Migraine in Pregnancy

7

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7.1 Occurrence/Incidence

Primary headache defined as migraine, tension-type headache, cluster headache, and other trigeminal autonomic cephalgias occurs in 10–17% of pregnancies [1, 2]. Ninety percent of those with one of the aforementioned primary headaches, presenting to primary care, is diagnosed with migraine. Although many women with migraine report avoiding pregnancy due to fear of worsening attacks [3], over half experience a marked improvement with reduced frequency and intensity during attacks. Improvement often begins during the first trimester and continues as the pregnancy progresses. Less than 10%, of those diagnosed with migraine prior to pregnancy, report an increased headache frequency or intensity during gestation [4]. For some women, migraine can worsen during the first trimester. A drop or big change in estrogen level can sometimes trigger a migraine attack, and there can be some drastic changes in estrogen early in pregnancy. Changes in hormone levels may off and improves in the second and third trimesters [5, 6]. Migraine attacks may start with pregnancy. Episodes without aura may begin in 1–10% of pregnant women. The onset of migraine with aura, with a pathophysiology believed related to endothelial reactivity linked to estrogen fluctuation, has an incidence of 11–14% [7]. Accurate diagnostic recognition is essential in managing migraine with and without aura during pregnancy. Another primary headache seen commonly in

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T. Mallick-Searle (ed.), *Holistic Pain Management in Pregnancy*,
https://doi.org/10.1007/978-3-031-06322-0_7

pregnancy is tension-type headache (TTH). Reported incidence of TTH in pregnancy is as high as 26% of headaches in pregnancy [8]. TTH would be expected to improve during gestation as female hormones modulate serotonin and endorphins, which are involved in TTH pathophysiology [9].

A common question is if having migraine increases your risk of complications during pregnancy. Clinicians must be knowledgeable and monitor patients for changes in their chronic migraine, especially during pregnancy, but currently there is no data to suggest that a migraine attack that occurs during pregnancy is harmful to maternal or fetal health. However, in people who have migraine, there is a higher risk of other medical issues, such as preeclampsia, hypertension, and possibly blood clotting disorders [10, 11], so monitoring for these disorders is an important part of perinatal care.

Management of secondary headache in pregnancy generally targets the underlying disorder, and, thus, is not the focus of this chapter. It is however important for the clinician to be able to differentiate between a primary and secondary headache, to be able to refer or initiate workup of urgent, such in the case of refractory hypertension, preeclampsia, intercranial hemorrhage, and tumor.

7.2 Diagnosis

Understanding the difference between primary and secondary headaches is fundamental. Primary headaches are those headaches where the headache disorder is the disease; in contrast, secondary headaches are a symptom of another underlying diagnosis, as in the example of a secondary headache because of increased intracranial pressure related to a tumor [12]. The International Classification of Headache Disorders-3 (ICHD-3) establishes guidelines in diagnosing migraine with and without aura [13]. These criteria are listed in Box 7.1a and 7.1b. These criteria, while useful and essential in clinical research, may be cumbersome for busy primary care clinicians. The ID Migraine Tool [14] is a reliable and valid alternative for screening. Composed of the following three questions, the tool may be completed by patients alone or during clinical interview.

- Has a headache limited your activities for a day or more in the last 3 months?
- Are you nauseated or sick to your stomach when you have a headache?
- Does light bother you when you have a headache?

This is a rapid reliable method for diagnosing migraine in a primary care setting. If two of the three questions are answered affirmatively, there is a 93% likelihood the patient has migraine.

A large majority of the secondary headaches seen in pregnancy and the puerperium are caused by vascular disorders, in particular conditions associated with gestational hypertension [15, 16]. Clinical findings that require additional workup, referral, and consultation include the following.

