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Migraine and pregnancy

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ABSTRACT

Background. Migraine is a frequent neurological disorder affecting mostly women in the childbearing age. It is influenced by fluctuation of female hormones, especially estrogen levels.
Objectives. This review aims to describe the expression of migraine during the reproductive ages summarizing the diagnosis and effective, available treatment options.
Materials and methods. We performed a systematic literature review searching information on the subject in PubMed and Medscape databases between 2000-2022.
Outcomes. It reveals that during the first trimester due to symptoms of hyperemesis gravidarum, migraine attacks can exacerbate, while, through second and third trimester when estrogen levels rise, women report relief of symptoms. Therapy includes firstly behavioural approach and secondly pharmacological drugs along with non-invasive procedures, some still under investigation for pregnant state. For mild cases the first line is acetaminophen alone or together with antiemetics and in more severe cases or in women with past history of migraine triptans can used as the mainstay therapy.
Conclusions. Despite recent discoveries on therapy and drugs, our understanding of the way medications may affect the fetus or new-born is incomplete and further evidence is needed, bringing potential for improved management of migraine during pregnancy.

Keywords: migraine, pregnancy, estrogen, triptans, calcitonine gene-related peptide

INTRODUCTION

Migraine is a common neurovascular disorder with a sex ration prevalence of about 3:1, with a female preponderance and a peak prevalence in women of childbearing age [1]. The increased burden of migraine relates to both developmental and variable action of women's hormones during life. Approximately 2% of women develop their first migraine during pregnancy, usually along the first trimester [2]. Understanding its pathophysiology can help prevent, treat, and develop new treatment options, especially during pregnancy when its management can be challenging.

Migraine is the type of headache most affected by alterations of estrogen levels, resulting from biological processes as menstruation, pregnancy or menopause or exogenous mechanisms as contraceptive use or in-vitro fertilization.

Diagnosis is usually clinical, based on history and physical examination. It is typically unilateral, localised pain (frontotemporal and/or ocular area) that tends to have a throbbing or pulsatile characteristic and it can be associated or not with aura. Patients define pain as moderate to severe, augmenting with movement or physical activity, lasting for about 4 to 72h, associated with nausea and/or photophobia and phonophobia; this is migraine without aura (MO). Aura commonly occurs before headaches begin or sometimes accompany the headache and symptoms of it include visual, sensory, speech or language, motor or retinal manifestations, fully reversible; this is migraine with aura (MA) [3].

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MATERIALS AND METHODS

We performed a systematic literature review searching relevant information, written in English, on the subject in PubMed and Medscape databases. We used the following five keywords: migraine, pregnancy, estrogen, triptans, calcitonine gene-related peptide, in different combinations to achieve as many reliable results as possible. Being a subject intensively discussed for long period, we aimed to asses by our databases search a comparison between treatments and management used at early 2000 and recent therapies and protocols to follow. Thus, the search was made in both databases between 2000 and 2022. The research revealed 76 articles in total for the 2 databases. On one side, the inclusion criteria for our research focused on women diagnosed with migraine during pregnancy and postpartum state, of all races, patients with the need of preventive treatment, as well as acute treatment. On the other side, the exclusion criteria reunited: articles about migraine during menopausal state and adolescence, treatments including holistic therapy, but also novel treatments with calcitonin gene-related peptide monoclonal antibodies (CGRP Atb), currently restricted during pregnancy and also articles about other types of cephalic pain. After applying the inclusion and exclusion criteria we found 25 articles matching our research, which represented the foundation of our paper.

Pathophysiology

The pathophysiology of this disorder relates to the modifications in neural networks concerning pain. Arousal of central pain pathways from both cortex and brainstem stimulated the trigeminal vascular system with efferent fibres to dura mater and cranial blood vessels causing release of vascular inflammatory substances as calcitonin-gene related peptide (CGRP), cytokines and prostaglandins. The afferent fibres of these structures go to the trigeminocervical complex (TCC) explaining the area of action of migraine at the level of frontotemporal area and ocular area [4,5]. Estrogens can modulate this pathway and proofs support the genetic influence of this hormone in women with menstrual migraine [3,6,7]. It also has the capacity to augment the sensitivity to nociceptive responses to central and peripheral stimuli [8,9].

