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REVIEW

Menstrual migraine: what it is and does it matter?

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Abstract
The diagnostic criteria of menstrual migraine (MM), migraine related to menstruation and pure menstrual migraine, are placed in the appendix of the International Classification of Headache Disorders and are still primarily considered as research criteria that need validation. Although there is a great wealth of knowledge about the neurobiological processes underlying MM and its symptoms, the mechanisms by which an attack starts during the menstrual cycle remain baffling, and the disease is still undertreated. In this narrative review, we aim to summarize recent data on pathophysiology, epidemiology, burden of disease and treatment of MM. The vast majority of the literature focuses on the relationship between MM and hormonal factors. The role of falling in estrogen levels is believed to increase the susceptibility of blood vessels to prostaglandins, which have been implicated in neurogenic inflammation. Moreover, fluctuations of ovarian steroid hormone levels modulate calcitonin gene-related peptide in the trigeminovascular system. In addition, it has been observed that gonadal hormones modulate cortical spreading depression susceptibility in animal models. Sex hormone influences on MM affect not only the frequency and severity of headache attack but also its treatment. Understanding the mechanisms that contribute to neuroendocrine vulnerability in some women and some menstrual cycles may yield possible marker of the disease opening treatment options specifically targeting MM. An increased interest for future research on the subject will further elucidate how to manage this debilitating type of migraine.

Keywords Burden of disease · CGRP · Estrogen · Headache · Treatment options

Introduction

Hormonal factors play a relevant impact on migraine. Menstruation is a common migraine trigger among female migraineurs. The International Classification of Headache Disorders ICHD-3 [1] recognizes two types of menstrual migraine (MM): migraine related to menstruation (MRM) and pure menstrual migraine (PMM). Women with a diagnosis of MM report that menstrual attacks are more painful, longer lasting, more disabling and less responsive to treatment [2–7]. During the last few years, the literature concerning this topic has added some relevant information widening definition and meaning of the relationship between hormonal events and migraine. According to new scientific evidence, ICHD-3 criteria for MM have been revised [1]. Considering the various lines of findings implicating the impact of hormonal and biochemical cyclic changes on trigeminovascular system in menstrual migraineurs, we aim to provide an updated overview of the literature to date on the subject. We hope also to inspire an increase in interest for future research aimed at further elucidating how to manage this type of debilitating migraine.

Methods

We searched the literature from MEDLINE, PubMed, Cochrane Library, and EMBASE databases for publications from 1972 to October 2019. Key search terms "Menstrual Migraine", "Estrogen and migraine", "Hormones and Migraine", "CGRP and Hormones", "CGRP and Menstrual Migraine". were used. This narrative review included both quantitative and qualitative studies in addition to reviews and abstracts. Relevant literature was reviewed by the authors.

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Only English language studies were included. The final reference list was generated on the basis of relevance to the topics covered in this review.

Results

Diagnostic criteria

The definition of "menstrual migraine" appeared in the International Classification of Headache Disorders I in 1988 [8], although accepted criteria for this entity were not yet available. In ICHD II 2004, MM criteria were added in the Appendix, defined as migraine without aura occurring in the perimenstrual period, i.e. on day − 2 to + 3 of menstruation in at least two out of three menstrual cycles and subdivided into PMM without aura and MRM without aura [9]. PMM without aura was defined as migraine without aura attacks occurring exclusively in the perimenstrual period, while MRM without aura might have also migraine without aura attacks outside the perimenstrual period [9]. In ICHD III beta version published in 2013, MM diagnostic criteria appeared unchanged from ICHD II version [10]. At beginning, 2018 ICHD-3 criteria were published. MM criteria, although always added in the Appendix, were updated [1]. Which is the main novelty about MM in ICHD-3 criteria? The diagnostic criteria for PMM and MRM now include not only that one for PMM and MRM without aura, but also those for PMM and MRM with aura [1]. In both cases, as clearly pointed out in the guidelines, MM are defined attacks on day − 2 to + 3 of menstruation in at least two out of three menstrual cycles. The definition of the first day of menstruation which is day 1 and the preceding day is day − 1; there is no day 0. For research purposes, a prospective diary is recommended although not mandatory for clinical diagnosis. In the notes, some relevant information are again outlined including the criteria of menstruation considered to be endometrial bleeding resulting either from the normal menstrual cycle or from the withdrawal of exogenous progestogens, as in the use of combined oral contraceptives or cyclical hormone replacement therapy [1]. Since, as ICHD-3 guideline outlines, the mechanisms of migraine may be different with endometrial bleeding resulting from the normal menstrual cycle and bleeding due to the withdrawal of exogenous progestogens research should separate these distinct subpopulations even though the diagnostic criteria do not (Table 1).

