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Menstrual Migraine: Use of Steroid Hormones

Migraña menstrual: uso de hormonas esteroideas

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SUMMARY

Menstrual migraine is a condition in females where headaches are linked with menstruation. Hormonal fluctuations could have a key role in migraine pathogenesis, as several women experience that their migraine attacks correlate with their menstrual cycle. Estrogen withdrawal appears to have a significant role in migraine associated with menstrual cycles, even though its pathophysiology is not well known. Although clinical and basic science studies have advanced our understanding of the mechanisms of sex hormones, many questions remain, and our understanding of this topic continues to evolve. This article highlights the use of sexual hormones in women who suffer from menstrual migraine.

Keywords: *Headaches, menstrual migraine, estrogen therapies, combined hormonal contraceptive, oral contraceptives, phytoestrogens*

RESUMEN

La migraña menstrual es una afección que afecta a las mujeres que se relaciona con la menstruación. Las fluctuaciones hormonales podrían tener un papel clave en la patogénesis de la migraña, ya que muchas mujeres experimentan ataques de migraña que se correlacionan con su ciclo menstrual. La abstinencia de estrógenos parece tener un papel importante en la migraña asociada con los ciclos menstruales, aunque su fisiopatología no se conoce bien. Aunque los estudios clínicos y de ciencia básica han avanzado en nuestra comprensión de los mecanismos de las hormonas sexuales, aún quedan muchas interrogantes y nuestra comprensión de este tema continúa evolucionando. Este artículo destaca el uso de hormonas sexuales en mujeres que sufren migraña menstrual.

Palabras clave: *Dolores de cabeza, migraña menstrual, terapias con estrógenos, anticonceptivos hormonales combinados, contraceptivos orales, fitoestrógenos.*

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INTRODUCTION

Migraine is a disabling headache characterized by moderate to severe head pain, usually accompanied by nausea, photophobia, phonophobia, and osmophobia (migraine without aura, MO); 30 % of patients' migraine attacks are preceded by transient focal neurologic symptoms, which are called aura (migraine with aura, MA). Migraine has a high socio-economic impact. In fact, during migraine attacks, most migraineurs

reported severe impairment or the need for bed rest and almost 40 % of migraine patients have five or more headache days monthly (1). Worldwide, millions of patients suffer from migraine headaches (2). Migraine prevalence varies by race and geography (3). Despite regional variations, headache disorders are a worldwide problem, affecting people of all ages, races, income levels, and geographical areas. In 2016, the World Health Organization (WHO) (4) estimated that the prevalence among adults of current headache disorders (symptomatic at least once within the last year) is about 50 % worldwide.

Half to three-quarters of adults aged 18-65 years in the world have had headaches in the last year, and among those individuals, 30 % or more have reported migraine. Headache on 15 or more days monthly affects 1.7-4 % of the world's adult population. The prevalence of migraine during childhood is similar in boys and girls. Still, after puberty, it rises differently in sexes, becoming two to three times more prevalent in women than in men, with 17 % of all women meeting the diagnostic criteria for migraine (5). Four of every ten women and two of every ten men will contract migraine in their lifetime, most before age 35 years (6). More than 50 % of women with migraine report an association between migraine and menstruation (1-10). For most women with menstrual attacks, migraine also occurs at other times of the month (11). Fewer than 10 % of women report migraine exclusively with menstruation and at no other time of the month (9-12).

The incidence of migraine headaches increases significantly between the ages of 15 and 19 years, peaks in women in their late 30s to early 40s, and falls after menopause (8). Up to 70 % of women with migraine headaches observe an association with menses; 7 %-25 % have pure menstrual migraine (MM), and the remainder have menstrual-related migraines (MRM) (5,13). Most MM attacks are without aura, even in women who have attacks with aura at other times of the cycle (7,11). Compared with headaches that occur at different times of the month, MM is usually more resistant to treatment, generally not associated with aura, of longer duration, and associated with more functional disability (14,15).

