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Migraine in pregnancy. A narrative review

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Abstract

Migraine is one of the most common types of headaches, affecting almost all group ages and both sexes. Nevertheless, it is known that migraine can modify its characteristics during pregnancy and that nearly 60-80% of pregnant women with migraine will suffer attacks, especially during the first trimester. In this narrative review, we describe critical aspects of this frequent neurological pathology during pregnancy and provide a reference hallmark to guide diagnosis and treatment.

Keywords: *Migraine. Pregnancy. Migraine treatment. Migraine drugs.*

Migraña en el embarazo. Revisión narrativa

Resumen

La migraña es uno de los tipos de dolores de cabeza más comunes y afecta a casi todos los grupos de edades y a ambos sexos. Sin embargo, se sabe que la migraña puede modificar sus características durante el embarazo y que cerca del 60-80% de las mujeres embarazadas con migraña sufrirán ataques, especialmente durante el primer trimestre. En esta revisión narrativa, describimos aspectos críticos de esta patología neurológica frecuente durante el embarazo y proporcionamos referencias para guiar el diagnóstico y el tratamiento.

Palabras clave: *Migraña. Embarazo. Tratamiento de la migraña. Medicamentos para la migraña.*

Introduction

The term migraine originates from the Greek word hemicranias, which means “half of the head”[1]. Nevertheless, there are historical recordings of headaches dating back nearly 600 years. In the 17th century, a migraine was called a “hypoglycemic headache,” and the term “chronic migraine was coined during the early 20th century”[2].

Definition

Migraine is a chronic brain disease with episodic manifestations that typically involve unilateral headache of throbbing or pulsating quality, associated with complex sensory disturbances such as photophobia and phonophobia and neurovegetative symptoms such as nausea or vomiting. Migraine can occur in episodic or chronic forms, with or without aura[1,3,4].

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An aura consists of focal neurological symptoms with positive and negative manifestations, most commonly visual disturbances. Approximately one-third of patients will report an associated aura with their migraine[5].

Epidemiology

Migraine accounts for 20% of all outpatient neurology consultations[6] and thus is considered the most common cause of disability worldwide[7,8]. Yearly, it affects one billion people worldwide[9].

Migraine has racial disparities in its incidence, being more common among Caucasians[1], in its episodic form, it affects nearly 12-18.5% of adult subjects. In contrast, chronic migraine affects ~2% of the general population[4], particularly those younger than 50[6]. There is also an apparent sex disparity among females in a proportion 1:2 or 1:3 (20.2% to 24.4% vs. 9.4%)[4,5,10], but only in adults, in young childhood, the prevalence of migraine are marginally higher in boys than in girls. In contrast, in pre-pubertal populations**,** prevalence is similar among both genders. However, after menarche, migraine prevalence increases in girls (6.4%) compared with males (4.0%)[11-13]. The disparity in the incidence of migraine between men and women seems to be related to the hormonal differences between sexes; specifically, estrogens and progesterone appear to play a pivotal role in producing the disease[14,15].

The incidence of migraine in women between 30 and 39 years (the central period of reproductive age) is 24%[16]. Migraine symptoms also vary due to other hormonal states, such as hormonal contraception, pregnancy, and menopause[16-18]. During the reproductive age, migraine prevalence becomes 3 times higher in women than men[12]. Then, after age 60, prevalence decreases in both sexes (5.0% women, 1.6% men)[6].

The pathophysiologic mechanism by which menstruation favors the susceptibility to migraine attacks is not well understood, but sudden decreases in estrogen serum levels appear to be implicated. Still, similar drops in circulating estrogen during ovulation do not seem to provoke migraine attacks[19].

Migraine in pregnancy

Nearly 60-80% of pregnant women with migraine will suffer attacks, which can be especially burdensome during the first trimester. After the first trimester has passed, about half of the patients will improve; by the last trimester, up to 80% will have improved[16,20].

