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REVIEW

Menopause, Perimenopause, and Migraine: Understanding the Intersections and Implications for Treatment

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ABSTRACT

Migraine affects women three times more often than it does men, and various mechanisms may explain this incidence, including the key role of female sex hormones. Fluctuations in the levels of these hormones and their feedback control regulate the menstrual cycle, pregnancy, puerperium, perimenopause, and menopause. They can influence the occurrence and severity of migraine throughout the reproductive period. Of particular importance seems to be the perimenopausal period, which is associated with an increase in migraine, especially menstrual migraine, which is considered more disabling and less amenable to treatment than non-menstrual attacks. This article reviews the available evidence documenting the relationship between perimenopause, menopause, and migraine and diagnostic considerations in an attempt to determine the management of these periods of a woman's life. Special considerations, future directions, and unmet needs for perimenopausal and menopausal migraine are also discussed.

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Key Summary Points

Migraine affects women three times more often than it does men, and the key determinant of this relationship is most likely female sex hormones.

Migraine is one of the most debilitating neurological diseases, and in addition, hormonal fluctuations during the reproductive period can affect migraine occurrence and intensity.

The relationship between perimenopause, menopause, and migraine is still poorly explained and requires further observation.

INTRODUCTION

The female reproductive cycle is regulated by the hypothalamic–pituitary–ovarian system through the release of estrogen and progesterone. Fluctuations in the levels of these hormones and their feedback control regulate the menstrual cycle, pregnancy, puerperium, perimenopause, and menopause [1, 2]. Migraine affects women three times more often than it does men. Various mechanisms may explain this prevalence, including the important role of female sex hormones in migraine occurrence and higher genetic heritability in women [3, 4]. Hormonal fluctuations during the reproductive period can affect migraine occurrence and intensity, both positively and negatively [5]. The Stages of Reproductive Aging Workshop has developed a classification of the stages of reproductive aging, dividing women's lives into three stages: premenopausal (or reproductive), perimenopausal (or menopausal transition) and menopausal (or postmenopausal) [6, 7].

Premenopause is the period of several years preceding the last menstrual period, during which the clinical, hormonal, and metabolic changes associated with the extinction of ovarian function begin. Menstrual cycle disorders then manifest themselves to varying degrees and severity. It lasts an average of 5–6 years and is underpinned by a process of the extinction of ovarian hormonal function along with a rapidly progressive reduction in the number of ovarian follicles [7, 8]. In premenopause, the number of ovulatory cycles drops from 50% at age 35 to 5% at age 45 [9].

Perimenopause is the immediate perimenopausal period and includes the period 1–2 years before menopause and 12 months after menopause. During this period, irregular cycles accompanied by vasomotor symptoms may occur. Due to these constant, rapid changes in ovarian hormone concentrations, 60–70% of perimenopausal women experience symptoms such as headaches, hot flashes, mood swings, depression, decreased libido, and sleep disturbances [1, 7].

Menopause is the last menstrual bleeding, followed by no further menstruation for 12 months (and cannot be justified by any other condition). The average age for a woman to experience natural menopause is 49–51 years, but some women may experience menopause earlier or later [2]. Menopause in women under the age of 40 is called premature menopause or primary ovarian failure. Many factors influence the age at which menopause occurs, including genetic factors, socioeconomic factors, smoking, and alcohol intake [1–3].

Postmenopause is the period of a woman's life following menopause characterized by stable low levels of ovarian hormones [6, 7].

Migraine is a common neurological condition, and according to the 2021 Global Burden of Disease (GBD) study estimates, its prevalence is 15.2% worldwide (18.9% among women and 11.4% among men) [10, 11]. The two subtypes of this disease are migraine without aura (MwoA) and migraine with aura (MwA). The main symptom of migraine is a moderate to severe, usually unilateral headache, accompanied by nausea, vomiting, phonophobia and photophobia, which are aggravated during physical activity. Untreated or ineffectively treated attacks last from 4 to 72 h [12]. In about 30% of cases, reversible neurological symptoms lasting 5–60 min may occur before, during, or in the absence of headache (migraine aura without subsequent

headache), the most common of which are visual symptoms [12, 13]. Migraine often coexists with other chronic diseases including depression, anxiety, vascular diseases, or other pain syndromes, which further increases its burden [14, 15]. Despite significant disability, migraine is often underreported by patients and underdiagnosed by health care professionals [16]. Globally, this situation is complicated by the fact that about 80% of people with migraine live in low- and middle-income countries with limited access to medical care [17].

