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CLINICAL ASPECTS OF HEADACHES

# Migraine in perimenopausal women

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**Abstract** Hormonal changes during the reproductive cycle are thought to account for the variation in migraine occurrence and intensity. Although the majority of women and the specialists treating them do not consider migraine as a component of the climacteric syndrome, many women, in fact, do experience migraine during perimenopause. If a woman already suffers from migraine, the attacks often worsen during menopausal transition. Initial onset of the condition during this period is relatively rare. Women with the premenstrual syndrome (PMS) prior to entering menopause are more likely to experience, during late menopausal transition, an increased prevalence of migraine attacks. Hormone replacement therapy (HRT) can be initiated during the late premenopausal phase and the first years of postmenopause to relieve climacteric symptoms. The effect of HRT on migraine, either as a secondary effect of the therapy or as a preventive measure against perimenopausal migraine, has been variously investigated. HRT preparations should be administered continuously, without intervals, to prevent sudden estrogen deprivation and the migraine attacks that will ensue. Wide varieties of formulations, both systemic and topical, are available. Treatment with transdermal patches and estradiol-based gels is preferable to oral formulations as they maintain constant blood hormone levels. Natural menopause is associated with a lower incidence of migraine as compared with surgical menopause; data on the role of hysterectomy alone or associated with ovariectomy in changing the occurrence of migraine are till now unclear.

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## Introduction

Adult women experience migraine attacks more commonly than men by a ratio of three to one. Hormonal changes during the reproductive cycle are thought to account for the variation in migraine occurrence and intensity. It is widely believed that migraine symptoms improve with menopause, and many women await this phase of their reproductive life in the hope that headache attacks will eventually subside. Statistically this may be true, but menopause proceeds through various stages, each of which can differently influence migraine. Other factors that can affect migraine expression are whether a woman enters menopause naturally or has undergone surgery or has begun hormone therapy to counteract the many different symptoms menopause can cause on her body and mind. Here we discuss several of the many factors that can influence the clinical expression of migraine during menopause.

## Menopausal stages and clinical evolution of migraine

The stage of reproductive aging workshop *STRAW + 10 criteria* (Table 1) delineates the stages of menopausal transition and postmenopause according to the characteristics of the menstrual cycle and serum sex hormone levels [1]. Two phases of *menopausal transition* are distinguished: the *early phase* is characterized by variable cycle duration ($\geq$7 days) and the *late phase* by amenorrhea, which may last between 2 and 11 months. Similarly,

**Table 1** Some of the STRAW + 10 criteria for staging reproductive aging in women

| Menarche ⇩ | | | | | Last menstrual period ⇩ | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Stage | -5 | -4 | -3b | -3a | -2 | -1 | +1a | +1b | +1c | +2 |
| *Terminology* | REPRODUCTIVE | | | | MENOPAUSAL TRANSITION | | POSTMENOPAUSE | | | |
| | early | peak | late | | early | late | early | | | late |
| | | | | | PERIMENOPAUSE | | | | | |
| *Duration* | variable | | | | variable | 1-3 years | 2 years (1+1) | | 3-6 years | Remaining lifespan |
| PRINCIPAL CRITERIA | | | | | | | | | | |
| *Menstrual Cycle* | Variable to regular | regular | | Subtle changes in flow/ length | Variable length<br>Persistent ≥ 7 day<br>Difference in length of consecutive cycles | Interval of amenorrhea of ≥ 60 days | | | | |

*postmenopause* is divided into two phases: the *early phase* lasts between 5 and 8 years, is characterized by amenorrhea for ≥1 year and low serum estrogen and high follicle stimulating hormone (FSH) levels; the *late phase* is characterized by stably low ovarian hormone levels and continues for the rest of a woman's life. Finally, the term *perimenopause* refers to a period of 2–8 years between the last menses (*menopausal transition*) and 1 year after the last menses (*postmenopause*).

Migraine incidence peaks about age 50, coinciding with fluctuations in reproductive hormone levels which produce typical symptoms (the so-called climacteric symptoms) such as hot flashes, night sweats, vaginal dryness, irritability, sleep disturbances, and headache [2]. If a woman already suffers from migraine, the attacks often worsen during menopausal transition. Initial onset of the condition during this period is relatively rare [3]. Usually, symptoms will improve when a woman enters postmenopause and hormone levels have stabilized. About two-thirds of women migraineurs report that migraine intensity and frequency diminish significantly during postmenopause [4].

