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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Agency for Healthcare Research and Quality

Supplemental Evidence and Data Request on Management of Primary Headache  
during Pregnancy

AGENCY: Agency for Healthcare Research and Quality (AHRQ), HHS.

ACTION: Request for Supplemental Evidence and Data Submissions.

SUMMARY: The Agency for Healthcare Research and Quality (AHRQ) is seeking scientific information submissions from the public. Scientific information is being solicited to inform our review on *Management of Primary Headache during Pregnancy*, which is currently being conducted by the AHRQ's Evidence-based Practice Centers (EPC) Program. Access to published and unpublished pertinent scientific information will improve the quality of this review.

DATES: *Submission Deadline* on or before 30 days after date of publication.

ADDRESSES:

*E-mail submissions:* [epc@ahrq.hhs.gov](mailto:epc@ahrq.hhs.gov)

*Print submissions:*

Mailing Address:

Center for Evidence and Practice Improvement

Agency for Healthcare Research and Quality

ATTN: EPC SEADs Coordinator

5600 Fishers Lane

Mail Stop 06E53A

Rockville, MD 20857

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FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION:

The Agency for Healthcare Research and Quality has commissioned the Evidence-based Practice Centers (EPC) Program to complete a review of the evidence Management of Primary Headache during Pregnancy. AHRQ is conducting this systematic review pursuant to Section 902(a) of the Public Health Service Act, 42 U.S.C. 299a(a).

The EPC Program is dedicated to identifying as many studies as possible that are relevant to the questions for each of its reviews. In order to do so, we are supplementing the usual manual and electronic database searches of the literature by requesting information from the public (e.g., details of studies conducted). We are looking for studies that report on *Management of Primary Headache during Pregnancy*, including those that describe adverse events. The entire research protocol is available online at: <https://effectivehealthcare.ahrq.gov/products/headaches-pregnancy/protocol>

This is to notify the public that the EPC Program would find the following information on Management of Primary Headache during Pregnancy helpful:

- A list of completed studies that your organization has sponsored for this indication. In the list, please *indicate whether results are available on ClinicalTrials.gov along with the ClinicalTrials.gov trial number.*

- *For completed studies that do not have results on ClinicalTrials.gov, a summary, including the following elements: study number, study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, primary and secondary outcomes, baseline characteristics, number of patients screened /eligible /enrolled /lost to follow-up /withdrawn /analyzed, effectiveness/efficacy, and safety results.*
- *A list of ongoing studies that your organization has sponsored for this indication. In the list, please provide the ClinicalTrials.gov trial number or, if the trial is not registered, the protocol for the study including a study number, the study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, and primary and secondary outcomes.*
- *Description of whether the above studies constitute ALL Phase II and above clinical trials sponsored by your organization for this indication and an index outlining the relevant information in each submitted file.*

Your contribution is very beneficial to the Program. Materials submitted must be publicly available or able to be made public. Materials that are considered confidential; marketing materials; study types not included in the review; or information on indications not included in the review cannot be used by the EPC Program. This is a voluntary request for information, and all costs for complying with this request must be borne by the submitter.

The draft of this review will be posted on AHRQ's EPC Program website and available for public comment for a period of 4 weeks. If you would like to be notified when the draft is posted, please sign up for the e-mail list at:  
<https://www.effectivehealthcare.ahrq.gov/email-updates>.

*The systematic review will answer the following questions. This information is provided as background. AHRQ is not requesting that the public provide answers to these questions.*

## **Key Questions (KQ)**

**KQ 1:** What are the (comparative) benefits and harms of interventions *to prevent* attacks of primary headache in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding?

**KQ 1a.** Do the (comparative) benefits and harms vary by phase (i.e., preconception, first trimester of pregnancy, second trimester of pregnancy, third trimester of pregnancy, postpartum, breastfeeding)?

