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Menopause hormone therapy, migraines, and thromboembolism

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A B S T R A C T

Migraine, a common form of headache, is a highly prevalent and disabling condition with a predilection for females. Migraines are neurovascular diseases. The two main types of migraines are migraines with and without aura, and several subtypes exist. There is a strong link between sex steroids and migraines. In women, migraine remissions are associated with stable and critical oestrogen levels. The literature reveals an association between migraine with aura and stroke, with a higher incidence in the young compared with that in the old. The absolute risk of stroke is low; tobacco use and a high dose of oral oestrogens may increase the risk. Early diagnosis, follow-up, and nonhormonal symptomatic and preventive treatments address the neglected area of migraines. Judicious use of hormones throughout the lifespan as needed would improve the quality of life.

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Introduction

The word migraine originates from the Greek word "hemicrania" meaning "half the head," a partial description of the disease. Migraines, a common type of headache, are highly prevalent and a disabling condition. In 2019, among young adult females (15–49 years), the Global Burden of Disease Study showed that headache is the second leading cause of disability-adjusted life years (DALYs), and estimates of years lived with disability (YLDs) varied, with headache positioned between second in Europe and Central Asia to sixth in North America [1]. Migraines may not lead to premature mortality but are responsible for more years of lost healthy life in young women.

Migraines are neurovascular diseases, with recurrent attacks of moderate-to-severe headache associated with nausea, vomiting, and light and sound sensitivity, which may last up to 72 h. Aura, a temporary neurological disturbance of the sensory or motor functions, may or may not be associated with migraines.

Emerging literature links migraines with aura (MA) to cardiovascular disease (CVD) and cerebrovascular diseases such as ischaemic stroke, Raynaud's disease, mitral valve prolapse, and angina/myocardial infarction [2,3]. Migraines are associated with comorbidities including psychiatric disorders, with epilepsy, essential tremor, benign positional vertigo, and restless legs syndrome being the commonest [4,5]. In a registry-based cohort, it was observed that younger subjects with migraine were more likely to develop incident chronic kidney disease (CKD) compared with the patients in the non-migraine cohort. Age and symptomatic relief agents such as non-steroidal anti-inflammatory drugs and propranolol were found to be independent risk factors for CKD within the migraine cohort [6].

The clinical or subclinical brain lesions and common risk factors and comorbidities show the causal association of migraine and stroke. The literature indicates the link between oestrogens and vascular disease, and the outcome depends on the presence of healthy or damaged endothelium. In migrainous women, a hypercoagulable state is present, and oestrogens may further stimulate this.

Effective symptomatic and preventive treatments are available; hence, early diagnosis and follow-up are needed to address the neglected area of headache. Before elaborating on the relationship among menopause hormone therapy (MHT), migraine, and thromboembolism (TE), the basics of migraine, gender and migraine, and MHT and TE have to be discussed, as described in the following section.

Migraines

Types of migraines as described by the International Headache Society (IHS) are given below [7]. Migraines are classified as:

1. Migraines without aura (MO).
2. Migraines with aura (MA).

Several well-characterized migraine subtypes include migraine with brainstem aura, hemiplegic migraine, retinal migraine, vestibular migraine, menstrual migraine, and chronic migraine. Migraines-like headache secondary to another disorder is called symptomatic migraine. There may be associated episodic syndromes with migraines. Some neurological disorders may mimic migraines. The following features describe migraines and the diagnostic criteria as described in the guidelines by the Headache Classification Committee of the International Headache Society.

MO

Recurrent headaches (minimum five attacks) lasting for 4–72 h, in the presence of any two of the following characteristics – unilateral location, pulsatile quality, moderate to severe intensity, and aggravated by physical activity; and at least one of the symptoms of nausea and vomiting, photophobia and phonophobia. Fig. 1

Migraines with aura (MA)

Recurrent headaches that last for minutes with fully reversible unilateral symptoms of aura. The diagnostic criteria are a minimum of 2 attacks with one or more of the aura symptoms – visual, sensory, speech and language, motor, brainstem, and retinal; and three of the six characteristics – one aura symptom spreads gradually over ≥5 min, two or more aura symptoms occur in succession; each aura symptom lasts 5–60 min, unilateral aura symptom, at least one aura symptom is positive, the aura is accompanied, or followed within 60 min.

