



Evidence-based Practice Center Systematic Review Protocol

Project Title: *Management of Primary Headache During Pregnancy*

I. Background and Objectives for the Systematic Review

Headache, one of the most common symptoms in the general population, is also common during pregnancy. Primary headache refers to conditions where the headache itself is the disorder. In contrast, secondary headaches are caused by an underlying disorder, such as stroke, venous thromboembolism,^{1, 2} or pituitary tumors.^{3, 4} Therapy for secondary headache in pregnancy generally targets the underlying disorder, and is thus not the focus of this review.

Primary headaches that occur in pregnant women are classified into four types: migraine, tension headache, cluster headache, and other trigeminal autonomic cephalgias (TACs).⁵ Migraine is by far the most frequent type, accounting for about 90 percent of primary headaches in pregnant women.² The lifetime prevalence of migraine disorder among pregnant women is approximately 30 percent.^{6, 7} Other types of primary headache during pregnancy (i.e., tension headache, cluster headache, and other TACs) are rarer.⁸ Primary headaches can be pre-existing (i.e., they began before pregnancy) or can occur for the first time during pregnancy, postpartum, or breastfeeding. The stress of pregnancy and imminent infant care may exacerbate the frequency and/or severity of primary headaches. Migraine remains the most common type of both pre-existing and pregnancy-onset primary headache.

Both pre-existing and pregnancy-onset primary headaches can have significant consequences for the mother, the fetus/child, and mother-child bonding.⁸ Outside of pregnancy, migraine frequency and severity can vary with a woman's menstrual cycle. During pregnancy, hormonal fluctuations can precipitate attacks of migraine and can make them more severe.^{9, 10}

From a management standpoint, pregnancy constrains the options available and poses major decisional dilemmas. Treatments for primary headaches may harm the fetus and breastfed newborn. Radiation and/or contrast agents may harm the fetuses of pregnant women who undergo diagnostic testing (primarily neuroimaging).¹¹⁻¹³ Regarding treatment for acute attacks of migraine, many of the commonly prescribed drugs with the highest level of evidence in the general population can be harmful during pregnancy. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to be associated with a higher risk of spontaneous abortion and of developmental malformations in the fetus.¹⁴ Similarly, sodium valproate, a commonly used drug for prophylaxis against migraine attacks, is contraindicated in pregnancy due to its teratogenicity and to adverse neurocognitive outcomes in the offspring.^{15, 16}

Other therapies used outside of pregnancy, such as complementary and alternative therapies and biologic drugs (e.g., monoclonal antibodies), have unclear and/or mixed safety profiles during pregnancy and lactation. Therapies that are commonly used in patients with migraine during pregnancy include pharmacologic therapies, such as acetaminophen, antihistamines, caffeine, and magnesium. The first-line agents used for prophylaxis (i.e., migraine prevention) are typically magnesium oxide and low-dose tricyclic antidepressants, such as amitriptyline.¹⁷ Non-

pharmacologic interventions for treatment and prophylaxis include hydration and physical therapy. Pericranial nerve blocks, including occipital nerve block, are increasingly used for treatment and prophylaxis against headaches in pregnancy.¹⁸

Treatment of the other types of primary headache also presents decisional dilemmas. While patients with tension headache respond best to NSAIDs, they can be treated with acetaminophen, although often with only moderate success. Because cluster headache and other TACs are rare and inadequately studied during pregnancy, little is known about ideal treatments and prognostic strategies for them. While some subtypes of TACs, such as paroxysmal hemicrania, hemicrania continua, and primary stabbing headache, respond to indomethacin (an NSAID), it is contraindicated in the latter phases of pregnancy. Little is known about nonpharmacologic treatments for non-migraine types of primary headache during pregnancy.

Unique aspects of the pregnancy and postpartum phases present distinct challenges for managing primary headaches. Given the heightened sensitivity about the potential impact of pharmacotherapy on the developing fetus, there is a tension between treatment decisions that might be best for the mother's health and those that might be best for the fetus/infant. Women with migraine during pregnancy have been shown to have higher rates of adverse maternal-fetal outcomes, such as maternal hypertension, preterm birth and cesarean section, and neonatal low birth weight, respiratory distress, and other adverse outcomes.¹⁹ Sound risk-benefit assessments that optimize the health of both mother and fetus/infant require clinical expertise and careful shared decisionmaking between providers and patients.