Estrogen withdrawal hypothesis and pathophysiological implications

There is some evidence that MM attacks, at least in some women, result from oestrogen withdrawal, although other hormonal and biochemical changes at this time of the cycle may also be relevant (Fig. 1). Actually, the "estrogen withdrawal hypothesis" of migraine triggering described by Somerville in 1972 [11] has been confirmed and some further relevant information have been gained exploring menstrual hormonal patterns in women with migraine or

Table 1 ICHD-3 criteria for menstrual migraine

A1.1.1 Pure menstrual migraine without aura	A1.1.2 Menstrually related migraine without aura
Diagnostic criteria A. Attacks, in a menstruating woman[a], fulfilling criteria for 1.1 Migraine without aura and criterion B below B. Occurring exclusively on day 1 ± 2 (i.e. days − 2 to + 3) of menstruation[b] in at least two out of three menstrual cycles and at no other times of the cycle[c]	*Diagnostic criteria* A. Attacks, in a menstruating woman[a], fulfilling criteria for 1.1 Migraine without aura and criterion B below B. Occurring on day 1 ± 2 (i.e. days − 2 to + 3) of menstruation[b] in at least two out of three menstrual cycles, and additionally at other times of the cycle[c]
A1.2.0.1 Pure menstrual migraine with aura	A1.2.0.2 Menstrually related migraine with aura
Diagnostic criteria A. Attacks, in a menstruating woman[a], fulfilling criteria for 1.2 migraine with aura and criterion B below B. Occurring exclusively on day 1 ± 2 (i.e. days − 2 to + 3) of menstruation[b] in at least two out of three menstrual cycles and at no other times of the cycle[c]	*Diagnostic criteria* A. Attacks, in a menstruating woman[a], fulfilling criteria for 1.2 migraine with aura and criterion B below B. Occurring on day 1 ± 2 (i.e. days − 2 to + 3) of menstruation[b] in at least two out of three menstrual cycles, and additionally at other times of the cycle[c]

[a]For the purposes of ICHD-3, menstruation is considered to be endometrial bleeding resulting either from the normal menstrual cycle or from the withdrawal of exogenous progestogens, as in the use of combined oral contraceptives or cyclical hormone replacement therapy

[b]The first day of menstruation is day 1 and the preceding day is day 1; there is no day 0

[c]For research purposes a prospective diary is recommended, but this is not mandatory for clinical diagnosis of A1.2.0.1 menstrual migraine with aura and A1.2.0.2 menstrually related migraine with aura