At some point during childhood and adolescence, 60% of girls and half of boys suffer from headaches, with the prevalence increasing significantly in girls and remaining stable in boys [18]. In the prepubertal period, both sexes are similarly affected by migraine. However, approximately around age of 9, it becomes more prevalent among girls [19]. The onset of migraine often occurs during menarche, when cyclic hormonal changes begin, and early menarche appears to be a risk factor for migraine development [7]. Headaches are reported in more than 50% of adolescent girls at the onset of menarche. Migraine with aura has a peak incidence between the ages of 12 and 13, while migraine without aura usually appears several years later [7, 20, 21]. Women have a 3.25-fold higher risk of developing migraine than men [20]. The peak incidence is observed in women between the ages of 35 and 45, and they also report a significantly higher burden of disease and more frequent use of pain medications than men [7, 21].

Almost half of patients with migraine report a link between headache and menstrual cycle [20]. Depending on whether migraine occurs exclusively during the perimenstrual period or at other times as well, the International Headache Society in its appendix to the third edition of the International Classification of Headache Disorders (ICHD-3) identifies pure menstrual migraine and menstrual-related migraine, which have an overall incidence of 1% and 7%, respectively [13, 22]. The perimenopausal period and menopause consist of several phases having a unique hormonal pattern; therefore, they all have different effects on migraine. Another very important factor is whether menopause is a natural process or surgery-induced and whether hormone replacement therapy (HRT) is used [6, 23]. The reported prevalence of migraine during menopause varies between 10% and 29%, depending on various studies [24, 25]. Data from available studies suggest that the prevalence of migraine remains stable or increases during the perimenopausal period and decreases after menopause. Additionally, it should be noted that population-based studies have supported this trend more so than those conducted in hospital settings [1, 24].

Given the above, it is crucial to understand the relationship between migraine and perimenopause and menopause. Further research in this area is needed to develop targeted management strategies during this period. This paper reviews the available evidence documenting the relationship between perimenopause, menopause, and migraine, with an attempt to determine management during these periods of a woman's life. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Hormonal Fluctuations and Migraine Pathophysiology

Role of Hormones

The mechanism for gender differences in migraine is not clear, even though endogenous sex steroids, which can passively cross the blood–brain barrier, are thought to play an important role [26, 27]. Most of the available literature focuses on the effect of estrogen, which is known to modulate serotonergic neurotransmission, activate the endogenous opioidergic system, and induce vascular changes by suppressing inflammatory responses [28–30]. The role of progesterone has not been well defined, but experimental studies suggest that it may play a protective role by inhibiting neurogenic edema and mast cell histamine secretion, reducing trigeminal nociception, and decreasing prostaglandin production [3, 7, 21]. The role of testosterone in migraine pathogenesis has also not been sufficiently studied, but there are several

reports suggesting that testosterone may play a role in migraine in women [31]. Mechanisms potentially could include modulation of cerebral blood flow, effects on the serotonergic system, and susceptibility to cortical spreading depression [7, 31]. There are also some reports suggesting the possible involvement of the hypothalamus–pituitary–adrenal axis on the development of migraine. Cortisol and dehydroepiandrosterone-sulfate (DHEA-S) could play a role; however, solid scientific evidence supporting this involvement is lacking [32]. Rustichelli and colleagues demonstrated lower levels of allopregnanolone, which is a neurosteroid, in women with menstrual-related migraine and postmenopausal migraine than in control groups. These observations suggest that reduced GABAergic inhibition, caused by low serum levels of allopregnanolone, may contribute to menstrual-related migraine and the persistence of postmenopausal migraine [33].

Menstruation is the most common trigger for migraine during reproductive life. Estrogen's serum levels [in particular those of estradiol (E2), but possibly its metabolites (estrone E1 and estriol E2) as well] are some of the determinants in menstrual-related migraine, and only decreases in their concentration are associated with the onset of migraine [34, 35]. In fact, with the continuous extremely high estrogen concentrations of the second and third trimesters of pregnancy, migraine often disappears. In nonpregnant women, estrogens are produced primarily by the ovaries, and in much lesser quantities by adipocytes, adrenal glands, the liver, and breasts [36, 37].

