REVIEW ARTICLE

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Headache in Pregnancy

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ABSTRACT

PURPOSE OF REVIEW: **Headache disorders are extraordinarily common and disproportionately impact women of childbearing age. This article reviews the importance of proper diagnosis, natural history, and management of headache disorders in pregnant and postpartum women.**

RECENT FINDINGS: **Red flags for secondary headache specifically among pregnant women include elevated blood pressure and lack of a previous headache history, as well as a prolonged duration of the headache attack in those with a prior history of migraine. Migraine improvement is typical for most pregnant women, but the prognosis for women who have migraine with aura or chronic migraine is less predictable. Migraine is now an established risk factor for the development of preeclampsia. Recent data suggest hazards for compounds containing butalbital and possibly a better safety profile for triptans than previously believed during pregnancy. Peripheral nerve blocks and noninvasive neurostimulation devices are procedural and emerging therapies that have promising safety profiles for pregnant women with headache disorders.**

SUMMARY: **Acute headache occurring in pregnancy and the postpartum period is a red flag requiring diagnostic vigilance. Migraine frequency in women typically improves during pregnancy, although this trend is less certain when aura is present and after delivery. Acute and preventive treatment plans during pregnancy and lactation are plausible but may require shifts in therapeutic hierarchy. Relatively safe oral, parenteral, and procedural therapies are available for pregnant women. Noninvasive neuromodulation devices are already available and will likely play a greater role in the coming years. Migraine is associated with medical and obstetrical complications during pregnancy, and women with frequent migraine attacks may need to be considered high risk.**

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RELATIONSHIP DISCLOSURE:
Dr Robbins has received personal compensation for serving as a section editor for *Current Pain and Headache Reports* and serves (without compensation) on the board of directors and as a member-at-large of the American Headache Society and as associate editor of *Headache: The Journal of Head and Face Pain*. Dr Robbins has received book royalties from John Wiley & Sons.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Robbins discusses the unlabeled/investigational use of medications and devices for the treatment of headache disorders in pregnant and breast-feeding women, including all analgesics, neuromodulation devices, preventive therapies, and triptans.

INTRODUCTION

Primary headache disorders such as migraine are extraordinarily common in women of childbearing age. The importance of the diagnosis and management of headache in pregnant and postpartum women is underscored by the high rate of secondary headache disorders in this population based on hormonal, vascular, homeostatic, and procedural factors. In addition, treatment decisions must consider both maternal and fetal or newborn health. This article first approaches the diagnosis of headache in pregnancy and carefully distinguishes primary from secondary headache disorders that are state specific. The article then reviews

migraine, the most common headache disorder, and how it may be managed during pregnancy. The diagnosis and management of headache in the peripartum and postpartum state is then addressed, followed by a review of headache management during lactation. Finally, the impact of migraine on pregnancy itself is discussed, with a focus on adverse labor and delivery outcomes, including preeclampsia.

HEADACHE DIAGNOSIS IN PREGNANCY

Many traditional red flags in the diagnosis of headache that raise alarms for secondary causes have been well described.[1] These factors include systemic symptoms or signs, focal neurologic signs or symptoms including papilledema, an older age of onset, an abrupt onset of severe headache (thunderclap), a pattern change at variance with a preexisting headache disorder, precipitation by Valsalva maneuver or exertion, or a postural headache. However, recent evidence suggests that new headache in pregnancy and in the puerperium (within 6 weeks postpartum) is also a red flag for secondary headache.[2,3] Specific clinical clues heightening the suspicion for secondary headache disorders in pregnancy and the puerperium are listed in TABLE 7-1.

Secondary headache disorders that may have a predilection for occurrence during pregnancy and the puerperium fall under many different categories. Symptomatic headache attributed to cerebrovascular disorders may occur with an increased incidence in women during this time and include aneurysmal subarachnoid hemorrhage, acute ischemic or hemorrhagic stroke, cerebral venous thrombosis, cervical artery dissection, and reversible cerebral vasoconstriction syndrome (RCVS) (FIGURE 7-1). Congenital or space-occupying lesions such as a Chiari malformation, a third ventricle colloid cyst, or a neoplasm may present during labor when Valsalva maneuvers can provoke transient rises in intracranial pressure. CASE 7-1 illustrates a patient who developed headache attributed to pituitary disease, which may also manifest more commonly in pregnant women. Disorders of homeostasis can also feature headache during pregnancy or the postpartum state, including acute severe hypertension with or without preeclampsia, eclampsia, and posterior reversible encephalopathy syndrome (PRES) (FIGURE 7-3). Finally, derangements of intracranial pressure may also develop during this period, including idiopathic intracranial hypertension that may present or worsen in the setting of weight gain associated with pregnancy. Post–dural puncture headache after epidural or combined epidural and spinal anesthesia is a common cause for postpartum headache. Pneumocephalus may also occur with epidural or spinal anesthesia when air is introduced into the intrathecal space, migrates cranially, and leads to a sudden headache, typically with onset during or shortly after insertion of an epidural or spinal needle and catheter.

A 2015 study addressed acute headache diagnosis in pregnancy and included 140 women who presented to acute care with severe headache requiring inpatient neurologic consultation.[2] In this sample, primary headache was diagnosed in 65% of patients, and secondary headache was diagnosed in 35% of patients. The most common diagnosis overall was migraine at 59.3%, and the second most common disorder (and the most common in the secondary headache disorder category) was hypertensive disorders of pregnancy, which mostly featured preeclampsia but also included PRES, eclampsia, acute arterial hypertension, and RCVS. In this study, a number

KEY POINTS

- Recent evidence suggests that new headache in pregnancy and in the puerperium (within 6 weeks postpartum) is a red flag for secondary headache.
- Among women with a history of headache, a changed feature of a longer attack duration was associated with a secondary headache disorder diagnosis.
- A diagnostic strategy for acute headache in pregnant women should feature liberal use of noncontrast MRI and monitoring for preeclampsia, particularly in those with an elevated blood pressure and without a headache history.

