▪ Headache Medicine 2026, Supplement ▪ p-ISSN 2178-7468, e-ISSN 2763-6178

Headache Medicine

ID: 295

Menstrual migraine: neuroendocrine mechanisms and therapeutic challenges

Rhaissa Soledade Couto, Ana Beatriz Estanek Lota, Ana Thereza Sampaio Mendes, Brenda Talyta de Sousa Santos, Clara de Azevedo Teles de Oliveira, Daniel Paulo de Lima Maciel, Geovanna Karla Cardoso Ferreira, Kellyan Manasselly de Lima França, Luiz Felipe Montenegro Cardozo, Maria Luísa Albuquerque Menezes de Andrade, Maria Luiza Fragoso Pereira Neta, Matheus Fausto Barbosa Gonçalves, Vitor Gabriel Rodrigues de Oliveira

Afya School of Medical Sciences of Jaboatão dos Guararapes, Jaboatão dos Guararapes, Pernambuco, Brazil

Rhaissa Soledade Couto
rhaissacouto@gmail.com

Introduction
Menstrual migraine is a common form of primary headache in women of reproductive age, characterized by attacks associated with the menstrual period. The diagnosis, based on the criteria established by the International Classification of Headache Disorders (ICHD-3), considers the temporal relationship with menstruation and typical symptoms, such as unilateral throbbing pain, nausea, photophobia, and phonophobia. Its identification can be complicated by clinical variability and overlap with other headaches. In addition to physical symptoms, it has a significant psychosocial impact and affects quality of life.

Objective
To understand the neuroendocrine mechanisms underlying menstrual migraine, highlighting the limitations and advances in the therapeutic management of this condition.

Methods
A systematic review with meta-analysis was conducted in accordance with PRISMA 2020 guidelines. Searches were performed in PubMed, MEDLINE, Embase, Cochrane Library, and SciELO for studies published between 2020 and 2026. Randomized clinical trials and observational studies addressing neuroendocrine mechanisms and therapeutic challenges of menstrual migraine were included. Extracted data focused on pathophysiology, diagnostic criteria and pharmacological treatment, synthesized into a translational explanatory.

Results
Menstrual migraine is directly related to hormonal fluctuations, particularly the sharp drop in estrogen during the late luteal phase, a phenomenon known as "estrogen withdrawal", which is considered the primary trigger of attacks. This hormonal fluctuation lowers the pain threshold, induces neuronal excitability, and destabilizes the trigeminovascular system during the perimenstrual period. In this process, neurotransmitters and neuropeptides, such as CGRP, are released, promoting meningeal vasodilation, nociceptive sensitization, and pain maintenance. Treatment is divided into mini-prophylaxis and continuous prophylaxis. Mini-prophylaxis, indicated for women with regular cycles, uses NSAIDs and triptans initiated before menstruation to reduce the intensity and duration of attacks. Continuous prophylaxis, on the other hand, is represented by hormonal contraceptives and aims to reduce hormonal fluctuations in patients with irregular cycles or frequent attacks. In addition, anti-CGRP therapies and gepants represent advances in disease management, particularly in patients with contraindications to triptans or therapeutic refractoriness.

Conclusion
The findings reinforce the notion that menstrual migraine is associated with perimenstrual fluctuations in estradiol, which are responsible for destabilizing the trigeminovascular system and triggering the release of pro-inflammatory neuropeptides. Mini-prophylaxis with triptans and NSAIDs is effective in regular cycles, while continuous hormonal therapies, CGRP antagonists, and gepants expand treatment options for chronic or refractory cases, reducing functional and social impact as well as absenteeism.

Keywords:
Menstrual migraine
Menstrual cycle
Neuropharmacology

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