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Review

# Estrogen replacement and migraine

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ABSTRACT

Four of every 10 women will experience migraine at some time in their lives, with peak prevalence in middle life. Evidence supports estrogen 'withdrawal' as one of the important triggers of menstrual attacks of migraine without aura. Improvement of migraine without aura postmenopause is generally attributed to the absence of variations in sex hormone levels. Maintaining a stable estrogen environment is best achieved using non-oral estrogen replacement. Unlike migraine without aura, migraine with aura is recognized as a marker for increased risk of ischemic stroke. Research suggests that aura may be more likely to affect women with underlying coagulation disorders. This could, at least in part, account for both increased risk of stroke and the dose related effect of estrogen replacement on the development of aura. Hence women with migraine with aura requiring estrogen replacement should be given the lowest effective dose necessary to control menopause symptoms, by a non-oral route.



**Contents**



## 1. Introduction

Migraine is prevalent episodic headache disorder affecting otherwise healthy individuals. It is an important target for public health interventions as it is highly prevalent and disabling. The World Health Organization (WHO), recognizes migraine as 19th among all causes of years lived with disability (YLDs), 12th in women [1]. Headache disorders impose recognizable burden on sufferers including sometimes substantial individual suffering, impaired quality of life and financial cost [2]. Four of every 10 women and two of every 10 men will contract migraine in their lifetime. This sex difference is recognized to be the result of the additional hormonal triggers affecting women. The median age at onset is 25 years but prevalence does not peak until middle life [3].

Of the two main types of migraine seen in clinical practice, migraine without aura is most prevalent, particularly in women [4]. In migraine without aura, typical symptoms are of episodic disabling attacks of headache associated with nausea and photophobia, which last between part of a day and three days. Migraine with aura is characterized by specific neurological symptoms that gradually develop over 5–20 min, last under 1 h, and usually completely resolve before the onset of headache [5]. Homonymous visual symptoms are most common, experienced in 99% of auras [6].

Both menopause and hormone replacement therapy (HT) can have significant effects on migraine. Given the high prevalence of migraine, it is important for all healthcare professionals to understand the association between migraine and estrogen in order to develop effective management strategies for their patients.

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## 2. Role of estrogen in migraine pathophysiology

Around 50% of women report an association between migraine and menstruation during the reproductive years [7–10]. Evidence supports estrogen 'withdrawal' in the late luteal phase of the menstrual cycle as one of the important triggers of menstrual migraine, which are typically attacks of migraine without aura [11–13]. Somerville found that migraine could be postponed by maintaining high plasma estradiol levels with an intramuscular injection of long-acting estradiol valerate in oil; migraine subsequently occurred when the plasma estradiol fell [11]. He then tried daily progesterone injections, beginning three to six days before expected menstruation [14]. Menstruation was delayed in four of these women but, in spite of this, five experienced migraine at their customary time, unrelated to plasma progesterone levels.

Several other studies support the importance of estrogen 'withdrawal' as a migraine trigger. Epstein et al. noted that the extent of decline from peak to trough estrogen was greater in all 14 women with migraine in their study compared to 8 women in the control group who did not have migraine. They concluded that variation in hormonal activity might be a potentially relevant factor in all women with migraine; factors additional to the hormonal environment could account for the development of 'menstrual' attacks [15]. Lichten et al. studied 28 postmenopausal women challenged with estrogen confirming that in women with a history of premenopausal menstrually-related migraine, a drop in serum estrogen, in the absence of progesterone, could precipitate migraine and that a period of estrogen priming was a necessary prerequisite [16].

If estrogen 'withdrawal' triggers migraine, then maintenance of a stable hormonal milieu should be associated with fewer migraine attacks. In accordance with this hypothesis, several studies have used perimenstrual estrogen supplements to prevent the natural late luteal fall in estrogen.

Placebo-controlled trials with 25 μg or 50 μg estradiol patches seemed to have little effect in reducing the occurrence of menstrual or menstrually-related migraine [17–19]. These doses achieve mean estradiol serum levels of 25 pg/ml and 40 pg/ml respectively. However, trials using 100 μg estradiol patches or 1.5 mg estradiol gel, which maintain mid-luteal phase estradiol levels, have shown efficacy [18,20,21].

de Lignières et al. studied 18 women (mean age 42.5 years (range 32–53)) with strictly defined menstrual migraine who completed a double-blind placebo-controlled crossover trial using 1.5 mg estradiol or placebo gel. Treatment was started two days before the earliest expected onset of menstrual migraine and continued for seven days during three consecutive cycles [20]. Only eight menstrual attacks occurred during the 26 estrogen treated cycles (30.8%) compared with 26 attacks during the 27 placebo cycles (96.3%). Further, attacks during estrogen treatment were considerably milder and shorter than those during placebo.

