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Review

Migraine and perimenopause

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ABSTRACT

Perimenopause and migraine are closely linked. The hormonal instability during the perimenopausal period not only causes vasomotor symptoms and mood disturbances, but also increases migraine incidence. Women do report new onset migraine during this period, but the increased incidence is reported by women with menstrually related migraine (MRM). The hormonal fluctuations can be stabilized with hormone replacement therapy (HRT), while simultaneously improving the migraine in some patients. The increased stroke risk in women with migraine with aura (MA) should be taken into consideration when intending to treat perimenopausal women with migraine with HRT.

Contents

1. Introduction

The onset of the perimenopausal period, the period of 2–8 years prior to the menopause as well as the year after the end of menses, is usually characterized by a sequence of symptoms caused by an estrogen deficit that occurs due to a decline in ovarian function. These symptoms consist foremost of night sweats, hot flushes, joint pain and vaginal dryness, however sleep disturbances and irritability are also prevalent. There is a link between the menopausal transition and migraine as well. Preexisting migraine can remain unchanged, improve, but may also worsen during perimenopause [1,2]. Consequently, perimenopause is a turbulent period in women's life, not only with regard to migraine. Unfortunately, prospective studies documenting the course of migraine during and after the menopausal transition remain rare.

2. Migraine pathophysiology

Migraine is a paroxysmal disorder of a neurovascular origin, with great adverse effects on the quality of life. According to the Global Burden of Disease Survey 2010 conducted by the World Health Organization, migraine is ranked as seventh highest cause

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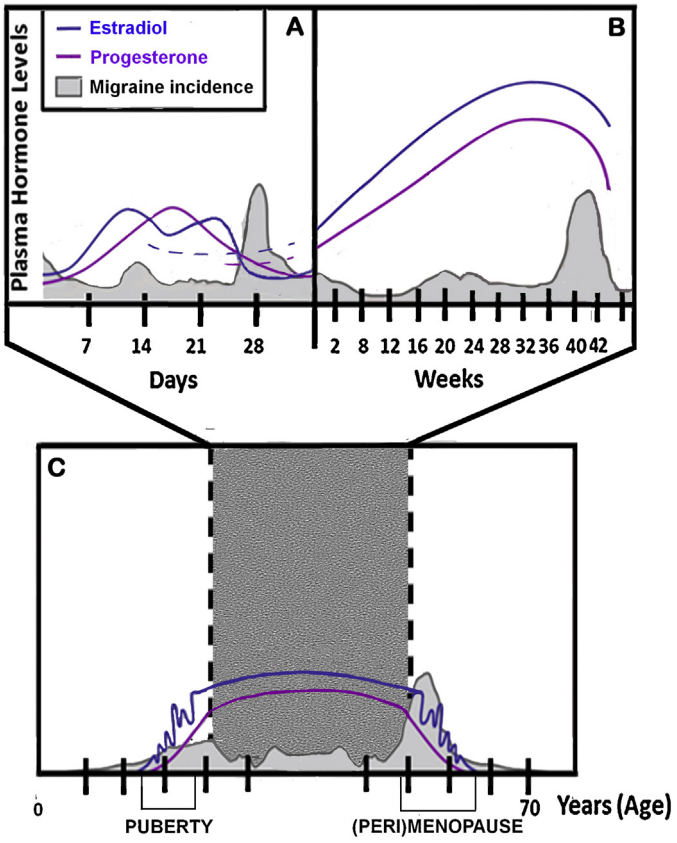

Fig. 1. Migraine incidence and female hormones during the menstrual cycle, pregnancy and a woman's life.
Adapted from Sacco et al. [43].

of disability in the world [3]. The distinctive pulsating headaches manifest as attacks that can last from 4 up to 72 h and are located unilaterally. The headaches worsen with physical activity and/or are associated with photophobia and phonophobia. When the headache is preceded and in some cases accompanied by gradually developing visual, sensory or other central nervous system symptoms (aura), then it is diagnosed as migraine with aura (MA) otherwise it is considered migraine without aura (MO) [4]. Migraine is thought to originate from neural events that results in dilation of cranial blood vessels, inducing headache and further nerve activation [5]. Calcitonin gene-related peptide (CGRP) is a key neuropeptide in migraine pathophysiology. Indicative of its importance, CGRP levels are elevated in jugular blood and saliva during migraine attacks and normalize after the use of antimigraine drugs [6,7]. CGRP receptor antagonists and antibodies against CGRP or its receptor are currently being developed as acute migraine therapy [8,9].

