Migraine in Women

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Abstract

Migraine is one of the most common neurological disorders, affecting women disproportionately at a rate of 3:1. Prior to puberty, boys and girls are equally affected, but the female preponderance emerges after puberty. Migraine pathophysiology is not fully understood, and although the hormonal effect of estrogen is significant, other factors are at play. This article will focus on the hormonal influence on migraine in women. Here we review our most recent understanding of migraine and menstrual migraine, including epidemiology, pathophysiology, and treatment strategies for this challenging disorder, as well as migraine during pregnancy, postpartum period, breastfeeding, perimenopause, and menopause. We also review the risks and benefits of exogenous hormone use in this population and discuss stroke risk in women with migraine aura. By understanding these aspects of migraine in women, we hope to arm practitioners with the knowledge and tools to help guide treatment of this debilitating disorder in this large population.

Keywords
► hormones
► menstrual migraine
► pregnancy
► contraceptives
► stroke

Epidemiology of Migraine

Migraine is among the most common patient complaints seen in a neurology practice, accounting for up to 20% of all outpatient neurology consultations. Migraine is one of the most prevalent health conditions worldwide and the most frequent cause of headache consultation in the Americas, Europe, South-East Asia, and the Western Pacific. In the United States, as many as 32 million Americans will be affected by migraine at some point in their lives, with the significantly greater proportion of the patients being females.

The global prevalence of migraine is 18.5%; 11.5% of these patients have definite migraine and 7.5% have probable migraine (patients who meet all but one of the diagnostic criteria for migraine). The prevalence of migraine with aura ranges from 1.2 to 5.8%, approximately one-quarter of adults with migraine. Chronic migraine is less common, with the average cross-study estimate of chronic migraine at 0.5% (range: 0.2–2.7%). Prevalence estimates are comparable around the world and have been consistent for several decades.

Migraine prevalence varies with age, with women consistently shown to have higher rates of migraine at all ages. In the American Migraine Prevalence and Prevention (AMPP) study, migraine prevalence was found to be highest among adults 30 to 39 years where prevalence among women (24.4%) was more than three times that in men (7.4%). Prevalence was found to be lowest in those older than 60 years (5.0% women, 1.6% men). Even among those aged 12 to 17 years, females had a higher prevalence of migraine at 6.4% compared with males at 4.0%.

It is well established that sex hormones play an important role in the epidemiology of migraine. Before puberty, girls are afflicted with migraine at approximately the same rates as boys. It has been noted that migraine tends to occur earlier in boys. The incidence of migraine with aura peaks at around age 5 in boys and age 12 to 13 in girls. Migraine without aura peaks at age 10 to 11 in boys and age 14 to 17 in girls. The incidence of migraine peaks between the age of 15 and 19 years in men (6.2/1,000 person-years) and between the age of 20 and 24 years in women (18.2/1,000 person-years). By adulthood, up to three times as many women as men suffer with migraine, with a cumulative incidence of 43% in women and 18% in men. Four of every 10 women and 2 of every 10 men will contract migraine in their lifetime, most before the age of 35 years.
Many women migraineurs note an increase in attacks during the perimenstrual period. The International Criteria for Headache Diagnosis 3-β version Appendix divided menstrual migraine (MM) into pure menstrual migraine (PMM) and menstrually-related migraine (MRM). PMM is defined by migraine without aura that occurs during menstruation over at least three consecutive cycles, exclusively on day 1 + / – 2 of menstruation (i.e., days – 2 to +3 where day 1 reflects the onset of bleeding in at least two of three menstrual cycles). The term MRM uses the same menstrual associated criteria, but refers to women who are also having migraines outside of this.

MM develops most frequently around the onset of menarche with prevalence peaking around the age of 40 years and declining as menopause approaches. The AAMP study found that nearly 60% of women with migraine reported an association between migraine and menses. PMM was seen in 5.5% of the women surveyed and MRM was seen in 53.8%. Women with MM had an older age of migraine onset. Compared with nonmenstrual migraineurs, women were more likely to cause impairment, were longer, and were more likely to relapse within 24 hours, increasing the burden of MM.