The stresses on women during pregnancy and the ethical challenges in designing studies in this vulnerable population have been obstacles to conducting studies in these women to identify the best therapies. The uncertainty about the comparative effectiveness and harms among various treatment options has meant that specific clinical practice guidelines for management of primary headaches during pregnancy do not exist. Existing guidelines on perinatal care from organizations, such as the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG), do not discuss primary headaches.²⁰ Existing guidelines on the management of headache from the American Headache Society (AHS) do not discuss pregnancy.²¹⁻²³ To address the gap related to the overlap of primary headaches and pregnancy, ACOG nominated this evidence synthesis.

Purpose of Review

This systematic review will assess the prevention and treatment of primary headache during pregnancy, postpartum, and breastfeeding. Specifically, the review will address: (1) the (comparative) benefits and harms of pharmacologic and nonpharmacologic interventions *to prevent* attacks of primary headache in women who have a history of primary headache and are pregnant (or attempting to become pregnant, i.e., in the preconception phase), postpartum, or breastfeeding, and (2) the (comparative) benefits and harms of pharmacologic and nonpharmacologic interventions *to treat* acute attacks of primary headache in women who are pregnant (or attempting to become pregnant), postpartum, or breastfeeding.

The intended audience for this systematic review includes guideline developers, clinicians and other providers of care for pregnant, postpartum, and breastfeeding women with primary headache. It is expected that the findings will inform a future ACOG guideline for management of primary headaches during pregnancy.

II. Key Questions

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)
 - Chemodenervation (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: 5HT₃ 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:

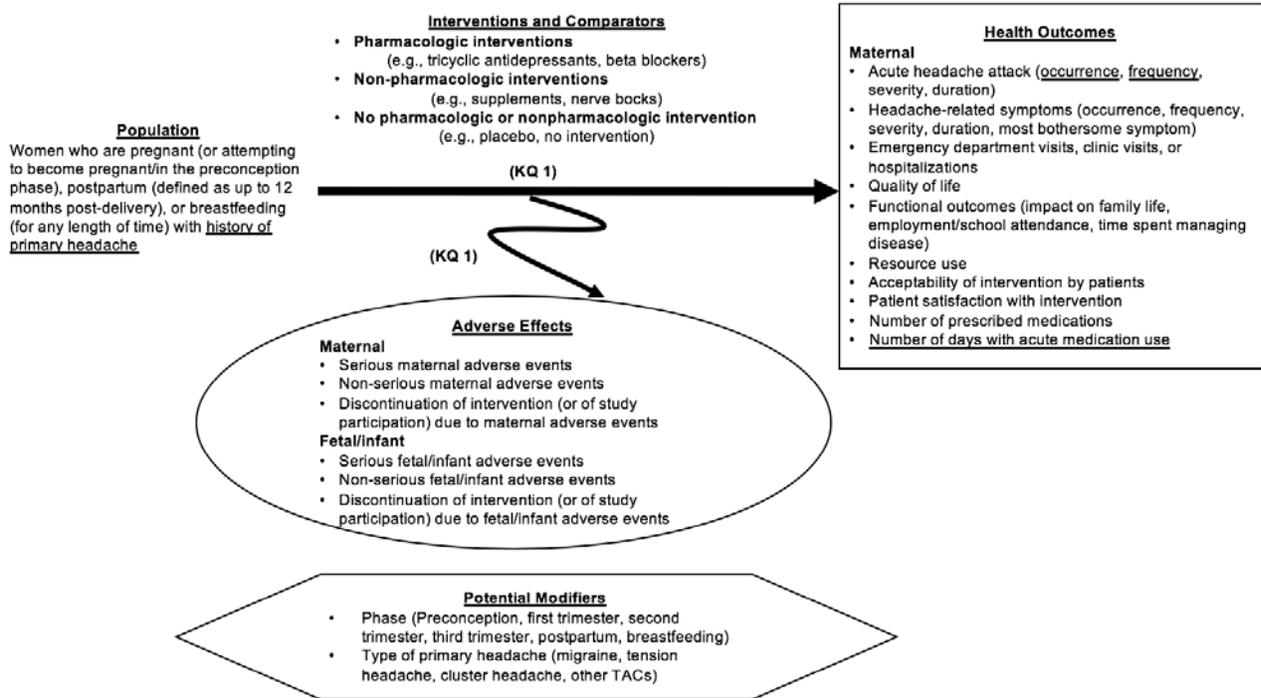
- Any

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.

