence and burden of migraine in the United States:data from the American Migraine Study II. Headache. 2001;41:646-657.
3. Launer IJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort. Neurology. 1990;53:537-542.
4. Martin VT, Behbehani M. Ovarian Hormones and Migraine Headache: Understanding Mechanisms and Pathogenesis-Part I. Headache. 2006;46:3-23.
5. Sommerville BW. The role of estrogen withdrawal in the etiology of menstrual migraine. Neurology. 1972;22:355-365.
6. Edelson RN. Menstrual Migraine and other hormonal aspects of migraine. Headache. 1985;25:376-379.
7. Massiou H. Is menstrually associated migraine difficult to treat? Cephalalgia. 1999;19 (Suppl 24):S13-S18.
8. MacGregor EA, Hackshaw A. Prevalence of migraine on each day of the natural menstrual cycle. Neurology. 2004;63:351-353.
9. Granella F, Sances G, Allais G, et al. Characteristics of menstrual and nonmenstrual attacks in women with menstrually related migraine referred to headache centres. Cephalalgia. 2004;24:707-716.
10. Visser WH, Jaspers NMWH, deVriend RHM, et al. Risk factors for headache recurrence after sumatriptan:a study in 366 migraine patients. Cephalalgia. 1996;16:246-249.
11. Calhoun A. Adjusting estradiol concentrations reduces headache frequency and severity in female migraineurs. Cephalalgia. 2001;21:448-449.
12. Pradalier A, Vincent D, Beaulieu P, Baudesson G, Launay J-M. Correlation between oestradiol plasma level and therapeutic effect on menstrual migraine. Proceedings of the Tenth Migraine Trust International Symposium. 1994:129-132. [Au: Please provide location of 1994 symposium.]
13. Sumatriptan Pregnancy Registry Interim Report, 1 January 1996 through 30 April 2006. Data on file with GlaxoSmithKline Pharmaceutical.
14. Silberstein SD. Migraine and pregnancy. Neurol Clin. 2004;22:727-756.
15. Martin SR, Foley MR. Approach to the pregnant patient with headache. Clin Obstet Gynecol. 2005;48:2-11.
16. American Academy of Pediatric Committee on Drugs. Transfer of drugs and other chemicals into human milk. Pediatrics. 2001;108:776-781.
17. Neri et al. Maturitas. 1993;17:31-37.
18. Nappi RE, Cagnacci A, Granella F, et al. Course of primary headaches during hormone replacement therapy. Maturitas. 2001;38:157-163.
19. Silberstein S, Lipton R, Goadsby P. Migraine: Ddiagnosis and treatment. In: Headache in Clinical Practice. 2nd edition. London: Martin Dunitz Ltd; 2002: 105-7.

SUSAN L. HUTCHINSON, MD, is board certified in Family Practice and has a subspecialty in Headache. She is Director and Founder, Orange County Migraine & Headache Center, Irvine, California. She is also an Associate Clinical Professor in the Department of Family Medicine at UC-Irvine Medical Center. She concentrates on management of migraine and mood disorders with a special interest on the relationship of both conditions to hormones. Dr. Hutchinson is a national speaker on both migraines and depression and was awarded the National Headache Foundation Lectureship Award in February 2003 in recognition of her contribution to headache education. She was selected as a Physician of Excellence by the Orange County Medical Association in January 2007. In recent years, she has co-authored numerous journal articles and chapters on the subject of migraine.