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Migraine in Pregnancy: A Mini-Review

David Vo[1]* and Suzan Khoromi[1]

Abstract

Despite emerging treatments for migraine, there are limited treatments available for pregnant women. There is a lack of research available to guide treatment because of the risk of possible harm to the pregnant woman and the fetus. However, migraines tend to improve in the majority of women during pregnancy because of the steady increase in estrogen level. This paper serves as a mini-review of migraine in pregnancy and we will discuss the management of migraines, secondary headache disorders that can mimic migraines during pregnancy, and future directions.

Keywords: Migraine in pregnancy; Headache in pregnancy; Management of migraine; Management of headache; Migraine; Headache; Lactation

Introduction

Migraine is a neurological disorder that can cause significant disability. From the International Classification of Headache Disorders, migraine is defined as a headache lasting 4-72 hours with features such as unilateral location, pulsating, moderate to severe pain, aggravation by physical activity. Migraine is often accompanied by nausea, vomiting, and photo- and phonophobia [1]. The pathophysiology of migraines is complex and involves a network of molecules and neurotransmitters that activate nociceptors that trigger headaches, along with other symptoms [2].

Approximately 30% of women develop migraine by the age of 45. [3,4] With the high prevalence of migraine in women, it is important to know how to effectively manage migraines during pregnancy. Reassuringly, migraine headaches tend to improve as women advance through pregnancy. It is believed that the rise in estrogen level is associated with decrease in migraine burden in pregnant migraineurs. Conversely, approximately 18-25% of patients with migraine have headaches in association to their menstrual cycle, thought to be secondary to dropping estrogen level during this time [5]. The effects of estrogen on migraine are also supported by the fact that postmenopausal women who do not experience fluctuations in estrogen level experience a reduction in their migraine headaches [6]. There are far fewer treatments available to women during pregnancy because the management of migraine has not been well studied in this group. Given the lack of literature, patients and their clinicians need to anticipate pregnancy and develop a plan that is safe for the patient and the fetus. Starting a plan at least 6 months prior to conception is recommended in order to avoid teratogenic effects of potential medications [7]. The newer therapies in the class of calcitonin gene-related peptide (CGRP) inhibitors, CGRP monoclonal antibodies (CGRP mAbs) for example, have longer half-lives and there is a lack of research evaluating their safety in pregnancy. Women should be aware of the options available to them that are regarded as safe and also understand the potential risks that can be associated with treatment options. For instance, retrospective studies

Affiliation:

[1]University of California San Diego

***Corresponding author:**
David Vo, Specialist, University of California San Diego, USA.

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have shown that OnabotulinumtoxinA (botox) does not pose any additional risk to the fetus or infant as compared to the general population [8]. However, this treatment has not been studied prospectively in pregnant patients.

Studying various therapies and management of migraine in women who are planning pregnancy and those who are pregnant is difficult because of safety concerns. However, it is important to continue to conduct research in this group of patients because many women of reproductive age are affected by migraine. Studies have also revealed that women who suffer from migraine prior to pregnancy are at increased risk for adverse outcomes during pregnancy. Pregnant women with migraine may be at increased risk of preeclampsia, stroke, and have low birth weight infants at higher rates when compared to patients who do not have migraine [9,10,11]. This paper serves as a mini-review on migraine in pregnancy and it will discuss the management of migraines, secondary headache disorders that can mimic migraines, and future directions.

Methods

Literature search was performed in Pubmed by searching key words, such as "migraine in pregnancy", "headache in pregnancy", "management of migraine", "management of headache", "migraine", and "headache".

Discussion

Pregnancy Planning and Prevention

Management of migraines in pregnancy should ideally start at least 6 months prior to conception out of concern for adverse effects from prophylactic and/or abortive therapies affecting the pregnancy. During this time, it is essential for the physician and the patient to discuss what are the safest ways to manage migraines from both a preventive and abortive point of view. This can be distressing to patients because the number of options available to them is limited. For some patients, the fear of migraine can make them not want to become pregnant.