The presentation of MO and MA may be transient, called episodic migraines (EM), chronic migraines (VM) and oestrogen-related migraine.

Chronic migraines

Migraines are classified under the chronic category if the headache occurs 15 or more days per month for over three months, which, on at least eight days/month, has the features of migraines with or without aura.

Oestrogen-related migraines

Oestrogen-associated migraines are precipitated concerning the woman's endogenous or exogenous hormonal status through their life span, starting from menarche to menopause. Oestrogen-associated migraines include both MO and MA that are triggered by fluctuations in oestrogen levels.

Endogenous oestrogen-associated migraines are classified as pure menstrual MO, related only to the menstrual cycle. Menstrual-related MO may occur at oestrogen withdrawal during the luteal phase.

Nonmenstrual MO may occur any time with and without relation to the menstrual cycle [8].

The exogenous hormone used for contraception or hormone therapy (HT) can be associated with an increase in frequency or new development of headache, and the migraine is referred to as an exogenous hormone-induced headache. Oestrogen withdrawal follows the cessation of a course of exogenous oestrogen, such as during the pill-free interval of combined oral contraceptive (COC) or following a course of sequential HT.

Migraine complications are status migrainosus (attack lasting for more than 72 h), persistent aura without infarction, migrainous infarction (neuroimaging demonstrates ischaemic infarction in a relevant area), and migraine aura-triggered seizure [8].

Diagnosis

Migraine is a clinical diagnosis based on the criteria established by the International Headache Society. We should perform a complete neurological examination during the first visit to exclude other disorders. Neuroimaging is unnecessary in a typical case, but it may lead to other diagnostic investigations to guide management. The consensus document on the diagnosis and management of migraine in ten steps is simple for the clinician to screen and manage a case of migraine [9].

Gender bias and migraines

Studies have reflected that the prevalence, severity, persistence, and sequelae of migraines are more in females [6,8,10]. Females had a higher prevalence of migraines than males, beyond ten years; the prevalence ratio is the highest during the female reproductive/child-bearing years, consistent with a relationship between menstruation and migraines. After the age of 42, the prevalence ratio was approximately 2-fold higher in women [11–13]. MO (70–80%) are more prevalent and influenced by hormones than MA (20–30%) from menarche to menopause [14].

Migraines trigger and improvement change during different phases of a woman's life span depending on the endogenous or exogenous sex steroids. It is thought that stable and critical levels of sex steroids are needed to prevent an attack. Menarche, menses, pregnancy, and menopause transition may carry a different migraine risk because of fluctuating oestrogen levels; in general, migraine

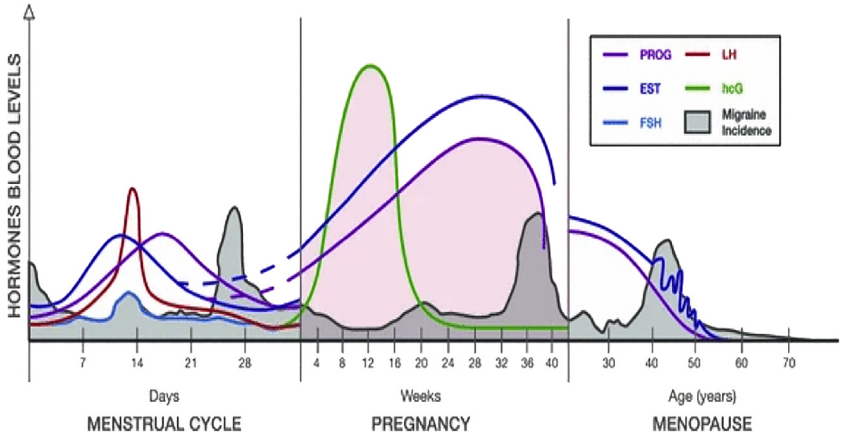

Fig. 1. Hormonal changes and incidence of migraine without aura in women.

frequency is associated with declining oestrogen levels. MA have a different hormonal response, with high oestrogen levels such as in cases of pregnancy, combined hormonal contraception, or MHT, which may lead to an increased incidence of MA [15–17].

