Migraine Headache in Perimenopausal and Menopausal Women

E. Anne MacGregor, MD, MFSRH

Corresponding author
E. Anne MacGregor, MD, MFSRH
The City of London Migraine Clinic, 22 Charterhouse Square, London EC1M 6DX, United Kingdom.
E-mail: anne.macgregor@migraineclinic.org.uk

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Perimenopause marks a time of change in a woman's hormonal environment, which is apparent from the resultant irregular periods and vasomotor symptoms. These symptoms can start in the early 40s and continue through to the early 50s. Migraine is also affected by hormonal fluctuations, particularly the natural decline in estrogen in the late luteal phase of the menstrual cycle. This effect of estrogen "withdrawal" on migraine appears to become more predominant during perimenopause. Despite the increased prevalence of headache and migraine in women in their 40s, migraine is underdiagnosed in this population. In women attending with symptoms suggestive of perimenopause, it is important to ask about headache symptoms. Once diagnosed, a number of strategies can be used to manage both perimenopausal migraine and menopausal symptoms effectively, with the potential to reduce the associated morbidity.

Introduction

Perimenopause describes the time in a woman's life when she experiences symptoms such as hot flashes and a change from a regular to an irregular menstrual cycle as a consequence of fluctuating ovarian activity. Perimenopause continues through to postmenopause, which is at least 12 months after menopause. Perimenopausal symptoms can be observed as early as age 43 [1]. The average age at menopause, defined by the last menstrual period, is 51 years. Hence, perimenopause can affect women for a significant number of years.

Migraine occurs in both sexes, but it is predominantly a female disorder, with a cumulative lifetime incidence of 43% for women compared with 18% for men [2]. Although migraine starts during the teens and 20s, the perimenopausal years are a time of increased migraine prevalence. Of all the migraine triggers, menstruation is the most important in increasing the risk and persistence of migraine [3•]. Hyperestrogenism coupled with decreased luteal phase progesterone disrupt the menstrual cycle and are the likely causes of the increased morbidity from migraine and other gynecological disorders that characterize this stage of life.

Epidemiology of Headache and Migraine

Perimenopause

Headache is a common but underreported complaint in perimenopausal women. In a study of 74 women attending a UK menopause clinic, 57% had experienced headache and 29% had migraine in the preceding 3 months [4]. Migraine was associated with significant disability, with 80% of women affected reporting attacks more often than once a month, 75% reporting severe attacks, and 50% reporting attacks lasting longer than 1 day. Of 1000 women attending a separate UK menopause clinic, 85% reported recurrent headache, of which 73% experienced headache more often than once a month. Migraine was reported by 24% of women [5]. Whether or not migraine is directly associated with menopause symptoms is unclear. Although a population-based retrospective study of 728 women reported no correlation between migraine and menopause symptoms [6], a more recent cohort study of 28,118 French women suggested a significant association (HR, 1.11; 95% CI, 1.07–1.16; $P = 0.007$) [7••].

Menopause

In a study of 1436 women at various stages of menopause, spontaneous menopausal women reported a prevalence of migraine of 10.5% compared with 16.7% in premenopausal and perimenopausal women (OR, 0.6; 95% CI, 0.4–0.9; $P = 0.03$) [8].

Spontaneous menopause is also associated with a lower prevalence of migraine compared with surgical menopause [9–11]. A retrospective questionnaire of 47 postmenopausal women with migraine noted eight women (17%) reporting new onset of headache with menopause [9]. Of those women who had physiological menopause, 67% reported improvement or complete remission of headache following menopause, 24% reported no change, and 9% reported worsening headache. Of those women

who had surgical menopause, 38% reported improvement of headache following menopause, 33% reported improvement, and 67% reported worsening headache.

In a retrospective study of 164 postmenopausal women with migraine without aura attending two headaches centers in Italy, worsening of migraine was significantly more frequent following surgical menopause than natural menopause ($P < 0.01$); improvement occurred only with natural menopause ($P < 0.01$) [10].