TABLE 7-1 **Clinical Clues in the Diagnosis of Secondary Headache Disorders in Pregnant and Postpartum Women**[a]

Clinical Clue	Diagnosis	Timing
Orthostatic headache pattern	Post-dural puncture headache	Postepidural anesthesia (hours to days)
Relapsing thunderclap headaches	Reversible cerebral vasoconstriction syndrome (RCVS)	Postpartum more often than antepartum
Single thunderclap headache	Aneurysmal subarachnoid hemorrhage	Antepartum and postpartum
	RCVS	Postpartum more often than antepartum
	Cerebral venous thrombosis	Antepartum and postpartum
	Cervical artery dissection	Postpartum
	Pituitary apoplexy	Antepartum more often than postpartum
	Pneumocephalus	Postepidural anesthesia (immediate)
Hypertension	Preeclampsia/eclampsia	Antepartum more often than postpartum
	Posterior reversible encephalopathy syndrome (PRES)	Antepartum more often than postpartum
	RCVS	Postpartum more often than antepartum
Visual loss	Preeclampsia/eclampsia	Antepartum more often than postpartum
	PRES	Antepartum more often than postpartum
	Pituitary apoplexy	Antepartum more often than postpartum
	Idiopathic intracranial hypertension	Antepartum more often than postpartum
	Cerebral venous thrombosis	Antepartum and postpartum
Seizures	Eclampsia	Antepartum more often than postpartum
	Cerebral venous thrombosis	Antepartum and postpartum
	PRES	Antepartum more often than postpartum
	RCVS	Postpartum more often than antepartum
Horner syndrome	Cervical artery dissection	Postpartum
Papilledema	Cerebral venous thrombosis	Antepartum and postpartum
	Idiopathic intracranial hypertension	Antepartum more often than postpartum
	Space-occupying lesion (eg, neoplasm)	Antepartum and postpartum
Focal neurologic findings	Ischemic stroke	Antepartum and postpartum
	Intracranial hemorrhage	Antepartum and postpartum
	Cerebral venous thrombosis	Antepartum and postpartum
	PRES	Antepartum more often than postpartum
	RCVS	Postpartum more often than antepartum

[a] Modified with permission from Glover RL, Headache.[3] © American Headache Society.

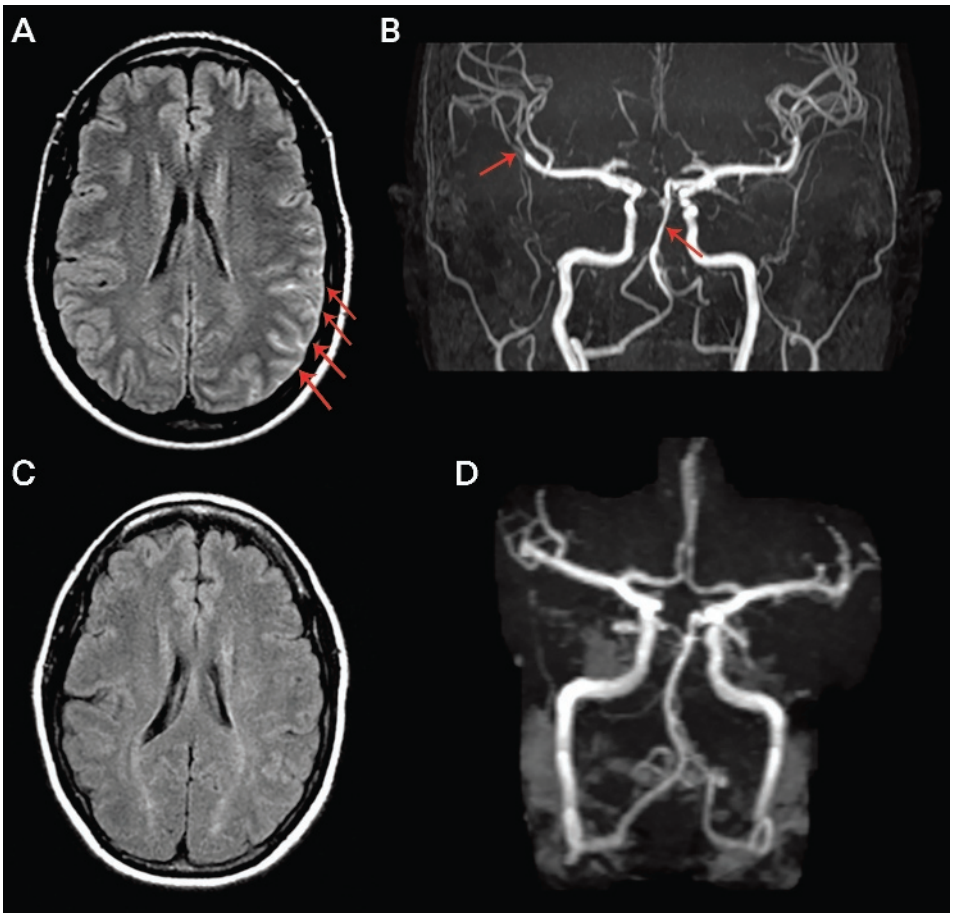

FIGURE 7-1
MRI and magnetic resonance angiogram (MRA) in a patient with acute postpartum headache. A 32-year-old woman at 3-weeks postpartum presented with relapsing thunderclap headaches followed by abulia that gradually resolved with nimodipine and IV magnesium. Initial brain MRI with fluid-attenuated inversion recovery (FLAIR) sequences (*A*) revealed left convexity subarachnoid hemorrhage (*arrows*). *B*, Initial brain MRA demonstrated multifocal areas of vasoconstriction including the middle cerebral artery branches and distal basilar artery (*arrows*) as well as attenuated flow in the anterior cerebral arteries. Repeat brain MRI (*C*) and MRA (*D*) demonstrated improvement of the convexity subarachnoid hemorrhage and resolution of the multifocal areas of vasoconstriction. Convexity subarachnoid hemorrhage can occur in association with reversible cerebral vasoconstriction syndrome.