Somerville demonstrated the story of the initial link between oestrogen and migraines in 1972, where he observed that migraines were mainly triggered when oestradiol levels declined below 45–50 pg/mL during the perimenstrual period. The attacks were delayed by up to 9 days by treating participants with supplemental oestrogen. Lichten (1996) thought that there might be a genetic component in migraine pathogenesis, and a decline in oestrogen levels after priming with higher levels can be a migraine trigger. Cachrimanidou's and MacGregor's findings indicated that preventing oestrogen withdrawal before menses can delay oestrogen withdrawal migraines. Martin demonstrated that both oestrogen withdrawal and increase can precipitate migraines and that patients with a history of menstrual migraines are susceptible to changes in serum oestradiol levels. Murray also concluded that minimizing fluctuations in oestrogen can reduce migraine incidence. Women with a history of migraines have an increased sensitivity to physiological fluctuations in oestradiol levels [18].

Pavlovic et al. showed that oestrogen withdrawal is not a direct trigger of migraines, but rather an endogenous characteristic and a marker of neuroendocrine vulnerability in females with migraines due to the disruption of the trigeminovascular system [19]. There is a hypothesis that hormonal imbalance of oestrogen and progesterone, which have a neuromodulatory effect within the brain, may increase the susceptibility to migraines. It is known that oestrogen stimulates neural excitability and progesterone exhibits inhibitory actions in central neutrons [20]. Rustichelli found that migraineurs, either menstrually related or postmenopausal, had lower allopregnanolone serum levels than non-headache control women, leading to the inhibition of an allopregnanolone-mediated enhancement of the gamma-aminobutyric acid-ergic (GABAergic) transmission causing inflammatory and algogenic stimuli and precipitate migraines and may contribute to menstrually related migraines and the persistence of migraines even after menopause [21].

To summarise, migraine is a multifactorial disorder that originates in the genetically predisposed brain and can be precipitated by various internal and external factors, with sex steroids being one of them. Hence, it would be very simplistic to consider it to be related only to hormonal cycles. Oestrogen addition and oestrogen withdrawal may trigger migraines, and women who are sensitive and susceptible to hormonal fluctuations need a stable oestrogen level. There may be a role of progesterone in the pathogenesis of migraines.

Pathophysiology of oestrogen-related migraines

A migraine attack occurs probably due to complex neurovascular events [22]. Migraines are thought to be a primary neuronal dysfunction, with secondary changes in cerebral perfusion. At baseline, a migraineur who does not have any headache has a state of neuronal hyperexcitability in the cerebral cortex, especially in the occipital cortex [23].

The trigeminovascular pathway is activated by pain signals originating in peripheral intracranial nociceptors, coupled with the dysfunction of the central nervous system (CNS) structures that modulate neuronal excitability and pain. Aura is most likely related to the phenomenon of cortical spreading depression (CPD), a self-propagating wave of neuronal and glial depolarization that spreads across the cerebral cortex. CPD activates the trigeminal nerve afferents and stimulates the trigeminal vascular system, causing vascular inflammatory substances, such as calcitonin gene-related peptide (CGRP), cytokines, and prostaglandins in pain-sensitive meninges leading to pain. Oestrogen modulates this pathway in complex ways through variable effects on the vascular inflammatory substances at different doses. Furthermore, oestrogen affects neuronal excitability through neurotransmitters such as serotonin, norepinephrine, dopamine, and endorphin [24].

Life-course of migraines in women

Menstruation

In the reproductive age, MO usually start two days before menstruation and continue through the first three days. Menstrual migraines are thought to be triggered because of oestrogen withdrawal and the production and release of prostaglandins into the systemic circulation. It affects about 20–60% of women [25].

Pregnancy and postpartum

Most women report an improvement in migraine attacks during pregnancy starting from the first to the third trimester. If migraines persists in pregnancy, they pose a risk to the mother and the neonate by increasing the risk of developing gestational hypertension, preeclampsia, or other vascular complications. Nearly all women report the return of migraine attacks after delivery [26].

Menopause transition

The early menopause transition is a vulnerable time wherein migraine attacks worsen due to the fluctuations of serum oestrogen. Migraines improve when oestrogen levels stabilize in the late menopause transition and following menopause. In late perimenopause, the presence of migraines may predict the risk of vasomotor symptoms [24]. Women with a history of premenstrual syndrome experience worsening of migraines compared with those who do not have this syndrome (31 vs 21%).