Fortunately women experience improvement in their migraine headaches throughout pregnancy. During the first trimester, approximately 46% of patients have improvement in their migraine. For some women, however, there is a potential for increase in migraine burden during pregnancy because of the imbalance in hormones and the rapid increase in estrogen level [1]. However, by the third trimester, upwards of 87% of pregnant women experience improvement in their migraine [5]. This is thought to be attributed to the change in hormone levels, specifically increase in estrogen level, as well as endorphins [1,3,9]. Migraine patients without aura tend to have higher rates of remission in migraine attacks during pregnancy compared to those who experience aura [3].

Despite restrictions in therapy during pregnancy, there are some available preventive treatments for patients (Table 1). Beta blockers, such as propranolol and metoprolol, are considered first line treatment for migraine prevention, but their pros, and cons need to be discussed with pregnant patients. Although beta blockers are used for hypertensive disorders during pregnancy, there are reports of associated risks of hypoglycemia, fetal cardiovascular and orofacial defects, neural tube defects and fetal growth restriction with their use [13,14]. Calcium channel blockers are used for hypertension and can also be used for migraine prevention. In a population study in the US, there was an increased risk of neonatal seizures in mother's exposed to calcium channel blockers, but the data did not show increased risk in congenital anomalies. A subsequent large cohort study did not observe an association between calcium channel blockers and neonatal seizures in women who were exposed to this type of medication in the last month of pregnancy [15]. The ACOG Clinical Practice Guidelines recommend to consider using calcium channel blockers, such as amlodipine and nifedipine, as first line if calcium channel blockers are being considered [7].

Tricyclic antidepressants, like amitriptyline, are also commonly used for migraine prevention adults who are not pregnant. In pregnant patients, the possible risks and benefits should be discussed. A study published in the Journal of Maternal-Fetal and Neonatal Medicine conducted a meta-analysis of antidepressant exposure during pregnancy, and there is a potential association between usage of tricyclic antidepressant medications and gestational diabetes. Pregnant women on amitriptyline had a relative risk of 1.52 for development of gestational diabetes as compared to pregnant women who were not exposed to this type of medication [16]. The ACOG Clinical Practice Guidelines recommend weighing the risks and benefits of using tricyclic antidepressants because a systematic review and metanalysis by McDonaugh et al. showed that their usage was associated with major congenital malformations (OR 1.31, 95% CI 1.04–1.65), cardiac malformations (OR 1.58, 95% CI 1.10–2.29), neonatal convulsions (OR 7.82, 95% CI 2.81-21.8), and neonatal respiratory distress (OR 2.11, 95% CI 1.57-2.83). [14,17]

The angiotensin receptor blocker, candesartan, has also been shown to be an effective preventive treatment for migraine in patients who are not pregnant. However, it should be avoided in pregnant women because of teratogenicity of the fetal renal system [18,19], Similarly, the seizure medications, valproate and topiramate, should be avoided and stopped prior to conception, given their known teratogenicity, such as neural tube defects and cleft palate, respectively [2,11].

CGRP monoclonal antibodies (CGRP mAb) and Gepants, CGRP receptor blockers, are the newest class of migraine medications, but they have not been studied in pregnant patients. It is not recommended to continue or start these

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Table 1: Preventative Treatments for Migraine and Safety.

Treatment	Safety	Possible Side Effects and Comments
Remote Electrical Neuromodulation (Nerivio)	Safe	Site irritation.
Calcium channel blockers (amlodipine, nifedipine)	Discuss with provider prior to continuation or use.	Possible risk of neonatal seizures. Considered first line therapy per ACOG.
Beta blockers (propranolol, metoprolol)	Discuss with provider prior to continuation or use.	Cardiovascular congenital defects, neural tube defects, fetal growth restriction, hypoglycemia.
Tricyclic Antidepressants	Discuss with provider prior to continuation or use.	Gestational diabetes, congenital defects, neonatal convulsions, and neonatal respiratory issues.
Botox	Discuss with provider prior to continuation or use.	Not directly studied in pregnant patients, but has low theoretical risk of harm to fetus.
Non-Invasive Vagus Nerve Stimulation	Avoid	Has not been studied in pregnant patients.
CGRP	Avoid	Not studied. CGRP may affect uteroplacental blood flow.
Angiotensin Receptor Blockers and Angiotensin Converting Enzyme Inhibitor	Avoid	Fetal renal dysfunction leading to oligohydramnios, skull hypoplasia, lung hypoplasia, and hypotension.[2]
Topiramate	Avoid	Cleft palate.
Valproate	Avoid	Neural tube defects.
Riboflavin	Avoid	Not studied in pregnancy.
Magnesium	Avoid	Neonatal death.