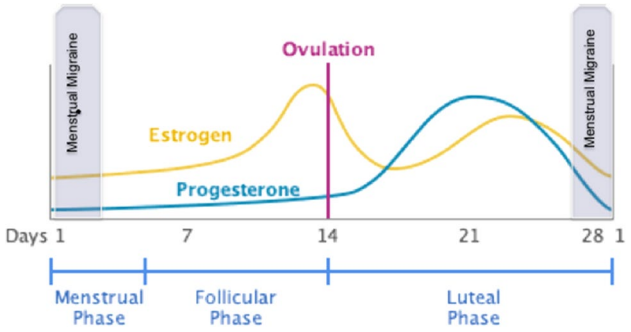

Fig. 1 Relationship between menstrual cycle days and menstrual migraine

comparing hormone levels and patterns between women with history of migraine and controls [4, 12–15]. More recently in the Study of Women's Health Across the Nation (SWAN) Daily Hormone Study (DHS), authors evaluated whether hormone levels and rates of change differ for women with migraine compared with controls [16]. To explore the hypothesis that women with migraine have distinct hormone patterns, they compared peak and daily hormone levels (up to 5 days post-peak) as well as mean within-woman daily rates of decline in ovulatory menstrual cycles for women with history of migraine and controls. Interestingly, in this study, it has been observed that there is no significant difference in estrogen peak levels or mean daily levels between migraineurs and controls. Conversely, there is a significant difference between the two groups in the rate of estrogen decline, specifically in the late luteal phase [16]. Moreover, among migraineurs, the rate of estrogen decline does not distinguish cycles with and without an acute headache [16]. This finding suggests that a neuroendocrine vulnerability characterizes women with migraine and it may facilitate initiation of migraine attack [16]. Interestingly, these pathophysiological considerations concerning migraineurs in respect of controls might underlie also the more specific condition of menstrual migraineurs. On the other hand, no obvious relationship between progesterone fluctuations across the menstrual cycle and migraine attacks was found [11, 16].

Ovarian hormones' cyclicity has been implicated in modulating also other chronic non-cancer pain conditions including endometriosis [17]. Indeed, there is good evidence of menstrual cyclicity to the pain in both these estrogen-dependent conditions [17].

A drop in estrogen may cause an increased susceptibility to prostaglandins (PGs). PGs might play a role in MM since a threefold increase in PG levels occurs from the follicular phase to the luteal phase, with a further increase occurring during menstruation [18]. PGs can cause neurogenic inflammation, leading to the release of neuropeptides such as substance P, neurokinins and calcitonin gene-related peptide (CGRP) [19–24].

Hormonal fluctuations of ovarian steroid hormone levels, estrogens and progesterone, influence CGRP in the trigeminovascular system during different reproductive milestones. In a clinical study, authors demonstrated that concentrations of immunoreactive plasma CGRP in healthy women were significantly increased throughout pregnancy and decreased after delivery [25]. Moreover, the sensitivity of various vascular beds to CGRP in rats appears to increase with advancing pregnancy. This increased sensitivity might be involved in regulating uteroplacental blood flow, in addition to other vascular adaptations that occur during normal pregnancy [26]. In addition, it was observed that in healthy subjects, immunoreactive plasma CGRP levels were significantly higher in females than in males and that women on contraceptive pills had significantly higher immunoreactive CGRP levels than women not taking contraceptives [27]. Moreover, circulating CGRP levels are influenced by menopausal status [28].

These data suggest that the CGRP system could be influenced directly by both endogenous and exogenous ovarian steroid hormones. In a rat model, 17β-estradiol enhanced neurogenic vasodilation, suggesting increased CGRP release from perivascular nerves [29, 30]. Authors suggested that this might be one of the mechanisms through which 17β-estradiol exacerbates migraine in women [29, 30]. In a clinical experimental model exploring gender differences in CGRP-dependent dermal blood flow in healthy subjects and migraineurs, dermal blood flow in males did not vary over time and was comparable between healthy subjects and migraineurs [31]. Conversely, in healthy women, fluctuations of ovarian steroid hormones influenced CGRP-dependent dermal blood flow. Interestingly, in female migraine patients, dermal blood flow responses were elevated, compared to healthy subjects, but these responses were independent of the menstrual cycle [31]. The authors postulate that their data confirm the preexisting theory that the premenstrual withdrawal of estradiol influences the trigeminovascular system. They conclude that this study supports the hypothesis of a disturbed systemic as well as trigeminovascular cyclicity in patients with menstrual-related migraine, which might augment their susceptibility to migraine around the time of menstruation [31].