III. Analytic Frameworks

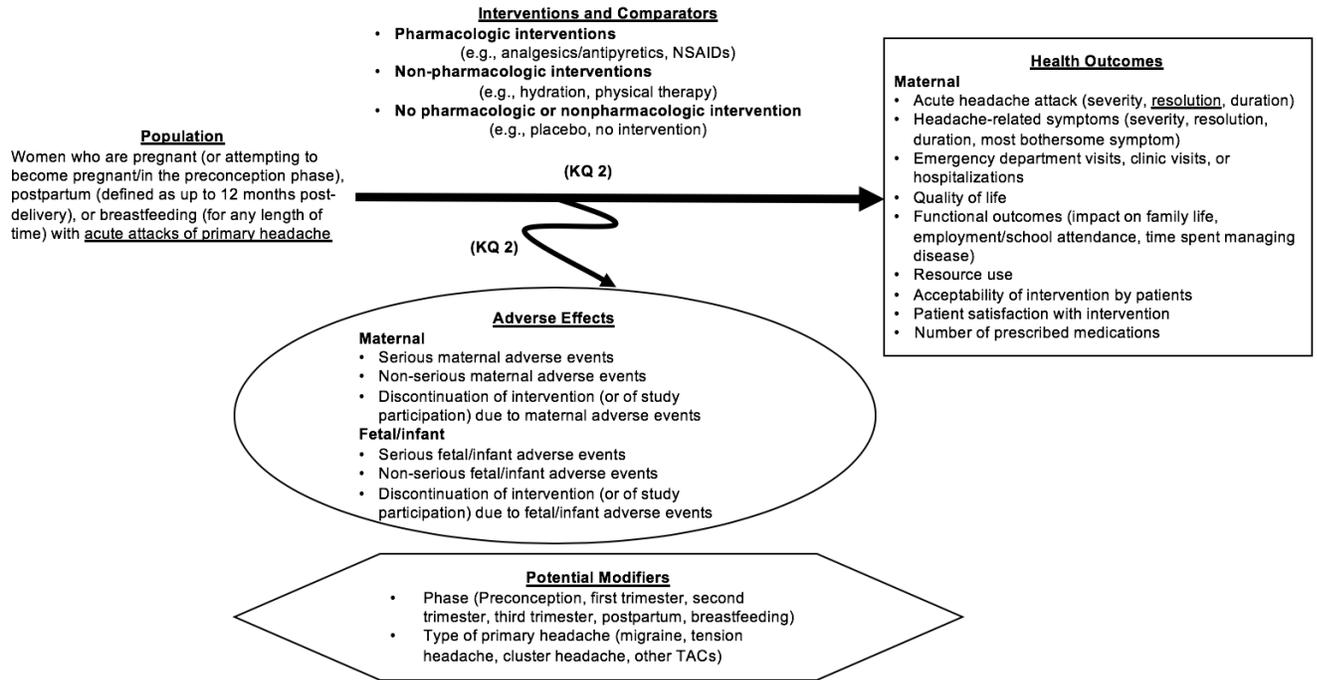
Figure 1. Analytic Framework for Key Question 1: Interventions to prevent attacks of primary headache during pregnancy, postpartum, and breastfeeding



Underlined text in regular font refers to aspects that are distinct to Key Question 1.

Abbreviations: KQ = Key Question, TACs = trigeminal autonomic cephalgias

Figure 2. Analytic Framework for Key Question 2: Interventions to treat Acute attacks of primary headache during pregnancy, postpartum, and breastfeeding



Underlined text in regular font refers to aspects that are distinct to Key Question 2.

Abbreviations: KQ = Key Question, NSAID = nonsteroidal antiinflammatory drug, TACs = trigeminal autonomic cephalgias

IV. Methods

The systematic review will follow Evidence-based Practice Center Program methodology, as laid out in its Methods Guide, particularly as pertain to reviews of comparative effectiveness, diagnostic tests, and complex meta-analyses.²⁴ As described below, the contextual question will be addressed using a nonsystematic approach.

Conducting the Systematic Review (KQ 1 and 2)

Criteria for Inclusion/Exclusion of Studies in the Review: See Study Eligibility Criteria in Section II.

Literature Search Strategies to identify primary studies for both Key Questions: We will search for primary studies in MEDLINE (via PubMed), The Cochrane Register of Clinical Trials, Embase, and CINAHL. Duplicate citations will be removed prior to screening. Searches will not have any date or language restrictions. Search strategies will include filters to remove nonhuman studies and articles that are not primary studies. The searches will include MeSH or Emtree terms, along with free-text words, related to pregnancy, postpartum, breastfeeding,

headache, migraine, tension headache, and cluster headache. The searches will be independently peer reviewed. The search strategy for each database (for primary studies) is included in Appendix A.