Two possible explanations exist for migraine symptoms decreasing after the first trimester of pregnancy. One is the physiological increase in estrogen and endogenous opioid levels, and the other is the disappearance of sudden fluctuation in hormone levels, a factor that usually triggers attacks[16]. Estrogens modulate neuronal excitability by upregulating serotonin, norepinephrine, dopamine, and endorphin levels and downregulating the endothelial nitric oxide synthase.

MacGregor and Hackshaw demonstrated that migraine attacks are more frequent during the late luteal and early follicular phase of falling estrogen; in contrast, attacks are less frequent during the increase of estrogen. Therefore, increased levels of estrogen protect women against migraine attacks[21].

The phenotype of migraine might be modified in pregnant women[20]. One of the most common changes is aura development[22]. In a retrospective hospital-based study, 70% of women diagnosed with migraine with aura had no prior history of aura[20].

Migraine without aura improves more frequently than other types of migraine during the first trimester; partial improvement is seen in 46.8% and remission in 10.6%. During the second trimester, remission rates increase to 53.2%, and in the third semester, the remission rate reaches 78.7%[16]. Pregnant migraineurs with aura also experience improvement in their symptoms. However, it is not as crucial as in women without aura.

Diagnosis

If the diagnosis of migraine does not precede the pregnancy, the International Classification of Headache Disorders, 3rd edition (beta version) (ICHD-3 beta)[23] diagnostic criteria for migraine can be applied regardless of the pregnancy state[24]. However, excluding other causes of headache in this particular population is vital since, especially in low-income countries, pregnant women are at a heightened risk of cerebral venous thrombosis (CVT), pre-eclampsia/eclampsia and posterior reversible encephalopathy syndrome, among several grave secondary causes of headache[25].

Differential diagnosis

There are several conditions that, such as migraine, also increase its frequency during pregnancy. The most important include[26]:

Table 1. Doses and risk class of medications used in pregnant women with migraine

Drug	Dose	Risk category
Aspirin	325-650 mg, oral, or rectal q4h	First and second trimester: C Third trimester: D
Ibuprofen	400 mg tablets 400-800 mg q3h, oral; maximum dose: 2400 mg/day	First and second trimester: B Third trimester: D
Diclofenac	100-200 mg tablets 75 mg, q12h, and oral 50 mg, q8h, and oral 100 mg, q12h, and oral	First and second trimester: B Third trimester: D
Naproxen	500/825 mg, oral	First and second trimester: B Third trimester: D
Ketorolac	Oral: 2 tablets q6h Intramuscular: 60 mg/2 mL; repeat in 4 h if needed	First and second trimester: B Third trimester: D
Acetaminophen	500 mg tablets 1 or 2 tablets q4h, oral. Do not exceed more than eight tablets per day	B
Acetaminophen/aspirin/caffeine	Tablets contain 250 mg of aspirin, 65 mg of caffeine, and 250 mg of acetaminophen 1-2 tablets q3h, oral; do not exceed more than four tablets per day	A (caffeine dose ≤ 200 mg daily)
Sumatriptan	Intranasal: 10 mg-20 mg Oral: 25, 50, 100 mg Subcutaneous: 4, 6 mg Dose Intranasal: 40 mg/d Oral: 50 and 100 mg q2h; maximum 200 mg/d Subcutaneous: 4-6 mg q3h maximum dosing: twice daily	C
Eletriptan	20 and 30 mg tablets 40 mg q4h, oral	C
Rizatriptan	5 and 10 mg tablets 10 mg q4h, oral	C
Almotriptan	6.25 and 12.5 mg tablets 12.5 mg q4h, oral	C
Frovatriptan	2.5 mg tablets 2.5 mg q4h, oral	C
Naratriptan	1 and 2.5 mg tablets 1 tablet q3h, oral; maximum three doses per day	C
Zolmitriptan	2.5 or 5 mg tablets 5 mg, q3h, oral, as needed	C
Dihydroergotamine	1 mg intramuscular or intravenous 0.33 or 0.50ml on its first administration	X
Opioids	Oral or intramuscular These are limited per day and month	C
Metoclopramide	5-10 mg tablets Migraine and nausea without vomiting: 10 mg/8 h, oral	A
Ondansetron	4-8 mg tablets 8 mg q3h, oral	B
Dexamethasone	4 mg q8h, oral, as needed. Maximum 8 mg/day	D
Prednisone	20 mg q8h, oral, as needed. Maximum 40mg/day	C
Ergotamine	0,5-1 mg, q6h -12h, oral	X