of factors were associated with primary versus secondary headache, including asthma, hypertension, any past psychiatric diagnosis, and any past headache history.[2] Among women with a history of headache, a changed feature of a longer attack duration was associated with a secondary headache disorder diagnosis in this group. Acute attack features associated more with primary headache included phonophobia only. Attack features associated with secondary headache included the presence of seizures, elevated blood pressure, fever, and an abnormal neurologic examination. In multivariate analysis, a lack of headache history was associated with a nearly fivefold risk of secondary headache, and elevated blood pressure was associated with a 17-fold risk of secondary headache. The study suggested that a diagnostic strategy for acute headache in pregnant women should feature liberal use of noncontrast MRI and monitoring for

KEY POINTS

- Migraine without aura typically improves or remits altogether in most women when pregnant, with improvement or remission observed in nearly 47% of women during the first trimester, in 83% of women during the second trimester, and in 87% of women during the third trimester.
- Migraine with aura is less likely to improve during pregnancy than migraine without aura. New-onset migraine with aura and even aura without headache may occur in the later stages of pregnancy.
- Management of migraine during pregnancy always starts with preconception counseling whenever feasible.
- Nonpharmacologic therapies should always be emphasized as an important aspect of migraine management, especially during pregnancy.
- Migraine prophylactic medication may be unnecessary in pregnancy because of the generally good prognosis and should be avoided because of teratogenic concerns.
- Butalbital compounds that are used in combination with acetaminophen or aspirin and caffeine have recently been associated with congenital heart defects and are generally not recommended.

CASE 7-1

A 23-year-old woman in her first pregnancy presented with 3 days of a sudden-onset severe headache in a fixed bifrontal location. Her history included rare attacks of migraine without aura during her teenage years, but her current symptoms were atypical of her remote migraine attacks. She described a perturbation in her binocular peripheral vision that was not demonstrable on neurologic examination, and fundoscopy, visual field testing, and pupillary reflexes were all normal.

MRI revealed an expanded sella with a fluid level and optic chiasm compression suggestive of pituitary apoplexy (FIGURE 7-2[4]). Automated perimetry revealed a bitemporal hemianopsia, and her serum prolactin level was 395 ng/mL (with the laboratory's normal range for pregnant women being 10 ng/mL to 209 ng/mL).

Because of visual loss, she required transphenoidal resection, which was uncomplicated. She was prescribed levothyroxine thereafter and peripartum hydrocortisone around the time of her otherwise uncomplicated cesarean delivery.

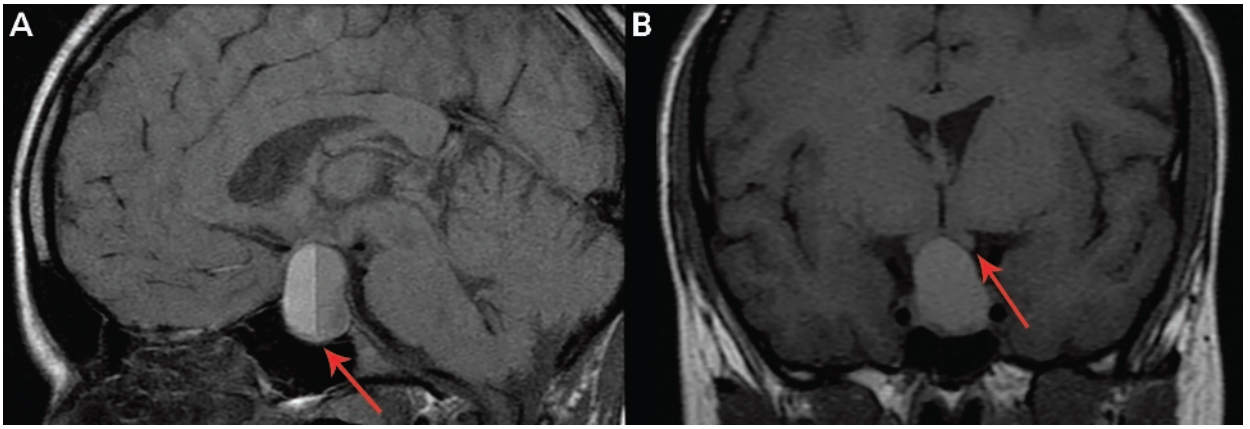

FIGURE 7-2

MRI of the patient in CASE 7-1. Sagittal (*A*) and coronal (*B*) noncontrast T1-weighted brain MRI showing a 1.7 cm by 1.8 cm by 2.5 cm suprasellar mass containing a fluid level (*A, arrow*) with upward compression of the optic chiasm (*B, arrow*). The findings were consistent with pituitary apoplexy, and the pathology revealed a lactotroph-secreting adenoma with hemorrhage.

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COMMENT

Pituitary apoplexy can present with acute headache that can be of gradual onset or thunderclap and can occur with increased frequency in pregnant women because of physiologic expansion of the gland during the antepartum period, which is attributed to lactotroph cellular activity and hyperemia.