In addition to the higher prevalence of migraine in women, the burden of the disease is likely to be greater in women. As described above, MM is more likely to cause disability when compared with non-MM. Gender is also a risk factor for chronicization of headache, likely due to hormonal differences; women have a higher prevalence of chronic daily headache than men. In addition, several studies have suggested that women have more frequent, more severe, and more long-lasting headaches when compared with men and experience more of the associated symptoms of photophobia, phonophobia, and nausea.

Migraine is comorbid with several medical disorders, including arterial disease, hypothyroidism, asthma, endometriosis, depression, anxiety, and somatic complaints, including fibromyalgia, chronic fatigue, irritable bowel syndrome, and interstitial cystitis. The underlying pathophysiology of these comorbidities has not yet been adequately elucidated.

Migraine poses an enormous personal and social burden in terms of direct and indirect costs. The Global Burden of Disease Study 2013 found that migraine is the sixth highest cause of disability worldwide. Over 80% of patients with migraine report some degree of disability. Migraine is the third cause of disability in those under 50 years of age. Despite the magnitude of disability associated with migraine, only approximately one-half of the patients with debilitating migraine seek professional help. With advances in treatment options, improved awareness of migraine and better delivery of interventions are essential.

Pathophysiology of Migraine

Our understanding of the pathophysiology of migraine has advanced significantly over the past several decades. Migraine is no longer considered as a disease of extracranial vascular dilatation. We now know migraine is an inherited disorder that involves central pain modulating dysfunction via a complex interplay between neurotransmitters, inflammatory peptides, and vasculature modulated by the trigeminovascular system involving both the peripheral and central nervous systems.

Initiating processes in migraine include activation and sensitization of the trigeminovascular pain pathway as well as cortical spreading depression in migraine aura. This activation of the trigeminovascular system results in neurotransmission to the trigeminal nociceptors that innervate the large blood vessels in the meninges. In turn, there is a release of calcitonin gene-related peptide (CGRP) and other vasoactive inflammatory peptides that trigger vasodilation, plasma extravagation, and further release of cytokines and proinflammatory molecules. This complex stimulates second- and third-order sensitization of the trigeminovascular system neurons, leading to the pain and allodynia of migraine. This is accompanied by baseline hyperexcitability of the cortex in people with migraine, which is likely due to dysfunction of central pain modulatory processes. In addition to the trigeminovascular complex, the periaqueductal gray, thalamus, hypothalamus, and cortex are brought into play. Other putative players in the production of migraine include nitric oxide (NO), vasoactive intestinal peptide (VIP), Fos expression, N-methyl-D-aspartate (NMDA) receptors, glutamate receptors, serotonin, gamma-aminobutyric acid (GABA), and prostaglandins, among others.

Estrogens have a profound effect on migraine, contributing to the larger percentage of women with migraine than men. Hormonal effect is also seen clinically in MM as well as migraine during pregnancy and postpartum and during perimenopause and menopause. Early studies revealed that the drop of estrogen (rather than progesterone) in the luteal phase of the menstrual cycle is an important trigger for MM. Further, implanted long-acting estrogen that delivered fluctuating estrogen levels was shown to lead to menstrual irregularity and triggered more migraines in some female patients. The literature does not offer a clear reason for this drop in estrogen to serve as a trigger for many female migraineurs. However, other findings involving estrogen have added to our understanding. Estradiol appears to have a direct effect on gene expression. In women with MM, β-estradiol at physiological doses appears to significantly reduce inflammation by reducing mRNA expression and therefore levels of CGRP, interleukin (IL)-1β, and inducible nitric oxide synthase (iNOS). However, pharmacological doses appear to significantly increase mRNA expression of CGRP in both patients with MM and controls, highlighting the differences between estrogen dose and response. Migraineurs have faster late luteal phase-conjugated urinary estrogen decline (greater absolute rate of decline and greater percent of change) compared with controls, whether the migraineur has MM or MRM. This suggests an innate neuroendocrine vulnerability to estrogen withdrawal in women with migraine.

The role of genetics in migraine is under investigation. Functional polymorphisms in estrogen metabolism genes COMT, CYP1A1, or CYP19A1 have not been found to be
associated with MM. However, several other hormone-related genes have been identified to be associated with predisposition to migraine and, in particular, MM. These include ESRR, PR, PROGINS, and possibly, ESRR2 and FSHR, as well as genetic variants in the SYNE1 and TNF genes.