In a cross-sectional survey of 986 hysterectomized women with one or both ovaries present and 5636 nonhysterectomized women with both ovaries present, 8.8% nonhysterectomized women reported moderate to severe migraine compared with 15.1% of hysterectomized women with ovarian retention ($P < 0.001$) [11].

Migraine prevalence has been reported as lowest in those with hysterectomy and bilateral oophorectomy, although not to a statistically significant level (hysterectomy only, 28.6%; hysterectomy with unilateral oophorectomy, 36.4%; hysterectomy with bilateral oophorectomy, 15.8%; $P = 0.3$) [8]. There are no studies assessing the effect of bilateral oophorectomy in the absence of hysterectomy.

Postmenopause

Studies support the clinical impression that migraine improves postmenopause [7]. In a longitudinal study of 404 women enrolled in the Penn Ovarian Aging Study, the percentage of women reporting moderate to severe headache fell from 34% during premenopause to 24% postmenopause ($P = 0.003$) [12••]. This improvement is generally attributed to the absence of fluctuations in sex hormone levels postmenopause. Consistent with this theory is that ovarian failure, with low levels of estrogen and high levels of follicle-stimulating hormone, is associated with a lower prevalence of migraine than menstruating women [8].

Pathophysiology

More than 50% of women with migraine, both in the general population and presenting to specialist clinics, report an association between migraine and menstruation [10,13,14]. The association appears most prevalent in women approaching menopause. Hence, the effects of menstrual cycle hormones are obvious candidates to study in relation to pathophysiology.

A series of elegant studies undertaken during the 1970s assessed the effects of estrogen and progesterone across the menstrual cycle and confirmed an association between migraine and estrogen "withdrawal" during the late luteal phase of the natural menstrual cycle [15,16]. It was noted that estrogen withdrawal can only trigger migraine if withdrawal follows a period of estrogen "priming" with several days of exposure to high estrogen levels [15]. This would explain why migraine is not associated with the transient estrogen surge at ovulation.

Subsequent studies have supported the estrogen withdrawal theory as a trigger for migraine as well as confirming the necessity of estrogen priming [17,18]. More recently, a study of 38 women with pure menstrual or menstrually-related migraine found migraine to be inversely associated with urinary estrogen levels across the menstrual cycle [19•]. Attacks were significantly more likely to occur in association with falling estrogen in the late luteal or early follicular phase of the menstrual cycle and significantly less likely to occur during the subsequent part of the follicular phase during which estrogen levels rose.

The role of progesterone in migraine is unclear. Estrogen withdrawal can trigger migraine in the absence of progesterone [15,16,18]. However, progesterone may play a role in modulating migraine during the luteal phase of the cycle [20].

But why does estrogen withdrawal not trigger migraine in all women? Why does the association between migraine and menstruation appear to be most prevalent in perimenopause? Perimenopause is marked by erratic fluctuations of estrogen and progesterone. By late perimenopause, estrogen levels can reach high magnitudes [1,21]. In one study, the mean peak luteal phase estradiol urinary metabolites in women with menstrual migraine were significantly higher than in normal fertile cycling women reported in population studies matched by menopause status [22]. One hypothesis is that high baseline estrogen would result in a greater luteal drop, which in a susceptive individual may tip the balance in favor of triggering migraine.

Although the focus has been on estrogen, an increasing body of research implicates serotonin in the pathophysiology of menstrual migraine. Estrogen is associated with increased production of serotonin, reduced serotonin reuptake, and decreased serotonin degradation [23••]. Studies in female mice have demonstrated that expression of the rate-limiting enzyme required for serotonin synthesis is regulated during the natural estrous cycle [24•]. The consequent cyclical changes in serotonin levels in trigeminal ganglia could contribute to the selective response to estrogen withdrawal. Future research should focus on the clinical association between vasomotor symptoms and migraine. Given that serotonin has also been implicated in the pathophysiology of vasomotor symptoms [25••], it is interesting to speculate on a common pathophysiology.

Management

Acute treatment

Acute treatment of migraine during perimenopause, including menstrual attacks of migraine, should be in accordance with standard strategies for acute migraine management [26].