Lipton et al. (16) reported that 85 % of 389 people with migraine reported substantial reductions in their ability to do household work and chores, 45 % missed family social and leisure activities, and 32 % avoided making plans for fear of cancellation due to headaches. Work-related disability is more often reported for premenstrual migraines than for non-menstrual attacks ($p = 0.006$) (17). Similarly, less than 50 % productivity time is greater for menstrual than non-menstrual attacks ($p = 0.01$) (18). Disability does not only affect the individual but also extends to the family and work environment. In one study, MacGregor et al. (9) found that living with or being related to a migraineur decreased non-migraineurs' ability to participate in home/family life (moderate/significant impact, 49 %) and social/leisure activities (moderate/significant impact, 47 %).

The prevalence of migraine is relatively high during perimenopause, especially in women with a history of MM (19). In the Women's Health Study, 11 % of more than 17 000 postmenopausal female health professionals reported migraine; current users of hormone therapy were more often affected than never users (OR = 1.42; 95 % CI = 1.24-1.62), and prevalence correlated with the dose of estrogen therapy (20).

The objective of this narrative review article is to review and analyze the use of different hormonal therapies on women who suffer from MM.

MATERIAL AND METHODS

The present narrative review was conducted to investigate and analyze recent and relevant studies about MM and the use of hormonal therapy. Studies published in the English and Spanish languages were included in the review. Following the PRISMA guidelines, we identified published studies through a systematic and electronic review of PubMed, Medline, ISI, DOAJ, Springer, and Embase literature searches. Web of Knowledge, DOAJ. Google Scholar for original articles written in English, Scielo, Lantidex, Imbiomed-L, Redalyc, and Google Scholar for original articles written in the Spanish language. The searches included the keywords

(Mesh): headache, migraine, menstrual migraine, and the following search terms: ("headache," AND "migraine" AND "menstrual migraine OR hormone treatment OR combined hormone contraceptives OR oral contraceptive OR phytoestrogens").

Selection criteria included randomized clinical trials, observational trials, open-label non-randomized trials, and reviews. Publications from 1970 to April 2024 were reviewed and analyzed. The author evaluated the electronic search and eligibility of the studies.

Hormonal therapy

Different authors have discouraged the hormonal treatments contained in migraineurs, especially in those with MA, due to an increased risk of ischemic stroke and venous thromboembolism (VTE). Women who have MA have twice the risk of stroke as women without migraines (5.9 *vs*. 2.5 events per 100 000 persons annually), and the risk is nearly six times as great with contraceptive use (14.5 events per 100 000 persons) (1,21-24).

However, there are two main categories of hormonal treatments evaluated in MM prevention: 1. Combined hormonal contraception (CHC): oral, vaginal ring, and patches, to avoid unintended pregnancies with different regimens and doses of ethinylestradiol (EE) administration according to the duration of the hormone-free interval (standard regimens 21/7, variable extended regimens, continuous regimens without hormonal-free interval (HFI); 2. Estrogen treatments do not ensure contraception, which replaces the fall in estrogen during the perimenstrual period both in patients with MM and in those with premenstrual migraine (PMM) (5,7,25).

Data on hormonal treatments in MM prevention are scarce and heterogeneous, but they suggest their ease of use, versatility, and good safety profile (23). They have been administered as short-term preventive strategies during the perimenstrual period to replace the fall in endogenous estrogens in those suffering from PMM with predictable menstruations (7,25). They have also been administered at low doses in a continuous modality to counterbalance physiological hormonal fluctuations or in combination with progestogens to stabilize hormonal levels and ensure contraception (22).

Estrogens

Estradiol

Perimenstrual estrogen can only be used when menstruation is regular and predictable. If the woman has an intact uterus, no additional progestin is necessary as long as she is ovulating regularly (7). Macgregor et al. (7,25) recommended prophylactic use during the perimenstrual period of 1.5 mg estradiol (E_2) gel applied daily, 2 to 3 days before expected menstruation for seven days. Alternatively, 100 μg E_2 transdermal patches can be used from 2 to 3 days before expected menstruation until the 4th or 5th day of menstruation (twice a week). The study showed that some women who responded to E_2 supplementation experienced a delay in the onset of attacks when additional E_2 administration was stopped. The authors (7, 14) suggest extending the use of the gel until day 7 of the menstrual cycle but reducing the dose in the last two days.