An estrogen receptor-mediated mechanism contributes also to spreading depression (SD) events and pain in ovariectomized and intact rats [32]. This finding suggests that estrogens play multiple actions in migraine when intense hormonal fluctuations occur [32]. Gonadal hormone-mediated modulation of cortical SD susceptibility in female FHM1 mutant mice has also been observed [33]. The authors also found that ovariectomy and senescence influence cortical SD susceptibility in wild-type and homozygous R192Q mutant

mice [33]. All these findings, even if obtained in different experimental and clinical models of migraine, may also have a relevance for the pathophysiology of a more specific condition such as MM.

The serotoninergic system and ovarian hormones play a complex and interconnected role in migraine pathogenesis. The cortical SD suppressive effect of 5-hydroxytryptophan has been shown to occur only in the presence of ovarian sex hormones and it is more pronounced during the estrous phase in cycling rats as well as after chronic estradiol administration in oophorectomized animals [34]. Estrogens and estrogen receptors are widely expressed in the brain and in the trigeminovascular system [35]. The density of estrogen receptors changes with changes in estrogen levels over the menstrual cycle [36, 37]. Estrogen receptors are mainly localized in periaqueductal grey, thalamus, amygdala, brain regions critically controlling pain perception [38] (Fig. 2).

The cyclic fluctuations of gonadal hormones may directly alter neuronal, glial and astrocyte function throughout the brain. There is also evidence of brain alterations across the menstrual cycle in females. Estrogen may influence brain areas, potentially involved to some migraine-related behaviors such as allodynia, mood changes, and food cravings [35] (Fig. 3).

Menstrual migraine and genetic aspects

Although estrogen levels are thought to be involved in MM, an association of functional polymorphisms in the estrogen metabolism genes *COMT*, *CYP1A1* or *CYP19A1* with MM

Fig. 2 Left, estrogen expression in the human brain. Right, estrogen receptor expression in the human trigeminal pathway

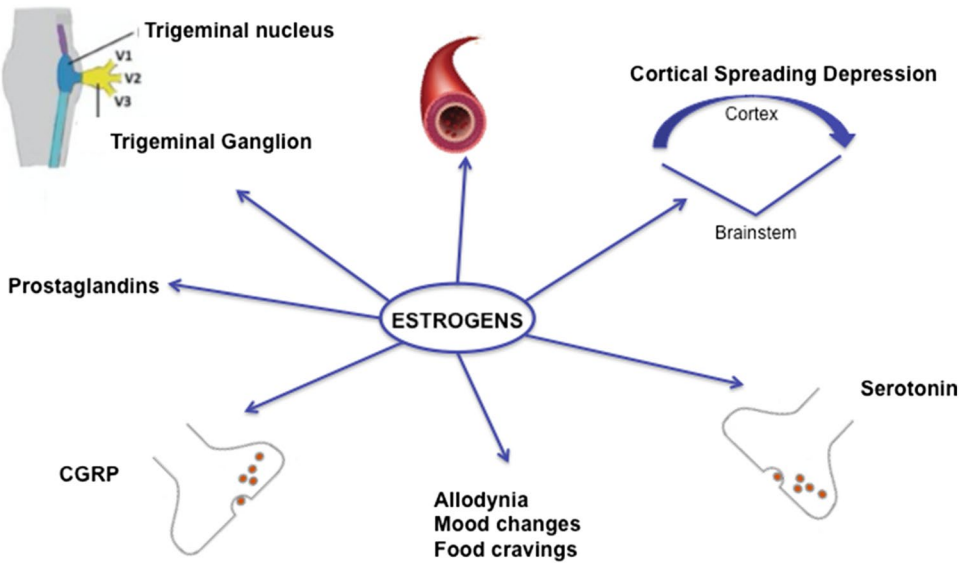

Fig. 3 Estrogen influences on menstrual migraine

has not been found [39]. Moreover, also variants in estrogen receptor 1 (ESR1) have not been found associated with MM, while SNPs in tumour necrosis factor alpha (TNFα) and Spectrin Repeat Containing Nuclear Envelope 1 (SYNE1), a gene neighbouring ESR1, were positively associated with MM [40]. The authors suggest that since TNFα is a pro-inflammatory cytokine, their finding might represent a link between the influence of estrogen and progesterone on inflammatory processes and MM. In addition, SYNE1, a spectrin repeat containing protein usually is directly adjacent to the estrogen receptor, and polymorphisms within SYNE1 have been linked strongly to other estrogen-mediated events [40].

