REVIEW

Migraine in menopausal women: a systematic review

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Abstract: Evidence suggests that migraine activity is influenced by hormonal factors, and particularly by estrogen levels, but relatively few studies have investigated the prevalence and characteristics of migraine according to the menopausal status. Overall, population-based studies have shown an improvement of migraine after menopause, with a possible increase in perimenopause. On the contrary, the studies performed on patients referring to headache centers have shown no improvement or even worsening of migraine. Menopause etiology may play a role in migraine evolution during the menopausal period, with migraine improvement more likely occurring after spontaneous rather than after surgical menopause. Postmenopausal hormone replacement therapy has been found to be associated with migraine worsening in observational population-based studies. The effects of several therapeutic regimens on migraine has also been investigated, leading to nonconclusive results. To date, no specific preventive measures are recommended for menopausal women with migraine. There is a need for further research in order to clarify the relationship between migraine and hormonal changes in women, and to quantify the real burden of migraine after the menopause. Hormonal manipulation for the treatment of refractory postmenopausal migraine is still a matter of debate.

Keywords: headache, female, menstrual cycle, sex hormones

Introduction

Migraine is a primary headache disorder with two major subtypes, ie, migraine without aura (MO) and migraine with aura (MA). MO is a clinical syndrome characterized by headache with specific features and associated symptoms (unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia); while MA is primarily characterized by transient focal neurological symptoms that usually precede or sometimes accompany a headache with migrainous features.[1]

Migraine occurs in both sexes, but it is predominantly found in females, with a cumulative lifetime prevalence of 43% in women and 18% in men.[2] There is strong evidence linking migraine with the hormonal status of women, and both the timing and frequency of migraine attacks are influenced by hormone-related events. Migraine occurrence may be influenced by the varying hormonal status of women through menarche, menstruation, pregnancy, and menopause, as well as use of oral contraceptives and hormone replacement therapy (HRT).

Migraine usually starts after menarche, occurs more frequently during menstruation, and ameliorates during pregnancy and after menopause.[3] The "estrogen withdrawal" hypothesis, more than 40 years after having been proposed for the first time, is still the most commonly referred to, in order to explain the mechanism through which migraine is triggered by ovarian hormones.[4] According to this hypothesis,

migraine is triggered by the sudden decline in estrogen levels occurring immediately before menses and during the transition toward menopause or in the early postmenopausal period.[3,5] Menopause is a normal physiological event, defined as the final menstrual period and reflecting loss of ovarian follicular function.[6] The menopausal transition, known as perimenopause, is associated with fluctuating ovarian function. Through a process of continuous depletion called atresia, the human ovary steadily loses follicles; as fewer and fewer ovarian follicles remain, the anterior pituitary gland attempts to compensate by releasing more follicle-stimulating hormone (FSH), which stimulates a recruited follicle to grow and produce estrogen. Chronic elevation of FSH makes the follicular cells insensitive to FSH leading to failure of the final maturation of ovarian follicles (anovulatory cycles). Transient increases in estradiol can occur during this time as surges of FSH stimulate the remaining follicles, but the luteal progesterone decreases as result from declining dominant follicle quality. Once no more follicles remain for stimulation, estradiol levels also decrease and menstruation ceases completely.[7] Thus, while the perimenopausal period is characterized by considerable fluctuations of estrogen and progesterone levels, greater than those occurring during the normal phases of menstrual cycle in the fertile period, menopause is characterized by hormonal stability due to decline of estrogen and progesterone production by the ovaries. Spontaneous or natural menopause is recognized retrospectively after 12 months of amenorrhea,[8] occurring on average at the age of 51 years, with an age range of 40–60 years.[9] Induced menopause refers to the cessation of menstruation that occurs after either bilateral oophorectomy or iatrogenic ablation of ovarian function (such as by chemotherapy or pelvic radiation).[10]