**KQ 1b.** Do the (comparative) benefits and harms vary by type of primary headache (i.e., migraine, tension headache, cluster headache, and other trigeminal autonomic cephalgias)?

**KQ 2:** What are the (comparative) benefits and harms of interventions *to treat* acute attacks of primary headache in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding?

**KQ 2a.** Do the (comparative) benefits and harms vary by phase (i.e., preconception, first trimester of pregnancy, second trimester of pregnancy, third trimester of pregnancy, postpartum, breastfeeding)?

**KQ 2b.** Do the (comparative) benefits and harms vary by type of primary headache (i.e., migraine, tension headache, cluster headache, and other trigeminal autonomic cephalgias)?

## **Contextual Question:**

What is the available evidence concerning levels in maternal serum/blood, fetal/infant serum/blood, breast milk, amniotic fluid, meconium, cord blood, or child urine of drugs used to prevent or treat attacks of primary headache in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding?

## **Study Eligibility Criteria**

We had discussions with a Technical Expert Panel (TEP) during which we reviewed the specific eligibility criteria. As part of the discussions, we asked the TEP to provide guidance on prioritizing outcomes and selecting among harms/adverse events of interest.

### **KQ 1 (Prevention of Primary Headache)**

#### **Population(s):**

- Women who are pregnant (or attempting to become pregnant/in the preconception phase), postpartum (defined as up to 12 months post-delivery), or breastfeeding (for any length of time) with history of primary headache
  - Migraine, tension headache, cluster headache or other trigeminal autonomic cephalgia (TACs)
  - Women attempting to become pregnant include those actively planning pregnancy, by any method, who may wish to use only treatments found to be safe and effective during pregnancy.
- Exclude: Women with history of secondary headache of any origin

#### **Interventions:**

- Pharmacologic interventions
  - Tricyclic antidepressants (e.g., amitriptyline, nortriptyline, imipramine)
  - Beta blockers (e.g., metoprolol, propranolol, nadolol, atenolol, timolol, nebivolol)

- Calcium channel blockers (e.g., verapamil, nimodipine, nifedipine, nicardipine)
  - Other antihypertensive medications (e.g., lisinopril, candesartan, clonidine)
  - Antiepileptic drugs (e.g., divalproex sodium, sodium valproate, valproic acid, topiramate, gabapentin, carbamazepine, lamotrigine)
  - Serotonin and norepinephrine reuptake inhibitors (SSNRIs) (e.g., venlafaxine, duloxetine)
  - Benzodiazepines (e.g., clonazepam)
  - N-methyl-D-aspartate (NMDA) receptor antagonists (e.g., memantine)
  - Calcitonin gene-related peptide (CGRP) inhibitors (e.g., erenumab, fremanezumab, galcanezumab)
  - Antihistamines (e.g., cyproheptadine)
  - Antimanic agents (e.g., lithium)
  - Tetracyclic antidepressants (e.g., mirtazapine)
  - Corticosteroids (e.g., methylprednisolone, triamcinolone acetonide, combinations of local anesthetics and corticosteroids)
  - Other pharmacologic interventions used to prevent primary headache (whether or not available or approved in the United States)
- Non-pharmacologic interventions

- Supplements (e.g., riboflavin, magnesium, coenzyme Q10, melatonin, feverfew, butterbur, frankincense)
- Nerve blocks (e.g., occipital nerve blocks, sphenopalantine ganglion blocks, trigger point injections)
- Chemodeneration (e.g., onabotulinum toxin A, abobotulinum toxin A)
- Physical therapy
- Hydration
- Noninvasive neuromodulation devices (e.g., transcutaneous electrical nerve stimulation, transcranial magnetic stimulation, transcutaneous vagal stimulation, remote electrical neurostimulation)
- Behavioral therapy (e.g., cognitive behavioral therapy, diet therapy, sleep therapy, exercise therapy, support group therapy)
- Complementary therapies (e.g., biofeedback, acupuncture, mindfulness-based stress reduction)
- Other non-pharmacologic interventions used to prevent primary headache