Headache intensity, as rated on a pain scale from 0 to 3 (0 = no pain, 1 = mild, 2 = moderate, 3 = severe), correlates with the different phases of menopausal transition. The percentage of women reporting moderate-to-severe headache pain is higher during both the early and late phases of menopausal transition than during postmenopause (24 vs. 36 and 32 %, respectively) [2].

The theory that best explains the hormone-mediated mechanism that triggers migraine is based on cyclical fluctuations in estrogen levels: the transient decrease in estrogen around menses triggers headache attacks (menstrually related migraine, pure menstrual migraine) in over 50 % of women [5, 6]. Estrogen fluctuations can also trigger migraine when estrogen deprivation persists for weeks or months, as occurs during late menopausal transition and early postmenopause [7].

Women with the premenstrual syndrome (PMS) prior to entering menopause are more likely to experience, during late menopausal transition, an increased prevalence of migraine attacks, which then diminish during postmenopause. In their study on migraine prevalence during menopausal transition, Wang et al. [8] found that, as compared with the patients in late menopausal transition, migraine prevalence was higher among those in early menopausal transition with a history of PMS (31 vs. 21 %, respectively). A history of PMS is considered a predictor for the development of migraine during the menopausal transition as it may indicate a higher sensitivity to hormonal fluctuations and greater predisposition to developing moderate-to-severe climacteric symptoms [2]. Furthermore, the intensity and duration of climacteric symptoms (hot flashes, palpitations, night sweats, and mood swings) can contribute to exacerbation of migraine attacks [9]. Worsening of migraine may also be secondary to concomitant conditions such as depression, which raises the risk of the development of chronic pain and insomnia that could increase migraine frequency [10, 11].

## Migraine and hormone replacement therapy

Hormone replacement therapy (HRT) can be initiated during the late premenopausal phase and the first years of postmenopause to relieve climacteric symptoms. Wide varieties of formulations, both systemic and topical, are available. Treatment with transdermal patches and estradiol-based gels is preferable to oral formulations as they maintain constant blood hormone levels [12, 13]. Although the majority of women and the specialists treating them do not consider migraine as a component of the climacteric syndrome, many women, in fact, do experience migraine during perimenopause. The effect of HRT on migraine, either as a secondary effect of the therapy or as a preventive measure against perimenopausal migraine, has been variously investigated. HRT preparations should be administered continuously, without intervals, to prevent sudden estrogen deprivation and the migraine attacks that will ensue. In her preliminary uncontrolled study, MacGregor et al. [14] reported that, as compared with oral formulations, transdermal estrogen replacement in premenopausal and postmenopausal women was associated with improvement in migraine. Moreover, in an earlier study she found that elevated doses can more easily induce new migraine with aura or exacerbate attack frequency and intensity, whereas the aura disappears with the administration of lower doses or switching from an oral to a topical formulation [15]. Similar results were obtained by Nappi et al. [13] who reported that migraine worsened in women receiving an HRT with oral estradiol plus medroxyprogesterone acetate but did not change in those receiving HRT with a transdermal patch plus medroxyprogesterone.

During perimenopause, women with intact uterus should be offered protection against the development of atypical endometrial hyperplasia and endometrial carcinoma. HRT strategies include the association of progestogen for 12–14 days in many cases. However, combined-continuous estrogen and progestin therapy is better tolerated than cyclical administration.

In their prospective longitudinal study, Facchinetti et al. reported that HRT increases migraine attack intensity and frequency in postmenopausal women. By comparing with other therapy regimens, combined-continuous HRT was found to be preferable in migraine as is it associated with shorter duration of attack and fewer days of migraine [16]. Nand et al. [17] studied whether progesterone dose had an effect on migraine. They tested three different doses of medroxyprogesterone acetate combined with estradiol in three different groups but found no differences between them. Aegidius et al. [19] evaluated a sample of 5507 patients receiving HRT and found a strong association between therapy, both oral and topical formulations, and migraine. In their study involving a sample of 10,107 menopausal women, Misakian et al. [18] found a significant correlation between HRT and migraine (OR 1.42, 95 % CI 1.24–1.62). It is also possible, however, that women with migraine more often receive exogenous hormone therapy to prevent exacerbation of the condition [20, 21].