Other factors have been proposed over the years as contributory to MM. Prostaglandins (PGs) have long been identified as possible factors in MM. PGs are fatty acid derivatives of arachidonic acid and are believed to promote neurogenic inflammation and inhibit norepinephrine release. It appears that PG levels significantly increase in the luteal phase and menstruation.

Platelet abnormalities or alterations in platelet homeostasis have also been observed.

Central processing of the trigemino-cervical reflex in women with MM appears to be different from controls. Women with MM appear to have different trigeminal excitability compared with controls, with significantly shorter latencies, when the supraorbital nerve is stimulated during perimenstruation compared with during the follicular phase.

Women with and without migraine seem to have reduced habituation and increased pain perception to peripheral stimuli during the estrogen withdrawal phase of migraine. This may partly explain why MM is more painful and debilitating than migraine outside the menstrual cycle.

Animal models have shed some light on the pathophysiology of MM. In one animal model of MM, high estrogen levels in the estrous cycle were seen to induce increased neuronal excitability and peripheral sensitization of trigeminal ganglia neurons. In another experiment, exogenous estrogen and progesterone exposure in mice with an ovariec- tomy led to increased cortical spreading depression (CSD), which may be why aura may worsen in pregnancy or with combined oral contraceptive (COC) use. In the mouse model of familial hemiplegic migraine-1 (FHM1), hormonal influence on CSD was clear: female mice showed reduced susceptibility to and higher velocity and frequency of CSD compared with male mice. Ovariec- tomy reversed this.

Serotonin has also been implicated in both migraine and MM. Migraine is thought to be a low 5-hydroxytryptophan (5-HTP) condition. A recent study looking at the effect of hormones, 5-HTP (a precursor to serotonin), and cortical excitability in a mouse model of migraine found that

1. 5-HTP decreased CSD occurrence in the presence of ovarian hormones, particularly during estrus, suggesting its potential benefit as prophylaxis in women with migraine with aura,
2. elevated estradiol levels increased CSD susceptibility, while estrogen withdrawal decreased CSD, and
3. mice with oophorectomy who then received estradiol replacement showed increased CSD, decreasing after estradiol was removed. These findings may explain why migraine aura can emerge with pregnancy as estrogen levels rise and why MRM is rarely associated with MA.

This study built upon work which had demonstrated that enzymes involved in the synthesis of serotonin are expressed in mouse trigeminal ganglion, and the level of these enzymes is dependent on the gender and estrus cycle stage, suggesting that ovarian steroids might play a role in the regulation of serotonin synthesis.

**Treatment of Menstrual Migraine**

Because MM is more severe, lasts longer, and causes associated nausea and disability more than migraine outside the menstrual cycle, special treatment strategies are often necessary. The first step is to have the patient keep a headache diary over a 3-month period to determine the link to menstruation as well as total migraine frequency and any other patterns. Once this is determined, diagnosis and treatment options should be discussed and implemented. Both pharmacological and nonpharmacological strategies should be employed. Pharmacological approaches include acute treatments, daily prophylaxis, and short-term prophylaxis leading up to and during menses. Nonpharmacological strategies include trigger avoidance, consistent sleep hygiene, hydration, exercise, and complementary treatment approaches.

**Acute treatments:** Many women will respond well to typical non-MM acute treatment approaches using triptans or nonsteroidal anti-inflammatory drugs (NSAIDs). However, because of the high prevalence of associated nausea during MM compared with non-MM, antiemetics and prokinetics, such as metoclopramide, may be required. There are seven triptans on the market, and the choice of a particular agent should take into account the patient’s prior success or failure and personal preferences, as well as speed of onset, associated features, such as nausea or vomiting, and recurrence. Although any triptan can be used for MM on an as-needed basis, published data for acute treatment in MM are available on frovatriptan 2.5 mg, almotriptan 12.5 mg, naratriptan 2.5 mg, sumatriptan 6 mg injectable, sumatriptan 50 and 100 mg tablets (with the 100 mg tablet showing a slight trend in better efficacy than the 50 mg dose in one study), rizatriptan 10 mg, and zolmitriptan 2.5 mg and 5 mg. Although frovatriptan has been shown to be as effective as almotriptan and zolmitriptan, there appears to be a lower rate of recurrence with frovatriptan due to its long half-life and duration of action, making it a particularly appealing choice for MM.

