

# THE PATIENT WITH HEADACHES, HORMONES, AND HOT FLASHES

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Although the perimenopausal years are often a frustrating time for women who suffer with headaches, new insights into the effects of fluctuating hormones have provided us with a clearer picture, and the tremendous advances in the understanding of migraine have led to new therapeutic options. Following a logical step-by-step approach, with therapy tailored to the individual, usually leads to success.

## Case History

A married 49-year-old right-handed woman presented with worsening headaches. She experienced her first headache at around age 14 years, and thereafter experienced “regular headaches” throughout her lifetime on an episodic basis. Generally speaking, she used over-the-counter (OTC) medication to treat these headaches, albeit not very successfully. Now, she presents with a 4-year history of increased frequency and severity of headaches, as well as a change in headache pattern.

Previously, her headaches were described as bifrontal and throbbing, with intolerance to light, odor, and aversion to food. In her twenties and thirties, her headaches occurred monthly, and responded reasonably well to the anti-inflammatory she had been prescribed for menstrual cramps. After the birth of her third child, at age 37 years, she underwent a tubal ligation and discontinued her birth control pill. For a few years, her headaches were under fairly good control, and the frequency was reduced.

Over the last 3 to 4 years, however, the headaches became more severe, with intense nausea, irritability, and inability to function. Whereas they used to be once a

month or so with her menstrual cycle, they were now occurring at least five times a month and lasting for 2 to 3 days each time. Her anti-inflammatory medication was no longer effective. She was also beginning to use OTCs more frequently, for dull “tension” headaches, which were coming quite frequently in between her more severe headaches.

Four years ago, her menstrual cycle became irregular, she felt quite irritable at times, and was having trouble sleeping due to night sweats. Two years prior to presentation, when her period became very irregular, her gynecologist put her on cyclical oral combined estrogen-progesterone supplementation.

At presentation, she is experiencing about 20 headache days a month.

Past medical history is unremarkable. She is a non-smoker, and her cholesterol is normal. Family history is positive for “stress headaches” in her mother and sister, and “sinus headaches” in her 12-year-old daughter.

Medical and neurologic examinations are within normal limits.

Subsequently, changes were made in her medical therapy, resulting in improvement in her symptoms.

## Questions on the Case

Please read the questions, try to answer them, and reflect on your answers before reading the author’s discussion.

- What is her headache diagnosis?
- Why did her headache pattern change?
- Are investigations necessary?

- Can she continue to use her hormone replacement therapy (HRT)?
- If so, which one is best?
- How should her headaches be managed?

## Case Discussion

Generally speaking, migraine tends to improve with advancing age. In particular, women who had menstrually associated migraine often experience a marked improvement after menopause. However, many women with migraine may actually notice a worsening of their migraines in the years preceding menopause, the perimenopause, which unfortunately can last several years. Since nearly 18 million American women are afflicted with migraine, many of them baby boomers who are now “40-something” in age, millions of women with migraine are at risk for worsening headaches.

In the United States, menopause occurs around age 50 years, with most women reaching menopause (one year of amenorrhea) by age 55 years. The climacteric or perimenopause is a transitional phase, which may begin in the mid- to late-thirties and can last 10 years or more. During the perimenopausal years, the orderly pattern of estrogen and progesterone secretion is lost, and episodic fluctuations in hormone levels occur, along with an overall decline in absolute levels. Although estrogen and progesterone levels may begin to decline in the thirties, most women do not become aware of symptoms until they enter their forties. These perimenopausal symptoms can include irregular periods, insomnia, night sweats, hot flashes, irritability, forgetfulness, a drop in libido, difficulty concentrating, and fatigue, as well as a drop in high-density lipoprotein, increase in low-density lipoprotein, and osteoporosis. In some women, the symptoms of perimenopause can be successfully managed with HRT.

In a woman with migraine, an important symptom heralding the onset of perimenopause may be worsening headaches. The chaotic, often unpredictable hormonal fluctuations of this time may even contribute to the new onset or return of previously abated migraine headaches. Women who have a history of menstrually related migraines often now begin to experience a worsening in both the severity and frequency of their migraines. As a woman enters the perimenopausal years, monthly menstruation may become a more significant trigger for migraine, and treatment becomes more difficult as irregular menstrual cycles make migraine attacks unpredictable. Other perimenopausal symptoms such as hot flashes and insomnia contribute to poor sleep, which in turn contributes to worsening headaches.