Outcomes

Effect of pregnancy on migraine

The occurrence and severity of migraine is influenced by the fluctuating levels of estrogens. About 60-70% of patients with past history of this headache (migraine with aura, menstrual migraine) report improvement over the course of pregnancy and only 5% describe worsening of the symptoms [10,11].

During the first trimester due to frequent symptoms of hyperemesis gravidarum, migraine attacks can exacerbate. While, during the second and third trimester when estrogen levels rise, women report relief of symptoms, except the ones with history of migraine with aura. Also, current literature describes the appearance for the first time during first trimester of migraine with aura [12].

Moreover, in the first 3 to 6 days after delivery women can encounter an exacerbation of symptoms due to both environmental factors as change of status (especially for primigravida), sleep disturbance, stress, irregular meals and decreasing of estrogen levels. In the postpartum, some data suggest that breast feeding delays occurrence or recurrence of migraine, related to the anovulation mechanism [13,14].

Effect of migraine on pregnancy

Pregnant women with past history of migraine attacks are at increased risk for gestational hypertension, preeclampsia and preterm birth [15,16]. Studies evaluating pregnancy outcome in people affected by this headache conclude that whether treated or not, it is linked to an increased prevalence for hypertensive disorders of pregnancy.

Migraine is a risk factor for a secondary headache, for pregnancy associated stroke and preeclampsia. A new headache together with fever, hypertension or any neurological signs should raise suspicion and be investigated by MRI without contrast as gadolinium should be avoided during pregnancy.

Pregnant women diagnosed with migraine are at increased risk for gestational diabetes and postpartum depression compared to the one non affected, suggesting the need for more careful follow-up and recommendations for neurological investigation after delivery [17].

Preventive treatment

Migraine can be a deciding factor in pregnancy, thus its management should reunite preconception counselling and history of migraine attacks, preventive treatment options and most recent, effective medications to use both during pregnancy and postpartum.

The first-line actions for the management of migraine during pregnancy are the behavioural approaches, which are non-pharmacological options. It consists of improvement of sleep quality and duration, relaxation therapy and biofeedback, stress cessation, balanced and regular meals, good hydration and physical exercise [18]. The actual recommendations are for women to start these actions prior to conceive in order to reduce the frequency of attacks.

Vitamins and minerals can be an option for mild cases that do not want pharmacological agents. However, an important mention at this level is regarding the use of magnesium, because prolonged high doses administered intravenous can result into bone abnormalities and decreased fetal calcium, thereby it can be administered oral. Another vitamin recommended is riboflavin to reduce the risk for anemia and some studies show efficacy of coenzyme Q10 in migraine and preeclampsia prevention, but still extensive studies need to be performed [19,20].

Acute treatment during pregnancy

The management of acute migraine during pregnancy is different due to drug's adverse effects on fetus. Current literature indicates a start with a first-line drug- acetaminophen 1000mg, because of the maternal fetal safety during all trimesters. If migraine does not respond to it, a combined therapy can be indicated: acetaminophen 650 mg to 1000 mg and metoclopramide 10 mg or acetaminophen and codeine 30 mg, with attention that codeine should not be used more than nine days per month [21]. Acetaminophen was associated with some neurodevelopmental outcomes for fetuses exposed more than 28 days, but further studies developed by the European Medicine Agency found insufficient evidence [22, 23].

Non-steroidal anti-inflammatory drugs (ibuprofen, naproxen, diclofenac) are also used as first-line drugs, considered safe during the second trimester, but raising concerns during the first one regarding the risk of miscarriage and the third one for the risk of premature closure of ductus arteriosus [1,24]. From all, ibuprofen offers the best data concerning safety of use.

Antiemetics are second-line drugs used in the management of migraine attacks, alone or along with acetaminophen. Metoclopramide is the preferred antiemetic, while data regarding ondansetron and fetal effects are still conflicting, some show risks for palate and heart defects [25].

Triptans are a mainstay therapy for migraine, with sumatriptan being the most studies and used. It is the most hydrophilic triptan with very difficult passage of the placental membrane, preferably administered as nasal spray than the 25 mg tablet, but with same efficacy [22,26].