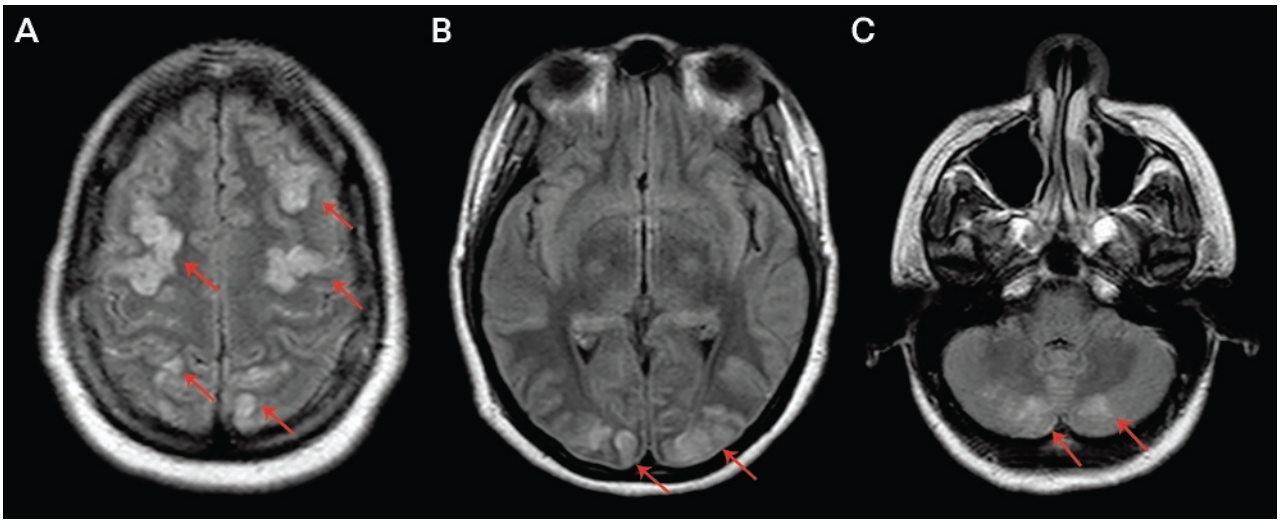

FIGURE 7-3

MRI in acute postpartum headache. A 23-year-old woman 4 days postpartum presented with progressive severe headache and generalized seizures. Axial fluid-attenuated inversion recovery (FLAIR) MRI revealed hyperintensities (*arrows*) throughout the bilateral cerebral (*A*, *B*) and cerebellar (*C*) hemispheres that resolved on follow-up imaging, consistent with posterior reversible encephalopathy syndrome.

preeclampsia, particularly in those with an elevated blood pressure and without a headache history.[2]

PROGNOSIS OF MIGRAINE IN PREGNANCY

Although migraine often improves during pregnancy, the epidemiology of migraine suggests that its enormous prevalence and incidence in women during their childbearing years renders it a frequent clinical problem during pregnancy. During childbearing years, migraine prevalence peaks to nearly 25%, and migraine incidence peaks at nearly 20 per 1000 person-years according to data from the American Migraine Prevalence and Prevention Study.[5,6] Migraine without aura typically improves or remits altogether in most women when pregnant, with improvement or remission observed in nearly 47% of women during the first trimester, in 83% of women during the second trimester, and in 87% of women during the third trimester.[7] Migraine improvement during pregnancy is related to increasing levels of estradiol during the gestational period, as well as the lack of cycling related to the menstrual cycle where estrogen withdrawal can serve as a major migraine trigger. However, more than 26% of pregnant women with migraine do report some degree of moderate or severe headache-related disability during their early pregnancy.[8]

Migraine with aura is less likely to improve during pregnancy than migraine without aura. New-onset migraine with aura and even aura without headache may occur in the later stages of pregnancy. In one study, among 91 women who had any primary headache disorder, 39.6% presented with aura while pregnant, and 69.4% of these women had no previous aura attacks.[2] Potential mechanisms driving the different prognosis of migraine with aura relative to migraine without aura include increased endothelial reactivity during pregnancy, as well

as a high estrogen to progesterone ratio, which may actually lower the threshold for cortical spreading depression.[9–11]

MANAGEMENT OF MIGRAINE IN PREGNANCY

Migraine treatment in pregnancy can be challenging because of concerns for both maternal and fetal well-being. Management of migraine during pregnancy always starts with preconception counseling whenever feasible. All women of childbearing age who are prescribed any therapy for migraine should know what the risks are if they are planning to become pregnant and should contact their physician immediately if an unexpected pregnancy occurs.

Nonpharmacologic therapies should always be emphasized as an important aspect of migraine management, especially during pregnancy. Recognizing and avoiding commonly reported migraine attack triggers such as diet and especially sleep disturbance may be particularly important during pregnancy, when previously stable routines may be disrupted.[12,13] Proactively addressing risk factors for migraine progression and comorbidities is also crucial since many of these factors are modifiable.[14] Medication overuse, excessive caffeine intake, psychiatric and pain comorbidities, obesity, sleep disturbance, and persistent frequent nausea may all be treatable risk factors for migraine progression or worsening. Nonpharmacologic treatments, many of which are evidence-based and safe during pregnancy, are highly recommended and include relaxation strategies, biofeedback, and cognitive-behavioral therapy.[15] Emphasizing the good prognosis for migraine in pregnancy is also helpful to relieve some of the anxiety for women planning to conceive, particularly for those who have episodic migraine without aura. Direct communication with the obstetrician is also helpful in the coordination of care for pregnant women with migraine.

For migraine management with medications, therapies can be divided into acute and prophylactic strategies. Acute treatments may need to be stepwise or stratified, and this plan should be discussed with the patient in advance of conception. Migraine prophylactic medication may be unnecessary in pregnancy because of the generally good prognosis and should be avoided because of teratogenic concerns. Finally, a pregnant woman who has an intractable migraine attack or status migrainosus should know what a backup plan might be during pregnancy to minimize worry and to have a safe and effective treatment strategy in place.