When all headaches in a diary study were combined, not only was the menstrual peak more prominent, but a post-ovulatory peak was revealed as well [38]. If the cyclic pattern of E2 concentration is simultaneously displayed, an important relationship emerges: the time when there is an increase in headache frequency in female migraineurs is when serum estrogen levels are declining [20, 23].

This relationship is also seen with oral contraceptives (OCs). Up to 70% of OC users experience headache during the placebo week of their pill pack, when exogenous estrogen concentrations drop precipitously [39]. The peak incidence of these headaches occurs on the third day of the placebo week (similar to the onset of migraine after childbirth, which usually occurs on about the third day after delivery). If migraine indeed occurs when the threshold for trigeminal activation is exceeded, then a decline in serum estrogen concentrations may represent a specific lowering of that threshold [40]. However, before menstruation there is a decline in serum concentration for both estrogen (produced by the granulosa cells of the follicle) and progesterone (produced by the corpus luteum) levels. In a series of studies from the mid-1970s, Somerville separated and considered the menstrual declines in E2 and progesterone levels and demonstrated that migraines coincided only with falls in E2 [41]. The menstrual cycle, including the levels of the different hormones throughout the cycle, is shown in Fig. 1.

Significant limitations to the use of combined (estro-progestin) hormonal contraceptives (oral, vaginal, or transdermal) (CHC) are documented in WHO Medical Eligibility Criteria for Contraceptive Use in women with migraine especially with aura, particularly the two- to fourfold increased risk of stroke in women who experience migraine with aura [42]. Given the contraindications to CHC use in a significant proportion of female migraine sufferers, including all women with migraine with aura, progestin-only oral contraceptives [progestin-only pills (POP)] are increasingly considered an alternative for patients with migraine, particularly those experiencing migraine with aura. The mechanism of POP in reducing migraine frequency and intensity is largely unknown but may relate to inhibition of ovulation and the maintenance of stable E2 levels throughout the cycle (between 30 and 70 pg/ml) [43, 44]. A recent meta-analysis demonstrated that desogestrel 75 mcg/day POP significantly but modestly reduced the number of migraine attacks and migraine days; reduced intensity and duration and reduced analgesic and triptan use were observed, along with improved headache-related quality of life. We have no data about any possible beneficial effect in this respect of the new drospirenone 4 mg 24+4-only pill, a newly launched POP [45, 46].