**Comparators:**

- Pharmacologic interventions
  - Other class
  - Other drug within class

- Same drug(s), different route, treatment duration, initiation time, or other aspect
- As comparator to nonpharmacologic intervention
- Nonpharmacologic interventions
  - Other nonpharmacologic intervention class
  - Other nonpharmacologic intervention, within class
  - As comparator to pharmacologic intervention
- No pharmacologic or nonpharmacologic interventions
  - Placebo
  - No intervention

**Outcomes:** (\* denotes important outcomes that will be used when developing Strength of Evidence tables)

- Acute headache attacks\*
  - Occurrence of acute headache attacks
  - Frequency of acute headache attacks
  - Severity of acute headache attacks
  - Duration of acute headache attacks
- Headache-related symptoms (e.g., nausea/vomiting, photosensitivity, dizziness)\*
  - Occurrence of headache-related symptoms
  - Frequency of headache-related symptoms

- Severity of headache-related symptoms
- Duration of headache-related symptoms
- Most bothersome symptom
- Emergency department visits, clinic visits, or hospitalizations\*
- Quality of life\*
- Functional outcomes
  - Impact on family life
  - Employment/school attendance
  - Time spent managing disease
- Resource use
- Acceptability of intervention by patients
- Patient satisfaction with intervention
- Number of prescribed medications
- Number of days with acute medication use
- Adverse events
  - Maternal
    - Serious maternal adverse events\*
      - “Serious” adverse events (including those that are composite outcomes), as defined by study authors
      - Cardiovascular outcomes, such as stroke, myocardial infarction

- Non-serious maternal adverse events
  - Nonobstetrical (e.g., maternal weight gain, tachycardia, hypertension, gastrointestinal)
  - Preterm labor, cesarean section
  - Reduced breast milk production
  - Symptoms related to withdrawal of medication
- Discontinuation of intervention (or of study participation) due to maternal adverse events\*
- Fetal/infant
  - Serious fetal/infant adverse events\*
    - “Serious” adverse events (including those that are composite outcomes), as defined by study authors
    - Death – spontaneous abortion, stillbirth, infant death
    - Preterm birth
    - Low birth weight for gestational age
    - Congenital anomalies or other newborn abnormalities
    - Perinatal complications, e.g., low APGAR score, respiratory distress, neonatal intensive care unit time
    - Neurodevelopmental – social, emotional, or cognitive delay or disability
  - Non-serious fetal/infant adverse events

- Breastfeeding – delayed initiation, cessation, reduced frequency, reduced volume of breast milk
- Poor infant attachment/bonding
- Symptoms related to withdrawal of medication
- Discontinuation of intervention (or of study participation) due to fetal/infant adverse events\*

**Potential Modifiers:**

- Phase
  - Preconception
  - First trimester
  - Second trimester
  - Third trimester
  - Postpartum
  - Breastfeeding
- Type of primary headache
  - Migraine
  - Tension headache
  - Cluster headache
  - Other TACs

**Timing:**

- Any

**Setting:**

- Any

**Design:**

- Randomized controlled trials
- Nonrandomized comparative studies, including pre-post studies
- Single group studies
- N-of-1 studies
- Case-control studies
- Case reports or series of case reports
- Cross-sectional studies/surveys
  - Prospective or retrospective (all applicable study types)
- For harms, we will start by searching for existing systematic reviews of interventions used during pregnancy, postpartum, or breastfeeding, regardless of their indication (i.e., for any disease/condition, not only primary headaches). We will not enforce a date restriction when screening for eligible systematic reviews, but when multiple eligible systematic reviews exist for a certain drug/class of drugs, we will use the most recent or most complete one.
  - We will subsequently search for, and include, large primary studies of interventions not adequately covered by the existing systematic reviews

of harms. The specific eligibility criteria (particularly pertaining to study design, minimum sample size, and publication date) will be determined based on available EPC resources, the number of interventions without adequate existing systematic reviews, and the volume of potentially eligible studies.