Searches will be conducted in the ClinicalTrials.gov registry for unpublished study protocols, unpublished study results, and ongoing studies. The reference lists of relevant existing systematic reviews will be screened for additional eligible studies. Additional articles suggested to us from any source, including peer and public review, will be screened applying identical eligibility criteria. Non-English language articles will be screened and data extracted either by readers of the relevant languages or after translation via Google Translate (<https://translate.google.com/>), if possible.

Literature Search Strategies to identify systematic reviews of harms of pharmacologic interventions for both Key Questions: We will search for systematic reviews in MEDLINE (via PubMed), The Cochrane Database of Systematic Reviews, and Epistemonikos. Duplicate citations will be removed prior to screening. Searches will not have any date or language restrictions. The searches will include MeSH and free-text words related to pregnancy, postpartum, breastfeeding, and each of the pharmacologic interventions and classes of interventions of interest (for both Key Questions). The search strategy for each database (for systematic reviews) is included in Appendix A.

All searches will be updated upon submission of the draft report for public review.

Screening process: This section describes our screening process for each of the searches described above. Citations from all searches will be entered into Abstrackr software (<http://abstrackr.cebm.brown.edu/>) to enable abstract screening. The team will conduct two or more rounds of pilot screening. During each pilot round, we will all screen the same 100 abstracts and discuss conflicts, with the goal of training the team in the nuances of the eligibility criteria and refining them as needed. After the pilot rounds, we will screen all remaining abstracts in duplicate. The Abstrackr software has machine learning capabilities that predict the likelihood of relevance of each citation. Daily, the list of unscreened abstracts will be sorted so that most potentially-relevant articles are presented first. This process will make screening more efficient and will enable us to capture the large majority of relevant articles relatively early in the abstract screening process.

Potentially relevant citations will be retrieved in full text. These articles will be rescreened in duplicate.

Data Extraction and Data Management: Data from eligible studies will be extracted into the Systematic Review Data Repository-Plus software (<https://srdplus.ahrq.gov>). Each article will be extracted by one researcher, and entered data will be confirmed by a second, independent researcher. Individual studies with multiple publications will be extracted as a single study (with a single entry in SRDR+). Each study will be entered into SRDR+ separately, even if two or more studies are reported within a single publication.

For each study, we will extract publication identifying data, study design features, population characteristics, intervention and comparator names and descriptions, relevant outcomes and their definitions, and funding source. In particular, we will extract, as available, data on phase (i.e., preconception, first trimester of pregnancy, second trimester of pregnancy, third trimester of pregnancy, postpartum, breastfeeding) and type of primary headache (i.e., migraine, tension headache, cluster headache, other TACs).

Assessment of Methodological Risk of Bias of Individual Studies: We will evaluate each study for risk of bias and methodological quality.

For randomized controlled trials, we will adapt the Cochrane Risk of Bias tool,²⁵ focusing on issues related to randomization and allocation concealment methodology; patient, caregiver, and outcome assessor blinding; loss to followup (omissions from analyses); adequacy of descriptions of study participants, interventions, and outcomes; and other issues. Questions related to outcome assessor blinding, loss to followup, and reporting adequacy will be assessed for each outcome.

For nonrandomized comparative studies, we will add assessments of specific elements from ROBINS-I,²⁶ in particular related to confounding and selection bias. The questions will be assessed for each outcome (e.g., whether each outcome was adjusted for potential confounders).

For single group studies, we will primarily assess specific elements from ROBINS-I, in particular related to selection of participants and completeness of outcome reporting (for each outcome separately).

We will assess the quality of the systematic reviews using specific items from AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews, version 2):²⁷ description of eligibility criteria (AMSTAR 2 item 1), comprehensive search strategy (item 4), duplicate study screening (item 5), duplicate data extraction (or with verification) (item 6), adequate description of details of included studies (item 8), use of a satisfactory technique for assessing risk of bias in included studies (item 9), appropriate meta-analysis methods (if applicable) (item 11), assessment of potential impact of risk of bias (item 12), explanation and discussion of any heterogeneity (item 14), and reporting of systematic review conflict of interest (item 16). We will omit questions about systematic review protocol timing, justification of excluded studies, study funding sources, and assessment of publication bias. We will consider a systematic review to be of high quality if each of the following four criteria is met: the eligibility criteria are appropriate (item 1), the search strategy is comprehensive (item 4), the potential impact of study-level risk of bias is adequately assessed (item 12), and the meta-analysis methods (if applicable) are appropriate. We will preferentially select higher-quality over lower-quality systematic reviews, as appropriate.