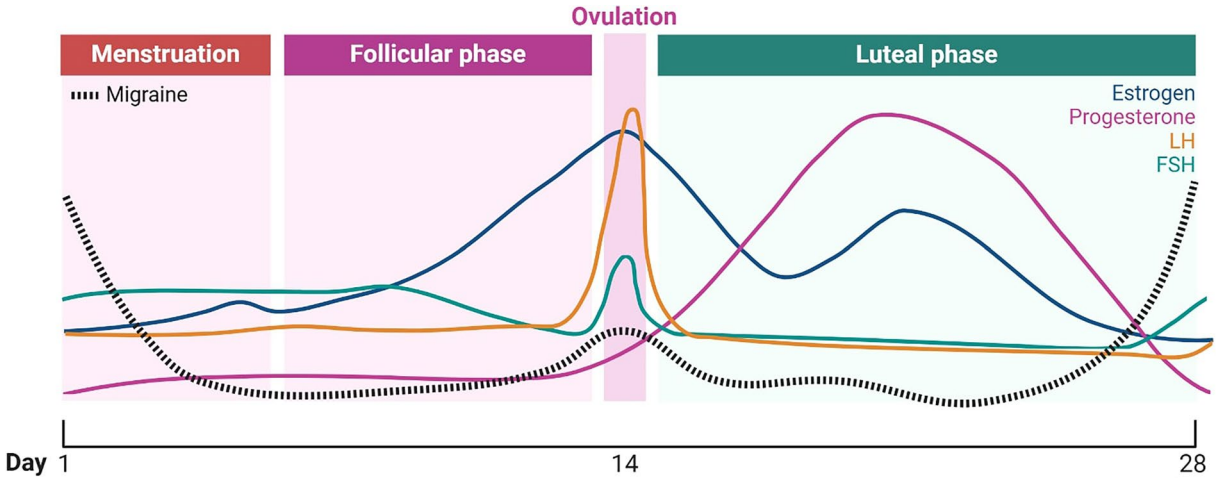

Fig. 1 Menstrual cycle rhythmicity

Pathophysiology of Migraine in the Context of Menopause

The mechanisms by which the menopausal transition influences migraine manifestations are complex and only partially understood. The brain contains receptors for estrogens and progestins that may act as pain modulators. Animal studies have shown that the cingulate cortex—a major cortical area for pain processing—can be activated to a pro-nociceptive state by increased estrogen levels [40]. In contrast, low estrogen levels might protect against facial pain [34]. In humans, receptors for female sex hormones have been found in the trigeminal system [47]. In addition, estrogens and progestins have a complex interplay with oxytocin, which is produced by the pituitary gland and can have anti-nociceptive effects via its connections with the trigeminovascular system [32]. The oxytocin pathway could be the link between the actions of female sex hormones in the brain and the pathways of migraine-related neuropeptides such as the calcitonin gene-related peptide (CGRP) pathway [35]. Notably, animal evidence points to sex differences in the expression of oxytocin and vasopressin receptors possibly due to the different degree of pituitary stimulation resulting from female sex hormones [48].

As the activation of the CGRP pathway is one of the best studied mechanisms of migraine, this pathway has also been studied in relation to the expression of female sex hormones. Notably, the injection of 17-beta-estradiol in rats increased dermal vasodilation compared with controls, suggesting that high levels of estradiol can increase CGRP release [49]. With regard to human studies, a crossover study in a real-world setting measured the CGRP levels in the tear fluid and plasma in several groups of women, including those with regular menstrual cycles and those on treatment with combined oral contraceptives; all the groups of women with migraine were compared with migraine-free subjects. Notably, CGRP levels were higher in women with migraine and regular menstrual cycles than in women without migraine; women in menopause or taking combined hormonal contraception did not show any difference in CGRP levels compared with migraine-free women [50].

Estrogen and progestin compounds also have some direct effect on neurons and the vasculature. While estrogens increase neuronal excitability, progestins have an inhibitory effect on that function [2]. Additionally, estrogens promote vasodilation whereas progestins might lead either to dilation or to constriction of vascular smooth cells [8, 51].

The abovementioned evidence might explain the influence of female sex hormones on migraine during the perimenopausal and menopausal periods. The association between female sex hormones and migraine exacerbations

follows the "estrogen withdrawal" hypothesis [29]. According to this hypothesis, there is a high risk of severe migraine when estrogen levels experience a rapid decline. This hypothesis explains the occurrence of menstrual migraine, as the premenstrual phase of the ovarian cycle is characterized by a rapid drop in estrogen levels. It also explains the increased risk of migraine in women using combined hormonal contraceptives with high estrogen content, as those compounds can increase the steepness of premenstrual estrogen decline. This hypothesis can also explain the transient exacerbation in migraine symptoms experienced by some women during the menopausal transition [1, 7]. This transition is characterized by ample fluctuations in the estrogen levels that precede the decline in estrogen levels that can be found years after the menopause. In this context, women can experience an exacerbation of migraine as shown by observational evidence [24]. An exacerbation of migraine can also occur with hormone replacement therapy, as it involves the exogenous administration of estrogens together with progestins [28, 52–54].

The Relationship Between Menstrual Migraine and Perimenopausal Migraine

The estrogen withdrawal hypothesis explains why the premenstrual phase of the ovarian cycle might trigger migraine attacks. However, it does not enable prediction of the course of migraine after menopause in women with menstrual migraine. The literature shows that women with a history of premenstrual stress disorder, menstrual migraine, and anxiety and/or depressive symptoms have an increased risk of climacteric symptoms, including hot flashes, night sweats, irritability, insomnia, joint aches, vaginal dryness, decreased libido, and headache [55–57]. Those symptoms can signal the presence of a "hormonal sensitivity" that can manifest itself during the perimenstrual phase in fertile women and can translate into climacteric symptoms and the persistence of migraine through the menopausal transition [57].

It should be noted that migraine pain and migraine aura have a different sensitivity to the effect of hormones. Migraine aura can be modulated by the effect of high estrogen level, indicating sensitivity of this phenomenon to female sex hormones [26, 27]. However, from a clinical point of view, migraine pain is more sensitive to hormonal fluctuations than is migraine aura. Perhaps this is a reason why migraine with aura can persist throughout pregnancy while migraine without aura usually improves during that period [58–60]. Similarly, migraine without aura usually improves after the menopause, while migraine with aura might worsen or even start after menopause, and attacks of aura without migraine can occur [3, 7, 61].