Therapeutic use of exogenous hormones may influence migraine course; regular use of those hormones may be associated with the development of "exogenous hormone-induced headache".[1] On the other hand, according to the theory of "estrogen withdrawal headache", headache or migraine may be caused by cessation of a course of exogenous estrogens. Many different cellular actions of estrogens have been described, including effects on vascular tone; the hormonal changes are often responsible for the clinical vasomotor signs and symptoms, such as hot flushes, and may favor migraine. While estrogens induce vasodilation through mechanisms involving the arterial endothelium and through endothelial-independent actions, progesterone has varying effects on arterial tone, including induction of vascular smooth muscle relaxation

as well as induction of smooth muscle constriction.[11] A link between hormonal imbalance and migraine may stem from the opposing roles of estrogen and progesterone within the brain; indeed, while estrogen stimulates neural excitability, progesterone exhibits inhibitory actions in central neurons. Therefore, imbalance between these neuromodulatory hormones may give rise to physiological conditions that alter susceptibility to migraine.[12] Although the focus has been on estrogen, we cannot exclude that other factors may contribute to migraine course and menopause. Estrogen is associated with increased production of serotonin, reduced serotonin reuptake, and decreased serotonin degradation. The consequent cyclical changes in serotonin levels in trigeminal ganglia could contribute to the selective response to estrogen withdrawal. Given that serotonin has also been implicated in the pathophysiology of vasomotor symptoms, it is interesting to speculate on a common pathophysiology.[13]

This paper reviews the available evidence documenting the relationship of menopause and migraine.

Search strategy and selection criteria

Data for this review were obtained through searches in BIOSIS, the Cochrane database, Embase, Google scholar, ISI Web of Science, and Medline, with a timeframe from 1960 up to December 2014. The search terms included "migraine" OR "headache" AND ("women", "menopause", "perimenopause", "menstruation", "hormonal fluctuations", "sex hormones", "estrogens", "hormone replacement therapy"). We also searched reference lists of identified articles and papers quoting identified articles. No language restrictions were applied. Cohort studies, case–control studies, and clinical trials evaluating the association between menopause and migraine in either hospital-based or population-based settings were included in the review. Studies dealing with the pathophysiological links between migraine and hormones, and letters, reviews and, comments related to this topic were also considered for the discussion but not included in the systematic review.

Results

Out of 6,326 records, we considered 46 papers after title and abstract review. Six more papers were retrieved from the reference lists of identified articles. We finally included 22 studies[14–35] in our review.

In this review, we discuss each issue addressed by the studies in a single paragraph. The characteristics of the included studies are summarized in Tables 1 and 2.

Table I Characteristics of observational studies evaluating the relationships between migraine and menopause