Novel treatments

There are several non-invasive neurostimulation devices available for the treatment of migraine like transcranial magnetic stimulation, vagal or transcutaneous supraorbital nerve stimulators, but their safety has not been determined during pregnant state [12]. The same goes for occipital and trigeminal peripheral nerve blocks (PNBs). They could become a suitable alternative in the future, but further data is required.

Comparing Romanian guidelines for management of migraine during pregnancy and postpartum state to European and American guidelines, we can observe the same protocole for first and second line acute theraphy, as well as for preventive treatment. The main difference comes from the recent introduction of symptomatic treatments, as cited by the American Society of Neurology, that includes nowadays local injections of a substance like lidocaine or bupivacaine into the scalp to target specific nerves, depending on the site affected by pain. These measures are considered safe during pregnancy and postpartum and can be used repeatedly throughout pregnancy as a prevention or treatment measure [27].

Also, another variant used in the United States of America includes the use of liquid lidocaine 4% as nasal spray. As for patients with diabetes, it exists a wearable neuromodulation device that emits a mild electrical current for migraine relief or prevention, still under debatable studies [27].

A revolution in the management of migraine attacks was the discovery of calcitonin gene-related peptide (CGRP Atb) monoclonal antibodies blocking a protein that cause inflammation and pain, but its use is still restricted during pregnancy and lactation because of the toxicity, risks for spontaneous abortion and unknown fetal effects. The US Food and Drug Administration has approved a calcitonin gene-related peptide receptor antagonist CGRP- atogepant (Qulipta), a novel calcitonin gene-related peptide (CGRP) for the prevention of episodic migraine, lacking the vasoconstrictor effect of triptans. The once-daily medication will be available in doses of 10 mg, 30 mg, and 60 mg [28,29]. Its safety during pregnancy and lactation is still not determined.

CONCLUSION

The expression of migraine in women is common and varies with the hormonal phases through their lives. The fluctuations of hormones during the reproductive years explain its higher prevalence compared to man. In order to optimize treatment in the prenatal period, preconception counselling and regular visits to specialists should be encouraged. Although recent discoveries on therapy and drugs have been made, our understanding of the way drugs may affect the fetus or new-born is incomplete and further evidence is needed, bringing potential for improved management of migraine.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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REFERENCES

