Comparative Effectiveness Review
Number 234

Management of Primary Headaches in Pregnancy

Evidence Summary

Main Points

- **Prevention** of primary headache in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding with a history of primary headache
  - Pharmacologic and nonpharmacologic interventions
    - There is no evidence regarding the effectiveness of any pharmacologic or nonpharmacologic intervention in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding.
    - A single primary study provided insufficient (direct) evidence to make conclusions about the harms of topiramate when used for preventing primary headache during pregnancy, but use during pregnancy outside the primary headache context (indirect evidence) suggests increased risk of fetal/child adverse effects. Indirect evidence also suggests that other antiepileptics, such as carbamazepine, gabapentin, and valproate may have similar adverse effect profiles, but lamotrigine may have a low risk of adverse effects.
    - Venlafaxine, tricyclic antidepressants (any), benzodiazepines (any), beta blockers (any), prednisolone, and oral magnesium use during pregnancy may have increased risk of fetal/child adverse effects, but calcium channel blockers (any, but nifedipine in particular) and antihistamines (any) may have a low risk of adverse effects (indirect evidence).

(continued on page 2)

Agency for Healthcare Research and Quality

- **Treatment** of patients with acute attacks of primary headache in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding
  - Pharmacologic interventions
    - Use of triptans for migraine during pregnancy may not be more harmful than their use before pregnancy (both direct and systematic review evidence). Compared with nonuse (either during or before pregnancy), triptan use may not be associated with spontaneous abortions or congenital anomalies, but may be associated with worse child emotionality and activity outcomes at 3 years of age.
    - A single primary study found that compared with oral codeine, combination metoclopramide and diphenhydramine may be more effective to reduce migraine or tension headache severity during pregnancy, and may not be associated with greater serious or nonserious maternal harms; fetal/child harms were not reported. Indirect evidence found that antihistamines (any) during pregnancy (used for indications other than primary headache) may have a low risk of adverse effects.
    - Systematic reviews of harms (regardless of indication) report that acetaminophen, prednisolone, indomethacin, ondansetron, antipsychotics (any), and intravenous magnesium use during pregnancy may be associated with fetal/child adverse effects, but low-dose aspirin use may not be associated with increased risk of adverse effects.
  - Nonpharmacologic interventions
    - There is insufficient direct evidence to make conclusions about the benefits or harms of acupuncture, thermal biofeedback, relaxation therapy, physical therapy, peripheral nerve blocks, and transcranial magnetic stimulation when used for treatment of primary headache during pregnancy.
    - No indirect evidence regarding harms of nonpharmacologic interventions in pregnancy was identified.

Background and Purpose

Primary headaches (i.e., conditions in which the headache itself is the disorder) are common in pregnancy and comprise four types: migraine, tension headache, cluster headache, and other trigeminal autonomic cephalgias (TACs). Although tension headaches are more common, migraine is by far the most common primary headache to present to clinical practice. Primary headache and its treatments can have significant consequences for the mother and fetus or infant. Given the heightened sensitivity about the potential impact of drugs on the fetus or infant, there is a tension between treatment decisions that might be best for the mother and those best for the fetus/infant. The uncertainty about the comparative effectiveness and harms of various treatment options underscores the importance of identifying effective interventions to treat primary headaches during pregnancy.

This systematic review (SR) aims to inform healthcare providers, policymakers, and the American College of Obstetricians and Gynecologists (ACOG) as developers of clinical guidance about currently available evidence on interventions for preventing or treating acute attacks of primary headaches in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding. The SR addresses both pharmacologic and nonpharmacologic interventions for migraine, tension headache, cluster headache, and other TACs.

Methods

We used methods consistent with those outlined in the Agency for Healthcare Research and Quality's Evidence-based Practice Center Methods Guidance (https://effectivehealthcare.ahrq.gov/products/cer-methods-guide/overview). Our searches covered published and unpublished primary studies (direct evidence) and case reports (supplemental evidence) in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding from database inception to June 5, 2020. For additional information on harms, we also searched for relevant SRs of interventions in women in the same phase, regardless of the indication for which the intervention was used (indirect evidence), from database inception to June 5, 2020.

Results

We found 16 primary studies (14,185 patients), representing direct evidence (3 randomized controlled trials, 8 nonrandomized comparative studies [i.e., observational studies that compared 2 or more interventions], and 5 single-group studies [i.e., studies without a comparison group]), and 26 SRs of interventions for any indication during pregnancy, representing indirect evidence. We also identified 19 case reports, representing supplemental evidence. Most primary studies enrolled patients with migraine and some with migraine and/or tension headache.

Table A provides a high-level summary of findings, summarized below.

Prevention—antiepileptics: There was insufficient direct evidence to make conclusions about harms of topiramate when used for migraine (one single-group study). However, we identified indirect evidence (i.e., systematic reviews regardless of indication) that carbamazepine, gabapentin, topiramate, and valproate use during pregnancy had increased fetal/child adverse effects (all moderate strength of evidence [SoE], except for gabapentin, which had low SoE). Lamotrigine may have a lower risk of adverse effects: no increased risk of spontaneous abortion, stillbirth, preterm birth, or congenital anomalies (moderate SoE), although increased risk of autism/dyspraxia but not other neurodevelopmental adverse effects (moderate SoE).