Study (year)	Type of study	Setting	Inclusion period	Included subjects	Age range (years)	Diagnostic criteria for migraine	Migraine ascertainment	Issues addressed
Whitty and Hockaday[19] (1968)	Cross-sectional	Headache clinic	NR	63 (all), 40 (women in menopause)	22–81 (all)	Recurring throbbing headaches and, in addition, two of the following five features: unilateral headache, associated nausea with or without vomiting, visual or other sensory aura, cyclical vomiting in childhood, and a family history of migraine	Face-to-face interview	Migraine evolution during menopause
Kaiser and Meienberg[31] (1993)	Case series	Headache clinic	NR	10	44–58	ICHD-I	Face-to-face interview	Effects of HRT on migraine
Granella et al[24] (1993)	Cross-sectional	Headache clinic	1984–1990	1,300	18–70	Ad hoc Committee on Classification of headache (1984–1988) ICHD-I (1989–1990)	Face-to-face interview	Migraine type and menopause Menopause type and migraine
Neri et al[20] (1993)	Cross-sectional	Menopause clinic	1990	556	<65	ICHD-I	Face-to-face interview	Migraine evolution during menopause Menopause type and migraine
Cupini et al[22] (1995)	Cross-sectional	Headache clinic	1991–1993	268	18–80	ICHD-I	Face-to-face interview	Migraine evolution during menopause Migraine type and menopause
MacGregor[32] (1999)	Case series	Headache clinic; menopause clinic	NR	4	44–72	ICHD-I	Face-to-face interview	Effects of HRT on migraine
MacGregor[28] (1999)	Case series	Association members	NR	112	NR	NR	Face-to-face interview	Effects of HRT on migraine
MacGregor and Barnes[14] (1999)	Cross-sectional	Menopause clinic	NR	74	32–74	ICHD-I	Face-to-face interview	Migraine prevalence during menopause
Hodson et al[15] (2000)	Cross-sectional	Menopause clinic	1998	1,000	29–73	Previous physician diagnosis of migraine	Self-report questionnaire	Migraine prevalence during menopause Effects of HRT on migraine
Mueller[21] (2000)	Cross-sectional	Headache clinic	1997	451	18–80	ICHD-I	Self-report questionnaire	Migraine evolution during menopause Effects of HRT on migraine
Mattsson[25] (2003)	Cross-sectional	General population	1997–1998	728	40–74	ICHD-I	Face-to-face interview	Migraine type and menopause Migraine and menopausal symptoms
Misakian et al[29] (2003)	Cross-sectional	Clinical trial (WHS)	1995	17,107	>45	ICHD-I	Self-report questionnaire	Effects of HRT on migraine
Wang et al[16] (2003)	Cross-sectional	General population (KIWI)	1998	1,436	40–54	ICHD-I	Self-report questionnaire	Migraine prevalence during menopause Menopause type and migraine Migraine and menopausal symptoms
Aegidius et al[30] (2007)	Cross-sectional	General population (HUNT)	1995–1997	6,007	>40	ICHD-I	Self-report questionnaire	Effects of HRT on migraine
Freeman et al[17] (2008)	Cohort	General population (POAS)	1996–1997	404	35–47	Answers "yes", "no", or "unknown" on history of headache	Face-to-face interview	Migraine prevalence during menopause
Sabia et al[26] (2008)	Cohort	Managed care cohort (E3N)	1990–2000	28,118	NR	NR	Self-report questionnaire	Migraine and menopausal symptoms
Oh et al[18] (2012)	Cross-sectional	Headache clinic	2003–2005	224	40–54	ICHD-II	Face-to-face interview	Migraine prevalence during menopause Migraine evolution during menopause
Karli et al[23] (2012)	Cross-sectional	General population	2008	2,600	18–65	ICHD-II	Face-to-face interview	Migraine evolution during menopause

Abbreviations: HUNT, Nord-Trøndelag Health Study; KIWI, Kinmen Women's Health Study; POAS, Penn Ovarian Aging Study; WHS, Women's Health Study; ICHD-I, International Classification of Headache Disorders, 1st revision; ICHD-II, International Classification of Headache Disorders, 2nd revision; HRT, hormone replacement therapy; NR, not reported.

Table 2 Clinical trials on hormonal replacement therapy in migraineurs

Study (year)	Period of inclusion	Design	Interventions	Population	Number of subjects	Outcome(s)	Assessment periods	Main findings
Nappi et al[34] (2001)	1997–1999	Randomized, open-label	1) Transdermal estradiol 50 µg every 7 days for 28 days plus MAP 10 mg/d from 15th to 28th day 2) Oral conjugated estrogens 0.625 mg/d for 28 days plus MAP 10 mg/d for the last 14 days	Consecutive patients with spontaneous menopause and MO or TTH (ICHD-I criteria)	30 (MO), 20 (TTH)	Attack frequency, days with headache, headache severity, analgesic use	Run-in, 1, 3, 6 months	All outcomes increased in oral vs transdermal HRT in subjects with MO; no differences in subjects with TTH
Facchinetti et al[33] (2002)	1999–2000	Nonrandomized, open-label	1) Estradiol hemihydrate 1 mg/d plus norethisterone 0.5 mg/d for 28 days 2) Oral conjugated estrogens 0.625 mg/d for 28 days plus medroxyprogesterone acetate 10 mg/d in the last 14 days 3) Estradiol valerate 2 mg/d for 21 days plus cyproterone acetate 1 mg/d from day 12 to 21	Consecutive patients with spontaneous menopause and MO (ICHD-I criteria)	33	Attack frequency, days with headache, severity, analgesic use	Run-in, 1, 3, 6 months	Progressive increase in attack frequency, days with headache, and analgesic consumption in all groups after 6 months; decreased duration and increased severity of attacks; increase in number of days with headache and number of analgesics used smaller with continuous combined regimen
Nappi et al[35] (2006)	NR	Randomized, open-label	1) 1 mg 17β-estradiol +0.5 mg norethisteroneacetate 2) 2.5 mg tibolone	Consecutive patients with spontaneous menopause and MO or TTH (ICHD-I criteria)	40	Days with headache, severity, analgesic use	Run-in, 3, 6 months	Tibolone noneffective in decreasing number of days with MO; significant decrease in number of hours during which pain intensity prohibited daily activities and number of analgesics after 3 months with tibolone; continuous estroprogestin increasing the number of days with head pain and the number of analgesics; both treatments effective in the management of TTH
Martin et al[27] (2003)	NR	Randomized, placebo-controlled, pilot trial with parallel-group design	1) Subcutaneous goserelin implant +100 µg estradiol patch 2) Subcutaneous goserelin implant + placebo patch	General population and headache clinic	23 (10 estradiol patch, 13 placebo patch)	Headache index[a] (primary) Headache disability, headache severity, headache frequency, percentage of headaches with a pain severity rating of 7 or greater (secondary)	Lead-in month, three subsequent phases of 2.5 months, 1 month, and 2 months' duration, respectively	Decrease in headache index with goserelin/estradiol compared with goserelin/placebo; similar improvements in the goserelin/estradiol and goserelin/placebo group for all secondary outcome measures with the exception of headache frequency