Menopause

A systematic review concluded that data on the prevalence and characteristics of migraines after menopause are sparse. Migraines during menopause may show improvement, remain stable and worsen sometimes. Migraines at menopause are associated with a higher incidence of mood disorders. Most women experience improvement, but few women may experience worsening of symptoms even after natural menopause.

Medical and surgical oophorectomy without oestrogen add-back generally results in more frequent and disabling headaches [25]. Hysterectomy appears to have a detrimental effect on migraines, even when the ovaries are retained. MA is unaffected by either natural or surgical menopause.

MHT

HT at menopause includes oestrogens, progestogens, combined therapies, androgens, tibolone, and selective oestrogen receptor modulator (SERM) (raloxifene, bazedoxifene). HT involves different routes of administration, potencies, and potentially different effects of each molecule; the risks and benefits differ in individuals and at different times of life span. The lowest effective dose is prescribed and titrated upwards until the desired therapeutic effect is achieved. Hence,it is not surprising that there exist discrepancies in the results related to MHT in various studies wherein fixed combinations and fixed doses have been used. Based on sound evidence, three indications of MHT, which have constantly withstood the test of time, are the beneficial effect of oestrogens on menopausal symptom relief, urogenital atrophy, and bone health in women under 60 years and or less than ten years since menopause [26].

Thromboembolism

Arterial thromboembolism

A disturbance in the cerebral blood flow due to occlusion or haemorrhage from a cerebral vessel leads to focal or sometimes global loss of cerebral function. Strokes are of three types: transient ischemic attack (TIA, mini-stroke), ischaemic stroke, and haemorrhagic stroke. A cryptogenic stroke is a brain infarction without a defined cause (a stroke of undetermined aetiology) despite extensive investigation [27].

Ischaemic stroke is the most common type of stroke, and sometimes, haemorrhage may occur in the cerebral vessel. We can divide all thrombotic strokes into either large- or small-vessel diseases. The thrombus in an artery produces a stroke either by occlusion and reduced blood flow distally or by an embolic fragment that breaks off and travels to a more distant vessel.

A TIA occurs when the neurological deficit resolves fully within 24 h and is because of micro-emboli. TIA is a type of ischaemic stroke in which there is only temporary blockage of a blood vessel in the brain, and symptoms and signs last only for a few minutes.

In women, the risk factors for stroke are hypertension, diabetes, cigarette smoking, and an atherogenic milieu, as seen in postmenopausal women.

Venous thromboembolism (VTE)

VTE commonly presents as deep venous thrombosis (DVT) of the lower limb and pulmonary embolism, a severe and potentially fatal event. The increased susceptibility to VTE is due to a genetic or an acquired cause leading to provoked or an unprovoked VTE. VTE occurs due to stasis in blood flow, vascular endothelial injury and alterations in the blood constituents, i.e., a hypercoagulable state referred to as Virchow's triad.

A provoked VTE is associated with either transient or persistent acquired risk factors, whereas an unprovoked or idiopathic VTE is associated with no apparent clinical risk factors. Chances of recurrence are high in unprovoked or idiopathic VTE.

Risk factors for VTE

Genetic and acquired conditions – Genetic predisposition such as hereditary thrombophilias account for only about 5% of the cases of thrombosis, and the rest are acquired conditions such as the antiphospholipid syndrome, hyperhomocysteinaemia, and elevated factor VIII levels; more often, there is a combination of genetic and acquired factors. Generally, the prevalence of severe thrombophilias (OR for VTE >8) is rare, whereas “mild” thrombophilias (OR for VTE <8) are very common in the overall population.

Constitutional factors – These include increasing age, overweight, and obesity.

Comorbidities – Comorbidities include cancer, heart failure, active systemic lupus erythematosus, antiphospholipid antibody syndrome, inflammatory polyarthropathy, in amatory intestinal disease,

nephrosis, diabetes mellitus type I with nephropathy, sickle-cell anaemia. The other comorbidities are prolonged surgery, immobilization, oral oestrogen, and selective oestrogen receptor modulators (SERMs).