Treating migraine in pregnancy with medication is challenging as no single medication is entirely free of any potential teratogenic effects. The US Food and Drug Administration (FDA) has recently phased out the pregnancy risk letter category system for medications and has replaced it with the new pregnancy and lactation labeling rule, which provides more qualitative description of the risks during pregnancy and lactation.[16] The FDA letter category system was useful as a hierarchical system, but these ratings will soon become outdated.

TABLE 7-2 reviews acute treatments and their safety concerns in pregnant women. The safest acute treatments may include acetaminophen and metoclopramide, which may be given both enterally or parenterally. However, even these agents carry potential risks including the later development of attention deficit hyperactivity disorder in children with antepartum acetaminophen exposure, and maternal cardiac conduction changes and extrapyramidal symptoms with metoclopramide exposure. Opiates are typically not indicated to treat migraine, but if necessary as a rescue therapy, oxycodone may be the safest specific drug within this class to use. However, major safety concerns for opioids

include neonatal respiratory suppression as well as maternal and fetal dependence. Butalbital compounds that are used in combination with acetaminophen or aspirin and caffeine have recently been associated with congenital heart defects and are generally not recommended.[17] Nonsteroidal anti-inflammatory drugs may have a niche in the second trimester, but this must always be prescribed in concert with the patient's obstetrician, as they have trimester-specific teratogenic profiles that generally prohibit their use in the first and third trimesters.

Triptans had all been rated FDA category C. The postmarketing registry maintained for sumatriptan demonstrated a birth defect rate of 4.2% (95%

Acute Headache Therapies and Their Potential Safety Concerns in Pregnant Women TABLE 7-2

Agent or Class	US Food and Drug Administration (FDA) Class[a]	Some Potential Risks and Comments
Acetaminophen	B	Attention deficit hyperactivity disorder
Lidocaine	B	Safety data largely from peripheral injection and not IV use, central nervous system depression
Ondansetron	B	Cleft palate
Dopamine antagonists (metoclopramide)	C (B)[b]	Prolonged QTc interval on ECG, extrapyramidal symptoms
Opiates (oxycodone)	C (B)[c]	All cross placenta, neonatal respiratory suppression (dependence [maternal and fetal])
Butalbital compounds	C	Congenital heart defects
Triptans	C	Preterm labor, uterine atony, postpartum hemorrhage
Bupivacaine	C	Maternal cardiac conduction abnormalities
Prednisone, methylprednisolone (dexamethasone)	C (D)[d]	Orofacial clefts, intrauterine growth restriction, some cross placenta
Nonsteroidal anti-inflammatory drugs	C (first trimester/second trimester)	First trimester: inhibit implantation, cardiac abnormalities, gastroschisis
	D (third trimester)	Third trimester: premature ductus arteriosus closure, oligohydramnios, periventricular hemorrhage
Magnesium sulfate	D	Bone loss[a]
Valproate	X	Neural tube defects, clefts, lower IQ and developmental delay, autism, cardiovascular and genitourinary abnormalities
Dihydroergotamine	X	Uterine ischemia, increased uterine contractility, prematurity

ECG = electrocardiogram; IQ = intelligence quotient; IV = intravenous; QTc = corrected QT interval.
[a] Although the FDA ratings have not been continued past 2015, for now they remain a useful hierarchical scheme in the organization of drug safety in pregnant women.
[b] Class B refers only to metoclopramide.
[c] Class B refers only to oxycodone.
[d] Class D refers only to dexamethasone.

confidence interval, 2.6% to 6.5%), which is in line with the general population.[18] A recent meta-analysis that analyzed prenatal triptan use included one case-control study and five cohort studies that totaled 4208 triptan exposures.[19] When comparing women with migraine exposed to triptans versus women with migraine not exposed to triptans, no significant increases were found in malformation rates (odds ratio of 0.84 [0.61 to 1.16]), prematurity (odds ratio of 0.90 [0.35 to 2.30]), or spontaneous abortions (odds ratio of 1.27 [0.58 to 2.79]). Compared to healthy nonmigraine controls, women exposed to triptans had a higher risk of spontaneous abortions (odds ratio of 3.54 [2.24 to 5.59]). Women with migraine not exposed to triptans compared to healthy controls had a higher rate of malformations (odds ratio of 1.41 [1.11 to 1.80]). A more recent prospective observational study of 432 pregnant women exposed to triptans demonstrated no increase of major birth defects, spontaneous abortions, preterm delivery, and preeclampsia in comparison to a nonmigraine cohort.[20] It may be that women with more severe migraine in pregnancy who have been studied take triptans, and the majority of evidence suggests triptans intrinsically may not adversely impact labor and delivery outcomes, but more studies among pregnant women stratified by migraine severity may provide further clarity.

Prophylactic medications for migraine during pregnancy also have variable safety profiles (TABLE 7-3). Medications that may be safe based on limited human and animal studies include pindolol, memantine, and cyproheptadine but have not been investigated extensively in rigorous clinical trials. Magnesium supplementation is often used as a preventive treatment in nonpregnant women and may be safe during pregnancy. However, the association of prolonged maternal IV magnesium sulfate exposure with fetal bone demineralization has raised concerns about the safety of magnesium oxide used daily in pregnant women, and further investigations are certainly indicated. Beta-blockers are generally thought to be safe and are commonly used for the treatment of hypertension in pregnancy but may be associated with intrauterine growth restriction. Antiepileptic drugs such as topiramate and valproic acid are avoided during pregnancy because of their more significant teratogenicity.