Combined Hormonal Contraception

Combined Oral Contraception

In 2019, WHO reported that 16 % (151 million) of women between 15-49 years old were using combined oral contraceptives (COC), which are the most common method of reversible contraception in the United States (26). The combined oral contraceptives composition has continuously evolved over the years to improve safety, efficacy, tolerability, and non-contraceptive benefits. While the estrogen (E) component has remained predominantly the same, ethinyl estradiol (EE), due to its good bioavailability, formulations have varied significantly in terms of progestogens (23,27). The estrogen component of modern combined oral contraceptives has been implicated in increasing stroke associated with migraine with

aura. Women who have MA have twice the risk of stroke as women without migraines (5.9 *vs*. 2.5 events per 100 000 persons annually). The risk is nearly six times as great with contraceptive use (14.5 events per 100 000 persons) (22); because of this, WHO and the Center for Disease Control and Prevention of the United States (CDC) (28) have MA as an absolute contraindication to use COC. Concerns over dose-dependent health risks (e.g., venous thromboembolism [VTE] and cardiovascular [CV] events), mainly associated with EE, have led to the development of alternative formulations with either reduced doses of EE, natural E, less androgenic progestogens or different routes of administration (29). Combined oral contraceptives are the most popular type of CHC, with a wide range of hormones, doses, and regimes. The estrogenic component is mainly EE, usually in a 20-30 μg dosage. Still, the newest formulations today also deliver natural forms of estrogen, such as E_2, estradiol valerate (E_2V), the ester of E_2, and estetrol (E_4), a fetal form of estrogen (30). The progestogenic component ensures the efficacy of the contraceptive and includes several types of progestogens at different doses depending on their biological potency (31). The most common way of administrating COCs is the 21/7 regimen, seven days of hormone-free interval (HFI) (32).

As mentioned before, since 2004, the World Health Organization (33,34) recommended that women with MA, because of the increased risk of ischemic stroke (35), should not use COCs. In 2016, the US CDC updated its medical eligibility criteria for contraceptive use in various medical conditions. In the case of MA, the guidelines note limitation to the use of combined hormonal contraceptives, regardless of the patient's age. The consensus was that the risk associated with combined hormonal contraception typically outweighs its benefits, noting "an unacceptable health risk if the contraceptive method is used" (24,28). However, the American Headache Society and the International Headache Society are less definitive about the contraindications of COC and recommend an individualized decision concerning OC that is based on benefits and risks, especially in the absence of other risk factors for stroke, such as age older than 35 years, tobacco use, hypertension, alcohol use, obesity, diabetes, or hyperlipidemia (36,37).

The availability of regimens with a shorter (6, 4, or 2 days) or absent HFI prevents the worsening of the migraine that sometimes characterizes the HFI. Indeed, observational studies showed that the reduction or the absence of HFI led to a significant decrease in the frequency, intensity, and duration of migraine attacks (38-40). Another strategy to improve MM during COC use would be an estrogenic supplementation during the HFI to prevent estrogen withdrawal (40,41). Both therapeutic approaches suggest that inhibiting the fall in estrogen or its replacement may be effective in the prevention of menstrual-related migraine: MM and PMM.

Short hormone-free interval

A significant amount of evidence has demonstrated the positive impact of a shorter HFI on MM. A prospective randomized study compared the administration of a COC containing 20 μg EE and 3 mg drospirenone (DRSP) in a standard 21/7 versus a 24/4 regimen in women suffering from PMM; patients receiving the 24/4 regimen reported a significantly lower intensity and duration of migraine attacks occurring during menstruation since the first cycle, and results gradually improved throughout the study period (37). Another prospective study evaluated the impact of a 26/2 regimen with a natural estrogen step-down (E_2V from 3 mg down to 1 mg) and a progestin step-up approach dienogest (DNG from 2 mg to 3 mg) in women with MRM, both switchers from a standard 21/7 COCs and never users, overall, women reported a significant reduction in headache frequency and duration, and acute medication consumption ($p < 0.001$) (39).