Prophylaxis

Short-term perimenstrual prophylaxis for the management of menstrual migraine may be appropriate for those

women with regular and predictable periods who experience inadequate relief from the usual forms of acute therapy or who are troubled by headache recurrence and require multiple doses of acute migraine medications [27]. There are grade B recommendations for perimenstrual use of transcutaneous estrogen 1.5 mg, frovatriptan 2.5 mg twice daily, and naratriptan 1 mg twice daily [28••]. However, in a perimenopausal population, irregular periods mean that accurate timing of perimenstrual prophylaxis can be difficult to predict [27]. In women who require prophylaxis but whose migraine attacks show no hormonal association, standard migraine prophylactic strategies are indicated. Women experiencing migraine and vasomotor symptoms may benefit from a trial of hormone replacement therapy (HRT).

Hormone Replacement Therapy

Few data exist on the association between headache and current use of HRT. Worsening of migraine at menopause has been suggested as a factor in predicting worsening migraine with HRT [5]. However, it is not known whether HRT is associated with increased incidence of headache and migraine, or if HRT is initiated because of headache. Evidence does suggest that HRT is often recommended for perimenopausal women with migraine [29]. Given the increased prevalence of migraine in women of perimenopausal age who are also likely to be experiencing vasomotor symptoms, it is sensible to consider the outcome of treatment options that have theoretical benefit for both conditions [30].

Of 120 women attending a headache clinic, 64.1% of responders reported improvement or complete remission of headache associated with HRT use, 22.5% reported no change, and 13.3% reported worsening headache [31]. In contrast, a cross-sectional questionnaire of 6007 postmenopausal women showed a significant association between headache and current use of HRT [32••]. This was irrespective of whether the route of delivery was local (OR, 1.3; 95% CI, 1.0–1.6) or systemic (OR, 1.3; 95% CI, 1.1–1.5).

In a cross-sectional analysis of 39,876 female health professionals ages 45 years or older enrolled in the population-based Women's Health Study, 21,788 were postmenopausal at baseline, of which 6588 (30.2%) had never used HRT and 10,519 (48.3%) were current users [33]. Of these 17,107 women, 1396 (8.2%) experienced migraine headaches that fulfilled modified International Headache Society migraine criteria during the year preceding baseline. In multivariate analyses controlling for age, race, smoking, alcohol use, ever use of contraception, age at menopause, and menopause type, current use of HRT was associated with a 42% increased risk of migraine headache (OR, 1.42; 95% CI, 1.24–1.62) in the preceding year compared with never users. When stratified by menopause type, the risk of migraine was increased in current HRT users with a surgical menopause (OR, 1.65; 95% CI, 1.18–2.29) and current users who experienced a natural menopause (OR, 1.39; 95% CI, 1.20–1.61). Compared with never users, estrogen-only HRT was associated with a 39% increased risk of migraine (OR, 1.39; 95% CI, 1.14–1.69) with a similar 41% increased risk in women using estrogen and progestin (OR, 1.41; 95% CI, 1.22–1.63). Duration of HRT had no effect on migraine. There were no significant differences in risk of migraine headache in users of cyclic versus continuous progestins.

Based on the estrogen withdrawal pathophysiology of migraine, estrogen should be given continuously to prevent estrogen withdrawal migraine [34]. There are theoretical and clinical benefits to non-oral estrogen replacement for all women wishing to use HRT. Observational evidence suggests that transdermal estrogens may be associated with a lower risk of venous thromboembolism (VTE) than oral administration, but no evidence exists from randomized controlled trials [35]. Non-oral routes are less likely to have a negative effect on migraine than oral formulations of estrogen replacement. In a study of continuous transdermal estradiol, 50 μg, plus cyclical medroxyprogesterone acetate (MPA), 10 mg per day, compared with continuous oral conjugated estrogens, 0.625 mg per day, cyclical MPA, 10 mg per day, both frequency of attacks and days with headache significantly increased during HRT in the subgroup taking oral estrogen, but not in the subgroup using the transdermal route [36]. This is probably the result of the more stable serum hormone levels associated with non-oral routes. If oral preparations are favored, tibolone may be the preferred option [37].