A variety of NSAIDs can be used in the treatment of MM. Since elevated prostaglandins have been observed in women with MM use of NSAIDs, which interfere with the production of PGs and other inflammatory molecules seen in the pathophysiology of migraine, seems to make sense, and some data support their use for “miniprophylaxis” (see below). Studies combining NSAIDs with triptans have also been positive. Frovatriptan 2.5 mg taken with dextromethorphan 25 or 37.5 mg showed higher pain free rate at two hours compared with frovatriptan 2.5 mg alone while retaining the benefit of low recurrence.

**Short-Term Prophylaxis:** For many women, however, the above treatments are insufficient, and short-term prophylaxis may be desirable. In this approach, treatment is initiated prior to the onset of menstruation or MM itself and is continued for
several days into menses. To be effective, a woman must have a regular and predictable menstrual cycle. Level 1 Evidence (effective) supports frovatriptan for the preventive treatment of MRM. Prophylaxis, 2.5 mg is used once or twice a day for 6 days starting 2 days prior to the onset of the expected MM. Studies have shown a statistically significant benefit compared with placebo for headache reduction, increase in headache-free time, and a reduction in severity. Although once daily dosing was beneficial, twice daily dosing appeared to provide even greater benefit. Level 2 Evidence (probably effective) supports zolmitriptan and naratriptan for MM prevention. Zolmitriptan 2.5 mg has been shown to be effective when used two to three times a day for 7 days starting 2 days prior to the expected onset of menstrual bleeding, resulting in reduced frequency and breakthrough pain. Naratriptan 1 mg taken twice daily for 5 days starting 2 days prior to the expected onset of menstrual bleeding showed benefit over placebo, although 2.5 mg was not seen to be efficacious. In one study, eletriptan (20 mg three times daily starting 2 days prior to the expected onset of menstruation and continued for a total of 6 days) significantly reduced headache activity compared with placebo; however, 9% may experience migraine in the 3 days immediately after discontinuing eletriptan. A follow-up study of eletriptan, comparing its use during MM with non-MM, showed similar 2-hour headache outcome measures between the two groups but a higher recurrence rate and a lower sustained response rate for nausea in the MM group. Sumatriptan 25 mg can also be effective; dosing is three times daily starting 2 to 3 days before the expected day of headache onset and continued for a total of 5 days. Short-term prophylaxis with triptans appears to be safe. In one study, frovatriptan for 6 days a month as “miniprophylaxis” was safe and well tolerated over a 12- to 15-month period. There was no evidence of increased cardiovascular risk, and rebound headache was not evident.

NSAIDs are also used for short-term prophylaxis of MM. Naproxen sodium 550 mg twice daily or mefenamic acid 500 mg three times daily, used 2 to 4 days prior to the onset of the MM and continued through day 3 of menstrual flow, can be an effective method and may address coexisting dysmenorrhea. The lack of response to one NSAID does not reflect a global lack of responsiveness to the class, and others NSAIDs may be tried.

For those without vascular contraindications, ergotamines have also been shown to be useful in MM miniprophylaxis. Given the relatively short duration of use, the risk of toxicity and dependence is low. Time-release dihydroergotamine (not available in the United States) has been shown to be beneficial in reducing MM intensity and duration, used daily starting 2 days prior to menses onset and taken for 7 days. In one study of DHE-45 nasal spray (2 mg per spray, used one spray every 8 hours) for MM prophylaxis, patients experienced significant benefit with good tolerability.