Estrogen supplementation during the HFI

Calhoun (40) evaluated the impact on MRM of a 21-day treatment with COC containing 20 μg EE followed by a 7-day treatment with 0.9 mg of oral conjugated equine estrogens (CEE) in women with MRM. He found that all patients reported a 50 % reduction in headache days per cycle and a remarkable reduction in headache severity with estrogenic supplementation in the HFI. Transdermal patches represent another route to replace the fall in estrogen during COCs HFI:

a crossover randomized placebo-controlled trial showed that 50 μg E_2 patches tended to reduce the frequency and severity of headaches and the occurrence of some bothersome migraine-related symptoms such as nausea, but the results were not statistically significant when compared with the placebo (41).

Extended and continuous regimens

Two further studies evaluated the extended and continuous administration of COCs for 168 days, both in patients with MRM (42) and in patients without migraine but reporting headaches during a 21/7 COCs regimen (43). The first study compared patients who previously received 21/7 COCs with never-user patients. The study population underwent a 168-day COC with 20 μg EE and 150-μg levonorgestrel (LNG). A 4-day hormone-free interval was scheduled after 84 days of continuous treatment (extended regimen) or in the case of reported bleeding (flexible regimen). Overall, the hormonal treatment led to a lower headache severity and disability in patients with MRM, and these results did not differ between patients previously receiving COCs in a 21/7 regimen and never-user patients (44). The second study prospectively compared the evolution of the headache in a sample of switchers from a 21/7 regimen to a 168-day regimen with 30 μg EE and 3 mg DRSP. Headache severity was significantly reduced during the 168-day COC, specifically in those who had previously reported more severe headaches during the 21/7 administration. Sacco et al. (22) mentioned that women with and without headaches supported more significant benefits of the extended regimen over the conventional one.

Finally, low-dose estrogen can be used even in women who have a simple visual aura, with careful monitoring and immediate discontinuation if the auras worsen. Preparations containing very low doses of estrogen (e.g., 10 to 20 μg of EE) are not clearly linked to the risk of stroke, as compared with the higher doses (e.g., 30 to 50 μg) investigated in earlier studies (37,40). In addition, a new era of contraception is coming using natural estrogens, including 17β-E, E_2V, and E_4 (a native estrogen of fetal origin). These show promise for conferring a lower risk of cardiovascular complications than that associated with EE and thus may become the most suitable option in women with migraine who need or want combined hormonal contraception (5,37).

Contraceptive Vaginal Ring

The transvaginal ring is an alternative route of administration of CHC. It releases 15 μg/day of EE and 120 μg/day of etonogestrel (ENG) and its typical use follows a 21/7 regimen, with three weeks of vaginal delivery plus one ring-free week; the vaginal route gives the advantage of stable hormonal levels during the 21-days of insertion (44). One study evaluated the efficacy of transvaginal hormonal treatment administered in an extended regimen in preventing MRM with aura (45). A significant reduction in aura frequency and an MRM resolution was observed in 91.3 % of patients. This was consistent with the stable hormonal levels and the absence of fluctuations allowed by the extended regimen (44). The study did not provide safety data, but the authors speculated that a decreased aura frequency might positively affect the risk of stroke as directly related to the frequency of auras (45,46).

Transdermal Estradiol Patches

The transdermal route is not affected by gastric absorption and hepatic catabolism. Moreover, transdermal E_2 has less impact on the synthesis of hepatic proteins, such as sex hormone-binding globulin (SHBG), coagulation factors, and angiotensinogen (47). Percutaneous E_2 should be preferred in women who suffer the most from hormonal fluctuations as they occur premenstrually and in perimenopausal women (48). However, some studies have evaluated the efficacy of transdermal E_2 patches in MM prevention as a short-term estrogen therapy during the perimenstrual period using a daily perimenstrual application of transdermal patches. Two randomized trials showed comparable results to placebo (PL) in preventing PMM and MM (49,50).