Box 7.1a: International Classification of Headache Disorders-3 Migraine Diagnostic Criteria [13]

Migraine without aura

Recurrent headache disorder manifesting in attacks lasting 4–72 h. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria:

A. At least five attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
    1. Unilateral location
    2. Pulsating quality
    3. Moderate or severe pain intensity
    4. Aggravation by or causing avoidance of routine physical activity (walking or climbing stairs)
D. During headache at least one of the following:
    1. Nausea and/or vomiting
    2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

Box 7.1b: International Classification of Headache Disorders-3 Migraine Diagnostic Criteria [13]

Migraine with aura

Recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory, or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C.
B. One or more of the following fully reversible aura symptoms:
    1. Visual
    2. Sensory
    3. Speech and/or language
    4. Motor
    5. Brainstem
    6. Retinal
C. At least three of the following six characteristics:
    1. At least one aura symptom spreads gradually over ≥5 min
    2. Two or more aura symptoms occur in succession

3. Each individual aura symptom lasts 5–60 min (when, for example, three symptoms occur during an aura, the acceptable maximal duration is 3 × 60 min. Motor symptoms may last up to 72 h)
4. At least one aura symptom is unilateral (aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.)
5. At least one aura symptom is positive (scintillations and pins and needles are positive symptoms of aura.)
6. The aura is accompanied, or followed within 60 min, by headache.

D. Not better accounted for by another ICHD-3 diagnosis.

Box 7.2 Red Flags in Clinical History or Neurologic Examination Requiring Further Evaluation [7, 17]

Clinical symptoms

- Sudden onset (thunderclap headache).
- Progressive, worsening.
- Change from prior headache type.
- Refractory to treatment.
- Worsening with valsalva maneuver, straining, coughing, or sneezing.
- Worsens with posture (sitting or standing).

Examination or laboratory findings

- Papilledema.
- Peripheral edema.
- Hypertension.
- Focal neurologic findings (numbness, weakness).
- Fever.
- Seizure.

7.3 Treatment

The optimal therapeutic approach for the management of primary headaches during pregnancy and lactation should be to consider non-pharmacological therapies first. It is important to initiate treatment timely, as an untreated migraine can lead to stress, sleep loss, depression, and poor nutritional intake, all of which can harm both the mother and the infant, leading to unfavorable outcomes. If non-pharmacological therapies are ineffective, a well-considered decision on the use of medicine should be taken, taking into account all of the advantages and potential risks.

7.4 Pharmaceutical

Acute and preventative medication treatment guidelines in adults with migraine with and without aura are well established (see Tables 7.1 and 7.2). Before applying these medication guidelines in pregnancy, potential maternal and fetal risk should be considered (Table 7.3). We have addressed many of the pregnancy considerations for commonly used pharmaceuticals for both TTH and migraine in Chap. 2.

Additional medications for migraine treatment and prevention, not currently recommended in pregnancy, but have established pregnancy registries (see Chap. 2), are onabotulinumtoxinA (Botox) and calcitonin gene-related peptide monoclonal antibody antagonists (CGRP mABs) [20].

7.5 Symptomatic/Acute Treatment in Pregnancy

Acetaminophen is considered the safest option to treat acute pain during pregnancy and breastfeeding [7]. Caffeine at moderate intake of caffeine seems safe for mother and child when breastfeeding [21]. NSAIDs (see Chap. 2). Considerable data is available on the use of sumatriptan in pregnancy. Due to its small molecular weight, sumatriptan can pass through the placenta [22]. However, the transfer is slow and passive, so that only about 15% of maternal dose reach the fetus after 4 h [23]. A few large pregnancy registries covering more than 3000 pregnancies have retrospectively reviewed the use of other triptans, in particular rizatriptan, zolmitriptan, and eletriptan [7]. Acute migraine medications (including triptans, NSAIDs, acetaminophen, caffeine) should not be used on a daily basis, to reduce the risk of medication overuse headache [24].

