

## Hormones and Headaches

**Introduction:** In women migraineurs, the female sex hormones, progestins and estrogens, exert a profound influence on the number and severity of migraine headaches. Why this occurs, and the mechanisms involved, remains unclear. Menstrual migraines generate an enormous amount of suffering because they tend to be more severe than nonmenstrually related headaches. In addition, they are often resistant to the usual migraine medication strategies. Headaches often decline in severity during pregnancy, but when present they are difficult to treat, because of the limited number of safe medications available. During menopause, headaches may follow any pattern, and they often improve after this time. When women require hormone replacement therapy, there are certain hormonal approaches that may help limit the headaches. Oral contraceptives may induce or exacerbate headache, or, less often, the headaches may improve. The majority of the time, the birth control pill does not influence migraine; however, it is important to be aware of the possibility of migraine exacerbation with the oral contraceptives.

**Menstrual Migraine:** Menstrually related migraine occurs prior, during, or after menstruation. Many women with menstrual migraine also experience an exacerbation with ovulation. Most often, the woman will also experience migraines that occur at other times of the cycle that are not hormonally influenced. Occasionally, women may suffer menstrual migraine alone, without other headaches.

In several studies, progestin and estrogen levels have been found to be increased premenstrually in women migraineurs. However, others have not discovered this difference. Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, as well as testosterone levels, have been the same in migraineurs as in controls. Estrogen withdrawal may produce migraine headaches, but the exact mechanism of this is uncertain.

Estrogen and progesterone influence serotonin receptors. Estrogen withdrawal exerts a profound effect on hypothalamic control mechanisms. Prostaglandins have been found in increased concentrations in women experiencing menstrual migraine.

Prostaglandin synthesis is blocked by the nonsteroidal anti-inflammatory drugs (NSAIDs), which may help to explain the role of the NSAIDs in treating menstrual migraine. Opioid peptide levels may be altered during menstrual migraine. All of the above factors may play a role in menstrual migraine. For any of the following medications, patients need to be informed of the side effects, as listed in the PDR and package insert.

**Treatment of Menstrual Migraine:** Menstrual migraine is often severe, refractory, and prolonged. However, many women suffer only a mild or moderate 1 day migraine, easily managed with the first line abortive migraine medications such as Excedrin or ibuprofen. At times, the standard migraine preventive medications help the .menstrual migraines, such as propranolol or amitriptyline. For those women who experience severe, prolonged menstrual migraines, the preventive approaches include the following:

1. NSAIDs, such as naproxen, ibuprofen, or the Cox-2 inhibitors (Vioxx, Celebrex) warrant consideration. The Cox-2 may not be as effective; this has yet to be determined.
2. Ergotamine derivatives such as Ergomar, ergonovine, DHE, or methysergide.
3. Hormonal approaches, such as tamoxifen, estrogen, or the birth control pill.
4. Triptans, such as naratriptan (Amerge), sumatriptan (Imitrex), or rizatriptan (Maxalt).

**Abortive Treatment:** Abortive treatment of menstrual migraine usually follows the abortive therapy of migraine. For severe menstrual migraines, cortisone is one of the more effective treatments, usually Decadron or Prednisone. Decadron, 4mg tablets, or Prednisone, 20 mg. pills, are usually limited to 3 pills per month at most, and are taken every 6 hours, as needed. The triptans are crucial in abortive therapy for menstrual migraines. Dexamethasone, 2 to 4 mg every 6 hours prn, or Prednisone, 20 mg every 6 hours prn, limited to three per month, are often helpful. The triptans, particularly SQ sumatriptan (Imitrex SQ), are also very effective. All three forms of sumatriptan, naratriptan (Amerge) or rizatriptan (Maxalt) may be used. IM Toradol, IM DHE, or Migranal nasal spray benefit some women. If these strategies fail, at times a strong narcotic, such as meperidine (Demerol) with a powerful antiemetic, such as chlorpromazine (Thorazine), helps to avoid emergency room visits. As a last resort, Stadol N.S. may be helpful. The intense severity of menstrual migraines necessitates stronger abortive measures in many women.