Transdermal Estradiol Gel

A few trials have proved the superiority of 1.5 mg E_2 gel to PL in short-term MM prevention. E_2 was administered for 7 or 8 days (from day −2 to +5 (51,52) or from day −6 to +2 of the menstrual cycle in 2.5 g of gel (41). These studies showed a significant reduction in MM frequency ($p < 0.01$, $p = 0.04$, respectively) with a significant effect on moderate to severe attacks ($p < 0.05$; $p = 0.003$, respectively) (41,51,52). A disease rebound might happen shortly after treatment discontinuation. Indeed, MacGregor et al. (41) reported a significant increase in migraine occurrence in the five days immediately following E_2 use compared to PL (RR 1.40, $p = 0.03$), with a spontaneous resolution after five days. This effect might be explained by an insufficient hormone dose or an inadequate start and treatment duration, maybe because the first two randomized controlled trials started the short-term prevention later in the menstrual cycle (41). Conversely, MacGregor et al. (41) started treatment six days before the expected menstruation to achieve the nadir of systemic estrogen concentration two days before menses, when migraines are more likely to occur. Further studies might provide information on the optimal treatment dose, duration, and start and might consider patients with MA.

Estradiol Implants

One study evaluating the efficacy of subcutaneous E_2 implants in a few patients with MM has proven the efficacy of this route of administration (53). Patients received implants containing 100 μg E2 at first and subsequently maintained doses of 50 μg together with cyclic 7-day oral norethisterone acetate (NETA) at 5 mg, leading to protection of endometrium. Most patients registered headache improvement: 46 % of women reported complete headache freedom and 37.5 % almost complete symptom relief (53).

Add-Back Therapy

Headache evolution has been studied in women using gonadotropin-releasing hormone (GnRH) analog, using transdermal E_2 patches, alone or combined with progestogen (add-back therapy). In one study, patients received 100 μg/daily transdermal E_2 and 2.5 mg/daily oral medroxyprogesterone acetate (MPA) to 3.75 mg monthly GnRH administered for ten months: patients reported a reduction in headache severity ($p < 0.001$) in both treatment phases (during GnRH administration alone and in combination with add-back therapy (54). Other studies compared transdermal patches of 100 μg E_2 with pl administered one month after the implant of a GnRH-releasing device. Transdermal E_2 proved superior to pl in reducing headache disability ($p < 0.035$), and severity ($p < 0.03$), but had no effects on headache frequency ($p = 0.7$) (13); also, patients without a diagnosis of MM reported a beneficial effect of the add-back therapy, supporting that the lack of hormonal fluctuations may also be helpful to prevent migraine attacks occurring outside the perimenstrual period.

Progestins

The progestin (Pn) component of hormonal contraceptives represents most of their contraceptive effects: inhibition of ovulation, suppression of endometrial activity, and thickening of cervical mucus. Progestin-only methods include pills, injectables, implants, and intrauterine devices (55). Progestins provide effective and reversible contraception; Pn-only contraception has many non-contraceptive health benefits, including improvement in dysmenorrhea, menorrhagia, premenstrual syndrome, and anemia (56). Progestins decrease the amount of menstrual bleeding (1). Progestin-only methods are appropriate for women who cannot or should not take CHCs because they have some contraindications to using estrogen and, therefore, have a higher risk of VTE (57) and a risk factor for stroke (58). The use of Pn-only contraception is not associated with an increased risk of VTE compared with non-users of hormonal contraception (59). In addition, Pn-only pills, injectables, or implants are not associated with an increased risk of ischemic stroke, according to a recent meta-analysis (OR 0.96; 95 % CI: 0.70-1.31) (60). The use of different types and doses of Pn has been studied in women with migraine without a specific focus on MM (61-63). Since the 1-year prevalence rates for migraine in women are 11 % for MO and 5 % for MA, respectively