Data Synthesis: We will summarize the evidence both qualitatively and, when feasible, quantitatively. Each study included in the *de novo* systematic review will be described in summary and evidence tables presenting study design features, study participant characteristics, descriptions of interventions, outcome results, and risk of bias/methodological quality. The existing systematic reviews (for harms of pharmacologic interventions) will be summarized narratively regarding their eligibility criteria, the included studies, and their conclusions. We will

critique these reviews within the narrative. Summary tables will briefly describe the systematic reviews and their findings, as needed.

For Key Questions 1 and 2, we will compare interventions (pharmacologic and nonpharmacologic interventions) with their comparators, for their effects, primarily with odds ratios (ORs) for dichotomous outcomes (e.g., occurrence of headache), “net differences” (between-intervention comparison of within-intervention changes) for continuous outcomes with both pre- and post-intervention data (e.g., headache or quality of life scales), and differences (between interventions) in continuous outcome data post-intervention (e.g., duration of hospitalization). Where there are sufficient studies reporting sufficiently similar results, we also plan to conduct a Bayesian network meta-analysis comparing the different interventions to each other and to placebo (or no intervention). Depending on the evidence base, we may conduct separate analyses by phase and by type of primary headache. We expect to summarize harms data semi-quantitatively (i.e., without meta-analysis).

For both Key Questions, we expect to qualitatively describe reporting of differences in effects and harms by different factors, subgroups, or predictors. We do not expect to be able to conduct statistical analyses on these evaluations. We expect to primarily rely on reported within-study differences in effects (or harms). However, we will look for opportunities to qualitatively or quantitatively compare results across studies.

Grading the Strength of Evidence (SoE) for Major Outcomes and Comparisons: We will evaluate the SoE addressing each major comparison or evaluation for each Key Question. We expect that these will include:

- Relative clinical effects of pharmacologic and nonpharmacologic interventions for preventing attacks of primary headache;
- Harms of pharmacologic and nonpharmacologic interventions for preventing attacks of primary headache;
- Relative clinical effects of pharmacologic and nonpharmacologic interventions for treating attacks of primary headache; and
- Harms of pharmacologic and nonpharmacologic interventions for treating attacks of primary headache.

We will grade the strength of the body of evidence as per the AHRQ Methods Guide on assessing SoE.^{28, 29} We will assess SoE for each of the important clinical outcome categories. We determined the relative importance of the outcomes with input from the TEP. These categories include acute headache attacks; headache-related symptoms; emergency department visits, clinic visits, or hospitalizations; quality of life; serious maternal adverse events or discontinuation of intervention (or of study participation) due to maternal adverse events; and serious neonatal/infant adverse events or discontinuation of intervention (or of study participation) due to neonatal/infant adverse events. This list of important outcome categories may be revised after further discussion with the TEP.

For each SoE assessment, we will consider the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the KQs, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, other limitations, and the overall findings across studies. Based on these

assessments, we will assign a SoE rating as being either high, moderate, low, or insufficient evidence to estimate an effect.

Outcomes with highly imprecise estimates, highly inconsistent findings across studies, or with data from only one study will be deemed to have insufficient evidence to allow for a conclusion (with the exception that particularly large and generalizable single studies could provide at least low SoE). This approach is consistent with the concept that for imprecise evidence “any estimate of effect is very uncertain,” the definition of Very Low quality evidence per GRADE.³⁰

We will summarize the data sources, basic study characteristics, and each SoE dimensional rating in a “Summary of Evidence Reviewed” table. This table will detail our reasoning for arriving at the overall SoE rating.

Assessing Applicability: For each Key Question (or specific subquestion), we will assess the applicability of the included studies primarily based on the studies’ eligibility criteria and their included participants, specifically related to such factors as severity of disease, prior history, age, and race/ethnicity. These will be qualitatively compared with typical distributions of these factors among pregnant women with primary headache in the U.S. For interventions with reviewed primary studies, we will determine whether the interventions are available and currently used in the U.S. for treatment of primary headache.