### **Preventive Medications:**

**Nonsteroidal Anti-inflammatories:** The anti-inflammatories remain the mainstay of menstrual migraine preventive therapy, not because they are extremely effective, but because the side effects are less than with the other medications that are used. The anti-inflammatory is usually begun 3 days prior to the expected onset of the headache; if the patient experiences migraine beginning on the first day of the period, the NSAID is instituted 3 days prior to the expected onset of menses. The medication is continued for several days past the point of the "expected" headache. When the menstrual periods are irregular, medication is usually started the first day of the period, or when the woman feels that the menses is about to begin. Women who tend to experience the headache prior to, during, or after the menses require a much longer period of preventive therapy than women with premenstrual migraines. The timing of preventive therapy for hormonal headaches is often extremely difficult.

Naproxen (Naprosyn, Anaprox, iNapreian, Aleve) has been the most widely studied medication for prevention of menstrual migraine. The usual dose is approximately 1,000 mg/day, taken with food. GI side effects are common, but otherwise the naproxen is well tolerated. Fluid retention may occur. The naproxen may also be utilized as an abortive agent once the headache begins.

Ibuprofen (Motrin) is available over the counter, and is well tolerated. It is also very effective for many women's menstrual cramps. The effective dose of ibuprofen varies widely, from as little as 400 mg per day to 2,400 mg per day in divided doses. As with naproxen, GI side effects are common. Ibuprofen may also be used as an abortive medication.

Flurbiprofen (Ansaid) is an effective and generally well tolerated anti-inflammatory. The usual dose is one 100 mg pill twice per day, or, if tolerated, the 2 tablets may be taken at the same time. GI side effects are common, as with any anti-inflammatory. Flurbiprofen may be used abortively.

Many other NSAIDs have been utilized for menstrual migraine prophylaxis. These include ketoprofen (Orudis and Oruvail), meclufenamate sodium (Meclomen), mefenamic acid (Ponstel), and fenoprofen (Nalfon). These are all probably as effective as naproxen or flurbiprofen. Some women will tolerate or respond to one anti-inflammatory significantly better than to another. It is sometimes worthwhile to attempt treatment with several anti-inflammatories as preventive medications prior to abandoning this class. The Cox-2 inhibitors (Vioxx, etc.) eliminate the (GI) gastrointestinal side effects. These are useful with a history of reflex or ulcers.

**Ergotamine Derivatives or Triptans:** Ergotamine or triptans may be utilized for the prevention of menstrual migraine, with minimal risk for developing rebound headaches. These may also be used abortively for the acute headache. The forms that are employed are: (1) ergotamine tartrate, (2) ergonovine, (3) DHE, and Triptans (Imitrex, Amerge, Maxalt, Zomig).

**Triptans (Imitrex, Amerge, Maxalt, Zomig):** For some women, triptans are the most effective abortive and preventive therapy. Ideally, the longer-acting ones (Amerge) may be best; however, Imitrex has been effective (preventively) for certain women. The usual dose would be one tablet twice per day, starting 1 day (or so) prior to the "usual" onset of the migraine. It would usually be continued for 3 to 5 days. Timing of the menstrual migraine is often difficult, however. Amerge (2.5 mg) is very well tolerated, and is particularly suited to this use. Triptans do not have an indication for this use from the FDA as of yet.

**Hormonal Approaches to Menstrual Migraine Prevention:** If the above therapies have not been effective and the menstrual migraines are very severe and debilitating, it is justified to consider stronger approaches, such as the use of hormonal therapies. Prior to utilizing hormonal therapies, women need to be informed of associated risks, as listed in a major drug reference guide.