Supplements for migraine (also see Chap. 4 for supplement recommendations during pregnancy):

- Magnesium at recommended doses (up to 350 mg daily) can be used during pregnancy and lactation [25].
- Coenzyme Q10 appears safe during pregnancy [26, 27].
- Melatonin has not been shown to have harmful effect during pregnancy [28].
- High-dose riboflavin, feverfew, and butterbur should be AVOIDED during pregnancy [26, 29].

7.6 Preventative Treatments in Pregnancy

Beta-blockers metoprolol and propranolol are the first-line agents recommended needed from migraine prophylaxis in pregnancy and breastfeeding [7, 30].

OnabotulinumtoxinA (Botox) has been used as a preventative treatment for chronic migraine since 2010. Given the tremendous benefit that patients receive with this treatment, and as many of the patients studied were women of childbearing age, the question was raised about the safety and efficacy of continuing treatment during pregnancy. Many studies, including reporting from the Allergan pregnancy

Table 7.1 Acute migraine treatments recommended by American Headache Society (AHS) [18]

Level A	Level B	Level C	Level U	Other
Analgesics Acetaminophen 1000 mg (for non-incapacitating attacks)	*Antiemetics* • Chlorpromazine IV 12.5 mg • Droperidol IV 2.75 mg • Metroclopramide IV 10 mg • Prochlorperazine IV/IM 10 mg, PR 25 mg	*Antiepileptics* Valproate IV 400–1000 mg	*NSAIDs* Celecoxib 400 mg	*Level B negative, Other* Octreotide SC 1000 mcg
Ergots DHE: nasal spray 2 mg, pulmonary inhaler 1 mg	*Ergots* • DHE: IV/IM/SC 1 mg • Ergotamine/caffeine 1/100 mg	*Ergots* Ergotamine 1–2 mg	*Others* • Lidocaine IV • Hydrocortisone IV 50 mg	*Level C negative, Antiemetics* • Chlorpromazine IM 1 mg/kg • Granisetron IV 40–80 mcg/kg
NSAIDs • ASA 500 mg • Diclofenac 50, 100 mg • Ibuprofen 200, 400 mg • Naproxen 500, 550 mg	*NSAIDs* • Flurbiprofen 100 mg • Ketoprofen 100 mg • Ketorolac IV/IM 30–60 mg	*NSAIDs* Phenazone 1000 mg		*NSAIDs* Ketorolac • Tromethamine nasal spray
Opioids Butorphanol nasal spray 1 mg		*Opioids* • Butorphanol IM 2 mg • Codeine 30 mg oral • Meperidine IM 75 mg • Methadone IM 10 mg • Tramadol IV 100 mg		*Analgesics* Acetaminophen IV 1000 mg

(continued)

Table 7.1 (continued)

Level A	Level B	Level C	Level U	Other
Triptans Sumatriptan, zolmitriptan, Rizatriptan, rizatriptan, etc.	*Others* • $MgSO_4$ IV (migraine w/ aura) 1–2 g • Isometheptene 65 mg	*Steroid* Dexamethasone IV 4–16 mg		
Combinations • Acetaminophen/aspirin/ caffeine 500/500/130 mg • Sumatriptan/naproxen 85/500 mg	*Combinations* • Codeine/acetaminophen 25/400 mg • Tramadol/acetaminophen 75/650 mg	*Others* • Butalbital 50 mg • Lidocaine intranasal *Combinations* • Butalbital/acetaminophen/ caffeine/codeine 50/325/40/30 mg • Butalbital/acetaminophen/ caffeine 50/325/40 mg		

Table 7.2 Preventative migraine treatments recommended by American Headache Society (AHS) [19][a]

Level A	Level B	Level C	Level U
Antiepileptics • Divalproex • Valproate • Topiramate	*Antidepressants* • Amitriptyline • Venlafaxine	*ACE inhibitors* Lisinopril	*Antidepressants* Fluoxetine
Beta-blockers • Metoprolol • Propranolol • Timolol	*Beta-blockers* • Atenolol • Nadolol	*ARBs* • Candesartan • Clonidine • α-Agonists	*Calcium-channel blockers* • Verapamil • Nifedipine
Triptans Frovatriptan	*Triptans* • Naratriptan • Zolmitriptan	*Antiepileptics* Carbamazepine	*Antiepileptics* Gabapentin
		Beta-blockers • Nebivolol • Pindolol	