Our patient, as with many other women, never received a formal diagnosis of migraine. She presumed that all

women got “regular” headaches with their periods and only briefly pursued medical help for proper management of the headaches even when the OTCs gave minimal relief. For a period of time, she got reasonably good relief from her nonsteroidal anti-inflammatory drug.

As she approached the perimenopausal years, however, in the same way as with many other women migraine sufferers, her headache pattern changed. Two years prior to presentation, her gynecologist prescribed oral HRT. Both of these factors played a role in the evolution of her migraine pattern, as did her analgesic overuse for “tension headaches.” Thus, at presentation, she meets Silberstein-Lipton criteria for a diagnosis of transformed migraine with medication (analgesic) overuse, as well as exogenous hormone-induced headache.

Given that she has a 35-year history of headaches, without associated neurologic symptoms, as well as normal physical and neurologic examinations, neuroimaging is not mandatory at this point in time. An evaluation with her gynecologist to check hormonal levels could be undertaken; however, their results are unlikely to sway the diagnosis and treatment plan significantly.

In female migraineurs, the beginning of perimenopause may have differing effects on her pattern of migraine headaches. There are several different patterns that may emerge; however, the reported percentages of women in each category vary widely.

- No change in headache pattern
- Improvement in migraine or resolution of migraine
- Change in character of attacks or worsening of attacks
- Transformation of episodic migraine to more frequent migraine attacks with intermixed “tension-type” headaches
- New onset of migraine
- New onset of late-life migraine accompaniments

In our patient, a previously undiagnosed migraineur, perimenopause led to a change in the frequency and quality of her headaches, as a result of transformation of the migraine with consequent analgesic overuse. Her migraine pattern changed, not only as a result of endogenously fluctuating hormones, but also due to the addition of oral HRT.

HRT has been heralded for its putative vascular and other benefits, in addition to relieving symptoms of menopause. Unfortunately, the doses of currently used exogenous estrogen may inhibit the vasodilating effects of estrogen, resulting in less cardiovascular benefit than expected and potentially an increase in thromboembolic risk. With the recent publication of data from the Women’s Health Initiative (WHI) Study, our thinking regarding HRT has changed to some degree.

One arm of the WHI trial was prematurely stopped due to an increased risk of breast cancer and vascular events

(myocardial infarction, venous thromboembolism, and stroke) in women receiving a particular type of oral HRT. Prempro, as it is known, consists of 0.625 mg of conjugated equine estrogen in combination with 2.5 mg of medroxyprogesterone acetate. Women on mixed conjugated equine-derived estrogen alone, Premarin, showed no increased risk.

As a result of this study, thousands of women and their physicians have contemplated or already discontinued their HRT. For women with migraine, an abrupt withdrawal has led to a flurry of migraine headaches. Critics question the clinical relevance of the WHI data, citing that women included in the WHI trial were not representative of the target population for HRT. On the whole, women in the WHI trial were much older and had numerous comorbid risk factors, which might have precluded their receiving HRT in the clinical world. Many have therefore concluded that HRT is clearly effective in the management of postmenopausal symptoms and prevention of osteoporosis, but that timing for initiation and then continued duration of therapy must be assessed on an individual basis.

There are no definitive clinical studies evaluating the effect of estrogen on the frequency or severity of migraine headaches. Varying effects of estrogen upon a woman and her migraines are likely the result of various methods of estrogen replacement, including different routes of administration, varying doses, cyclical versus continuous regimens, and the type of estrogen. Until recent years, peri- or menopausal women with migraine had been prescribed HRT quite liberally, but the recent WHI data are changing this practice.

## Management Strategies

If HRT is recommended for a woman with migraine, several strategies may be employed to counteract a “negative” effect of the HRT, if any, on migraine. For some women, stabilization of the perimenopausal estrogen fluctuations may actually prove beneficial, especially if the appropriate dose and delivery system are prescribed. As there is no evidence that migraine without aura poses an increased risk for stroke after age 45 years, in a peri- or postmenopausal migraineur, HRT may be considered safe provided the appropriate contraindications have been excluded. Our patient has no other risk factors for vascular or coronary heart disease and is therefore a candidate for HRT, if deemed necessary. Additionally, she did not experience new aura or associated neurologic symptoms with her migraines after starting HRT. This would have been a contraindication for estrogen therapy.