On the other hand, the neuropilin 1 gene (*NRP1*), a protein coding gene, was found to be significantly associated with MM suggesting that *NRP1* functions could be related to either the neuronal or vascular aspects of migraine pathophysiology [41]. *NRP1* encodes a transmembrane protein that acts as a receptor and is considered involved in pathways of neurovascular tissue and menstruation, the authors thus suggest that this transmembrane protein could play a role in the pathophysiology and etiology of MM [41].

Epidemiology and burden

PMM is uncommon with respect to MRM. Few women reported migraine exclusively with menstruation and at no other time of the month in both headache clinic studies [42–44] and population studies [2, 45]. The prevalence of PMM varies widely in these studies, this large variation might be related to differences in study methodology and patient samples. Two large population-based studies published in the last few years have added some information to the epidemiology and burden of MM [46, 47]. In the Norwegian study, among 5000 women aged 30–34 years screened for MM women with self-reported MM in at least half of their menstrual cycles were invited to an interview and examination. A total of 237 women were included in the study. The prevalence for MM was 7.6%. In particular, prevalence for MM without aura was 6.1%, while MM with aura was 0.6%. PMM prevalence was around 1% among all women. In this population-based study, the authors confirmed the observation of some previous clinical studies that MM might also affect subjects with migraine with aura [46]. Moreover, an ancillary study of the same group has shown that, in women who were prospectively diagnosed with MM by diary, the MM without aura attacks were longer and more frequently accompanied by severe nausea than non-menstrual migraine (NMM) without aura attacks [7]. Conversely, no significant differences between menstrual and NMM without aura attacks were found among women with migraine without aura, but no MM [7]. Thus, the authors' conclusion is that in women from the general population, MM without aura attacks differ from NMM attacks only in women fulfilling the ICHD criteria for MM [7].

In the American Migraine Prevalence and Prevention (AMPP) study [47], 1697 women aged 18–60 years old with at least 1 menstrual cycle in the previous 2 months have been investigated. MM was assessed by mean of a validated questionnaire asking: "Which statements best describe your headaches in relation to your period?" Respondents were divided into three groups: MM, attacks that only or predominantly occur at the time of menses; menstrual-associated migraine, attacks commonly associated with menses, but that also occur at other times of the month; menstrual-unassociated migraine self-reported menstrually unrelated migraine. Women with attacks that only or predominantly occur at the time of menses had a prevalence of 5.5% and an older age of migraine onset. Moreover, women with predominantly menstrually related attacks had fewer headache-days but appeared to be more impaired by attacks. Headache impact test (HIT-6) and the migraine disability assessment scale (MIDAS) scores, two well-known and validated clinical measures of headache-related disability, were found significantly higher for both the MM and menstrual-associated migraine groups compared with the menstrual-unassociated groups [47]. Although in this study, the subgroups of MM differed from the ICHD-recommended definitions and data relied on self-reported retrospective data; this descriptive study of women in the US population provides information on the self perception of these patients concerning the relationship between their migraine attacks and menstrual cycle and provide data on the burden of migraine associated with menstruation in a large demographic representative US population.

Moreover, in two different cohort of patients, it was observed that among patients with MRM attacks, allodynia was more frequent that in NMM-related attacks [48] and allodynia scores were higher in MRM attacks in comparison to NMM attacks [49]. These results suggest that hormonal factors might have a facilitating effect on the development of central sensitization and thus potentially play a role in the risk of chronicization.