[a]Not a complete list

Table 7.3 Commonly used acute and preventative medications for migraine (adapted partially from Burch R. Headache in Pregnancy and the Puerperium. Neurol Clin. 2019;37: 31–51.). Also see Chap. 2 for greater detail

Medication	Use	Safety	Hale's lactation risk rating
Acetaminophen	Acute	No increased risk of teratogenic effects	Compatible
NSAIDs	Acute	Use restricted to second trimester	Ibuprofen = compatible; diclofenac = probably compatible
Triptans	Acute	No increased risk of major congenital malformations. Evidence best for sumatriptan, naratriptan, rizatriptan. Conflicting studies about possible increase risk of premature birth	No data, probably compatible. Eletriptan is likely to have lowest concentration in breast milk. Avoid long acting triptans
Ondansetron	Acute; nausea	No increased risk of congenital malformations	Probably compatible. Evidence is lacking
Prednisone	Rescue	Increased risk of cleft lip/palate, low birth weight Risks increase with chronic versus episodic use. Benefit versus risk assessment strongly advised	Probably compatible
Lidocaine	Acute/rescue	Limited data, existing studies show no increase in congenital malformations. Intranasal formulation presumed to have a better safety profile to systemic [33]	Probably compatible
Propranolol	Preventative	Considered first-line option in pregnancy and breastfeeding. Potential side effects of intrauterine growth retardation, premature birth described in some studies [26, 29]	

registry [31], have shown no evidence of teratogenic effects on the fetus. Botulinum toxin is a large molecule and, when injected intramuscularly in recommended doses, is not expected to enter systemic circulation [32]. Therefore, onabotulinumtoxinA is unlikely to cross the placenta. Although not recommended to use during pregnancy or lactation, many clinicians have been encouraged by the long-term safety data and, in the right patient, have supported clinical use as a migraine preventative in patients that have established efficacy with treatment before pregnancy and when the benefits outweigh the potential risks.

Gabapentin, although not found to be highly effective as a migraine preventative, level U on the AHS list of preventative migraine medications [19], still might prove to be effective in some patients. Gabapentin has been seen as relatively safe in pregnancy and lactation (see Chap. 2).

7.7 Non-pharmaceutical

First and foremost, non-pharmacological treatment should start with education by a knowledgeable clinician about migraine management, about incidence of disease impact on pregnancy. This will instill confidence and reduce stress about the unknown in this patient population. We already established earlier in this chapter that many women with migraine report avoiding pregnancy due to fear of worsening attacks [3]. Secondly, as with migraine prevention in the setting of non-pregnancy, women should be counseled about the importance of trigger identification, modification, and avoidance. Triggers like sleep deprivation, skipping meals, dehydration, and emotional stress should be avoided. A balanced lifestyle with attention for physical activity and regular eating and sleeping habits is recommended. Acupuncture and behavioral therapies like biofeedback and yoga have been shown to be beneficial [26, 27, 34]. Also see Chaps. 5 and 10 for addition information.

Injection therapies have shown benefit in acute and chronic migraine treatment [35, 36]. The use of peripheral nerve blocks in regions of the greater, lesser, and third occipital, auricular temporal, and supratrochlear and supraorbital nerves proved effective in stopping a severe migraine or at times decreasing the frequency and intensity of recurrent headache [36]. In pregnancy, nerve blocks and trigger point injections should be administered with only lidocaine. Bupivacaine crosses the placenta and may induce fetal bradycardia and cardiotoxicity. Use is avoided during pregnancy [7, 37]. Also see Chap. 9 for additional information on nerve blocks.