- For harms, we will also search the U.S. Food and Drug Administration, other international equivalent agencies, and pharmacopoeia.

## **KQ 2 (Treatment of Primary Headache)**

### **Population(s):**

- Women who are pregnant (or attempting to become pregnant/in the preconception phase), postpartum (defined as up to 12 months post-delivery), or breastfeeding (for any length of time) with acute attacks of primary headache
  - Migraine, tension headache, cluster headache, or other trigeminal autonomic cephalgia (TACs)
  - Women attempting to become pregnant include those actively planning pregnancy, by any method, who may wish to use only treatments found to be safe and effective during pregnancy.
- Exclude: Women with attacks of secondary headache of any origin

### **Interventions:**

- Pharmacologic interventions
  - Analgesics/antipyretics (e.g., acetaminophen)

- Nonsteroidal antiinflammatory drugs (NSAIDs) (e.g., ibuprofen, naproxen, aspirin, celecoxib, ketorolac, indomethacin, ketoprofen, diclofenac, mefenamic acid)
- Other over-the-counter analgesics (e.g., combination aspirin, acetaminophen, and caffeine; combination acetaminophen, isometheptene, and dichloralphenazone)
- Antiemetics: dopamine receptor antagonists (e.g., metoclopramide, promethazine, prochlorperazine, droperidol, chlorpromazine)
- Antiemetics: 5HT<sub>3</sub> antagonists (e.g., ondansetron)
- Antihistamines (e.g., meclizine, diphenhydramine, dimenhydrinate, promethazine)
- Central nervous system stimulants (e.g., caffeine)
- Muscle relaxants (e.g., baclofen, tizanidine, metaxalone, carisoprodol)
- Corticosteroids (e.g., prednisolone, prednisolone, methylprednisolone, dexamethasone, betamethasone)
- Triptans/Serotonin receptor agonists (e.g., sumatriptan, frovatriptan, naratriptan, rizatriptan, almotriptan, eletriptan, zolmitriptan, combination sumatriptan and naproxen)
- Opioid containing analgesics (e.g., codeine, hydrocodone, oxycodone, morphine, meperidine, tramadol, butorphanol, nalbuphine)
- Butalbital-containing analgesics (e.g., butalbital; combination butalbital and acetaminophen; combination butalbital, aspirin, and caffeine)

- Ergot products (e.g., dihydroergotamine, ergotamine, combination ergotamine and caffeine)
- Sympathomimetic amines (e.g., isometheptene)
- Topical anesthetics (e.g., lidocaine)
- Antipsychotics (e.g., chlorpromazine, olanzapine)
- Somatostatin analogs (e.g., octreotide)
- Intravenous magnesium
- Other pharmacologic interventions used to treat acute attacks of primary headache (whether or not available or approved in the United States)
- Non-pharmacologic interventions
  - Hydration
  - Physical therapy
  - Procedures (e.g., occipital nerve blocks, sphenopalantine ganglion blocks, trigger point injections)
  - Noninvasive neuromodulation devices (e.g., transcutaneous electrical nerve stimulation, transcranial magnetic stimulation, transcutaneous vagal stimulation, remote electrical neurostimulation)
  - Behavioral therapy (e.g., cognitive behavioral therapy, diet therapy, sleep therapy, exercise therapy, support group therapy)
  - Supplements (e.g., magnesium, cannabidiol)

- Complementary therapies (e.g., biofeedback, acupuncture, mindfulness-based stress reduction)
- Other non-pharmacologic interventions used to treat acute attacks of primary headache