Notes: [a]Defined as the mean of pain severity ratings (0–10 scale) recorded three times per day by the use of a daily diary.
Abbreviations: HRT, hormone replacement therapy; ICHD, International Classification of Headache Disorders, 1st revision; MAP, medroxyprogesterone acetate; MO, migraine without aura; NR, not reported; TTH, tension-type headache.

Prevalence of migraine during menopause

Reported migraine prevalence during menopause ranges from 10% to 29%.[14–18] Prevalence data are not dissimilar among studies, despite heterogeneity in design, settings, number and age of subjects included, and diagnostic criteria for migraine. An early questionnaire survey performed in women attending a menopause clinic found that 57% of women reported headache and 29% reported migraine in the 3 months preceding the visit.[14] In that study, migraine was also associated with significant disability: 80% of women reported that attacks occurred more than once a month, 75% reported severe attacks, and 50% reported that attacks lasted longer than 1 day. A further questionnaire survey performed on 1,000 women, aged 29–73 years, attending a menopause clinic, showed that 85% of women presented with recurrent headache; among them, 73% experienced headache more than once per month and 24% had migraine.[15] Those two studies did not report details according to the menopausal stages,[14,15] but other studies reported this information.[16–18] In a cross-sectional study of 1,436 menopausal women aged 40–54 years, 69% reported having at least one headache in the previous year, and 16.5% were diagnosed with migraine according to International Headache Society criteria. Women with spontaneous menopause reported a migraine prevalence of 11%, while premenopausal and perimenopausal women reported a prevalence of 17% (odds ratio [OR], 0.6; 95% confidence interval [CI], 0.4–0.9; P=0.03).[16] In a population-based cohort study with 404 premenopausal women aged 35–47 years assessed prospectively for 9 years, 34% of premenopausal women but only 24% of postmenopausal women reported headache at the end of follow-up. Headache prevalence was lower in postmenopause (OR, 0.60; 95% CI, 0.42–0.83; P=0.003), but not in perimenopause, compared with reproductive period.[17] A cross-sectional study investigating the headache characteristics of 229 middle-aged women (aged 40–54 years) consecutively attending a headache clinic showed a comparable prevalence of migraine among women in the pre-, peri-, and postmenopausal period. The proportion of patients with a brief migraine history (<6 months) was significantly higher in the perimenopausal group (41%) than in the premenopausal (13%) or postmenopausal (17%) groups.[18] In summary, data from the available studies suggest that migraine prevalence remains stable or increases in perimenopause and declines after menopause compared with reproductive period. Population-based studies supported this trend more than those performed in hospital settings.