classes of medications for patients who are pregnant or who are planning to become pregnant within 5 to 6 months for CGRP mAbs (6,20). The CGRP molecule plays a role in the development and maintenance of the placenta as well as fetal development [21,22]. Using the medications in these classes can possibly disrupt the developmental pathways in pregnancy and fetal growth. Therefore, more studies need to be conducted to delineate their safety for pregnant patients.

Botulinum toxin A (botox) injections have not been studied in pregnant migraineurs either. Theoretically, these injections should be safe because the molecule is too big to cross the placenta. There was a 29-year retrospective analysis on the safety of pregnant patients who were exposed to botox for various reasons, but in the majority of patients the use of botox was for cosmetic reasons and headaches. The study found that the prevalence of birth defects in babies from women who were exposed to botox was not higher when compared to the general population [8]. Using these injections does not pose increased risk compared to the general population, but providers should have a risk/benefit discussion with patients if botox injections are considered.

Common supplements for migraine prophylaxis, such as magnesium and riboflavin, are not studied well and are not recommended. For magnesium, a Cochrane review that examined its use as a supplement during pregnancy found an increased risk of neonatal death (RR 2.21; 95% CI 1.02 to 4.75; four trials, 5373 infants). Ultimately, the authors concluded there was not enough high-quality evidence for magnesium use during pregnancy [23]. As for riboflavin, its use is generally safe, however, there is not enough data on its safety during pregnancy [24].

Other potential avenues for migraine prevention are non-pharmacologic modalities, specifically, neuromodulation devices. A study of the remote electrical neuromodulation device (Nerivio) has shown that its use is effective and safe in pregnant patients. This device is worn on the upper arm for both the acute and chronic treatment of migraine. The study, published in the journal Headache, compared gestational age, birth weight, miscarriage rate, preterm birthweight among other factors. There was no difference in these measures between participants who used the device compared to the control group [25]. Another device, non-invasive vagal nerve stimulator (gammaCore) has been approved for general treatment of migraine in patients older than 12 years old, but has not been studied in pregnant patients [26]. External trigeminal nerve stimulation (Cefaly) and external concurrent occipital and trigeminal neurostimulation (Relivion) are additional devices used to treat migraine, but have not been studied in pregnant patients. Biofeedback and cognitive behavioral therapy are other considerations for migraine management, but have not been properly studied either in pregnant women [29].

Acute Treatment

An important component of migraine management is abortive or acute treatment for migraine attacks. Because the majority of women with migraine experience improvement in their headaches in the second and third trimesters, acute treatment in the first trimester is important (Table 2).

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Paracetamol or acetaminophen is the preferred treatment for pregnant patients and has the most benign side effect profile [30]. Previously, there was concern that exposure to acetaminophen led to neurodevelopmental problems, such as ADHD (attention deficient hyperactivity disorder) and autism. A recent study published in JAMA observed a cohort of over 150,000 patients exposed to acetaminophen during pregnancy to evaluate if these patients developed autism, ADHD, or intellectual disability. In sibling control analysis, there was no evidence that exposure to acetaminophen was associated with any of these diagnoses. The article states that other studies that found an association between acetaminophen and autism, ADHD, and intellectual disability "may have been attributable to familial confounding" or genetic or other environmental factors [31].

Metoclopramide and diphenhydramine have also been deemed a safe combination to abort migraine attacks [32].