Ethnicity – Europeans have a significantly higher incidence of VTE compared with Maori, Pacific Island, and Asian populations [28].

Migraines and thromboembolism

MA are linked with an increased risk of stroke and possibly other CVDs involving the arteries or the heart. In a recent Bayesian meta-analysis, migraines probability increased total stroke risk was 0.978 (RR 1.31; 95% credible interval (CrI): 1.01–1.72) [29].

The relationship between migraines and arterial thromboembolism leading to stroke is complex. Elegant studies have described the pathophysiological factors causing stroke in migraines and are interlinked with three critical factors: cortical spreading depression; an increase in inflammatory markers, endothelial dysfunction, and vasoconstriction; and a hyper-coagulable state. Community studies have highlighted common factors observed in patients with migraines and stroke, such as hypertension, dyslipidaemia, obesity, insulin resistance, metabolic syndrome, increased homocysteine levels and coronary artery disease.

The question of whether the association is causal has not been definitively proven in clinical studies. Migraine is a multifactorial disease; the presentation and associations are varied. Migraines may have clinical features of stroke, and stroke may mimic migraine. Migraine may increase the risk of stroke or it may be a consequence or a cause, although coincidental occurrence is more likely to happen. The association of migraine with stroke may have the following presentations [8].

A diagnosis of migrainous infarction leading to stroke is made if the infarction occurs during an attack of MA, the presence of focal neurological deficits lasts for over one hour, and neuroimaging shows infarction. Migrainous infarction is relatively rare, mainly occurring in the posterior circulation and younger women.

Ischaemic stroke, which is more common, occurs in persons with active migraines but remote from an attack of migraine. Meta-analyses conclude that MO is not associated with an increased risk of ischaemic stroke in women, while MA is associated with an approximately 2-fold increased risk, especially in young women. Smoking and the use of high doses of oestrogen further increase the risk.

Associated syndromes, rarely migraines and stroke, can be associated with various clinical syndromes such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), mitochondrial encephalomyopathy, lactic acidosis, stroke-like symptoms (MELAS), hereditary endotheliopathy, retinopathy, nephropathy, and stroke. (HERNS) [30].

Symptomatic migraines and migraine mimics: Here, migraines and ischaemic stroke share a common cause and may be due to structural brain lesions, vasculopathy, and arteriovenous malformations (AVM) that cause recurrent symptoms typical of MA.

Migraines with cerebral ischaemia: migraine attacks triggered by cerebral ischaemia, particularly with severe carotid stenosis related to dissections, can trigger a migrainous aura.

Migraines and ischaemic stroke

Only 10% of ischaemic strokes occur in individuals under 50 years of age, the age group most commonly affected by migraines [31]. MA appear to be an independent risk factor, as demonstrated in numerous case–control and cohort studies in the young population [31–33].

Based on the results of the Women's Health Study, which consisted of 5125 women over the age of 45 and had a follow-up of 9–12 years, only active MA at baseline, and not a history, was a risk factor for ischaemic stroke. At the start of the study, the women were free of CVD; the unadjusted absolute ischaemic stroke event rate for MA was 3.4 per 1000 women-years, with the highest association seen among women younger than 50 years. The Women's Health Study did not find an association between ischaemic stroke and MO [34].

The prospective cohort atherosclerosis risk in communities (ARIC) study showed that the risk was significant for MA (adjusted HR 1.67, 95% CI: 1.1–2.4) but not for MO (adjusted HR 1.2, 95% CI: 0.8–1.7) [35].

Risk factors for migraneous ischaemic stroke

The conclusion from various meta-analyses is that MA is associated with an approximately twofold increased risk of ischaemic stroke, with a higher risk observed among women aged less than 45 years, smokers, and women who used oral contraceptives [3,32–39].

The risk was six-fold higher in women <50 years old, and in late-onset > 50 years of MA may place them at a higher risk of stroke [37]. The risk increases with increasing frequency of attacks, a twofold increase with <1 aura/month and a fourfold increase if the aura is > 1/week [40].

Women with MA may have a high prevalence of other vasculopathy, including antiphospholipid syndrome and systemic lupus erythematosus, and presence of risk factors like smoking and hypertension puts them at a higher risk of stroke. Studies have not shown a clear association with conventional stroke risk factors such as diabetes, hypertension, dyslipidemia, and obesity in people with MA compared with the rest of the population.