Migraine evolution during menopause

To date, there are very few large, prospective, population-based cohort studies to determine the true effect of menopause on migraine. The available studies are mostly retrospective and questionnaire-based. A retrospective study evaluating the course of MO, by means of a questionnaire, in 47 postmenopausal women aged 43–67 years, reported an improvement in 24 women (62%), a worsening in 7 (18%), and no changes in 8 (20%), while 8 (17%) had new onset of headache with menopause.[20] A cross-sectional study carried out on 268 women (36 postmenopausal) with migraine referring to a single headache center found an improvement of migraine with spontaneous menopause.[22] Conversely, another study involving 53 female migraineurs retrospectively assessed 15–20 years after their first attendance at a neurology ward did not find any consistent change in attacks after menopause in 64% of the participants. Moreover, a worsening of migraine status was reported in slightly more cases (21%) than an improvement or complete remission (14%).[19] A further retrospective study performed in 451 women with MA or MO aged 18–80 years did not find migraine improvement during menopause. In fact, among 160 women in the menopause, the course of migraine was improving in 41 patients (24%), worsening in 60 (36%), and unchanged in 67 (40%).[21] More recently, an analysis of headaches in perimenopausal patients attending a headache clinic and not receiving exogenous hormone treatment showed that current headaches were reported as new-onset by 48% of subjects, aggravations of prior headaches by 34% of subjects, and unchanged from prior headaches in 18% of subjects.[18] Meanwhile in a cross-sectional, population-based study evaluating 1,333 women aged 18–65, only 17% of migraineurs reported improvement during menopause,[23] although the low number of menopausal subjects may have affected the results. In general, according to population-based studies, menopause may bring an improvement of migraine course, while according to the studies performed in hospital settings, migraine may remain stable or even worsen following menopause.

Migraine type and menopause

There is some evidence to suggest that MA and MO are differently influenced by women's reproductive life events,[24,25] although, to date, available data are scarce and too heterogeneous to confidently accept that such a difference exists. In a cross-sectional study that included 10 postmenopausal women with MA and 26 with MO consecutively referring to a Headache Center, no difference was found between the two

groups of patients with regard to postmenopausal migraine onset and migraine course during menopause.[24] A subsequent population-based study performed on 728 women (301 postmenopausal) aged 40–74 years showed a decreased risk of MO in postmenopausal women as compared with women in their fertile period (OR, 0.47; 95% CI, 0.24–0.86). After adjusting for age differences, however, the association was not statistically significant. In that same study, MA was not associated with the menopausal transition. Notably, time since menopause was a predictor of MO improvement in postmenopausal women.[25] In summary, the available literature suggests that MO is more influenced by hormones than MA, not only in the fertile period but also during and after the menopause.

Effect of spontaneous and of induced menopause on migraine

The available data are relatively concordant in showing that spontaneous menopause is associated with a more evident improvement of migraine compared with induced menopause.[16,20,24] In a postmenopausal outpatient survey, migraine improvement occurred in 67% of women after spontaneous menopause and in 33% after surgical menopause; notably, migraine worsened in 9% of women after spontaneous menopause and in 67% after surgical menopause.[20] A retrospective study of 164 postmenopausal women with MO showed that worsening of migraine was significantly more frequent after surgical menopause than after spontaneous menopause; migraine improvement occurred only in women with spontaneous menopause.[24] Regrettably, that study did not clearly define the aspects of migraine worsening (increased frequency, severity, or duration of attacks). In a subsequent study, a higher migraine prevalence was found in women with surgical menopause than in those with spontaneous menopause, among patients with a history of premenstrual syndrome (44% vs 7%; $P<0.0001$), while surgical menopause did not significantly affect migraine prevalence among patients without a history of premenstrual syndrome (16% vs 12%; $P=0.35$).[16] In summary, data from the available studies suggest that migraine prevalence remains stable or increases in perimenopause and declines after menopause compared with the reproductive period. Population-based studies supported this trend more than those performed in hospital settings.

Migraine and menopausal symptoms

The association between migraine and menopausal symptoms, such as mood changes, poor sleep, irritability, and concentration difficulties, is unclear since data from available studies are conflicting.[16,25,26] A population-based retrospective study of 728 Swedish women reported no association between the presence of migraine and menopausal symptoms.[25] Conversely, the results of a subsequent cohort study of 28,118 French women suggested that the risk of onset of any menopausal symptom was higher in subjects with a history of migraine (hazard ratio [HR], 1.11; 95% CI, 1.07–1.16; $P=0.007$).[26] Another study analyzed the association between menopausal vasomotor symptoms (hot flushes, night sweating) and migraine and found that subjects with either hot flushes (22% vs 16%; OR, 1.5; 95% CI, 1.0–2.2; $P=0.044$) or night sweating (28% vs 16%; OR, 2.1; 95% CI, 1.3–3.4; $P=0.003$) had a higher migraine prevalence than those without these symptoms.[16] The differences among studies may be explained either by the confounders assessed in their adjusted models or by a different effect of migraine on each menopausal symptom. Different study designs and sample sizes may also have contributed to between-studies differences in the reported results.