**Table 1** Studied short-term prophylaxis regimens for menstrual migraine

<table>
<thead>
<tr>
<th>Medication</th>
<th>Regimen</th>
<th>FDA approved</th>
<th>Primary contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frovatriptan</td>
<td>2.5 mg BID × 6 d, starting 2 d prior to MM onset</td>
<td>No</td>
<td>History of stroke or MI, uncontrolled vascular risk factors, hypercoaguable state among others Presence of aura may be a contraindication</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>2.5 mg BID to TID × 7 d, starting 2 d prior to onset of menses</td>
<td>No</td>
<td>As above</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>1 mg BID × 5 d, starting 2 d prior to onset of menses</td>
<td>No</td>
<td>As above</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>20 mg BID × 6 d, starting 2 d prior to onset of menses</td>
<td>No</td>
<td>As above</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>25 mg TID × 5 d, starting 2–3 d prior to onset of MM</td>
<td>No</td>
<td>As above</td>
</tr>
<tr>
<td>Naproxen</td>
<td>550 mg BID × 5–7 days starting 2–4 d prior to MM</td>
<td>No</td>
<td>Renal disease, gastrointestinal bleeding</td>
</tr>
<tr>
<td>Mefenamic Acid</td>
<td>500 mg TID × 5–7 days starting 2–4 d prior to MM</td>
<td>No</td>
<td>Renal disease, gastrointestinal bleeding</td>
</tr>
<tr>
<td>Dihydroergotamine nasal spray</td>
<td>2 mg spray used one spray every 8 h for 6 d starting 2 d prior to onset of MM</td>
<td>No</td>
<td>As for triptans</td>
</tr>
</tbody>
</table>

Abbreviations: FDA, food and drug administration; MM, menstrual migraine.
exogenous hormones in women with aura may increase the risk of stroke, so their use in such patients must be evaluated on a case-by-case basis (see below). The concept behind hormonal intervention is to counterbalance the natural, steep decline of estrogen in the luteal phase that appears to be the main driving force for MM. Strategies include (1) supplementing estrogen when levels are dropping in the luteal phase or (2) using a noncycling combined oral contraceptive agent (COC) or progestin-only pill (POP) to inhibit follicular development and ovulation, and thereby reduce the large estrogen fluctuations that trigger migraine. Although many women do respond to exogenous hormones, it is important to alert the patient that some may experience more frequent migraines. Development of an aura for the first time during hormone use is an indication for immediate cessation of the hormone due to perceived stroke risk.

**Estrogen Supplementation:** Supplementation of falling estrogen levels near the onset of menstruation may provide relief. In one study, women who used 1.5 mg estradiol gel for 7 days starting 2 days prior to onset of expected MM experienced a statistically significant reduction in frequency and the use of acute treatments. Another study showed that a 0.1 mg per day estrogen patch starting just prior to onset of menses for a total of 7 days was effective in reducing MM, but lower doses were not. Patches and gels are believed to be more effective, because these have a steady state of absorption compared with the fluctuations seen in oral supplementation.

**Daily Hormonal Use:** There are many formulations of COCs, and the lower dose (35 µg or less) monophasic COCs may be safer and less disruptive to migraineurs than higher dose and triphasic formulations. Minimizing the number of placebo days by noncycling (elimination of the placebo week) may be beneficial in reducing MM. Elimination of the menstrual cycle with the use of hormonal preventatives has been correlated with a transformation from chronic to episodic migraine as well as a significant reduction in acute treatment use. Noncycling COC may lead to a decrease in headache severity along with improvement in work productivity and involvement in activities. Additionally, formulations, such as the patch or the vaginal ring, deliver a steady state of hormones compared with the peaks and troughs found in oral counterparts. This steady state may help minimize migraine vulnerability by reducing estrogen fluctuations. One study looking at the effect of noncycling use of the vaginal ring in women with migraine with aura and MRM showed an association with reduction in frequency of migraine aura with resolution of MRM. The stroke risk could not be assessed or extrapolated from this study.

The progestin-only pill (POP) may be beneficial for women with MM, reducing migraine frequency in women without aura and, in one study, addressing comorbid endometriosis pain. In a pooled analysis of four studies from 1980 to 2016, the effect of POP use on migraine in general showed that desogestrel 75 µg/day significantly reduced migraine frequency, intensity, duration, and acute treatment use. More studies are needed on the use of the POP pill for MM, but this may turn out to be a better option for women with aura.

Few data are available on induced menopause (hysterectomy or oophorectomy) for treatment of MM. In one study, two-thirds of patients who underwent surgical menopause reported a worsening of their headaches, but postoperative use of daily estrogen replacement confounds these results. There is no current role for these procedures for the management of MM.

**Complementary Approaches:** Although many patients experience benefit from the pharmacological approaches to MM, some have intolerable side effects or are looking for nonpharmacological approaches. Probably through its antiprostaglandin effect, vitamin E, 400 units taken daily for 5 days starting 2 days prior to menstruation, has been shown to reduce pain severity and disability and associated features compared with placebo. This regimen has also been found to improve the pain of dysmenorrhea significantly. Magnesium has been shown to reduce the pain of MM and premenstrual symptoms. There are no completed studies on the role of acupuncture in MM prevention; however, one study is underway.