The risk of stroke increased by 2.5-fold above the baseline rate in women with MA using COC [41]. The risk declined with decreasing dose of ethinyl estradiol (EE), OR 1.8 (95% CI: 1.6–1.9) for 30–40 mpg EE and OR 1.6 (95% CI: 1.4–1.8) for 20 mpg EE. Progestin-only pills had no impact on the risk of stroke. It is interesting to note that progestin-only pills reduced migraine frequency, the intensity of the associated symptoms, and the use of analgesics, as reported in a study by Nappi [42].

The absolute risk of ischaemic stroke in young women is low; the average yearly cumulative incidence of ischaemic stroke per 100,000 increases from 1 at ages 15–19 years to 30 at 45–49 years, with an estimated overall average yearly cumulative incidence of 11/100,000 woman-years [37,43]. Similarly, the absolute risk of stroke in migraineurs using COC is 18/100,000 person-years [44].

It is interesting to understand the other severe implications of MA. In a study of female health professionals aged at least 45 years, women with MA had a higher adjusted incidence rate of CVD than women without aura or no migraines [45].

A recent study showed that an association between migraines and ischaemic stroke is surgery. In a large prospective surgical patient registry study, migraines, especially MW, were associated with an increased risk of ischaemic stroke within 30 days of surgery, even in patients with a low estimated baseline stroke risk and those undergoing ambulatory surgeries [46].

Migraines and VTE

Few studies are available to understand whether migraines increase VTE risk, considering that migraines and VTE share certain risk factors.

Data indicate that in the presence of active migraines in young individuals, the risk of VTE was elevated in the short term following a migraine episode. Folsom et al. show that a history of migraines did not increase the long-term risk of venous thrombosis in an older population [47].

A cohort study from Denmark matched patients with a hospital-based diagnosis of MA and MO compared with an age- and sex-matched general population and found an approximately 1.5-fold increased risk of VTE among patients of MA and MO. The median age of the participants was 35 years with 19 years of follow-up [48]. Another study from Taiwan included patients with migraines, and a 2.5-fold increased risk of VTE among patients with MA was reported in a propensity-score-matched comparison cohort of individuals without headache. In contrast, the study found no association with VTE in patients with MO. Age did not modulate VTE risk when comparing women younger than 50 and women older than 50 [49].

A German cross-sectional population study involving 55- to 94-year-old patients with migraines had a 2-fold higher age- and sex-adjusted history of VTE than did non-migraine patients [50]. A population-based, cross-sectional sample of pregnant women showed that VTE during pregnancy was 3-fold more common in women with peripartum migraines vs those with no migraines [51].

The ARIC study has challenged the association of migraines with VTE. The study results do not support the hypothesis that migraine history is a risk factor for VTE in older adults and conclude that older patients with migraines should require only standard VTE prophylaxis [52].

The discrepancy of the results on VTE risk in the studies indicates that a history of migraines does not lead to long-term risk of venous thrombosis in an older population [46]. Prior publications indicated a link between active migraines and VTE, primarily in the younger population. VTE occurs due to venous stasis and coagulation factor activation. Migraine is not consistently associated with plasma haemostatic factors or genetic variants that predispose an individual to VTE. High oestrogen levels can contribute to migraines and VTE, but in that case, hyperestrogenemia would cause VTE, not migraines. Perhaps migraines could lead to immobility, predisposing an individual to VTE.

Potential mechanisms underlying the association between migraines and VTE are the common risk factors for migraines and VTE. Individuals with MA may have a higher prevalence of inherited coagulation abnormalities. Lifestyle behaviours predisposing one to the manifestation of VTE may be more common among patients with migraines. They have shown migraines attacks to trigger platelet hypercoagulability and activate the coagulation cascade putatively through endothelium-dependent pathways (endothelial activation) and induction of a systemic stress reaction. It supported the hypothesis because VTE occurs during the years of active migraines.

MHT and stroke

Oestrogens (endogenous or exogenous origin) have a differential effect on CVD, depending on whether the endothelium is healthy or damaged. HT used in the “window of opportunity” has favourable long-term effects on cardiovascular markers and is associated with reduced risk of atherosclerotic disease, although it may adversely affect thrombotic parameters in susceptible women.