A woman’s natural fluctuating levels of estrogen vary, irrespective of method of administered supplemental estrogen. In a migraineur, the type of estrogen prescribed

and the method of delivery can have a significant impact on the course of the migraine. If HRT worsens migraine, reducing the dose (as opposed to abrupt cessation) may be considered. Additionally, there is evidence that switching from a conjugated estrogen to pure estradiol or from a synthetic to a bioidentical estrogen may prove helpful. Particularly beneficial in the woman with migraine is transdermal estrogen supplementation.

With oral estrogen replacement, serum levels rise rapidly and thereafter decline until the next dose. Additionally, the amount of estrogen absorbed can vary with each dose. As such, these fluctuations may be the triggering mechanism for migraine, especially since a woman’s own endogenous estrogen levels are fluctuating as well. Transdermal estrogens, in contrast, provide more stable physiologic estrogen levels.

If adjustments in the estrogenic component of the HRT are unsatisfactory with respect to improving migraine, then manipulation of the progestagenic component can be undertaken. Medroxyprogesterone and norethisterone differ, with the latter having a more favorable clinical and pharmacologic profile. Oral cyclical progestogen therapy has been associated with migraine, with migraine being more frequently experienced by women using oral sequential estrogen with progestogen (women with an intact uterus) compared to hysterectomized women on oral continuous estrogen alone.

Strategies for adjustments in HRT may include the following.

With estrogen:

- Reduce estrogen dose
- Change from conjugated to pure estradiol to synthetic estrogen to pure estrone
- Use continuous dosing
- Change to parenteral (from oral)
- Add androgens
- Try a selective estrogen receptor modulator

With progestin:

- Switch to continuous
- Lower dose
- Change type
- Change delivery route (from oral to vaginal, for instance)
- Discontinue (caution in unhysterectomized women)

Hysterectomy has no place in the management of migraine. In women undergoing surgical menopause, two-thirds of them noted a worsening pattern of headache, compared to only one-third of women experiencing physiologic menopause.

Our patient was first provided with educational information regarding migraine and its management. She was prescribed a long-acting anti-inflammatory as well as a

triptan for acute treatment of her migraine. She was also placed on a sedating (nighttime) preventative agent to reduce the severity and frequency of her migraine and perhaps improve her sleep. Most importantly, in consultation with her gynecologist, she was switched from combined oral HRT to transdermal estrogen in a continuous fashion, along with cyclical bioidentical progesterone, with very good results. She will continue on this regimen for 9 to 12 months, with a reevaluation at that time.

Although migraine tends to improve with age, particularly after menopause, there is no need to wait until then. If a woman's migraines are worsened by the addition of HRT for perimenopausal symptoms, then approach her treatment first as a woman with migraine and then look to manipulation of her hormonal status. With perseverance, most women can achieve a balance between short-term HRT for symptomatic benefit without giving up effective control of migraine headaches.

### Selected Readings

Boussier MG, Conard J, Kittner S, et al. Recommendations on the risk of ischaemic stroke associated with use of combined oral contraceptives and hormone replacement therapy in women with migraine. The International Headache Society Task Force on Combined Oral Contraceptive & Hormone Replacement Therapy. *Cephalalgia* 2000;20:155–6.

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### Editorial Comments

Dr. Lay makes several key points about perimenopausal migraines:

- Migraines often worsen perimenopausally before they improve postmenopausally.
- The worsening of migraine perimenopausally may actually lead to accurate diagnosis for the first time in a patient's life, by forcing the patient to medical attention.
- Hormone replacement therapy stirs the pot, and its effects are variable and must be taken into account in the management of perimenopausal migraine.
- The treatment of perimenopausal migraine is the same as that for conventional episodic migraine, except for taking into account the unpredictable effects of the HRT.
- In general, steady HRT is better than cycled HRT.

#### FINAL DIAGNOSIS:

Perimenopausal episodic migraine without aura