Prevention—other pharmacologic interventions: We identified no direct evidence. We identified indirect evidence (i.e., systematic reviews regardless of indication) that the following, when used during pregnancy, were associated with fetal/child adverse effects: venlafaxine (a serotonin and norepinephrine reuptake inhibitor; moderate SoE), tricyclic antidepressants (moderate SoE), benzodiazepines (low SoE), beta blockers (moderate

SoE), prednisolone (low SoE), and oral magnesium (low SoE). But, calcium channel blockers (any, but nifedipine in particular) (low to moderate SoE for specific adverse effects) and antihistamines (moderate SoE) had low risks of maternal or fetal/child adverse effects.

Prevention—nonpharmacologic interventions: We found no direct or indirect evidence.

Treatment—triptans, ergot products, nonsteroidal anti-inflammatory drugs (NSAIDs: naproxen), and antihistamines (pizotifen): Eight observational NRCSs addressed adverse effects of triptans, ergot products, naproxen, and pizotifen, but none reported on treatment effectiveness. Among the studies that adjusted for underlying differences between study groups, child neurodevelopmental, behavioral, and social outcomes did not differ between use of any triptan during pregnancy and use only before pregnancy, except for worse emotionality and activity outcomes at 3 years of age with triptan use during pregnancy (low SoE). Triptan use during pregnancy was not associated with spontaneous abortion, elective or induced abortion, or major or minor congenital anomalies, compared with nonuse (low SoE). An existing SR found that triptan use was not associated with spontaneous abortion (moderate SoE), preterm birth (low SoE), or major congenital anomalies (moderate SoE). We also identified indirect evidence (not focused on primary headaches) regarding NSAIDs: indomethacin may be associated with neonatal periventricular leukomalacia, intraventricular hemorrhage, and necrotizing enterocolitis (low SoE), but low-dose aspirin was *not* associated with maternal (moderate SoE) or fetal/child adverse effects (low SoE).

Treatment—antiemetics (dopamine receptor antagonists), antihistamines, and opioids: One RCT found that, compared with codeine, combination metoclopramide and diphenhydramine reduced migraine or tension headache severity and was more likely to resolve headache (low SoE). No serious maternal adverse effects occurred (low SoE). We also identified indirect evidence (i.e., systematic reviews regardless of indication) that antihistamines were not associated with serious fetal/child adverse effects (moderate SoE).

Treatment—other pharmacologic interventions: We did not find any direct evidence. We identified indirect evidence (i.e., systematic reviews regardless of indication) that use of the following interventions during pregnancy may be associated with fetal/child adverse effects: acetaminophen (low SoE), prednisolone (low SoE), ondansetron (a 5HT3 antagonist antiemetic) (moderate SoE), antipsychotics (low to moderate SoE), and intravenous magnesium (low SoE).

Treatment—nonpharmacologic interventions: There was insufficient direct evidence to make conclusions about thermal biofeedback (one RCT and two single-group studies), acupuncture (one RCT), relaxation therapy (one RCT and two single-group studies), physical therapy (one RCT and one single-group study), peripheral nerve blocks (one single-group study), and transcranial magnetic stimulation (one single-group study). We found no indirect evidence.

Limitations

Evidence for intervention benefits and harms was often sparse or absent. Entire classes, such as tricyclic antidepressants, beta blockers, and calcium channel blockers, were not identified in any primary study of pregnant patients with primary headache. Similarly, no primary study addressed entire classes of nonpharmacologic agents, such as hydration and chemodenervation (see full report for full lists). Most studies focused on patients with migraine. We deemed individual studies to have high or moderate risk of bias, most commonly due to lack of adjustment for confounders; lack of blinding of participants, personnel, and outcome assessors; and/or incomplete outcome data.

Implications and Conclusions

Evidence regarding the benefits and harms of interventions in women who are pregnant or breastfeeding is insufficient or of at best low strength of evidence. The paucity of evidence emphasizes the need for further primary research to identify effective and safe pharmacologic and nonpharmacologic interventions for primary headaches during pregnancy. Future studies should either randomize patients or adequately account for important confounders and evaluate important maternal outcomes, such as headache-related symptoms, quality of life, functional outcomes, and important fetal/child adverse outcomes; we found negligible data for these outcomes.