Similarly, Dennerstein et al. studied 18 women who used 1.5 mg estradiol gel or placebo daily for seven days, beginning at least two days prior to the expected migraine, for four cycles [21]. The difference between estradiol gel and placebo was highly significant, favoring the estradiol gel, and less medication was used during active treatment.

MacGregor et al. studied 38 women with menstrual migraine (mean age 43 years (range 29–49)) in order to assess the effect of rising and falling estradiol levels across the menstrual cycle [22]. Urine collected daily over three menstrual cycles was analyzed for luteinizing hormone (LH), estrone-3-glucuronide ($E_1G$), pregnanediol-3-glucuronide (PdG) and follicle-stimulating hormone (FSH). Migraine was inversely associated with urinary estrogen levels: attacks were significantly more likely to occur in association with falling estrogen in the late luteal/early follicular phase of the menstrual cycle and significantly less likely to occur during the subsequent part of the follicular phase during which estrogen levels rose. During a further six cycles, women were randomized to treatment with 1.5 mg estradiol gel or placebo, starting five days before the onset of menstruation and continuing until the second full day of menstruation [23]. During estradiol treatment there was a significant reduction in the duration and severity of migraine compared to placebo. However, estradiol treatment only deferred migraine in some women, who experienced a significant increase in migraine post-treatment. This study failed to identify a critical 'threshold' for estrogen 'withdrawal' migraine, in line with the theory that falling levels are more important than absolute levels [11].

Martin et al. reported that a 100 mcg transdermal estradiol patch produced a modest preventative benefit for migraine headache in 21 women who had a medical menopause induced by a gonadotropin releasing hormone agonist [24]. Headache outcome measures were 45–50% higher during the first two days after application of a transdermal estradiol patch when compared to the fifth and sixth days after a patch change while no differences were seen between patch days in the placebo group. Within the estradiol treated group, serum estradiol levels were maintained in a very narrow range varying from 50 pg/mL during the first 2 patch days to 42 pg/mL during the last two days of the patch. Martin hypothesized that, despite an overall preventative effect with transdermal estradiol compared with placebo, a small rise in serum estradiol levels on the first two days of the patch might be sufficient to provoke migraine. These contrasting findings highlight the individual effects of estrogen, which can prevent migraine in some women but trigger migraine in others.

## 3. Effect of the perimenopause on migraine

Few studies have specifically addressed how migraine changes through the perimenopause, but they support the clinical impression that migraine without aura deteriorates with time since menopause being a significant factor in improvement [25,26].

A study of 1436 women showed a migraine prevalence of 10.5% in spontaneous menopausal women compared with 16.7% in premenopausal and perimenopausal women (OR 0.6, 95%CI 0.4–0.9, $p = 0.03$) [27]. This improvement is generally attributed to the absence of variations in sex hormone levels postmenopause. Consistent with this theory is that ovarian failure, with low levels of estrogen and high levels of follicle-stimulating hormone (FSH), is associated with a lower prevalence of migraine than menstruating women [27].

Natural menopause is associated with a lower prevalence of migraine compared to surgical menopause [8,28,29]. A retrospective questionnaire of 47 postmenopausal women with migraine and noted eight women (17%) reporting new onset of headache with menopause [28]. Of those women who had had a physiological menopause, 67% reported improvement or complete remission of headache following menopause, 24% reported no change, and 9% reported worsening headache. Of those women who had had a surgical menopause, 38% reported improvement of headache following menopause, 33% reported improvement, and 67% reported worsening headache.

In a cross-sectional survey of 986 hysterectomized women with one or both ovaries present and 5636 non-hysterectomized women with both ovaries present, 8.8% non-hysterectomized women reported moderate to severe migraine, compared with 15.1% of hysterectomized women with ovarian retention ($p < 0.001$) [29].

Migraine prevalence has been reported as lowest in those with hysterectomy and bilateral oophorectomy, although not to a statistically significant level (hysterectomy only, 28.6%; hysterectomy with unilateral oophorectomy, 36.4%; hysterectomy with bilateral oophorectomy, 15.8%; $p = 0.3$) [27].