**Estrogen:** During the normal menstrual cycle, there is a decrease in levels of estrogen during the late luteal phase. This may be a prominent factor in triggering the headache. Estrogen alleviates the headache in some women and exacerbates the headache in others. Progesterone is generally not effective for menstrual migraine, and will often increase headaches. Percutaneous estradiol gel, used perimenstrually, has been effective in the prevention of menstrual migraine, but this preparation is not available in the United States. I primarily use oral estrogen, usually ethinyl estradiol (Estinyl), 0.05 mg, or micronized estradiol (Estrace), 1 or 2 mg. Premarin, which is a natural conjugated estrogen, has an irregular absorption, and the fluctuating estrogen levels may contribute to headache. In addition, Premarin has miscellaneous natural compounds, equine-derived, that may possibly trigger headaches. The synthetic estrogen preparations are, in theory, better for headache patients. The estradiol transdermal system (Estraderm) gives very consistent absorption of estrogen, and is useful for menstrual migraine prophylaxis. Since the use of estrogens is contraindicated during pregnancy, this issue needs to be explained prior to initiating therapy.

The usual dose of estrogen is 0.05 mg of ethinyl estradiol (Estinyl), one tablet each day for 5 days prior to menses; this may be continued for 2 days after the onset of menstrual flow. I will usually utilize estrogen for a 1 week period of time. Alternatively, Estrace may be used, usually 1 mg per day. The estrogen transdermal patch, Estraderm, may be utilized, with the 0.05 mg patches. The total estradiol content is 4 mg, and the release rate is 0.05 mg per 24 hours. The patch is changed twice weekly, and utilized for a total of 7 days. The idea is to minimize the length of time on estrogen but to use the medication for a long enough time for it to be effective. The women who are placed on estrogens, or any hormonal therapy, have very severe, prolonged migraines. The debilitating nature of these severe menstrual migraines justified the use of stronger medication approaches.

Side effects of estrogens are many, and include: breakthrough bleeding, dysmenorrhea, amenorrhea, menstrual flow changes, endometrial hyperplasia, vaginal candidiasis, nausea, abdominal cramps, colitis or cholestatic jaundice, alopecia or hives, hirsutism, headache, dizziness, depression, decrease or increase in weight, edema, decreased libido, tenderness of the breasts, and chloasma. Estrogens may also increase the risk of endometrial carcinoma. Breast cancer may be influenced by estrogens. Estrogens are contraindicated during pregnancy or with a history of thrombophlebitis or thromboembolic disorders. Preexisting uterine leiomyomas may grow during estrogen therapy. Although small doses are utilized for limited periods of time, women on estrogens should be followed closely by their gynecologist.

**Continuous Birth Control Pill:** For some women with extremely severe, prolonged menstrual migraine, a birth control pill will be utilized for a number of months to decrease the devastating headaches for that period of time. This approach is relatively safe, and at times is the only effective therapy. While the

Birth control pill may help decrease headache, when it is used on a cyclical basis (in the usual manner), the menstrual migraines are often more severe. Women who smoke cigarettes should not be on the birth control pill.

**Oophorectomy as a Therapy for Severe Menstrual Migraine:** In very rare circumstances, in women past age 40 with prolonged, severe, refractive menstrual migraine, Lupron injections (to stop the menstrual cycle) have been given for a number of months. If the headaches are gone, even with added estrogens and progesterone, a few women have had an oophorectomy in order to stop the devastating headaches. It remains controversial whether this is ever indicated or appropriate.

**Vitamins and Minerals:** Magnesium oxide (250 to 500 mg. per day) has been helpful for some women with menstrual migraines. It is usually given daily, or for 1 week prior to and with menses. Long-term side effects, if any, are unknown. Calcium may be helpful as well (750 to 1500 mg. daily). In addition, vitamin B2 (riboflavin), 400 mg. per day, has been superior to placebo for migraine prophylaxis in several studies. Long-term side effects are not known.