Table A. High-level summary of benefits and harms of interventions

KQ	Intervention Type	Intervention Class	Intervention	Comparator	Condition	Maternal Benefits	Maternal AEs	Fetal/ Child AEs
1	Pharm	Antiepileptics	Topiramate	None	Migraine	-	-	?? (I)
				Nonuse	Various	-	-	↑ (++)
			Carbamazepine	Nonuse	Various	-	-	↑ (++)
			Gabapentin	Nonuse	Various	-	-	↑ (+)
			Lamotrigine	Nonuse	Various	-	-	↑ (++)
			Valproate	Nonuse	Various	-	-	↑ (++)
			Gabapentin	Nonuse	Various	-	-	↑ (+)
		SNRIs	Venlafaxine	Nonuse	Various	-	-	↑ (++)
		Tricyclic antidepressants	Any	Nonuse	Various	-	-	↑ (++)
		Benzodiazepines	Any	Nonuse	Various	-	-	↑ (+)
		Beta blockers	Any	Nonuse	Various	-	~ (+)	↑ (++)
		Calcium channel blockers	Any	Nonuse	Various	-	~ (+)	~ (++)
			Nifedipine	Nonuse	Various	-	-	~ (++)
		Corticosteroids	Prednisolone	Nonuse	Various	-	-	↑ (+)
		Antihistamines	Any	Nonuse	Various	-	-	~ (++)
		Oral magnesium	Oral magnesium	Nonuse	Various	-	~ (+)	↑ (+)
	Nonpharm	-	-	-	-	-	-	-
2	Pharm	Triptans, Ergot products, and NSAIDs	Sumatriptan	Naratriptan	Migraine	-	-	?? (I)
			Sumatriptan	Sumatriptan + naratriptan	Migraine	-	-	?? (I)

KQ	Intervention Type	Intervention Class	Intervention	Comparator	Condition	Maternal Benefits	Maternal AEs	Fetal/ Child AEs
			Naratriptan	Sumatriptan + naratriptan	Migraine	-	-	?? (I)
			Any triptan	Any ergot product	Migraine	-	-	?? (I)
			Any triptan	Pizotifen	Migraine	-	-	?? (I)
			Any ergot product	Pizotifen	Migraine	-	-	?? (I)
			Any triptan during pregnancy	Any triptan before pregnancy only	Migraine	-	?? (I)	↑ (+)
			Sumatriptan during pregnancy	Sumatriptan before pregnancy only	Migraine	-	?? (I)	?? (I)
			Any triptan during pregnancy	No triptan	Migraine	-	?? (I)	↑ (+)
		Antiemetics (Dopamine antagonists), Antihistamines, Opioid-like analgesics	Metoclopramide + Diphenhydramine	Codeine	Migraine or tension HA	Maternal benefit (+)	~ (+)	-
		NSAIDs	Any	Nonuse	Various	-	~ (++)	-
			Indomethacin	Nonuse	Various	-	-	↑ (+)
			Low-dose aspirin	Nonuse	Various	-	~ (++)	~ (+)
		Antiemetics (5HT3 antagonists	Ondansetron	Nonuse	Various	-	-	↑ (++)
		Antipsychotics	Any	Nonuse	Various	-	-	↑ (++)
		Corticosteroids	Prednisolone	Nonuse	Various	-	-	↑ (++)
		Analgesics/ Antipyretics	Acetaminophen	Nonuse	Various	-	-	↑ (+)
		IV magnesium	IV magnesium	Nonuse	Various	-	↑ (+)	-
		Antihistamines	Any	Nonuse	Various	-	-	~ (++)
	Nonpharm	Complementary, behavioral, and physical therapy	Acupuncture	Routine care	Migraine	?? (I)	-	?? (I)
			Thermal biofeedback, relaxation, physical therapy	Thermal biofeedback	Migraine or tension HA	?? (I)	-	-
			Thermal biofeedback and relaxation therapy	None	Migraine	?? (I)	-	-
		Procedures	Peripheral nerve blocks	None	Migraine	?? (I)	?? (I)	-
		Noninvasive neuromodulation devices	Transcranial magnetic stimulation	None	Migraine	?? (I)	-	-

For interventions with evidence of an increased risk of any fetal/child AE and evidence of no increased risk or unknown risk of other fetal/child AEs, this table includes only the indicator for increased risk. Table 38 in the full report includes further details.

Abbreviations: AE = adverse effect, HA = headache, IV = intravenous, KQ = Key Question, Nonpharm = nonpharmacologic, NSAID = nonsteroidal anti-inflammatory drug, Pharm = pharmacologic, SNRI = serotonin and norepinephrine reuptake inhibitor.

↑ = Increase in adverse effects, ~ = No increase in adverse effects, ?? = Direction unknown, - = No evidence, I = Insufficient strength of evidence, + = Low strength of evidence, ++ = Moderate strength of evidence, +++ = High strength of evidence (none in Table).

Full Report

Saldanha IJ, Roth JL, Chen KK, Zullo AR, Adam GP, Konnyu KJ, Cao W, Bhuma MR, Kimmel HJ, Mehta S, Riester MR, Sorial MN, Balk EM. Management of Primary Headaches in Pregnancy. Comparative Effectiveness Review No. 234. (Prepared by the Brown Evidence-based Practice Center under Contract No. 290-2015-00002-I.) AHRQ Publication No. 20(21)-EHC026. Rockville, MD: Agency for Healthcare Research and Quality; November 2020.
DOI: https://doi.org/10.23970/AHRQEPCCER234. Posted final reports are located on the Effective Health Care Program search page.