Addressing the Contextual Question

For drug levels, we will summarize data found in major databases such as the Drugs and Lactation Database (LactMed, <https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>). For drug levels not available from the databases, we will search for existing systematic reviews.

Based on data and input garnered from these sources, we will answer the contextual question in a narrative format. We will not systematically extract or review all eligible studies, create summary tables, or assess the strength of evidence.

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VI. Definitions of Terms and Abbreviations

Definitions of Terms

Acute headache attack	An occurrence of headache for 4 or more hours with moderate to severe pain intensity
Breastfeeding	The phase during which, according to the included studies, women were breastfeeding their infant(s)
Postpartum	The phase up to 12 months post-delivery
Preconception	The phase during which women are attempting to become pregnant
Primary headache	Conditions where the headache itself is the disorder
Secondary headache	Headaches that are caused by an underlying disorder, such as stroke, venous thromboembolism, or pituitary tumors

Definitions of Abbreviations

AAP	American Academy of Pediatrics
ACOG	American College of Obstetricians and Gynecologists
AHRQ	Agency for Healthcare Research and Quality
AHS	American Headache Society
BCBS	Blue Cross Blue Shield
COI	conflicts of interest
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
KI	Key Informant
KQ	Key Question
NICHD	National Institute of Child Health and Human Development
NSAID	nonsteroidal anti-inflammatory drug
OB/GYN	obstetrician and gynecologist
SoE	Strength of Evidence
TAC	trigeminal autonomic cephalgia
TEP	Technical Expert Panel
TOO	Task Order Officer

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section.

VIII. Review of Key Questions

The Agency for Healthcare Research and Quality (AHRQ) posted the Key Questions on the AHRQ Effective Health Care Website for public comment. The Evidence-based Practice Center (EPC) refined and finalized them after reviewing of the public comments and seeking input from Key Informants. This input is intended to ensure that the Key Questions are specific and relevant.

IX. Key Informants (KIs)

We included a panel of KIs during Topic Refinement.

KIs are end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the KIs' role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from KIs when developing questions for systematic review or when identifying high priority research gaps and needed new research. KIs are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

KIs must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as KIs and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. The Technical Expert Panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that fosters a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind; neither do they contribute to the writing of the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Members of the TEP must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with

potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. HHS290201500002I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The TOO will review contract deliverables for adherence to contract requirements and quality. The authors of this report will be responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XIV. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

Appendix A: Literature Search

Search 1 – headache treatment

PubMed

("Breast Feeding"[Mesh] OR "Fertilization"[Mesh] OR "Gestational age"[Mesh] OR "Lactation"[Mesh] OR "Maternal Behavior"[Mesh] OR "Maternal exposure"[Mesh] OR "Maternal-Fetal Exchange"[Mesh] OR "Perinatal Care"[Mesh] OR "Pregnancy"[Mesh] OR "pregnancy complications"[Mesh] OR "pregnancy trimesters"[Mesh] OR breastfeeding OR "fetal growth" OR "gestational age" OR postpartum OR pregnancy OR pregnant OR trimester OR lactation OR polycystic ovary syndrome OR IVF OR "In Vitro Fertilization" OR insemination OR "Polycystic Ovary Syndrome"[Mesh] OR "Fertilization in Vitro"[Mesh]) AND (Migraine OR "Migraine Disorders"[Mesh] OR "Tension-Type Headache"[Mesh] OR "Cluster Headache"[Mesh] OR headache OR "Headache Disorders, Primary"[Mesh] OR ((tension OR cluster) AND headache))

Cochrane and CINAHL

((breastfeeding OR "fetal growth" OR "gestational age" OR postpartum OR pregnancy OR pregnant OR trimester OR lactation OR polycystic ovary syndrome OR IVF OR "In Vitro Fertilization" OR insemination) AND (Migraine OR headache)) NOT ("post-dural" OR "post dural" OR postdural) AND puncture))

EMBASE

#20: #18 NOT #19
#19: 'postdural puncture headache'
#18: #13 AND #16 AND ([article]/lim OR [article in press]/lim) AND [humans]/lim
#17: #13 AND #16
#16: #14 OR #15
#15: 'headache'/de
#14: 'migraine'/de
#13: #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#12: 'insemination'
#11: 'in vitro fertilization'/de
#10: 'ovary polycystic disease'/de
#9: 'lactation'/de
#8: trimester
#7: 'pregnant woman'/de
#6: 'pregnancy'/de
#5: postpartum
#4: 'puerperium'
#3: 'gestational age'/de
#2: 'fetus growth'/de
#1: 'breastfeeding'/exp OR 'breastfeeding'