Interventional therapies and noninvasive neurostimulation devices have become prominent in recent years in the treatment of headache disorders, particularly migraine.[21] Such treatments include injectable therapies such as botulinum toxin, peripheral nerve blocks, trigger point injections, and sphenopalatine ganglion blocks. Three neuromodulation devices have been approved by the FDA for the treatment of migraine: a transcutaneous supraorbital nerve stimulator that is approved as a prophylactic and for acute treatment, a single-pulse transcranial magnetic stimulation device that is approved for both the acute treatment of migraine with aura attacks and as a preventive therapy, and noninvasive vagus nerve stimulation that has been approved for the acute treatment of episodic cluster headache attacks as well as for the acute treatment of migraine. These therapies have excellent safety profiles[22–24] and should be appropriate for pregnant women to use, although, of these devices, only limited investigations have been reported in pregnant women with single-pulse transcranial magnetic stimulation. A postmarketing study in Europe for both acute and prophylactic treatment with single-pulse transcranial magnetic stimulation included three patients who used the device while pregnant. All three patients used the device with good success as an acute treatment while pregnant and did not develop any known adverse delivery outcomes.[23]

Botulinum toxin had been previously rated by the FDA as a category C drug. It has a high molecular weight and theoretically should not cross the placenta, and reported cases of botulism have not been associated with adverse fetal outcomes. The pharmaceutical database, including patients in clinical trials and postmarketing studies, has reported 232 pregnancies, of which migraine was a clinical treatment diagnosis in 22 women. The majority of these botulinum toxin exposures were from 3 months preconception through the first trimester. The rate of fetal loss was 20.9% in comparison to 35.4% in the US population. The rate of major birth defects was 2.7% compared to the 3% US population birth defect rate.[25] However, most physicians still avoid using botulinum toxin during pregnancy because of safety concerns.[26]

Preventive Headache Therapies and Their Potential Safety Concerns in Pregnant Women TABLE 7-3

Agent	Class	US Food and Drug Administration (FDA) Class[a]	Potential Risks and Comments
Magnesium oxide	Nutraceutical	Not ranked	Neonatal hypotonia, bone demineralization associated with IV use
Riboflavin	Nutraceutical	Not ranked	Largely unknown in typical migraine doses of 400 mg/d
Memantine	*N*-methyl-D-aspartate (NMDA) receptor antagonist	B	Unknown
Cyproheptadine	Antihistamine/serotonergic	B	Unknown
Propranolol (pindolol)	Beta-blocker	C (B)[b]	Intrauterine growth restriction
Amitriptyline	Tricyclic antidepressant	C	Limb reduction, cardiac defects, neonatal withdrawal
Verapamil	Calcium channel blocker	C	Intrauterine growth restriction, fetal bradycardia, tocolysis
Gabapentin	Antiepileptic	C	Unknown, but crosses placenta
OnabotulinumtoxinA	Neurotoxin	C	Largely unknown
Aspirin	Cyclooxygenase inhibitor	C/D	Safe <150 mg/d
Candesartan	Angiotensin receptor blocker	D	Renal agenesis, oligohydramnios, craniofacial and limb deformities
Topiramate	Antiepileptic	D	Oral cleft, hypospadias, low birth weight
Valproic acid	Antiepileptic	X	Neural tube defects, clefts, lower IQ and developmental delay, autism, cardiovascular and genitourinary abnormalities

IQ = intelligence quotient; IV = intravenous.

[a] Although the FDA ratings have not been continued past 2015, for now they remain a useful hierarchical scheme in the organization of drug safety in pregnant women.

[b] Class B refers only to pindolol.

Occipital and trigeminal pericranial nerve blocks are a treatment used for migraine, cluster headache, and other headache disorders as an acute therapy as well as for short-term prevention and are appealing to use in pregnancy because of their peripheral administration and presumed safety. Most headache specialists are comfortable using peripheral nerve blocks during pregnancy.[27] It seems prudent to use lidocaine instead of bupivacaine because of its more favorable teratogenicity profile. One case series that examined 13 pregnant women who received a total of 27 peripheral nerve blocks for migraine or chronic migraine showed efficacy for both status migrainosus and short-term prophylaxis. The treatment seemed to be safe, although one patient developed a brief vasovagal attack, and two patients with no acute pain reduction ultimately developed preeclampsia and had postpartum resolution of their headache.[28] CASE 7-2 illustrates a patient in whom peripheral nerve blocks were utilized for status migrainosus in the second trimester.

CASE 7-2

A 33-year-old woman presented for preconception migraine management. She had a history of episodic migraine without aura that had been treated effectively with rizatriptan and naproxen. Preconception counseling included the natural history of migraine in pregnancy and the risks, benefits, and alternatives of antimigraine therapies in pregnancy.

She intentionally became pregnant for the first time, and once pregnant, acetaminophen and metoclopramide were prescribed for acute attack therapy. In the first trimester, her headache frequency was 1 to 2 days per week, but at 24 weeks gestational age she developed status migrainosus for 5 consecutive days and presented in follow-up.

Neurologic examination was normal, but because she had never experienced such a prolonged attack previously, a noncontrast brain MRI and magnetic resonance venogram (MRV) were performed and were normal. A 3-day course of prednisone helped only temporarily and her symptoms returned. Bilateral greater occipital, auriculotemporal, supraorbital, and supratrochlear nerve blocks with lidocaine were performed with definitive relief after 1 day. Migraine attacks diminished in frequency thereafter, and she had an uncomplicated spontaneous vaginal delivery at term.

COMMENT

This patient underwent preconception counseling, which is the most ideal way to frame risks and benefits and implement treatment plans including rescue therapies. As a prolonged attack duration is a specific red flag for pregnant women with a history of migraine, neuroimaging was obtained and fortunately was normal. Nerve blocks are an appealing therapy for status migrainosus or short-term migraine prevention in pregnancy because of their peripheral administration and favorable safety profile. The remainder of her migraine course in pregnancy with amelioration in the third trimester was typical of women who have migraine without aura.