**Migraine in Pregnancy, Postpartum, and Breastfeeding**

Migraine affects a significant number of women during childbearing years. Given that almost half of all pregnancies are unintended, practitioners should counsel their female patients about potential teratogenicity or other adverse fetal outcomes with migraine treatments, stressing the importance of adequate birth control. Several preventive agents are Category D in pregnancy, including valproic acid, topiramate, candesartan, nortriptyline, imipramine, and magnesium. When planning pregnancy, it is recommended that practitioners develop a plan for the woman to taper off medications in advance of conception, taking into consideration the half-life of the particular medication.

For some women, a worsening of migraine may be the first indication of pregnancy. However, 60 to 87% of women with MRM improve in the second or third trimester. Four to 8% of women may worsen, with a disproportionate number of women with aura in this group. Migraine may start for the first time during hormone use is an indication for immediate cessation of the hormone due to perceived stroke risk. Surveillance of the mother’s health is essential, as the developing fetus is at risk of stroke, so their use in such patients must be evaluated on a case-by-case basis (see below). The concept behind hormonal intervention is to counterbalance the natural, steep decline of estrogen in the luteal phase that appears to be the main driving force for MM. Strategies include (1) supplementing estrogen when levels are dropping in the luteal phase or (2) using a noncycling combined oral contraceptive agent (COC) or progestin-only pill (POP) to inhibit follicular development and ovulation, and thereby reduce the large estrogen fluctuations that trigger migraine. Although many women do respond to exogenous hormones, it is important to alert the patient that some may experience more frequent migraines. Development of an aura for the first time during hormone use is an indication for immediate cessation of the hormone due to perceived stroke risk.

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When these strategies are not sufficient, some acute treatments are considered safe in moderation. Although treatment options are limited, several strategies can be employed working in coordination with the patient’s obstetrician. Limited use of acetaminophen (category B) may be helpful, especially when combined with caffeine. Although causality has not been determined, two studies have observed an association between acetaminophen use in pregnancy and ADHD and other hyperactive kinetic disorders in children.\textsuperscript{86,87} One study has suggested an association of acetaminophen with autism spectrum symptoms in males.\textsuperscript{88} More research needs to be done to better understand these relationships given how widespread acetaminophen use is. Meanwhile, women should be advised to limit use of acetaminophen during pregnancy.

All NSAIDs are category D in the third trimester, but a few, including ibuprofen, naproxen, indomethacin, and ketorolac, are category B in the first and second trimester. Several opioids, such as meperidine and morphine, are category B until the third trimester when these should be used with caution. Codeine, hydrocodone, and oxycodone have been associated with major birth defects, including cardiac malformations, but it is not clear if this relationship is causal.\textsuperscript{89} Antiemetics are often used in migraine management. Pyridoxine and doxylamine are category B, while diphenhydramine, dimenhydrinate, cyproheptadine, ondansetron, and metoclopramide are category B. Ondansetron may confer a small risk of cardiovascular malformations.\textsuperscript{90} Ginger may be a safe alternative for nausea. If steroids are indicated, prednisone (category C) is preferred to dexamethasone, because prednisone is more efficiently metabolized by the placenta and excluded in its active form from the fetal circulation. Ergotamines and aspirin should be avoided during pregnancy. Triptans are category C during pregnancy carrying the risk of vasoconstriction and should be avoided. However, a meta-analysis looking at over 4,000 women who took triptans during pregnancy did not show an association with developmental issues, an increased rate of major congenital malformations, or prematurity; triptans may confer an increased risk of spontaneous abortions.\textsuperscript{91,92} More research needs to be done on agents in this class given their efficacy and the great disability of the disorder.

For severe attacks, IV fluids and IV antiemetic agents are often helpful. Lidocaine—only blocks nerves to interrupt status migrainous as well as intranasal lidocaine (category B) can be beneficial acutely. Daily oral preventive agents are reserved for women with frequent, severe attacks or significant vomiting, where the benefit might outweigh the potential risks to the developing fetus. Because most preventive agents are category C or higher, a decision to use these agents should follow a full discussion with the patient, her partner, and her obstetrician, and full consent should be obtained from all parties. Commonly used treatments include lebetalol, propranolol, sertraline, and occasionally amitriptyline. Memantine is category B; however, this designation is based on animal studies, and therefore the full risks to humans are not known. Acupuncture, biofeedback, and the transcutaneous nerve stimulator device are considered safe preventive therapies during pregnancy.