Genetics and Environmental Factors in Postmenopausal Migraine

Migraine is a biopsychosocial disease in which the genetic predisposition and biological components of each individual interact with psychological and environmental factors to determine the disease-related burden [62]. While there is no specific genetic study about the influence of genetic factors on the expression of migraine after the menopausal transition, there is evidence that some genetic polymorphisms in estrogen receptors overlap between migraine and endometriosis [63] and might therefore constitute a genetic link between migraine and hormonal condition. Additionally, it has been found that hormone levels are different in postmenopausal women with and without migraine, with lower levels of allopregnanolone in women with migraine compared with those without, suggesting that the expression of genes linked to female sex hormones is different in women with and without migraine. Further studies might better elucidate the relationship between the expression of genes linked to female sex hormones—or their receptors—and the manifestations of migraine [64].

Clinical Presentation of Migraine During Menopause and Perimenopause

Changes in Migraine Patterns

Migraine undergoes a significant change in its clinical characteristics during perimenopause

and menopause, where there is an alteration of the orderly pattern of estrogen and progesterone secretion [65]. This is especially true during the perimenopausal period, where a significant fluctuation of estrogen levels is observed, along with a transient increase in vasomotor symptoms and migraine prevalence. Furthermore, it has been observed that high blood estrogen levels are associated with an increase in the prevalence of aura symptoms during the perimenopausal period [23, 35]. In such situations, the physiological stabilization of estrogen levels within the physiological range is likely to reduce the migraine burden in terms of intensity and frequency [36, 65]. However, there is significant uncertainty about the epidemiological impact of migraine during perimenopause. Approximately 30% of women are affected by a peak in their migraine symptoms during perimenopause. A prior history of migraine seems to be a predominant risk factor for worsening symptoms during the perimenopause [66]. Seven percent of premenopausal patients with migraine are affected by a pain which occurs only in the perimenstrual period. This condition is known as pure menstrual migraine (PMM) of the perimenopause [67]. Perimenopausal pain is classically described as pulsating, unilateral ,and associated with nausea and vomiting but sometimes can have a pressure pattern with mid-facial localization and vestibular symptoms [68].

During menopause, there is a physiological decline in endogenous estrogen levels, which is associated with a progressive improvement of migraine symptoms, reaching complete relief in some patients [24]. However, in a smaller but not negligible percentage of patients, the pain may persist and be resistant to common analgesics [69, 70]. The risk of chronification is another emerging issue of the menopausal period, and the issue is even more complex because the use of triptans is often contraindicated for the occurrence of other comorbidities (e.g., uncontrolled arterial hypertension) or in patients who are above 65 years of age. The cardiovascular risk could increase significantly, becoming a strong limit to the therapeutic approach to symptomatic cases [71]. The use of new drugs targeting CGRP is changing the natural history of chronic migraine, especially during the menopause period, where other treatments have failed [72].

Co-occurring Symptoms

Despite menopause being generally associated with a global relief of migraine symptoms in many women, sleep alterations, anxiety, and depression, which often accompany menopause, may exacerbate migraine symptoms [55, 67]. Moreover, other pain disorders characterized by central sensitization and widespread pain, such as fibromyalgia, can negatively affect perimenopausal and menopausal women with migraine by reducing the pain threshold [73].

Another issue to consider is the association between migraine and menopausal weight gain. It has already been described how obesity could be strictly linked to a worsening of migraine. The chronic release of inflammatory mediators and substance P from adipose tissue and the persistent activation of the trigeminal system from CGRP, which is highly expressed in obese individuals, are some of the mechanisms which contribute to the vicious cycle of pain in menopausal women who gain weight [74]. The benefits of weight loss toward migraine symptoms confirm the need for strict weight control in menopausal women, who are at potential risk of cardiovascular disease after estrogenic decline [75]. Moreover, an unfavorable lipid profile of the menopausal period might negatively affect cardiovascular risk, and it has also been hypothesized that there is a correlation between migraine severity and cholesterol levels [76].

Another disorder directly related to a specific phase of the menstrual cycle is premenstrual syndrome (PMS). It manifests as a wide range of physiological and psychological symptoms occurring during the luteal phase, which resolve during or shortly after the onset of menstruation [22, 36]. The relationship between PMS and menstrual migraine is controversial and poorly studied, and observations to date provide conflicting results [77].