PERIPARTUM AND POSTPARTUM HEADACHE

Women presenting with acute headache in the peripartum and postpartum period also require high diagnostic vigilance for secondary headache causes. Different clinical clues may also be associated with more specific secondary headache diagnoses during this period (TABLE 7-1). One large study of postpartum headache evaluated 985 women prospectively and documented a rate of headache at 39% including incapacitating headache at 4%.[29] Median onset was 2 days postpartum, with primary headache diagnosed in more than 75% of women. Post–dural puncture headache occurred in about 5% of women. Risk factors for postpartum headache included known dural puncture, previous headache history, multiparity, and increasing age. Another study retrospectively examined 95 women with more acute postpartum headache and revealed a mean onset of 3.4 days postpartum. The rate of secondary headache was 53%, most commonly featuring preeclampsia/eclampsia (24%) and post–dural puncture headache (16%), and potentially life-threatening causes of cerebrovascular etiology were also encountered.[30]

A recent study of 63 consecutive neurologic consultations for acute postpartum headache revealed an even higher rate of secondary headache (73.0%), of which post–dural puncture headache (45.7%), postpartum preeclampsia (26.1%), and cerebrovascular headache disorders (21.7%) were the most common diagnoses.[31]

However, headaches associated with spinal or epidural anesthesia could also be attributed to pneumocephalus as well as post–dural puncture headache. Post–dural puncture headache is more common and results from leakage of CSF, typically featuring an orthostatic headache pattern that, in comparison with a postpartum migraine attack, typically emerges within 24 hours of delivery and features a lack of side predominance of the head pain.[31] If performed, neuroimaging may reveal brain sag, pachymeningeal enhancement, subdural fluid collections, pituitary hyperemia, and dilation of venous sinuses. Treatment typically includes conservative measures such as IV fluids and nonspecific analgesics. IV caffeine sodium benzoate may also be used. If initial conservative therapies fail, a lumbar epidural autologous blood patch is typically effective.

Post–dural puncture headache is distinguished from pneumocephalus, which may also develop when the loss of resistance to air technique is used by anesthesiologists. This secondary headache results when air is introduced intrathecally and migrates cranially, leading to obstruction or compression of pain-sensitive intracranial structures, and may feature a thunderclap headache within seconds or minutes of the anesthetic procedure. Treatment also may be conservative but can require use of 100% oxygen inhalation to improve the rate of reabsorption of intrathecal air. CT reveals hypodensities in the ventricles, cisterns, and subarachnoid space (FIGURE 7-4). MRI may reveal hypointensities in the same regions on gradient echo sequences.[32]

HEADACHE AND LACTATION

Over half of all women who have migraine will have an attack postpartum, so the management of postpartum headache, particularly in breast-feeding women, is an important clinical problem. Treatment of headache during lactation requires special consideration of the effects of the medication on the patient and the effects the treatment may have on the breast-fed baby. Lactation may be protective by inducing amenorrhea and reducing the cycling estradiol levels that may trigger migraine attacks in susceptible women, but this is not universal. All

KEY POINTS

- The majority of evidence suggests triptans intrinsically may not adversely impact labor and delivery outcomes, but more studies among pregnant women stratified by migraine severity may provide further clarity.
- Occipital and trigeminal pericranial nerve blocks are a treatment used for migraine, cluster headache, and other headache disorders as an acute therapy as well as for short-term prevention and are appealing to use in pregnancy because of their peripheral administration and presumed safety.
- Headaches associated with spinal or epidural anesthesia could take two forms: post–dural puncture headache and pneumocephalus.
- Over half of all women who have migraine will have an attack postpartum, so the management of postpartum headache, particularly in breast-feeding women, is an important clinical problem.
- Of the triptans, eletriptan is likely the most compatible medication with breast-feeding based on its low milk to plasma ratio.
- The evaluation of a pregnant or postpartum woman with suspected preeclampsia is also confounded by migraine serving as a preeclampsia risk factor. The distinction is crucial as migraine and preeclampsia are managed differently, with antepartum severe preeclampsia managed by expedited delivery.

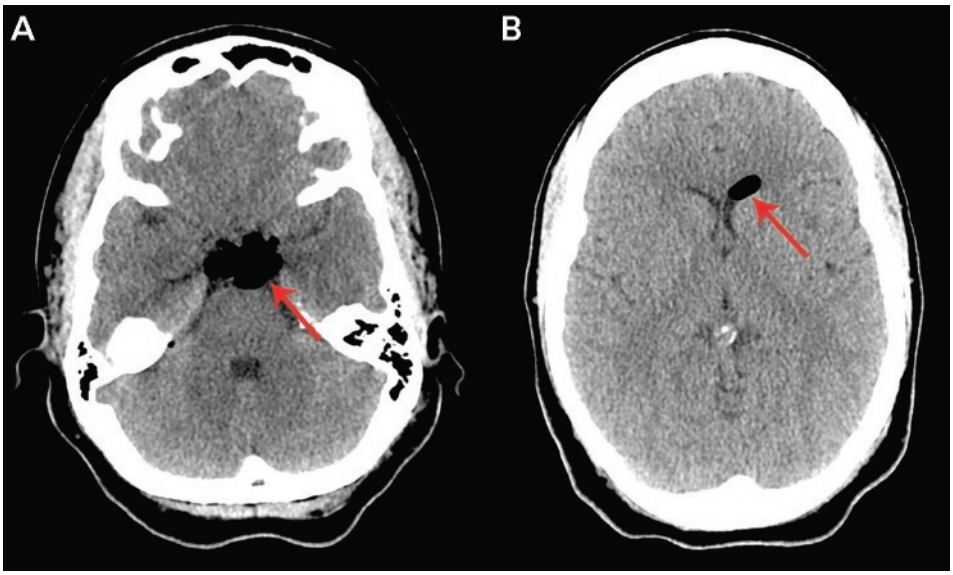

FIGURE 7-4
Head CT performed in a patient with thunderclap headache during anesthesia for labor. A 30-year-old woman who was in labor at term and otherwise healthy experienced a thunderclap headache coinciding with the lack of resistance to air during needle insertion in combined lumbar spinal-epidural anesthesia. Axial head CT revealed hypodensities (*arrows*) in the prepontine cistern (*A*) and left lateral ventricle (*B*) consistent with pneumocephalus.