(Continues)

Table 1. Doses and risk class of medications used in pregnant women with migraine *(continued)*

Drug	Dose	Risk category
Lasmiditan	50-100 mg, oral, per event	NA
Amitriptyline	10-25 mg up to 400mg, oral every bedtime	C
Imipramine	10-25 mg up to 400mg, oral every bedtime	D
Topiramate	Titrate over 4 weeks until effect. Week 1: 25 mg, oral every bedtime Week 2: 25 mg, oral q12h Week 3: 25 mg, oral in the morning and 50 mg oral every bedtime Week 4: 50 mg, oral q12h	D
Sodium Valproate	250 mg, oral q12h for 1 week May increase up to 1000 mg/day if needed	D
Propranolol	80 mg/day, oral, divided q6-8h; may be increased by 20-40 mg/day every 3-4 weeks; not to exceed 160-240 mg/day split q6-8h	C
Flunarizine	5-10 mg, oral every bedtime	NA
Onabotulinum toxin A	The recommended total dose is 155 units, as 0.1 mL (5 units) of intramuscular injections per site divided across seven head/neck muscles q12 weeks. Frontalis: 20 units divided into four sites Corrugator: 10 units divided into two sites Procerus: 5 units in 1 site Occipitalis: 30 units divided into six sites Temporalis: 40 units divided into eight sites Trapezius: 30 units divided into six sites Cervical paraspinal muscle group: 20 units divided into four sites	C
Erenumab	70 mg, subcutaneous once monthly OR 140 mg subcutaneous once monthly (administered as two consecutive 70-mg subcutaneous doses)	NA
Galcanezumab	Loading dose: 240 mg subcutaneous once (i.e., two consecutive 120 mg subcutaneous injections) Maintenance dose: 120 mg subcutaneous monthly	NA
Fremanezumab	225 mg subcutaneous once monthly OR 675 mg every 3 months, administered as three consecutive 225 mg subcutaneous doses	NA
Eptinezumab	100 mg intravenous every 3 months OR 300 mg intravenous dose every 3 months	NA
Lidocaine nerve block	Every 2 or 4 weeks	B

Idiopathic intracranial hypertension

It can appear during the first half of the pregnancy; its physiopathology is related to pregnancy-related weight gain. The headache is continuous, holo cranial, progressive, and aggravated by the Valsalva maneuver. Abnormalities in the neurological examination can include papilledema, visual disturbances, tinnitus, or paresis of the VI cranial nerve[27].

Pre-eclampsia and eclampsia

It commonly occurs after the 20th week 20 of pregnancy and during the puerperium. The headache is bilateral, pulsatile, and aggravated by physical activity. Its course is toward progressive deterioration without response to symptomatic treatment until the end of pregnancy. Additional clinical features include significant visual disturbances, seizures, and confusion[26].

Table 2. Pregnancy risk category definitions

A	Commonly acceptable. Controlled studies in pregnant women show no evidence of fetal risk.
B	It can be acceptable. Either animal or human studies demonstrated no harm, human studies are unavailable, or animal studies demonstrated minor risks.
C	Use with precaution only if the benefits outweigh the risks. Animal studies have demonstrated fetal risk, but human studies have not been available or demonstrated no risk.
D	Only use in cases where life is compromised. There is evidence of human fetal risk. The benefits may outweigh the risks.
X	Contraindicated, do not use in pregnancy. Use alternatives as risks outweigh benefits.

NA: information not available

Cerebral Venous Thrombosis

It can occur during any stage of pregnancy and puerperium. The headache is the most common presenting symptom. It tends to be paroxysmal, severe, and throbbing. It can be holocephalic or unilateral and have migraine-like features. Accompanying focal neurological symptoms include seizures, blurred vision, nausea, and vomiting[28].