2.1. Estrogen fluctuations and migraine

The prevalence of migraine is according to the recently published American Migraine Prevalence and Prevention study 17% in women and 6% in men [10]. Especially hormonal milestones accompanied by fluctuations in estrogen levels such as menarche, pregnancy and menopause seem to have vast effects on migraine prevalence and frequency (Fig. 1). The onset of migraine in women usually coincides with menarche and a close relation between migraine occurrence and the menstrual cycle remains during the reproductive years [11]. Approximately 50% of women with migraine are affected by MRM [12]; migraine without aura that occurs on day 1 ± 2 of the menstrual cycle in at least 2 of 3 consecutive menstrual cycles with additional attacks with or without aura that can occur at other times of the month [4]. During perimenopause changes in migraine prevalence have been reported [13]. Major fluctuations in estrogen levels take place during perimenopause, ultimately leading to dropping levels [14]. The prevalence of migraine headaches during this period seems to be higher in patients who previously had a history of MRM and premenstrual syndrome [15,16].

3. Perimenopausal migraine

During the perimenopausal period serum estradiol levels are low (10–20 pg/ml). Nevertheless, 8–13% of women with migraine report the onset of their migraine during this period [17,18]. Interestingly, the type of menopause (surgical or spontaneous) influences the effect of the menopausal transition on pre-existing migraine. Improvement of migraine occurs in two-thirds of women after spontaneous menopause, but migraine worsens in two-thirds after surgical menopause [19]. With the increase of time after the start of the menopausal transition, there is a decrease of migraine prevalence [16,20], which is most pronounced in MO [15]. It is not surprising that, given the improvement of migraine in women after spontaneous menopause, oophorectomy has been considered as preventive migraine therapy in perimenopausal women. Pharmacological oophorectomy induced by a gonadotropin-releasing hormone agonist with estrogen add-back therapy seems to improve headache pain severity, but not the headache frequency [21]. Anecdotal evidence suggests that total hysterectomy with bilateral oophorectomy and add-back estrogen therapy may be successful in the treatment of migraine [22]. This kind of drastic surgical intervention is considered by some doctors in cases of women suffering from severe and debilitating migraine that has improved after pharmacologically induced menopause. These claims have an insufficient scientific base, so gynecological operations like this should be discouraged.

4. Treatment/management

During perimenopause, HRT may be prescribed to women to fight the symptoms of dropping estrogen levels [23]. HRT can have an improving or worsening effect on migraine in perimenopausal women [24]. Transdermal estrogen patches or gel are preferred in treating women with migraine during this period, since oral treatment can lead to estrogen fluctuations and consequently worsening of the migraine [25]. Estrogen replacement in perimenopausal patients with MA has been associated with an increase in headache severity and visual auras [26]. Prescribing the lowest effective dose of estrogen seems to prevent this undesired effect [27]. This is also prudent considering MA is a risk factor for ischemic stroke, see below [28–30]. When systemic estrogen is used, endometrial protection is needed in perimenopausal women with an intact uterus. Progesterone, preferably micronized as this may be safer with regard to breast cancer risk [31], should be prescribed next to estrogen. Independent of the HRT to regulate estrogen levels, (pre)menopausal migraine can be treated with prophylactics or acute antimigraine therapy according to standard treatment strategy. While guidelines differ internationally and even nationally [32], generally migraine attacks are initially treated with acutely acting medication. According to a treatment ladder, therapy is usually started with an oral analgesic (acetaminophen or NSAID's) combined with an anti-emetic. When migraine relief is not achieved, triptans are prescribed. Migraine prophylaxis consisting of beta-blockers, topiramate, depakine of other prophylactics are prescribed in patients with frequent attacks or in case of insufficient efficacy or overuse of acutely acting drugs [33].