Although historically migraine has not been felt to confer a greater risk of complications of pregnancy, several new studies bring this judgment into question. Recent studies of pregnant women with migraine have shown an increased risk of adverse delivery outcomes. These include increase risk of low birth weight, preterm delivery, preeclampsia, cesarean section, and severe nausea and vomiting.\textsuperscript{93–95} Given these studies, it is important that gynecologists and obstetricians screen their patients for migraine.

Migraine symptoms often emerge in the postpartum period as estrogen levels rapidly fall. Breastfeeding may delay the return of migraines by keeping estrogen levels elevated. Treatment principles in breastfeeding are similar to those in pregnancy. Ibuprofen, ketoprofen, and sumatriptan are generally regarded as safe, though some physicians recommend the pump and dump method several hours after treating. Working with the patient’s pediatrician to find the safest approach for both mother and infant is recommended.

### Migraine during Perimenopause and Menopause

For many women, the perimenopausal time brings worsening migraines. While the average age of menopause in the United States is 51 years, perimenopause starts in the preceding decade (in some as early as the mid to late 30s) and marks the end of the reproductive years. This transition is caused by fluctuating ovarian function with fluctuating hormone levels resulting in irregular periods, hot flashes, insomnia, difficulty concentrating, and a reduction in libido. This chaotic hormonal variation can lead to higher migraine frequency and worsening severity, and some women with prior quiescent disease may see a return of migraine attacks. For women with MRM, irregular cycles set in making migraine attacks unpredictable and treatment more challenging. In particular, women with a history of premenstrual syndrome appear to have a significant increased risk for high frequency headache during this time period.\textsuperscript{96} Although tests may confirm perimenopause, these are unlikely to alter diagnosis or management.

Approaches to management include typical migraine preventive agents and acute treatments. When these fail and there are significant vasomotor symptoms and no contraindications, the use of hormone replacement therapy (HRT) may be helpful to some. HRT doses are typically lower than COC doses but do help stabilize estrogen withdrawal, thereby minimizing migraine induction. Patches and gels are less likely to aggravate migraine frequency compared with oral formulations because of their steady state. For women with an intact uterus using estrogen, the addition of progesterin for endometrial protection is typically employed. Continuous progesterin use rather than cycling of progesterin may be less provocative for women with migraine.\textsuperscript{98} If migraine worsens with HRT, reducing the dose, utilizing a noncycling method, or switching from conjugated estrogens to pure estradiol may be beneficial.\textsuperscript{99}

For women who have contraindications to HRT or who otherwise do not wish to use or have failed HRT, venlafaxine, paroxetine, fluoxetine, and gabapentin have been shown to help reduce the vasomotor symptoms of perimenopause.\textsuperscript{100} These four agents have some efficacy in migraine prevention,
with venlafaxine rated as probably effective (level B) and fluoxetine and gabapentin rated as level U, with insufficient or conflicting evidence.57

The effect of menopause on migraine is still not clearly understood. It has been observed that migraine typically improves after menopause in general population studies, but worsens in women in headache clinic studies.101,102 Overall, it appears that women with a history of premenstrual syndrome do better after menopause.103

**Vascular Risk in Women with Migraine**

It has long been recognized that there is an association between migraine and ischemic stroke.104 This risk is primarily attributed to migraine with aura in younger women, and it appears to be independent of other risk factors.105–107 A meta-analysis reported that the risk of stroke was doubled in those with migraine with aura and tripled in the female cohort.108 It also appears that aura frequency of more than once a month as well as a life-time duration of less than a year is associated with an even higher stroke risk.104,105 There are no data to date that suggest that effective treatment of migraine with aura to reduce frequency actually reduces this risk.106 Hemorrhagic stroke appears to be consistently increased in MA, MO, and uncategorized migraine.109