Contrary to guidelines on the use of estroprogestinic contraceptives, according to which migraine with aura is an absolute contraindication to take these drugs, migraine with aura is not an absolute contraindication to HRT when the route of administration is topical with low dose natural estrogens as they involve a minor risk of thromboembolism. If new migraine with aura occurs during HRT, a transient ischemic attack or other vasomotor events need to be excluded. If the aura recurs or worsens, HRT should be discontinued [22].

Migraine with aura is associated with a two-fold higher risk of ischemic stroke [23, 24]. In their meta-analysis, Spector et al. found an association between migraine and stroke, with an overall pooled effect estimate of 2.04 (95 %

CI 1.72–2.43). Subgroup analysis showed a difference between migraine with and without aura (OR 2.25, 95 % CI 1.53–3.33 vs. OR 1.24, 95 % CI 0.66–1.79). Despite the difference, the confidence intervals for the pooled adjusted ORs overlap, so that it cannot be considered statistically significant [24]. These data were consistent with another meta-analysis which reported a relative risk (RR) of 1.73 (95 % CI 1.31–2.29) for any type of migraine and ischemic stroke. Subanalysis of women aged >45 years showed a RR of 1.22 (95 % CI 0.88–1.68), not statistically significant. The RR rose to 10.0 (95 % CI 1.4–73.3) in women with migraine with aura who take estroprogestinic contraceptives and smoke. In women with migraine with aura, the risk of stroke was 2.08 (95 % CI 1.3–3.31), while the association with migraine without aura was not statistically significant. The risk of death due to cardiovascular causes in women with migraine was 1.60 (95 % CI 1.06–2.42) [23]. The limitations of these two studies were that they included data from men and women, without distinguishing between the sexes in some cases, and that no subanalysis of postmenopausal women was carried out.

In their prospective randomized study, Nappi et al. compared the effect of tibolone vs. continuous combined HRT on migraine in women requiring exogenous hormone replacement. Although tibolone did not reduce the number of days with migraine without aura, after 3 months of therapy it did significantly reduce the number of hours during which pain impeded activities of daily living and the amount of pain killer taken [25].

## Migraine and surgical menopause

Natural menopause is associated with a lower incidence of migraine as compared with surgical menopause [4, 26, 27]. The difference was present also when these two groups of women were compared, considering only those with PMS [8]. In their study involving a large sample of postmenopausal women, Neri et al. reported an improvement in migraine as compared with the premenopausal period in two-thirds of cases, while tension-type headache improved less. In the women who had undergone ovariectomy, however, the course of migraine was worse than in those who had entered menopause naturally ($p = 0.003$). Among the women who had received surgery, 67 % reported worsening of migraine and 33 % improved. Among those who entered menopause naturally, 67 % reported improvement, 24 % no change, and 9 % worsening of their condition [4].

In a cross-sectional survey involving 986 hysterectomized women with one or both ovaries preserved and 5636 non-hysterectomized women with both ovaries, far fewer of the non-hysterectomized reported worsening of migraine compared to the hysterectomized group (8.8 vs. 15.1 %, respectively) [26]. This finding contrasts with previous observations and appears to emphasize only the importance of the presence or absence of the uterus.

In their study on migraine prevalence, Wang et al. also examined whether it was related to type of surgery: hysterectomized women with bilateral annexectomy were found to experience improvement as compared with hysterectomized women with unilateral annexectomy or only hysterectomized. The difference was not statistically significant, however [8].

Moreover, a study on compliance with HRT showed that migraine occurs more often in women with intact uterus who receive sequential HRT than in hysterectomized women receiving continuous oral estrogens [28].

Martin et al. reported that pharmacological ovariectomy with gonadotropin-releasing hormone (GnRH) analogs plus systemic estradiol appears to reduce pain severity but not episode frequency. The study included 21 women with migraine (age range 21–45 years) randomized to two treatment groups: one group received goserelin (a GnRH analog) then 1 month later a patch containing 100 mcg of 17 beta estradiol. The other group received a placebo patch. At 2 months into therapy, the group that had received the 17 beta estradiol patch reported improvement in pain intensity, disability, and severity but not in episode frequency [29].

**Conflict of interest** The authors certify that there is no actual or potential conflict of interest in relation to this article.

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