In the two above-mentioned large population studies [46, 47], it has been confirmed and widened the knowledge concerning the significant impairment and impact of headache in menstrual migraineurs' daily activities. These studies provided also methodological information relevant for the disease definition. However, the real prevalence of MM should be ascertained using three-step approach. First, in the general population, a validated questionnaire should screen women with possible MM; second, a clinical interview by a physician should confirm the suspect for MM; finally, the use of a prospective headache and menstruation diary will allow a defined diagnosis.

MM may change over a woman's reproductive life and for this reason, this clinical condition might be underestimated either in the early reproductive life or in the proximity of the menopausal period.

Interestingly, a higher frequency of MM among female university students living together compared with a control group of university students living alone has also been observed [50]. The authors studied a group of migraineur female university students aged 18–30 years who lived together with two or more other students and a control group of age-matched students who lived alone. Subjects were interviewed with a specific questionnaire and assessed for 3 months by means of a paper pain diary. A higher occurrence of MM among women living together compared with women living alone was detected. This finding was not related to the main influencing factors detected such as use of a contraceptive, test stress, or sleep deprivation. These women also showed menstrual cycle synchrony with their roommates and the presence of headache crises during the menstruation of their colleagues [50]. The menstrual cycle synchrony is a controversial issue that might cause a further confounding element and might be one of the possible explanations concerning the high variability of prevalence data of both clinical and epidemiological studies in MM.

The natural history

The menstrual relation with migraine may change over a woman's reproductive lifetime. Women with MM had a late age of migraine onset in the AMPP study (age at onset ≥ 30 in 34.4% of cases) [47]. Interestingly, women with MM reported higher headache intensity during early pregnancy and postpartum compared to migraineur women without MM [51]. However, both groups showed improvement during the second half of pregnancy, in line with the continuous extreme high estrogen concentrations of the second and third trimesters of pregnancy, and after delivery [51].

Major fluctuations in estrogen levels take place during perimenopause, ultimately leading to dropping levels. During the perimenopausal period, serum estradiol levels are low. Nevertheless, 8–13% of women with migraine report the onset of their migraine during this period [43, 44].

Moreover, fifty percent of subjects reported MRM during menopausal transition in a cross-sectional community-based survey [52]. However, since longitudinal studies have not yet been performed on menstrual migraineurs, the natural history of the disease remains incompletely defined.

Treatment options

Attacks of MM are usually more debilitating, of longer duration, more prone to recurrence, and less responsive to acute treatment than NMM attacks [2, 5–7, 47, 48]. Nevertheless at present, there is no specific treatment for MM approved by the Food and Drug Administration (FDA) or the European Medicine Agency (EMA). Treatments used in traditional migraine therapy are used for PMM and menstrual-related migraine as well. The greater severity and duration of MM requires pharmaceutical targeting with anti-migraine drugs. However, there are no treatment options licensed specifically for MM and ICHD-3 does not give any treatment recommendations. Thus, the validation of both symptomatic and preventive treatment options in MM represents an unmet need.

Currently available acute treatments include mainly triptans, nonsteroidal anti-inflammatory drugs (NSAIDs) and ergot derivatives for acute attacks [53]. The efficacy of a triptan in combination with a second agent has also been evaluated. Rizatriptan combined with dexamethasone in a randomized, double-blind, cross-over study was found more effective than rizatriptan alone, although was associated with higher rate of adverse events [54]. In an open-label trial, it was tested the efficacy of frovatriptan and dexketoprofen for treatment of acute attack of MM [55] and encouraging data concerning the benefit derived from combining dexketoprofen with frovatriptan rather than using frovatriptan alone was observed [55]. Since women suffering from MM often do not respond completely to abortive therapies, they may be candidates for preventive treatment. Women with a regular menstrual cycle and MM may benefit from short-term strategies with drugs administered some days before or during menses. On the other hand, in women with irregular menstrual cycles a continuous preventive treatment may be helpful. Various options are available for both short-term and continuous prophylaxis [53]. However, evidence supporting most categories of prophylactic MM and/or menstrual-related migraine treatments is weak [53]. Among short-term prophylactic therapies administered only during perimenstrual period there are triptans, oestrogen, and naproxen [53]. Continuous prophylactic treatment with hormonal contraceptives are a further option tested and shown to be effective in some open-label trial [53].