Diagnostic Considerations

The perimenopausal period may pose a challenge in diagnosing headache due to multiple symptoms that can occur in this period. Importantly, apart from migraine, perimenopause has been linked to other types of headache including tension-type headache or new-onset headaches [29]. It is certainly important to have new neurological symptoms (red flags) in this age group at higher risk of developing cardiovascular or oncological diseases, which may suggest secondary headaches [78, 79]. Sleep disorders and depressive disorders more common for the elderly population should be monitored and treated, because migraine treatment may be complicated by their comorbidity [5, 80–82].

Despite associations between sex hormones and migraine, there are limited data supporting the role of estrogen, progesterone, follicle-stimulating hormone (FSH), or luteinizing hormone (LH) testing in the diagnosis or management of headache. This is especially valid in menopausal transition, when levels of hormones of the hypothalamic–pituitary–ovarian axis may be highly variable. Generally, mean FSH concentrations start to increase 2 years prior to menopause and stabilize 4 years later. The opposite situation is observed for estradiol, with a decrease starting 2 years before menopause that reaches a plateau 2 years after last ovulation [83]. However, in the transition period, both FSH and estradiol levels may follow different patterns, with elevated estradiol levels or decreased FSH concentrations in individual cases [84]. Studies looking for associations between sex hormones and migraine during perimenopause are few. One study showed that lower estradiol and higher FSH levels were associated with lower migraine prevalence in women with premenstrual syndrome symptoms during the menopausal transition [83, 84]. Due to limited data, sex hormone testing currently does not play a generally accepted role in migraine diagnosis or management during perimenopause.

This variability in hormone levels during the perimenopausal period should influence diagnostic strategies in the future. It is important to develop practical recommendations for distinguishing between hormonal and non-hormonal headache triggers in this demographic group. Despite the current lack of recommendations, it would be worth exploring the use of detailed headache diaries to track hormonal triggers of migraine attacks. It could also be important to introduce specific hormone tests in specific groups of patients and in certain recurrent scenarios, and to identify the limitations of current diagnostic tools.

Treatment Approaches

Migraine management during the perimenopausal transition involves a combination of [5] standard migraine treatment, in accordance with national and international guidelines, and [36] specific therapeutic strategies tailored to the hormonal fluctuations characteristic of this life stage (Fig. 2).

A key specific treatment approach during perimenopause is hormone replacement therapy (HRT). The perimenopausal phase is marked by increasing hormonal fluctuations, which are associated with a rise in migraine frequency and severity [5]. Hormone substitution to stabilize these fluctuations may represent a plausible strategy for preventing migraine, similar to the management of menstrual migraine [36]. However, the evidence on the efficacy of HRT in preventing perimenopausal migraine remains limited and inconsistent [23]. Some evidence suggests that HRT can improve migraine in this population, with over 60% of women reporting reduced migraine frequency while on HRT [37]. In contrast, other large cohort studies have indicated a significant association between HRT use and the presence of migraine, with both oral and local forms of delivery. It remains unclear whether HRT itself triggers migraine or is more frequently prescribed to women with pre-existing migraine [53, 85]. One smaller study suggested that continuous transdermal estradiol may be superior to oral estrogen formulations in terms of migraine control. Among oral options, tibolone has been suggested as more beneficial than estradiol/norethisterone for migraine