Search 2 – SRs of AEs

PubMed

("Breast Feeding"[Mesh] OR "Fertilization"[Mesh] OR "Gestational age"[Mesh] OR "Lactation"[Mesh] OR "Maternal Behavior"[Mesh] OR "Maternal exposure"[Mesh] OR "Maternal-Fetal Exchange"[Mesh] OR "Perinatal Care"[Mesh] OR "Pregnancy"[Mesh] OR "pregnancy complications"[Mesh] OR "pregnancy trimesters"[Mesh] OR breastfeeding OR "fetal growth" OR "gestational age" OR postpartum OR pregnancy OR pregnant OR trimester OR lactation)

AND

("Antidepressive agents, Tricyclic"[Mesh] OR "Adrenergic beta-Antagonists"[Mesh] OR "Calcium Channel Blockers"[Mesh] OR "Anticonvulsants"[Mesh] OR "Serotonin Uptake Inhibitors"[Mesh] OR "Benzodiazepines"[Mesh] OR "Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR "Neuromuscular Blocking Agents"[Mesh] OR "Histamine Antagonists"[Mesh] OR "Central Nervous System Stimulants"[Mesh] OR "Tryptamines"[Mesh] OR "narcotics"[Mesh] OR "Analgesics, Opioid"[Mesh] OR "Antimanic Agents"[Mesh] OR "Antipsychotic Agents"[Mesh] OR "Antiemetics"[Mesh] OR "Anesthetics, Local"[Mesh] OR "Analgesics"[Mesh] OR "Tricyclic antidepressants" OR amitriptyline OR nortriptyline OR imipramine OR "Beta blockers" OR metoprolol OR propranolol OR nadolol OR atenolol OR timolol OR nebivolol OR "Calcium channel blockers" OR verapamil OR nimodipine OR nifedipine OR nicardipine OR lisinopril OR candesartan OR Antiepileptic* OR "divalproex sodium" OR "valproic acid" OR "sodium valproate" OR topiramate OR carbamazepine OR lamotrigine OR gabapentin OR ((Serotonin OR norepinephrine) AND "reuptake inhibitor") OR venlafaxine OR duloxetine OR benzodiazepines OR clonazepam OR (NMDA AND receptor AND (inhibitor OR antagonist)) OR memantine OR (CGRP AND (inhibitor OR antagonist)) OR erenumab OR fremanezumab OR galcanezumab OR riboflavin OR "coenzyme Q10" OR melatonin OR feverfew OR "herbal supplement" OR feverfew OR butterbur OR frankincense OR cannabidiol OR cyproheptadine OR acetaminophen OR paracetamol OR (Nonsteroidal AND (antiinflammatory OR anti-inflammatory)) OR NSAID OR Excedrin OR ibuprofen OR naproxen OR aspirin OR celecoxib OR ketorolac OR indomethacin OR ketoprofen OR diclofenac OR "mefenamic acid" OR Midrin OR isometheptene OR dichloralphenazone OR Antiemetics OR metoclopramide OR Antihistamines OR meclizine OR dimenhydrinate OR diphenhydramine OR promethazine OR prochlorperazine OR (("Central Nervous System" OR "CNS") AND "Stimulant") OR caffeine OR "muscle relaxant" OR baclofen OR cyclobenzaprine OR tizanidine OR metaxolone OR carisoprodol OR "neuromuscular block" OR OnabotulinumtoxinA OR botox OR AbobotulinumtoxinA OR dysport OR magnesium OR corticosteroids OR methylprednisolone OR triamcinolone OR prednisolone OR prednisone OR triptans OR sumatriptan OR frovatriptan OR naratriptan OR rizatriptan OR almotriptan OR eletriptan OR zolmitriptan OR narcotics OR opioids OR codeine OR nalbuphine OR butorphanol OR hydrocodone OR oxycodone OR morphine OR meperidine OR tramadol OR Fioricet OR Fiorinal OR butalbital OR dihydroergotamine OR ergotamine OR ("5HT3" AND ("inhibitor" OR "antagonist")) OR ondansetron OR "Sympathomimetic Amine" OR isometheptene OR "topical anesthetics" OR lidocaine OR bupivacaine OR Antipsychotics OR chlorpromazine OR droperidol OR olanzapine OR antimanic OR lithium OR "Tetracyclic antidepressant" OR mirtazapine OR "Somatostatin analog" OR octreotide)