medications can be graded by a milk to plasma ratio and, generally, a less than 10% value is a safe threshold for drugs that do not concentrate in breast milk. However, other factors include the lipophilicity, small size, low protein binding, and oral administration of drugs. Other issues related to lactation include the prematurity of a baby where a brain of a newborn may be more susceptible to any central nervous system–sedating properties of drugs used. In addition, the timing of medication may also be important, and patients can be advised to discard pumped milk after taking any medication that may have side effects to the breast-fed baby.[33]

TABLE 7-4 illustrates medications that have favorable safety profiles in breast-feeding women. For acute treatments, acetaminophen and ibuprofen generally are the safest nonspecific medications in lactation. Of the triptans, eletriptan is likely the most compatible medication with breast-feeding based on its low milk to plasma ratio. Antiemetics also are generally safe, particularly ondansetron and promethazine. If a patient requires a corticosteroid, prednisone may be the most compatible in comparison to other drugs of its class. No prophylactic therapy is perfectly safe for lactation, but many have more favorable lactation profiles, including the tricyclic antidepressants amitriptyline and nortriptyline; gabapentin; beta-blockers including propranolol and timolol; riboflavin; and magnesium. OnabotulinumtoxinA is probably compatible with breast-feeding given its peripheral administration and large molecular size.

IMPACT OF MIGRAINE ON PREGNANCY

The impact of migraine on pregnancy itself is another important consideration in women. A systematic review has revealed that many cardiovascular or cerebrovascular complications of pregnancy in women with migraine are apparent, including gestational hypertension, preeclampsia, ischemic stroke,

heart disease, and venous thromboembolism.[34] More specific labor and delivery complications have been examined in two population studies in Taiwan[35] and Hungary,[36] and both studies consistently showed an elevated risk of preeclampsia in pregnant women with migraine. It is not clear if pregnant women who have "active migraine" during pregnancy are at a particularly higher risk of adverse delivery outcomes. One single-center retrospective study in a sample enriched with pregnant women with chronic migraine and status migrainosus presentations during pregnancy found that rates of preeclampsia, preterm delivery, and low birth weight were markedly elevated compared to historical controls from the same population.[37]

Preeclampsia and migraine are interrelated clinical problems in pregnant women. Phenotypic overlap occurs in the symptomatology as both disorders may feature severe headache that can be throbbing, have otherwise typical migraine-associated features, and also feature varied visual phenomenology that can be specific to preeclampsia or migraine aura.[2] The evaluation of a pregnant or postpartum woman with suspected preeclampsia is also confounded by migraine serving as a preeclampsia risk factor. The distinction is crucial as migraine and preeclampsia are managed differently, with antepartum severe preeclampsia managed by expedited delivery. It is not known whether migraine influences how preeclampsia is clinically expressed or if its prognosis is different in those with migraine. In addition, little is known about postpartum preeclampsia and its relationship with migraine. Recent evidence from a multicenter randomized placebo-controlled trial suggests that the use of low-dose aspirin as a preventive therapy against preterm preeclampsia in pregnant women at higher risk is safe and effective, and it may also be effective as a migraine preventive agent, particularly in women who have migraine with aura.[38]

CONCLUSION

The occurrence of headache in pregnant and postpartum women is a frequent clinical consideration. Acute headache that occurs in pregnancy and the

Medications Used to Treat Headache and Their Relative Safety in Breast-feeding Women[a] TABLE 7-4

Therapy Category	Considered Safe	Use With Caution	Contraindicated
Acute	Acetaminophen, ibuprofen, caffeine, aspirin (≤162 mg/d), eletriptan, sumatriptan, ondansetron, prednisone, lidocaine, bupivacaine	Naproxen, indomethacin, ketorolac, other triptans, codeine and opioids, metoclopramide, prochlorperazine, butalbital, dexamethasone	Dihydroergotamine, aspirin (higher doses)
Preventive	Propranolol, timolol, amitriptyline, nortriptyline, verapamil, onabotulinumtoxinA, magnesium, riboflavin	Topiramate, valproic acid, metoprolol, candesartan	Atenolol, nadolol

[a] Lactation safety concerns also include timing of administration as well as neurologic health of the baby, including prematurity.

postpartum period is a red flag that requires high diagnostic vigilance. Although migraine prognosis is largely favorable in pregnancy, the prognosis of migraine with aura is not certain, and postpartum migraine attacks are common even in the presence of lactation. Acute and preventive treatment plans during pregnancy and lactation are plausible but often require shifts in therapeutic hierarchy. Many relatively safe rescue therapies exist for pregnant women with migraine including oral or IV corticosteroids, antiemetics, and peripheral nerve blocks. Noninvasive neuromodulation devices are already available and likely will play a greater role in migraine treatment in pregnant women in the coming years, assuming no unexpected safety data emerge. Migraine is associated with medical and obstetrical complications during pregnancy, particularly preeclampsia. Close coordination and communication between neurologists and obstetricians is crucial in the diagnosis and management of primary and secondary headache disorders in pregnant and postpartum women.

USEFUL WEBSITE

DRUGS AND LACTATION DATABASE (LACTMED)
The LactMed database from the National Institutes of Health US National Library of Medicine provides information related to medication effects on breast-feeding.
toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

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