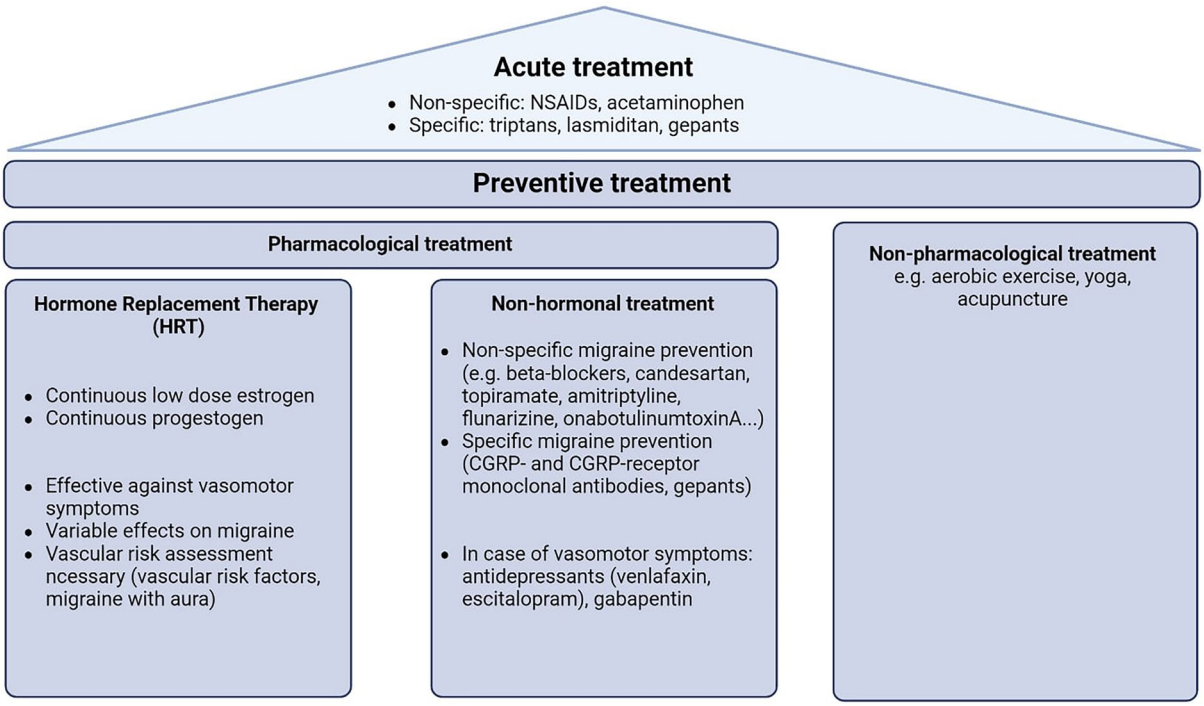

Fig. 2 Acute and preventive treatment options for perimenopausal women with migraine

management. As a general principle, it is recommended to prescribe the lowest effective dose of estrogen [53, 86, 87]. Phytoestrogens, such as soy isoflavones, have also been proposed as an alternative to mitigate perimenopausal symptoms, although evidence regarding their effect on migraine is limited [88]. Continuous progestogen formulations, especially the levonorgestrel intrauterine system, may be advisable as part of HRT due to their minimal systemic effects and potential positive impact on migraine [23, 89].

Since HRT is frequently recommended for perimenopausal women to alleviate vasomotor symptoms, it may be particularly beneficial for women with both migraine and vasomotor symptoms, as it can potentially address both conditions [23, 53, 89].

A critical consideration when prescribing HRT to women with migraine is the increased risk of ischemic stroke, particularly in those with migraine with aura and estrogen therapy. However, most data pertain to younger women, with the odds ratio for stroke in women with migraine higher in those under 50 [90]. In the context of HRT, the Oxford Vascular Study (OXVASC) observed a nonsignificant trend between HRT use and cryptogenic ischemic events in patients with migraine [91]. This area requires further research to clarify the risk profile.

In addition to these specific considerations, standard migraine treatments remain applicable, although it is essential to account for age-related restrictions and contraindications. Acute migraine treatments typically include nonspecific medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, alongside migraine-specific agents like triptans, ditans, and CGRP-receptor antagonists (gepants) [92]. Preventive options for migraine include nonspecific drugs: beta-blockers, the angiotensin II receptor blocker candesartan, the calcium channel blocker flunarizine, anticonvulsants such as topiramate and valproate, the tricyclic antidepressant amitriptyline, serotonin norepinephrine reuptake inhibitor (SNRI), and onabotulinumtoxinA for chronic migraine [93]. In perimenopausal patients with vasomotor symptoms, antidepressants such as escitalopram and venlafaxine can be useful, since they

treat vasomotor symptoms and may also exhibit migraine-preventive properties [94]. Gabapentin, which is effective for hot flashes, may also be beneficial for migraine prevention [95]. Specific preventive options include CGRP-targeted therapies, such as monoclonal antibodies and gepants [96, 97]. In postmenopausal women, caution is warranted with triptans and CGRP antagonists, as their formal indication only extends to patients under 65 due to concerns about their vasoactive properties and potential cardiovascular risks. Despite this, their use in clinical practice in patients beyond 65 is common, and no significant safety concerns have emerged so far [98–100].

As with all migraine treatments, pharmacological prevention should be complemented by non-pharmacological approaches: neuromodulation or nerve blocks. For women transitioning through perimenopause and menopause, evidence supports the potential benefits of acupuncture, vitamin E, black cohosh, aerobic exercise, and yoga in alleviating both headaches and vasomotor symptoms [95, 101].