**Comparators:**

- Pharmacologic interventions
  - Other class
  - Other drug within class
  - Same drug(s), different route, treatment duration, initiation time, or other aspect
  - As comparator to nonpharmacologic intervention
- Nonpharmacologic interventions
  - Other nonpharmacologic intervention class
  - Other nonpharmacologic intervention, within class
  - As comparator to pharmacologic intervention
- No pharmacologic or nonpharmacologic interventions
  - Placebo
  - No intervention

**Outcomes** (\* denotes important outcomes that will be used when developing Strength of Evidence tables)

- Acute headache attack\*
  - Severity of acute headache attack
  - Resolution of acute headache attack
  - Duration of acute headache attack
- Headache-related symptoms (e.g., nausea/vomiting, photosensitivity)\*
  - Severity of headache-related symptoms
  - Resolution of headache-related symptoms
  - Duration of headache-related symptoms
  - Most bothersome symptom
- Emergency department visits, clinic visits, or hospitalizations\*
- Quality of life\*
- Functional outcomes
  - Impact on family life
  - Employment/school attendance
  - Time spent managing disease
- Resource use
- Acceptability of intervention by patients
- Patient satisfaction with intervention

- Number of prescribed medications
- Adverse events
  - Maternal
    - Serious maternal adverse events\*
      - “Serious” adverse events (including those that are composite outcomes), as defined by study authors
      - Cardiovascular outcomes, such as stroke, myocardial infarction
    - Non-serious maternal adverse events
      - Nonobstetrical (e.g., maternal weight gain, tachycardia, hypertension, gastrointestinal)
      - Preterm labor, cesarean section
      - Reduced breast milk production
      - Symptoms related to withdrawal of medication
    - Discontinuation of intervention (or of study participation) due to maternal adverse events\*
  - Fetal/infant
    - Serious fetal/infant adverse events\*
      - “Serious” adverse events (including those that are composite outcomes), as defined by study authors
      - Death – spontaneous abortion, stillbirth, infant death
      - Preterm birth

- Low birth weight for gestational age
- Congenital anomalies or other newborn abnormalities
- Perinatal complications, e.g., low APGAR score, respiratory distress, neonatal intensive care unit time
- Neurodevelopmental – social, emotional, or cognitive delay or disability
- Non-serious fetal/infant adverse events
  - Breastfeeding – delayed initiation, cessation, reduced frequency, reduced volume of breast milk
  - Poor infant attachment/bonding
  - Symptoms related to withdrawal of medication
- Discontinuation of intervention (or of study participation) due to fetal/infant adverse events\*

**Potential Modifiers:**

- Phase
  - Preconception
  - First trimester
  - Second trimester
  - Third trimester
  - Postpartum
  - Breastfeeding

- Type of primary headache
  - Migraine
  - Tension headache
  - Cluster headache
  - Other TACs

**Timing:**

- Any

**Setting:**

- Any

**Design:**

- Randomized controlled trials
- Nonrandomized comparative studies, including pre-post studies
- Single group studies
- N-of-1 studies
- Case-control studies
- Case reports or series of case reports
- Cross-sectional studies/surveys
  - Prospective or retrospective (all applicable study types)

- For harms, we will start by searching for existing systematic reviews of interventions used during pregnancy, postpartum, or breastfeeding, regardless of their indication (i.e., for any disease/condition, not only primary headaches). We will not enforce a date restriction when screening for eligible systematic reviews, but when multiple eligible systematic reviews exist for a certain drug/class of drugs, we will use the most recent or most complete one.
  - We will subsequently search for, and include, large primary studies of interventions not adequately covered by the existing systematic reviews of harms. The specific eligibility criteria (particularly pertaining to study design, minimum sample size, and publication date) will be determined based on available EPC resources, the number of interventions without adequate existing systematic reviews, and the volume of potentially eligible studies.
  - For harms, we will also search the U.S. Food and Drug Administration, other international equivalent agencies, and pharmacopoeia.

Dated: 19 November 2019.

Virginia Mackay-Smith,  
Associate Director.

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