(64), there is potentially a high number of women in whom CHCs may be contraindicated according to WHO guidelines and Pn-only contraception may be safely used (57,65). When the Pn-only pills were tested, among other contraceptive options, in a small sample of women with MM, amenorrhea was associated with a significant reduction in headaches (66). Progestogens have a lower stroke risk than E (67) and are effective in preventing MA (62,63), making them a preferable option for women with risk factors (22). The use of progestins at ovulation-inhibiting dosages likely decreases cortical excitability by maintaining low estrogen levels and avoiding estrogen withdrawal (39). A study comparing 75 μg oral desogestrel (DSG) with an extended-cycle regimen of 150 μg DSG and 20 μg EE showed that both treatments effectively prevent migraine. Still, the Pn-only contraceptive was superior in reducing the days with acute medication consumption ($p = 0.044$) (64). The potential advantages of using Pn-only contraception in women with migraine are 1) continuous use; 2) absence of estrogen peak; 3) no influence on the threshold for cortical spreading depression; 4) no evidence of an increase in cardiovascular, stroke, and thrombo-embolic risk; 5) no data on Pn inducing migraine.

Phytoestrogens

Phytoestrogens are natural agents, which have estrogenic activity in target tissues such as genistein and daidzein. They have been considered helpful in the relief of hot flashes, menopausal symptoms, and MM. They exert their action as selective estrogen receptor modulators (SERMs) because of their structure, which is similar to E_2. An open-label study showed the efficacy of 56 mg of genistein and 20 mg of daidzein administered 10 days per month (from day –7 to +3 of menstruation) as MM prophylaxis in 10 women (68). Patients observed an average reduction of 62 % of days with headache from the baseline ($p < 0.005$) and a reduction in headache intensity ($p < 0.005$); half of them also reported the resolution of autonomic symptoms (nausea and/or vomiting) related to migraines (68). A randomized controlled trial confirmed the efficacy of 24-week treatment with 60 mg soy isoflavones, 100 mg *dong quai*, and 50 mg black cohosh, which proved superior to pl in reducing the frequency of MRM attacks and headaches, triptans, and other acute medication consumption, and headache severity ($p < 0.001$) (69). Therefore, phytoestrogens represent a suitable therapeutic option for women not willing to take or with contraindications for hormonal treatments (68).

Testosterone

Testosterone (T) has been used in migraine prevention, and it has been found that subcutaneous T implants in patients with androgen insufficiency symptoms reduced the severity of headaches (70). The T mechanisms of action in migraine pathogenesis are unknown, but preclinical studies showed that they could modulate the central neurotransmitter pathways suppressing the cortical spreading depression (71).

Tibolone

A selective tissue estrogenic activity regulator with mild androgenic properties is suggested as an excellent option to manage migraine at menopause to avoid scheduled bleeding (72).

Gonadotrophin-releasing hormone analogs

Although they are effective, adverse effects of estrogen deficiency, such as hot flushes, restrict their use. The hormones are also associated with a marked reduction in bone density and should not usually be used for longer than 6 months without regular monitoring and bone densitometry. 'Add-back' continuous combined estrogen and progestogen can be given to counter these difficulties, but due to their high cost, their use is limited (6).

Menopause/Post-menopause

The treatment of migraine in menopausal women is not different from that in premenopausal women so hormone regimens that minimize changes in circulating estrogen levels are preferable; therefore, continuous treatment is a better choice than cyclic therapy, and the addition

of a progestin, when needed, does not affect the frequency of migraines (20).

CONCLUSION

MM is a common and disabling condition and recent studies continue to support that drops in estrogen concentrations precipitate MM, and minimizing this decline may prevent these headaches (73). Many women report that migraines associated with their menses are more severe and more debilitating than migraines occurring at other times in the menstrual cycle. The specific characteristics of MM attacks, particularly the longer duration and increased relapse rate compared with non-MM attacks, present challenges for treatment efficacy. Limited data also suggest that specific regimens of CHC use in MM and PMM may decrease both headache frequency and aura. The role of female sex hormones in migraine is continuing to develop. Future research to firmly establish the role of CHC and HRT in those with migraine, including those with aura, is still needed. The treatment of migraine in menopausal women is not different from that in premenopausal. Additionally, studies with a particular focus on delineating the role and complex relationships between different sex hormones (i.e. estrogen, progesterone/progestin, and testosterone) in headaches would be of particular interest. Although clinical and basic science studies have advanced our understanding of the mechanisms of sex hormones, many questions remain, and our understanding of this topic continues to evolve.

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