Special Considerations, Future Directions, and Research Needs

Menopause is not only a physiological condition, but also a cultural phenomenon. It is an important moment in women's reproductive life as it is associated with physical, cognitive, and social transformations. Therefore, different attitudes toward menopause can influence the symptoms experienced by women during the menopausal transition and vice versa. There are many studies in the literature showing that the attitude toward the menopausal transition differs between cultures [102]. Although there are no systematic studies on the role of attitude toward menopause in influencing migraine after the menopausal transition, it is reasonable to speculate that attitudes toward menopause can influence the manifestations of migraine during that period.

Given the high prevalence of migraine, the increased incidence of attacks associated with menstruation and the worsening of migraine associated with the transition to menopause, perimenopausal women should be routinely asked about migraine and should receive appropriate specialized counselling. There should be individualized treatment plans that include both acute and preventive migraine treatment and also hormonal strategies. Given the additional health burdens or medication use due to other chronic diseases, the importance of personalized approaches based on patient history, preferences, and risk factors should be emphasized. This is particularly important in the group of patients with chronic or refractory migraine during menopause, where the key treatment pattern seems to be avoidance of polypharmacy [103].

Globally, it is important to educate the public and properly educate medical professionals to increase awareness of the burden of migraine and effective treatments. It is also important to change the paradigm of migraine treatment, which is currently still dependent on the significant cost of new specific drugs [17, 104, 105].

Future research will benefit from the identification of the interplay between female sex hormones and the mechanisms of migraine pathogenesis, including the CGRP pathway and new potential therapeutic targets [106]. Long-term observations evaluating efficacy and safety, especially of new drugs used to treat migraine but also of hormonal drugs often used in gynecological practice, are important. It is also important to develop practical diagnostic tools to help monitor this population group.

In addition it is important to emphasize the limitations of this review, which were difficult to avoid given the breadth of the topic. Some studies on hormonal changes discussed in this review did not address variability in methodologies, such as differences in hormone measurement techniques or timing of sample collection. These studies often differed in methodology and had strengths but also limitations. Undoubtedly, this is a very interesting and developing area of science, which should also systematize the principles of clinical and preclinical research in the years to come.

CONCLUSION

Migraine patterns show a temporal evolution that correlates with hormonal changes in a woman's life cycle. These observations suggest that both female and male sex hormones may play an important role in the pathophysiology of primary headaches, and the role of estrogen in particular in female patients with migraine has been well studied. The period of the perimenopause and menopause should be a time for careful observation of the course of migraine. Detailed studies are warranted to clarify the role of sex hormones not only in migraine but in all primary headaches.

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Declarations

Conflict of Interest. Marta Waliszewska-Prosół is a member of the Editorial Board of The Journal of Headache and Pain; reports personal fees from AbbVie, Pfizer, Polpharma and Teva for speaker activities. Giovanni Grandi received honoraria for sponsored lectures and participation in advisory boards from Organon, Bayer AG, Teva/Theramex, Exeltis, Italfarmaco, Opocrin and Gedeon Richter outside of the scope of this manuscript. Raffaele Ornello reports personal fees and non-financial support from AbbVie, Eli Lilly, Lundbeck, Novartis, Pfizer, and Teva; received research grants from Novartis; is Associate Editor for the Headache and Neurogenic Section of Frontiers in Neurology and for Arquivos de Neuropsiquiatria; is a Junior Editorial Board Member of The Journal of Headache and Pain; is an Editorial Board Member of Confinia Cephalalgica. Bianca Raffaelli is a member of the Editorial Board of The Journal of Headache and Pain; reports personal fees from AbbVie, Eli Lilly, Lundbeck, Novartis, Organon, Perfood and Teva for participating in advisory boards and/or speaker activities as well as research funding from Lundbeck, Novartis, Else Kröner-Fresenius-Stiftung, German Research Foundation and German Migraine and Headache Society. Marcin Straburzyński reports personal fees from Pfizer, Teva, Bausch, AbbVie, Neuca and Novartis for speaker activities. Claudio Tana is a member of the Editorial Board of The Journal of Headache and Pain and Editor of the Primary Care Section of Annals of Medicine. Paolo Martelletti is the Editor-in-Chief of The Journal of Headache and Pain and of SN Comprehensive Clinical Medicine. Paolo Martelletti and Raffaele Ornello are Editorial Board members of Neurology and Therapy. Paolo Martelletti and Raffaele Ornello were not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

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