Triptans are the most common abortive therapies for migraine patients. Sumatriptan is the most studied out of the other medications in this class. There was a registry of 558 infants who were exposed to sumatriptan during the first trimester. The rate of major birth defects among these patients was 4.6% (95% CI 2.9-7.2%) [33]. Another registry also showed a 4.2% (20/478 [95% confidence interval [CI] 2.6%–6.5%]) risk of birth defects in fetuses exposed to sumatriptan in the first trimester of pregnancy [34]. A German registry has reported that the rate of placental abruption was higher in patients with migraines exposed to triptans compared to patients who did not have migraines. However, this was found to be not be statistically significant [35]. A systematic review conducted by Saldanha et al. showed that infants exposed to triptans had increased risk of emotionality (adjusted relative risk [RR] 2.18, 95% CI 1.03–4.53) and hyperactivity by the age of 3 (adjusted RR 1.70, 95% CI 1.02–2.80). A study published in 2018 did not show an association between triptan exposure and birth defects [35].

NSAIDs inhibit the enzyme cyclooxygenase-1 and this is a common category of medications that help abort headaches. In pregnancy, their use has been associated with a risk of miscarriage and teratogenicity in the first trimester [11]. In the third trimester, there is a risk of closure of the patent ductus arteriosus [2,10]. Given these risks, some clinicians avoid NSAIDs for headaches during pregnancy, however, they are safe in the second trimester. Aspirin also falls in this category. Aspirin is used in high-risk preeclampsia patients [37]. It can also be used for the management of headache and it has risks similar to NSAIDs.

Occipital nerve blocks can also be considered for acute management of pregnant patients with migraine. A prospective study followed pregnant women exposed to local anesthetics during dental procedures and compared them to a participant pool without exposure. There was no significant difference in rate of miscarriages or major birth anomalies between the two groups [38]. When compared to acetaminophen 650 mg and caffeine 200 mg together in one randomized trial, the efficacy of occipital nerve blocks were similar to acetaminophen, but the time to relief was faster in patients who received occipital nerve blocks [39]. Non-pharmacologic therapies, such as the remote electrical neuromodulation device, is an alternative that can be safely used to acutely treat migraine during pregnancy [25].

Management of Migraines in Postpartum/Lactation

A study has shown that migraines in the postpartum period recur at greater than 30% after the first week and greater than 50% after a month [5]. Another study also showed that 4.5% of

Table 2: Acute Treatments for Migraine and Safety

Treatment	Safety	Side Effects and Comments
Acetaminophen	Safe	Preferred treatment.
Diphenhydramine	Safe	Preferred treatment.
Metoclopramide	Safe	Preferred treatment.
Remote electrical neuromodulation (Nerivio)	Safe	No significant different between patients who used devices compared to control.
Ibuprofen	Discuss with provider prior to use	Avoid due to risk of miscarriage, congenital malformations, and PDA closure.
Nerve blocks	Safe	There are possible dose dependent (higher doses) cardiac and neurologic side effects [48].
Triptans	Considered safe	No increased teratogenic effects compared to general population.
CGRP Inhibitors	Avoid	Not studied. CGRP affects uteroplacental blood flow.
Opioid	Discuss with provider before use.	Respiratory depression, sedation, neonatal withdrawal syndrome.
Ergotamine	Avoid	Risk of causing uterine contractions and decreasing fetal blood supply, low birth weight, and prematurity [49].

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women can experience their first migraine attack after giving birth [40]. With the fluctuations in hormones after delivery, it is important to properly manage migraine headaches during this period. Women who are not breastfeeding are able to resume their previous therapy as there is no risk for the infant. However, therapies available for women who are breastfeeding do have restrictions because of medications passing through the breastmilk to the infant.