Central nervous system tumors

Although intracranial tumors do not have a higher incidence during pregnancy, tumors such as pituitary adenomas and meningiomas may grow during pregnancy. Therefore, the clinical presentation of brain tumors during pregnancy tends to occur in the second half of the pregnancy. Although headache is a common presenting feature of brain tumors, it is rarely its only manifestation, and focal neurological complaints and symptoms of increased intracranial pressure, such as nocturnal headache, nausea, vomiting, and blurred vision, are almost universally present[29].

Treatment

Treatment for acute migraine should be tied to the severity of the headache. For mild-to-moderate headaches, treatment is initially based on first-line drugs. Paracetamol is safe during pregnancy. However, long-term use has been recently associated with hyperactivity and behavioral disorders[30]. Metoclopramide is also considered safe if nausea is prominent and concomitant to the pain.

Non-steroidal anti-inflammatories are possibly safe to take under certain circumstances but have also been associated with premature closure of the ductus arteriosus and pulmonary hypertension. Ibuprofen, diclofenac, naproxen, and piroxicam during the second trimester have also been associated with low birth weight. Ibuprofen during the second and third trimesters was associated with asthma. During the third trimester, diclofenac was related to maternal vaginal bleeding. Finally, indomethacin has been associated with miscarriage[31].

Triptans are also classified as possibly safe to take during pregnancy but are mainly reserved for migraine with aura and severe migraine[32]. These 5-HT 1B/D agonists are safer during the first trimester of pregnancy. Still, during the second and third trimesters, a small association has been demonstrated between the risk of atonic uterus and post-delivery bleeding. Triptans are contraindicated in patients with poorly controlled hypertension, hemiplegic migraine, severe hepatic and renal impairment, basilar migraine, and coronary artery disease[33].

Lasmiditan, a 5-HT 1F receptor antagonist, might be a safer alternative for acute migraine in pregnant women with cardiovascular conditions[34]. Onabotulinum toxin A has been used for chronic migraine in Europe[1].

Calcitonin gene-related peptide (CGRP) antibodies monoclonal antibodies.

In recent years, the US FDA has approved CGRP monoclonal antibodies as a promising preventive treatment for migraine. Current options vary according to the route of administration and dose schedules and include erenumab, galcanezumab, fremanezumab, and eptinezumab[35]. Nevertheless, safety data on migraine preventive monoclonal antibodies targeting the CGRP system in pregnancy are limited[36].

No specific maternal, fetal, or neonatal toxicity patterns were observed in a pharmacovigilance assessment of the safety reports related to pregnancy associated with erenumab, galcanezumab, fremanezumab, and eptinezumab. Spontaneous abortion was not more frequently reported with CGRP monoclonal antibodies compared with the use of other prophylactic drugs (ROR 1.1, 95% confidence interval, CI, 0.8-1.5), and triptans (ROR 1.2, 95% CI 0.8-1.9)[33]. However, a relatively limited number of adverse drug reactions are reported, and long-term safety data is lacking. Therefore, its use in pregnant women is anecdotal and case-by-case. In the event of prescription, continuous surveillance is required in pregnant and lactating women exposed to these drugs[37]. Table 1 lists medications' doses and risk class with documented use during pregnancy. Table 2 shows the risk classification system in pregnancy and breastfeeding.

Conclusion

The treatment objective is to reduce the severity of headaches as possible, restore functioning ability, reduce the use of drugs, and promote management with minimal side effects. These goals are not different when treating pregnant women. Still, non-pharmacological treatment of migraine is preferable whenever possible, and preventive migraine drugs should be used only in severe and selected cases. After balancing risks and benefits, the lowest effective dose and frequency should be prescribed. Pregnant women should be counseled to avoid migraine triggers by having a regular sleeping schedule, avoiding missing meals, and practicing relaxation techniques such as mindfulness and yoga.

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Conflicts of interest

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appears in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

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