The differing effect of transdermal and oral replacement estrogen on migraine may be a consequence of the effect of these different routes of delivery on serotonin metabolism. A study to determine the effect of transdermal and oral estradiol on serotonin metabolism measured the urinary serotonin metabolite 5-hydroxyindole acetic acid (5-HIAA) after 2 and 4 weeks of estradiol treatment in postmenopausal women, and showed that estradiol produced a significant increase in 5-HIAA [38]. However, compared with the oral route, serotonin turnover was more effectively induced by the consistent and continuous low delivery associated with the transdermal route of delivery.

Progestin therapy is a necessary adjunct to estrogen replacement in a woman with an intact uterus. There are no data regarding the effect on migraine of different types, routes of delivery, or doses of progestins used for HRT. Continuous progestin appears to be better tolerated by migraineurs than cyclical progestins [39].

In addition to increased risk of VTE, estrogen replacement therapy has been associated with increased risk of stroke, myocardial infarction and, after some years of use, endometrial cancer (reduced by a progestin), and breast cancer [40]. However, cardiovascular risk is dependent on the age at which HRT is initiated. A meta-analysis of 23 trials of HRT compared results of younger women (< age 60 or < 10 years since menopause) versus older women, and showed that risks were

significantly reduced with the use of HRT in younger group [41]. Continuation beyond the age of 60 should be based on individual risk–benefit analysis [42].

Migraine aura is not a contraindication to the use of non-oral HRT on the basis that physiologic doses of natural estrogens are used. This is in contrast to high doses of synthetic contraceptive estrogens necessary to inhibit ovulation. At an individual level, estrogen replacement therapy can have an adverse effect on migraine aura. Of 10 women seen in an ophthalmology clinic who were using transdermal estrogen patches, 50 μg daily, six had a history of migraine (3, migraine with aura; 3, migraine without aura) before using replacement therapy [43]. All six women developed increased headache severity and accompanying visual scintillations. One patient with no previous history of migraine developed visual scintillations with no accompanying headache. Withdrawal of estrogens and additional migraine prophylaxis led to marked improvement in all women, with complete cessation of migraine in four patients.

However, complete withdrawal of HRT may be unnecessary, as case reports on four women developing migraine aura following initiation of HRT showed that, in all cases, aura resolved with either a reduction in estrogen dose or change in route of delivery of estrogen [44]. There are no data regarding risk associated with developing a first attack of migraine with aura when using HRT.

On a practical level, new onset headache should be carefully evaluated for secondary causes. If aura starts for the first time, transient ischemic attacks should be excluded. The dose and route of delivery of estrogen replacement should be assessed to provide the lowest effective dose necessary to control menopause symptoms. If aura does not resolve, assess the effect of withdrawal of estrogen and consider nonhormonal strategies as symptoms dictate.

Nonhormonal Options

Reviews and recommendations for effective alternatives to HRT in women with vasomotor symptoms support the use of fluoxetine, paroxetine, venlafaxine, or gabapentin [42].

Fluoxetine and venlafaxine have evidence of efficacy for migraine prophylaxis [45–48]. As with estrogen replacement therapy, initial exacerbation of migraine in the first few weeks of treatment can occur; therefore, it is important not to stop treatment too early. Gabapentin can also be considered for migraine prophylaxis, although evidence of efficacy is limited [49,50].

Conclusions

Migraine during perimenopause is a common problem; when coupled with menopausal symptoms, it can result in considerable disability. Migraine can be managed with standard acute and prophylactic treatments as symptoms dictate. If estrogen replacement is indicated for the management of menopause symptoms, low doses of transdermal estrogens may be used. If progestins are required, continuous progestins are less likely to aggravate migraine than cyclical progestins. The association between migraine and vasomotor symptoms should be a target for future research.

Disclosure

Dr. E. Anne MacGregor has acted as a consultant for Endo Pharmaceuticals.

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