The safest options for breastfeeding mothers are the non-pharmacologic therapies, such as neuromodulation devices, transcranial magnetic stimulation, cognitive behavioral therapy, and biofeedback as there are no systemic side effects or possibility of passing on the effects to the newborn. Similar to pregnancy, the safest option would be intermittent use of acetaminophen, as a very low percentage is excreted in breast milk. NSAIDs, such as ibuprofen and naproxen, are also considered safe. Metoclopramide is excreted in breast milk, but low levels are detected in infants [11]. Therefore, intermittent use is likely safe. The triptans are not studied well and should be used with caution. Eletriptan has the lowest level in breast milk compared to sumatriptan, rizatriptan, almotriptan, zolmitriptan and naratriptan. Some clinicians recommend waiting 12 hours after use of eletriptan before breastfeeding again. Tricyclic antidepressants, such as amitriptyline and nortriptyline, have low levels when measured in breast milk, and side effects are rarely reported. There have been few reports of infant sedation from mother's who took a tricyclic antidepressant, so patients should be counseled prior to using this class of medications [42].

Valproate has low levels in breast milk, but can be teratogenic if the mother becomes pregnant again. Topiramate has higher levels in the breastmilk and can possibly cause irritability and sedation [11]. The class of CGRP inhibitors and "ditans," which are 5 HT1-F agonists should be avoided as they have not been studied well and ACOG has formally recommended against their use because of this [6]. Botox for migraine prophylaxis has not been studied during breastfeeding. However, in the few reports of botox exposure in breastfeeding mothers, the level of toxin was not detectable to detectable in minute amounts [42].

Evaluation of Headaches

Complaints of headache during pregnancy should be taken seriously out of concern for secondary headaches. Secondary headaches are head or facial pain that is caused by another disease or medical diagnosis. A study conducted by Robins et al. revealed that 35% of pregnant patients who present to the hospital have headaches due to another cause. Some of these patients either did not have a history of headache or the character of the headache was different from their prior headaches [43]. Most commonly, patients should be evaluated for preeclampsia and HELLP (Hemolysis, Elevated Liver enzymes and Low Platelets) syndrome as both of these can happen in pregnancy and are potentially dangerous to the patient and the fetus. Other secondary headaches will be further discussed. The mainstay of evaluation of headache is obtaining a thorough history and neurological evaluation to identify any neurological deficits, such as mental status changes, weakness, vision changes, and sensory disturbance. Red flags elicited from the history or discovery of neurological findings warrant imaging for further investigation of the patient's headaches. The preferred imaging modality in pregnant patients is MRI brain without contrast, however, for urgent or emergent concerns, patients should have immediate CT. MR studies do not have radiation that can be oncogenic. Contrast should be avoided as much as possible in pregnant patients because of possible thyroid dysfunction to the fetus.

Secondary Headaches

Headaches deserve further evaluation in pregnancy because of concern for secondary causes, especially when there are neurological findings on exam. One study demonstrated that out of 140 women who presented to the hospital for headache, up to 35% of patients had a secondary cause to their headache. The majority of the causes (~50%) was due to hypertensive disorders. For patients with preeclampsia, the risk of stroke is even higher. Patients who have migraine are also at higher risk for stroke. Wabnitz and Bushnell found that patients with diagnosis of migraine have higher risk of gestational hypertension (OR range from 1.23 to 1.68) and preeclampsia (OR range 1.08 to 3.5), as well as other cardiovascular conditions, such as myocardial infarction and stroke [44].

There are many causes for secondary headache during pregnancy, including, but not limited to preeclampsia/eclampsia, HELLP syndrome, stroke, subarachnoid and intracranial hemorrhage, pituitary apoplexy, CVST (cerebral venous sinus thrombus), PRES (posterior reversible encephalopathy syndrome), RCVS (reversible cerebral vasoconstriction syndrome), and mass lesions [45].

When patients do have a neurological change, it is vital to obtain immediate head imaging to investigate for secondary causes. Symptoms can vary from headache, weakness, numbness, speech changes, and confusion. Because there are therapies such as thrombectomy and tPA, are available for stroke in the acute window, emergent evaluation by a physician is indicated.

Conclusion

Management of migraine during pregnancy can be challenging because of the limited available treatment options. However, with proper planning and discussion of these options with women, migraine can still be successfully

treated. There are many avenues for research in this field, such as the safety of the newer neuromodulatory devices and other non-pharmacologic therapies, such as biofeedback, botox injections, or short acting CGRP inhibitors.

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