Effects of menopausal HRT on migraine

Women with menopause occurring before 45 years of age are at increased risk for long-term health consequences, including premature cardiovascular disease, mortality, Parkinsonism, cognitive decline, depression, anxiety, and sexual dysfunction.[36] HRT is typically recommended for these women until the age of expected natural menopause in order to reduce the risks as well as to relieve menopausal symptoms and to slow down the decrease in bone density that occurs after menopause.

HRT has a variable effect on migraine. A survey questionnaire performed on 112 perimenopausal or postmenopausal female members of the British Migraine Association using HRT (oral or transdermal conjugated estrogens combined with cyclical oral progestogen) showed a trend toward greater improvement of migraine in women using transdermal estrogen compared with oral conjugated estrogens and found that headache was often associated with the progestogen phase of cyclical therapy.[28] Two studies reported an increased risk of migraine among users of HRT.[29,30] Among 17,107 postmenopausal women selected from the Women's Health Study, 62% were current users of HRT and 39% had never used HRT, and 11% of all postmenopausal women – both users and nonusers – experienced migraine. Current HRT use was associated with higher risk of migraine than nonuse (OR, 1.42; 95% CI, 1.24–1.62), both for users of estrogen alone (OR, 1.39; 95% CI, 1.14–1.69) and users of estrogen plus progestin (OR, 1.41; 95% CI, 1.22–1.63). There were no significant differences in

the risk of migraine headache in users of cyclic versus continuous doses of estrogens, and no dose–response relationship was reported.[29] Among 5,507 postmenopausal women selected from the Nord-Trøndelag Health Study (HUNT) study, 2,375 (43%) reported use of HRT (26% previous, 20% local, 54% systemic). Migraine prevalence in the groups of never, previous, and present (local or systemic) use of HRT was 49%, 11%, and 40%, respectively. An association was found between migraine and current use of HRT (OR, 1.6; 95% CI, 1.4–1.9), showing that migraine was more common in HRT users as compared with nonusers.[30]

Other studies showed that worsening of migraine in menopause may be a predictor of migraine worsening on HRT.[15,21] In a questionnaire survey performed in a UK menopause clinic, women were asked about headache and were invited to note its severity on a visual analog scale. Women with improved or unchanged headache during menopause generally followed a similar pattern on HRT use, however, the women with headache worsening during menopause showed a variable response to HRT. The probability of headache worsening at menopause and with use of HRT was significantly increased with reported history of migraine.[15] Moreover, a retrospective study conducted on 451 female migraineurs found an association between self-reported worsening of headache on HRT and worsening of headache during menopause (67% vs 27%, $P<0.01$).[21]

HRT may have adverse effects on MA. Among ten menopausal women using estrogen cutaneous patches and consecutively referring to a Headache clinic, three had MA worsening, three had new-onset visual aura without migraine, one had new-onset MA, and three switched from MO to MA.[31] Another study, in which consecutive patients referring to a menopause clinic were assessed, suggested that HRT could lead to migraine worsening.[32] Higher doses of estrogen replacement therapy may be more likely to lead to the development of aura symptoms; lowering the dosage or switching to another type of estrogen replacement may lead to an abatement of aura symptoms.[32] It should be noted, however, that as those studies evaluated consecutive patients in tertiary clinics, the possibility of selection bias cannot be excluded. As regards MO, one study showed that postmenopausal women on HRT did not have a different prevalence of MO compared with premenopausal women, while postmenopausal women not on HRT had a lower prevalence of MO compared with premenopausal women.[25]

Some clinical trials have investigated the relationship between various HRT regimens and migraine (Table 2).[27,33–35]