The mechanisms of the relationship between migraine with aura and stroke are complex; hormonal influences are thought to contribute. Increased estrogen levels may increase the risk of ischemic stroke via their effect on endothelial function, coagulation factors, and inflammation.110 The stroke risk appears to be greater in women, and the magnitude of the increase is greater in women who take higher dose COCs.111,112 As for many vascular risk factors, the risk appears to be compounded in the presence of other known risk factors.106 COCs alone pose a stroke risk, so there is much concern about women with aura using COC and increasing their stroke risk. Guidelines of the American College of Obstetricians and Gynecologists state that the risks of COCs are unacceptable in this group, whereas COCs are not contraindicated in migraine without aura in healthy, nonsmoking women 35 years of age or under.113 However, controversies remain around the interpretation of the data. In particular, it appears that estrogen dose matters when speaking of stroke risk as well as thrombotic risk. A meta-analysis shows that the risk of ischemic stroke among COC users decreases significantly with decreasing estrogen dose. Estrogen doses less than 50 µg confer a lower risk than higher doses of estrogen above 50 µg. Risk continues to go down as estrogen dose goes down to 35, 30, and 20 µg.114 Thrombotic risk may also correlate with dose and duration of exposure.115

This controversy highlights the need for more studies, so we can better advise our patients. It is generally agreed, however, that any form of hormonal therapy should be avoided in patients with prolonged aura (lasting longer than 60 minutes) or aura with multiple neurological symptoms, including migraine with brainstem aura and hemiplegic migraine. Women who do not have aura but are contemplating hormonal contraception should be carefully counseled to report new onset aura symptoms or any changes in cardiovascular risk status, and they should be evaluated on a case-by-case basis for safety. Discontinuation of COCs should be immediate if migraines worsen after the first few months of treatment or if an aura develops for the first time.116

For the large number of women with simple aura, an individualized rather than a one-size-fits-all approach appears to be more appropriate. Developing a risk–benefit assessment in coordination with the patient and her gynecologist that includes the circumstances of the need for hormonal use, age, the subtype of migraine, smoking status, and any other vascular risk factors allows practitioners to approach the problem systematically as we wait for more data to guide us.

**Conclusion**

Migraine is one of the most common neurological conditions and is the third most common disabling disorder globally; yet, up to 50% of sufferers do not receive medical care. Women are disproportionately affected by a ratio of 3:1, in part due to hormonal differences with changes in estrogen appearing to be the main driver. Many other factors, including serotonin, prostaglandins, and central processing, appear to play an important role in the pathophysiology of migraine.

Many treatment options exist for hormonally related migraine, including acute treatments, short- and long-term prophylaxis, and hormonal manipulation. Fewer options are available during pregnancy and breastfeeding, but by working with patients’ obstetricians and pediatricians, solutions can be found. Understanding and discussing risks and benefits with patients are essential parts of pharmacological treatment. Stroke is associated with migraine, particularly in women with migraine with aura, and hormone use is currently not recommended in this subtype. To improve our care of patients, more studies need to be done to expand our knowledge of migraine in women, including hormonal effects on the pathogenesis of migraine and stroke.

**Conflict of Interest**

Dr Broner reports personal fees from Allergan, outside the submitted work.

**References**

1 Stone J, Carson A, Duncan R, et al. Who is referred to neurology clinics?--the diagnoses made in 3781 new patients Clin Neurol Neurosurg 2010;112(09):747–751
4 Merikangas KR. Contributions of epidemiology to our understanding of migraine. Headache 2013;53(02):230–246


Schreiber CP, Cady RK. Diagnosis of menstrual headache and an open-label study among those with previously undiagnosed menstrual related migraine to evaluate the efficacy of sumatriptan 100 mg. Clin Ther 2007;29(Suppl 2):2511–2519


Edelson RN. Menstrual migraine and other hormonal aspects of migraine. Headache 1985;25(7):376–379


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Martin VT, Pavlovic J, Fanning KM, Buse DC, Reed ML, Lipton RB. Perimenopause and menopause are associated with high frequency headache in women with migraine: results of the American Migraine Prevalence and Prevention Study. Headache 2016;56(02):292–305


MacGregor EA. Perimenopausal migraine in women with vasomotor symptoms. Maturitas 2012;71(01):79–82


Calhoun A. Combined hormonal contraceptives: is it time to reassess their role in migraine? Headache 2012;52(04):648–660