However, the increased risk of vascular disease in women with migraine [56] and the controversial issue on increased risk of stroke in women who use hormonal contraceptives [57] might concern about their use in women with migraine, at least in those with additional stroke risk factors such as smoking and hypertension. Moreover, oral contraceptives should be discouraged in women suffering from MM with aura since they may lead to a further increase in the vascular risk [58]. In a systematic review and meta-analysis of studies on the use of desogestrel progestin-only pill, it has been suggested a potential benefit [59]. However, current evidence is observational and based on small samples of women using one oral progestin-only formulation. Thus, further randomized trials on additional progestin-only contraceptives are required to confirm their role in migraine

management [59]. Only two small studies have investigated the use of phytoestrogens, estrogen-like molecules derived from soy, for MM prophylaxis [60, 61]. Although both studies showed improvement in outcomes, the level of evidence is low. Moreover, non-invasive Vagus Nerve Stimulation mini-prophylaxis has been shown to be an effective treatment that reduces the number of MM and MRM days and acute analgesic use for subjects with MM and MRM without adding any treatment-related safety or tolerability concerns [62]. However, further randomised controlled studies are needed to validate these results.

Finally, concerning association of frovatriptan with oral contraceptive, it was observed a decrease in pain only in patients taking combined therapy [63]. In conclusion, so far, triptans have the strongest evidence for both preventive and acute MM treatment [53]. Available studies support the use of almotriptan, naratriptan, sumatriptan, and zolmitriptan as acute therapies and frovatriptan, naratriptan, and zolmitriptan as preventive therapies [53].

A therapeutic perspective with Onabotulinum A for the management of MM has also been hypothesized, although clinical trial on this topic are lacking [64].

The safety and efficacy of perimenstrual telcagepant, a CGRP receptor antagonist, for headache prophylaxis has been studied in a randomized, double-blind, placebo-controlled 6-month trial in women with migraine for ≥ 3 months who experienced perimenstrual headaches. Telcagepant 140 mg taken perimenstrually for 7 days was generally well tolerated, but was associated with transaminase elevations. Interestingly, telcagepant did not reduce monthly headache frequency, but reduced perimenstrual headaches [65].

Three novel antibodies directed against CGRP or its receptor are currently approved by both FDA and EMA and entered in clinical practice [66–68] and another is pending [69] for the prevention of migraine. Future studies should focus on how these drugs act in PMM and MRM attacks. Moreover, the development of ditans and gepants might represent a major progress also in MM acute treatment [70].

Discussion

The diagnostic criteria of MM are still placed in the appendix of the ICHD III and are primarily considered as research criteria that need validation, although have been updated at beginning of 2018 including those for MM with aura. Estrogen receptors are expressed in the trigeminovascular system. Fluctuations of estrogen levels modulate CGRP, serotonin and PGs. These factors might account for MM attacks. Further research investigating reasons behind the susceptibility to hormonal and biochemical changes in some MM attacks, migraine treatment target and preventative treatment options should be conducted. MM appears not rare in clinical practice. Currently, there is no specific preventive treatment for MM. It is important to treat women with PMM and MRM adequate, as the impact of MM attacks on daily life is high. The development of monoclonal antibodies, ditans and gepants might represent a major progress not only in migraine but also in MM treatment.

"Finally, although current ICHD-3 criteria for MM is more exhaustive in respect of the previous guidelines, we feel that this gender specific type of migraine might benefit from further extensive research efforts being considered as an entity in the next ICHD classification."

Author contributions Category 1, (a) conception and design: LMC, IC, PS; (b) acquisition of data: LMC, IC, PS; (c) analysis and interpretation of data: LMC, IC, PS. Category 2, (a) drafting the manuscript: LMC, IC, PS; (b) revising it for intellectual content: LMC, IC, PS. Category 3, (a) final approval of the completed manuscript: LMC, IC, PS.

Compliance with ethical standards

Conflicts of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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