The first randomized trial performed in women with MO found that both frequency of attacks and days with headache significantly increased during HRT in the subgroup consuming oral formulation, while no changes in the same parameters were found in the group taking transdermal treatment. The severity of migraine was unaffected by HRT, while analgesic consumption was significantly increased in the subgroup on oral treatment.[34] A subsequent trial found a significant increase in attack frequency, days with headache, and analgesic consumption in postmenopausal women receiving HRT; duration of attacks decreased, whereas severity worsened. The increase in number of days with headache and number of analgesics used was smaller in the group receiving a continuous combined regimen than in cyclical regimens.[33] Another randomized trial found that tibolone, a synthetic steroid hormone with estrogenic, progestogenic, and androgenic properties did not affect the number of days with MO, but significantly reduced the number of hours during which pain intensity prohibited daily activities and the number of analgesics consumed as compared with oral continuous HRT.[35]

Induction of menopause has been proposed as a therapy in patients with refractory migraine, with the rationale of minimization of hormonal fluctuations. Refractory migraine has been defined as a migraine disorder that causes significant interference with function or quality of life despite modification of triggers, lifestyle factors, and adequate trials of acute and preventive (at least two) medicines with established efficacy.[37] In a placebo-controlled trial, 23 such patients were randomized to receive chemical oophorectomy either with goserelin – a GnRH agonist – and estrogen add-back therapy, or with goserelin and placebo, with a follow-up period of 6.5 months. The women who received goserelin and estrogen add-back therapy had less pain intensity after 3 months than those receiving goserelin and placebo.[27] Overall, it should be noted that the small sample size, the lack of placebo groups, and the inappropriate or unclear endpoint definitions in these studies limit their ability to determine to what extent HRT is beneficial, or otherwise, for migraineurs.

Discussion

Our systematic review showed that the available studies on migraine course in menopause are relatively few, heterogeneous, and with conflicting results. Migraine improvement after menopause is a widely accepted notion, mostly because of common clinical experience rather than due to the presence of large epidemiological studies providing robust evidence for this. Although in many patients migraine ameliorates

with the menopause, during the transition to menopause, migraine attacks can become more severe and frequent due to fluctuating and changing hormonal levels in this period. Unfortunately, no longitudinal studies have been conducted to determine the exact effect of the perimenopausal period on migraine.

It is of note that an increased prevalence of migraine in perimenopausal women and a decreased prevalence in postmenopausal women, compared with premenopausal women, has been found only in community-based studies,[16] while studies performed in headache clinics do not show significant differences between pre- and postmenopause.[18] This may be because Headache clinics select patients with more severe headache compared with the general population. The same selection bias may occur for migraine evolution during menopause, with the highest percentages of migraine worsening coming from Headache clinics[18,20,24] and the highest percentages of migraine improvement reported by population-based studies.[17,26] The different results may also be due to differences in study populations, where the proportion of women in perimenopause and menopause differ. Dissimilar age ranges in menopausal stages may have also contributed to inconsistencies among the study results.

"Headache attributed to exogenous hormones" and "estrogen withdrawal headache" have already been internationally coded as headache diagnoses.[1] The fact that both estrogen addition and estrogen withdrawal may trigger a headache with migrainous features suggests that migraine is sensitive to hormonal fluctuations rather than to the amount of circulating hormones. There is some suggestion that hormonally sensitive women (eg, those who have experienced migraine changes in conjunction with previous hormonal events such as menstruation, pregnancy, and use of oral contraceptives) are more likely to have migraine worsening in the perimenopause. Women with a history of menstrual migraine may be more vulnerable to exacerbation of migraine during the hormonally unstable perimenopausal period.[16] The transition from reproductive to nonreproductive phase is the result of a progressive reduction in female hormonal production by the ovaries and usually lasts 4–8 years.[38] Although the perimenopausal period is characterized by considerable fluctuations of estrogen and progesterone levels, greater than those occurring during the normal phases of menstrual cycle in the fertile period, menopause is characterized by hormonal stability due to the decline of estrogen and progesterone production by the ovaries.[3] During perimenopause, the slower these hormonal changes occur, the greater the improvement of migraine.

