

Women's Issues and Migraine

BY SUSAN HUTCHINSON, MD

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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.

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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.

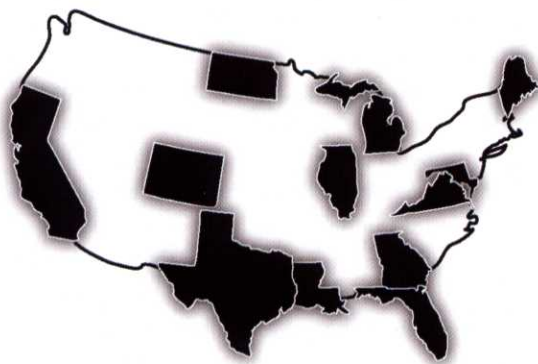
For women who don't need or want contraception, then supplementation with an estradiol patch during the perimenstrual time can be a useful preventive approach. Studies indicate greater efficacy if the 0.1 mg estradiol patch is used rather

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

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