Epidemiologic studies of oestrogen therapy and stroke risk are conflicting. The National Health and Nutritional Examination Survey (NHANES) findings indicated a significant reduction of risk. The age-adjusted incidence rate of stroke among postmenopausal hormone ever-users was 82 per 10,000 woman-years of follow-up compared with 124 per 10,000 among never-users [52]. Conjugated equine estrogen at an oral daily dose of 0.625 mg or greater increased the relative risk (RR) to 1.3, and in combination with progestin, the RR was 1.45 in the Nurses' Health Study [53]. No association was found in young HT users [54].

A meta-analysis of randomized trials indicated that HT was associated with increased ischaemic stroke but not hemorrhagic stroke or transient ischaemic attacks in all age groups. However, there was no absolute excess risk of stroke in the 50- to 59-year-old age group. The main limitation in the quality of evidence was that only about 30% of the women were 50–59 years old [55,56].

HT was associated with a reduced or null risk of future stroke if initiated relatively soon after the onset of menopause in women at low risk for CVD, regardless of regimen (type, active ingredient, and route of administration) and duration. This positive effect of and the timing hypothesis called the “window of opportunity” is observed in extensive observational studies, randomized trials with preclinical outcomes, and RCTs with clinical outcomes [57].

Observational studies, systematic reviews, and meta-analyses consistently report a two to three times greater risk of VTE among postmenopausal women on HT [58,59]. Women who have used HT in the past have a similar VTE risk to those who have never used the treatment, and among women on HT, the risk is most significant during the first year of treatment. However, there are no consistent data on the risk of VTE according to the method of HT, including the type and dose of oestrogens, route of administration, and the potential role of progestogens.

Based on the best available evidence, transdermal oestrogen combined with micronized progesterone or dydrogesterone appears to be the safest option for minimizing the risk of VTE among postmenopausal women requiring HT [60].

MHT, migraines, and stroke

In premenopausal women, the group at the highest risk of developing migraines and migraine-related stroke, the hypercoagulable state may be caused by high oestrogen levels, either endogenous due to pregnancy or exogenous due to COC or HT. As described earlier, oral oestrogen replacement is associated with a small increased risk of stroke; transdermal oestradiol is associated with minimal, if any, increased risk of stroke above the woman's own background risk. In MA, stroke is more likely to be associated with thrombophilia and not atherosclerosis and shows the safety of non-oral HT in women with past or current migraines and has some clinical evidence [61]. There are insufficient data on the effect of MHT on stroke in women with migraines.

The Oxford Vascular Study (OXVASC), a population-based cohort study, followed participants over ten years and assessed the association between migraines and incident cryptogenic TIA and stroke. Of the 92,728 participants, 1810 had an incident ischaemic event, of which 668 cases were cryptogenic. Although there was a trend towards increased risk of cryptogenic events in current HT users with migraines, the association was insignificant. There were no data on the type, dose, route of delivery, or duration of use of HT [32].

Limited evidence from the Women's Health Study indicates that the association between MA and ischaemic stroke is not statistically significantly modified by the use of postmenopausal HT [34].

MHT and migraines

The effect of MHT on migraines is variable, ranging from improvement or complete remission to worsening and no change [62].

The results of the studies on MHT and migraines are presented in Table 1 [63–68].

Management at menopause transition and menopause for migraines remains the same. Women needing HT for managing menstrual abnormality, contraception, or menopausal problems require evaluation to understand the baseline risk for stroke. MA is not a contraindication to the use of non-oral HT (transdermal and vaginal), and combined continuous oestrogen and progestin is better than a cyclical regimen. Another option is tibolone and progesterones such as levonorgestrel intrauterine system, natural progesterone, dydrogesterone, and dienogest are preferred.

If aura starts for the first time, the transient ischemic attack should be excluded, and the lowest effective dose necessary to control menopause symptoms should be tailored. If aura does not resolve, withdrawal of oestrogen and non-hormonal strategies should be considered.

In women who are at the highest risk, non-hormonal preparations such as fluoxetine, paroxetine, venlafaxine, escitalopram, or gabapentin may be more appropriate.