The achievement of hormonal stability on menopause is positively associated with migraine improvement.[17,25]

The type of menopause – spontaneous or induced – has a substantial effect on migraine. In spontaneous menopause, the likelihood of migraine improvement has been reported to be as high as 50%–60%,[39] although with high variability among studies. Surgically induced menopause (ie, oophorectomy with or without hysterectomy) appears to be associated with worsening of migraine in a substantial percentage of women.[20] However, the numbers vary widely among studies. Migraine worsening occurs even with retention of the ovaries or postsurgical estrogen therapy.[40] The reason for worsening is unclear, but it may be related to the abrupt, large change in hormones and/or the use of supplementary estrogen following surgery. Chemical oophorectomy with estrogen therapy has been performed for the prevention of refractory migraine[36] and has been suggested as a way of selecting women for surgical menopause. However, this approach is unproven. In women suffering from severe and disabling migraines which improve after pharmacologically induced menopause, hysterectomy with bilateral oophorectomy may be considered, but its effectiveness has not been demonstrated.

The effect of HRT on migraine is unpredictable. Either the usual contraceptive regimens or estrogen supplements can be used during the perimenopause. In addition to the use of hormonal formulations different from contraceptive regimens, the choice of estrogen supplements for the specific treatment of climacteric symptoms, including migraine, has been advocated.[41] The goal of hormonal treatment regimens for migraine is minimization of estrogen fluctuations. However, the erratic endogenous estrogen levels of perimenopause may increase the uncertainty of exogenous dosing.[42] HRT may have variable effects depending on the route of administration, type of estrogen, and type of administration (cyclical vs continuous). Transdermal preparations may be less likely to exacerbate migraine, but this has not been consistently shown.[41,43] Progesterone supplementation may be effective for treating menstrual migraine by suppressing menstruation. In general, progesterone dosing does not seem to change migraine frequency, duration, or severity.[41] A better understanding of the mechanisms linking migraine and hormonal fluctuations in menopause could lead to better treatment for patients suffering from migraine.

From a clinical perspective, in the absence of conclusive results, no specific therapies can be indicated for menopausal migraine. Most medications used in patients

in reproductive age, including both acute medications (as nonsteroidal anti-inflammatory drugs and triptans) and preventive medications (as β-blockers, calcium channel blockers, tricyclic antidepressants, selective serotonin reuptake inhibitors, and antiepileptic drugs), are also useful in healthy women in that age group. In menopausal women, additional factors may influence the onset or worsening of headache disorders, including migraine; among these factors, stress plays a major role.[15,17] Some migraine preventative drugs act on biological stress mechanisms and may be effective in migraineurs during menopause.

In migraineurs, HRT use may be challenging because of the potential worsening of migraine. Markers of "hormonal sensitivity" have been proposed, including menstrual migraine or onset at menarche,[21] history of improvement during pregnancy,[21] premenstrual syndrome,[16] and surgical menopause.[16,20,24] Recognition of these markers in migraineurs could help in planning the cautious use of HRT in order to avoid migraine worsening. Migraine worsening during menopause is associated with worsening also on HRT.[15,21] This association may also direct the therapeutic decisions of both clinicians and their patients. There is a paucity of scientific evidence to guide decision making regarding HRT for women who undergo surgical menopause and experience a worsening of headaches but need to take estrogen replacement to reduce long-term health consequences of premature estrogen deficiency. Further longitudinal studies should be performed to clearly identify markers of "menopausal migraine" and "HRT-associated migraine" and to plan specific treatments. To date, migraine does not represent a contraindication for HRT; in any case, it is reasonable to administer the lowest effective doses.[13] Moreover, there are also health risks associated with HRT use, such as the risk of cancer and cardiovascular diseases.[44] Due to evidences suggesting that migraine, particularly MA is associated with an increased risk of ischemic[45] and hemorrhagic stroke[46] and myocardial infarction,[47] we cannot exclude that this risk may be further elevated in the setting of combined estrogen–progesterone contraceptive use. There are no studies that directly assess the risk of stroke in migraineurs using HRT. For these reasons, the control of migraine via hormonal manipulation is still challenging, although the use of HRT to minimize fluctuations in estrogen may be a potentially helpful therapy in some menopausal women, and there is no enough scientific evidence to recommend it.

Disclosure

The authors report no conflicts of interest in this work.

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