1. Burch R, Rizzoli P, Loder E. The Prevalence and Impact of Migraine and Severe Headache in the United States: Figures and Trends From Government Health Studies. *Headache.* 2018 Apr;58(4):496-505.
2. Ertresvåg JM, Zwart JA, Helde G, Johnsen HJ, Bovim G. Headache and transient focal neurological symptoms during pregnancy, a prospective cohort. *Acta Neurol Scand.* 2005 Apr;111(4):233-7. doi:10.1111/j.1600-0404.2005.00350.x. PMID: 15740574.
3. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia.* 2018 Jan;38(1):1-211.
4. May A. Understanding migraine as a cycling brain syndrome: reviewing the evidence from functional imaging. *Neurol Sci.* 2017 May; 38(Suppl 1):125-130.
5. Akerman S, Holland PR, Goadsby PJ. Diencephalic and brainstem mechanisms in migraine. *Nat Rev Neurosci.* 2011 Sep 20;12(10):570-84.
6. Rodriguez-Acevedo AJ, Smith RA, Roy B, Sutherland H, Lea RA, Frith A et al. Genetic association and gene expression studies suggest that genetic variants in the SYNE1 and TNF genes are related to menstrual migraine. *J Headache Pain.* 2014 Oct 14;15(1):62.
7. Brennan KC, Romero Reyes M, López Valdés HE, Arnold AP, Charles AC. Reduced threshold for cortical spreading depression in female mice. *Ann Neurol.* 2007 Jun;61(6):603-6.
8. Paredes S, Cantillo S, Candido KD, Knezevic NN. An Association of Serotonin with Pain Disorders and Its Modulation by Estrogens. *Int J Mol Sci.* 2019 Nov 15;20(22):5729.
9. Amandusson Å, Blomqvist A. Estrogenic influences in pain processing. *Front Neuroendocrinol.* 2013 Oct;34(4):329-49.
10. Sances G, Granella F, Nappi RE, Fignon A, Ghiotto N, Polatti F, Nappi G. Course of migraine during pregnancy and postpartum: a prospective study. *Cephalalgia.* 2003 Apr;23(3):197-205.
11. Kvisvik EV, Stovner LJ, Helde G, Bovim G, Linde M. Headache and migraine during pregnancy and puerperium: the MIGRA-study. *J Headache Pain.* 2011 Aug;12(4):443-51.
12. Afridi SK. Current concepts in migraine and their relevance to pregnancy. *Obstet Med.* 2018 Dec;11(4):154-159.
13. Sances G, Granella F, Nappi RE, Fignon A, Ghiotto N, Polatti F et al. Course of migraine during pregnancy and postpartum: a prospective study. *Cephalalgia.* 2003 Apr;23(3):197-205.
14. Silberstein SD. Headaches in pregnancy. *Neurol Clin.* 2004 Nov;22(4):727-56.
15. Skajaa N, Szépligeti SK, Xue F, Sørensen HT, Ehrenstein V, Eisele O et al. Pregnancy, Birth, Neonatal, and Postnatal Neurological Outcomes After Pregnancy With Migraine. *Headache.* 2019 Jun;59(6):869-879.
16. Tanos V, Raad EA, Berry KE, Toney ZA. Review of migraine incidence and management in obstetrics and gynaecology. *Eur J Obstet Gynecol Reprod Biol.* 2019 Sep;240:248-255.
17. Anderson P. (2021, June 22) Women With Migraine ‚High-Risk' Patients During Pregnancy. Medscape.
18. Millstine D, Chen CY, Bauer B. Complementary and integrative medicine in the management of headache. *BMJ.* 2017 May 16;357:j1805.
19. Teran E, Hernandez I, Nieto B, Tavara R, Ocampo JE, Calle A. Coenzyme Q10 supplementation during pregnancy reduces the risk of pre-eclampsia. *Int J Gynaecol Obstet.* 2009 Apr;105(1):43-5.
20. Ma AG, Schouten EG, Zhang FZ, Kok FJ, Yang F, Jiang DC et al. Retinol and riboflavin supplementation decreases the prevalence of anemia in Chinese pregnant women taking iron and folic Acid supplements. *J Nutr.* 2008 Oct;138(10):1946-50.
21. Lipton RB, Baggish JS, Stewart WF, Codispoti JR, Fu M. Efficacy and safety of acetaminophen in the treatment of migraine: results of a randomized, double-blind, placebo-controlled, population-based study. *Arch Intern Med.* 2000 Dec 11-25;160(22):3486-92.
22. Calhoun AH. Migraine Treatment in Pregnancy and Lactation. *Curr Pain Headache Rep.* 2017 Oct 4;21(11):46.
23. European Medicines Agency. Pharmacovigilance Risk Assessment Committee (PRAC): minutes of the meeting on 5–8 May 2014. PRAC: Agendas, minutes and highlights [online], http://www. ema.europa.eu/docs/en_GB/document_library/Minutes/2014/06/ WC500169468.pdf (2014).
24. Nakhai-Pour HR, Broy P, Sheehy O, Bérard A. Use of nonaspirin nonsteroidal anti-inflammatory drugs during pregnancy and the risk of spontaneous abortion. *CMAJ.* 2011 Oct 18;183(15):1713-20.
25. Wells RE, Turner DP, Lee M, Bishop L, Strauss L. Managing Migraine During Pregnancy and Lactation. *Curr Neurol Neurosci Rep.* 2016 Apr;16(4):40.
26. Granella F, Sances G, Pucci E, Nappi RE, Ghiotto N, Napp G. Migraine with aura and reproductive life events: a case control study. *Cephalalgia.* 2000 Oct;20(8):701-7.
27. American Society of Neurology Guidelines. Accesed at : https://americanheadachesociety.org/topic/discussing-treatment-access. 12/07/2022.
28. Greb E. (2021, September 29) FDA Okays New Oral CGRP Antagonist for Migraine Prevention. Medscape.
29. JL, Davies R, Dean C, Xu C, Kim KH, Vargas HM, Chellman GJ, Balasubramanian G, Rubio-Beltran E, MaassenVanDenBrink A, Monticello TM. Nonclinical safety evaluation of erenumab, a CGRP receptor inhibitor for the prevention of migraine. Regul Toxicol Pharmacol. 2019 Aug;106:224-238.