7.7.1 Noninvasive Neuromodulation

Bhola 2015 reported in a prospective single-group study, using magnetic stimulation experienced resolution of their acute migraine, that three patients who received transcranial magnetic stimulation experienced resolution of their acute migraine-related symptoms [38].

Also see Chap. 9 for additional information on neuromodulation.

7.8 Clinical/Nursing Considerations

- Why you should discuss medication safety before pregnancy?
  A large percentage of pregnancies are unexpected or unplanned, and the majority of our patients at the headache clinic are women of childbearing potential.
- Study shows fears about pregnancy with migraine are common.
  The good news is we do have treatment options that can be effective during pregnancy; it's just a matter of talking to your healthcare provider about it and making sure they feel comfortable using different treatment options, whether it be for the prevention of migraine or for migraine attacks themselves. Allowing an open dialogue about patient's fears is therapeutic.
- How to plan for pregnancy when you have migraine?
  Planning for pregnancy includes learning which migraine treatments are safe during pregnancy and which lifestyle measures can help. Providing resources and reassurance is key.

7.9 Case Study

Twenty-seven-year-old female patient diagnosed with menstrual migraines in her teens, that became chronic around 3 years ago. She is now coming to your clinic every 3 months for onabotulinumtoxinA (Botox) injections via the PREEMPT paradigm for chronic migraine prevention and uses one of the new CRRP antagonist medications one to two times a month for acute migraine episodes. She informs you that she missed her last period and thinks that she maybe pregnant and is concerned how a pregnancy will affect her migraines. She and her husband are pleased about having a baby.

Plan:

- Educate her about what is known about reduction in migraine symptoms during pregnancy in many females, but you will monitor her symptoms and provide treatment options for possible worsening migraines.
- Tell her that you recommend stopping the Botox injections for now.
- Prescribe sumatriptan for acute migraine flares; stop the CRRP antagonist medication.
- Reinforce avoidance of triggers, behavioral management strategies, mindfulness, meditation, and diet.
- Offer to try propranolol if her migraines get worse during this time.

7.10 Summary

Headache is a common complaint, especially among women. As a result, it's not unexpected that it's a common occurrence in pregnant women. The majority of headaches in pregnancy are caused by primary headaches such as migraine and

tension headache. In the second and third trimesters of pregnancy, most women discover that their headaches disappear or significantly improve, probably due to a decrease in reproductive hormonal changes.

However, approximately 10% of women have an exacerbation of symptoms, and most women soon return to their prepregnancy migraine pattern after delivery. Because of the risk of certain drugs to the fetus and the fact that medications may be transferred in various degrees in a mother's milk, pregnancy and lactation might complicate therapy options for women with migraine.

Acetaminophen use in pregnancy is safe, and NSAIDs such as ibuprofen can be prescribed for short-term use in the first trimester. There are increasing safety data on triptans to treat migraine in pregnancy, and sumatriptan may be used to treat acute migraine attacks also while breastfeeding. Options in prescription preventive medications are limited, and it may be best to consider lifestyle changes and behavioral treatment for stress management. When preventive pharmaceutical treatment is needed for migraine, metoprolol and propranolol are the first choice followed by amitriptyline. Although still not widely recommended, safety data looks very good for onabotulinumtoxinA (PREEMPT) in pregnancy [31]. The new CGRP Abx all also has robust pregnancy registries, and hopefully some preliminary information will be forth coming.

7.11 Resources

- Hale's Medications and Mothers Milk 2021: https://www.halesmeds.comUpdated regularly, available as an online subscription and Published: Springer Publishing Company.
- Pregnancy registries are generally sponsored by interested organizations (pharmaceutical companies, academic institutions, government sponsored), ongoing for a finite period, and often listed on the U.S. FDA website: https://www.fda.gov/science-research/womens-health-research/pregnancy-registries Also see Chap. 2.
- American Headache Society: Pregnancy and Lactation – Migraine Management Toolbox https://americanheadachesociety.org/wp-content/uploads/2018/05/Pregnancy_and_Lactation_Toolbox.pdf

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