Summary

Migraine is a multifactorial neurovascular condition that is underdiagnosed and undertreated. The pathophysiology of migraines is complex, more so in oestrogen-related migraines. Hence, the challenge is to identify women who will benefit from HT and trigger those in which migraines. We associate MW with an increased risk of ischaemic stroke. Studies on oestrogen therapy in migrainous women are from COC's. The literature indicates that the risk of stroke in a woman with migraine who uses COCs is additional to the increased stroke risk associated with migraine and the risk associated with COC use. In studies on the risk of stroke in women without migraine using low oestrogen doses, non-oral COCs have been reassuring. Oestrogen replacement therapy should not be contraindicated for women with migraines, with or without aura. Tailoring MHT to the lowest effective dose and choosing the non-oral route to control menopause symptoms may be a safe option for women with MA.

Table 1
Studies on MHT and migraine and their outcomes.

Article/year	Number of participants	Study design	Intervention	Outcomes
Lichten, 1996 [67]	28	Open-label clinical trial	One-time dose of 5 mg depo-estradiol cypionate intramuscular injection	All had severe migraine on day 18 ± 4 of the study vs no migraine in the control group, with the average serum estradiol level on the day of migraine between 45 and 50 pg/mL
Nappi, 2001 [68]	50	Randomized, open-label	Continuous transdermal estradiol, 50 μg, plus cyclical medroxyprogesterone acetate (MPA), 10 mg per day, compared with continuous oral conjugated estrogens, 0.625 mg per day, cyclical MPA, 10 mg per day	Frequency and number of days of attacks significantly increased in the oral HRT group but not in the transdermal HRT group
Facchinetti, 2002 [65]	38	RCT (single-center study in Italy)	HRT with estradiol hemi-hydrate 1 mg/day plus norethisterone 0.5 mg/day for 28 days, in a continuous combined scheme; oral conjugated estrogens 0.625 mg/day for 28 days plus medroxyprogesterone acetate 10 mg/day in the last 14 days, in a sequential continuous scheme; and estradiol valerate 2 mg/day for 21 days plus cyproterone acetate 1 mg/day from day 12–21 in a sequential cyclical scheme	All 3 HRT treatments significantly increased migraine attack frequency and severity (2.2 days per month vs 3.8, $p < 0.001$), (3.4 days per month vs 4.9, $p < 0.001$), (3.4 days per month vs 5.6, $p < 0.001$) over the course of 6 months
Misakian, 2003 [25]	17,107	Cross sectional (Part of Women's Health Study)	Use of HRT	HRT use significantly increased the risk of experiencing a migraine in postmenopausal women (13% vs 9%, $p < 0.001$)
Brandes, 2006 [66]	18,221	Cross sectional (Part of Women's Health Study)	Estrogen dose Low (<0.3 mg/day), Intermediate (0.625 mg/day), High (>0.9 mg/day)	Intermediate-dose estrogen had a significantly lower risk of migraine occurrence or high dose compared with the general population
Nappi, 2006 [67]	40	Randomized trial	Tibolone vs estrogen-progestogen (EP)	Tibolone decreased headache intensity and frequency while estrogen-progestogen did not Tibolone decreased analgesic consumption while estrogen-progestogen increased it
A MacGregor, 2006 [8]	35	Double-blind placebo-controlled crossover	Effects of oral and transdermal estrogen replacement on migraine	22% reduction in migraine incidence while using percutaneous estradiol gel with 40% increase in migraine occurrence in the 5 days after discontinuing estrogen
Aegidius K, 2007 [68]	5507	Cross sectional (Part of Nord-Trøndelag Health Study 1995-97 HUNT 2)	HRT	Migraine was more common in HRT users than in nonusers

Practice points

- Oestrogen has a role to play in the pathophysiology of oestrogen-related migraines.
- The low-dose, non-oral route of MHT is not contraindicated in women suffering from migraines with and without aura.
- Continuous MHT regimes are preferred. New-onset migraine or trigger of migraine during therapy needs to be evaluated.

Research points

- Can MA be considered as a risk factor for CVD?
- Can we identify biomarkers for risk assessment for stroke in migraines?
- There is a need for evidence-based studies on ideal oestrogen–progesterone combinations for use in migraineurs at risk for stroke.

Declaration of competing interest

None.

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