AND

("drug-related side effects and adverse reactions"[MESH] OR "abnormalities, drug-induced"[MESH] OR birth defect OR congenital abnormality OR ((adverse or undesirable or harm or harms or harmful or toxic or injurious or serious or fatal) AND (effect* or reaction* or event* or outcome* or incident*)))

AND

(systematic[sb] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy* OR metanaly* OR metaanaly* OR met analy* OR (systematic AND (review* OR overview*)) OR "Review Literature as Topic"[Mesh] OR cochrane[tiab] OR embase[tiab] OR (psychlit[tiab] or psyclit[tiab]) OR (psychinfo[tiab] or psycinfo[tiab]) OR (cinahl[tiab] or cinhal[tiab] OR "cumulative index to nursing and allied health") OR science citation index[tiab] OR ibids[tiab] OR "international bibliographic information on dietary supplements" OR cancerlit[tiab] OR reference list*[tiab] OR bibliograph*[tiab] OR hand-search*[tiab] OR relevant journals[tiab] OR manual search*[tiab] OR ((selection OR inclusion OR exclusion) AND criteria[tiab]) OR data extraction[tiab] OR relevant journals OR "Systematic Review" [Publication Type])

Epistemonikos and Cochrane

(breastfeeding OR "fetal growth" OR "gestational age" OR postpartum OR pregnancy OR pregnant OR trimester OR lactation)

AND

(Tricyclic antidepressants" OR amitriptyline OR nortriptyline OR imipramine OR "Beta blockers" OR metoprolol OR propranolol OR nadolol OR atenolol OR timolol OR nebivolol OR "Calcium channel blockers" OR verapamil OR nimodipine OR nifedipine OR nicardipine OR lisinopril OR candesartan OR Antiepileptic* OR "divalproex sodium" OR "valproic acid" OR "sodium valproate" OR topiramate OR carbamazepine OR lamotrigine OR gabapentin OR ((Serotonin OR norepinephrine) AND "reuptake inhibitor") OR venlafaxine OR duloxetine OR benzodiazepines OR clonazepam OR (NMDA AND receptor AND (inhibitor OR antagonist)) OR memantine OR (CGRP AND (inhibitor OR antagonist)) OR erenumab OR fremanezumab OR galcanezumab OR riboflavin OR "coenzyme Q10" OR melatonin OR feverfew OR "herbal supplement" OR feverfew OR butterbur OR frankincense OR cannabidiol OR cyproheptadine OR acetaminophen OR paracetamol OR (Nonsteroidal AND (antiinflammatory OR anti-inflammatory)) OR NSAID OR Excedrin OR ibuprofen OR naproxen OR aspirin OR celecoxib OR ketorolac OR indomethacin OR ketoprofen OR diclofenac OR "mefenamic acid" OR Midrin OR isometheptene OR dichloralphenazone OR Antiemetics OR metoclopramide OR Antihistamines OR meclizine OR dimenhydrinate OR diphenhydramine OR promethazine OR prochlorperazine OR ("Central Nervous System" OR "CNS") AND "Stimulant") OR caffeine OR "muscle relaxant" OR baclofen OR cyclobenzaprine OR tizanidine OR metaxalone OR carisoprodol OR "neuromuscular block" OR OnabotulinumtoxinA OR botox OR AbobotulinumtoxinA OR dysport OR magnesium OR corticosteroids OR methylprednisolone OR triamcinolone OR prednisolone OR prednisone OR triptans OR sumatriptan OR frovatriptan OR naratriptan OR rizatriptan OR almotriptan OR eletriptan OR zolmitriptan OR narcotics OR opioids OR codeine OR nalbuphine OR butorphanol OR hydrocodone OR oxycodone OR morphine OR meperidine OR tramadol OR Fioricet OR Fiorinal OR butalbital OR dihydroergotamine OR ergotamine OR ("5HT3" AND ("inhibitor" OR "antagonist")) OR ondansetron OR "Sympathomimetic Amine" OR isometheptene OR "topical anesthetics" OR

lidocaine OR bupivacaine OR Antipsychotics OR chlorpromazine OR droperidol OR olanzapine OR antimanic OR lithium OR “Tetracyclic antidepressant” OR mirtazapine OR “Somatostatin analog” OR octreotide)

AND

(birth defect OR congenital abnormality OR ((adverse or undesirable or harm or harms or harmful or toxic or injurious or serious or fatal) AND (effect* or reaction* or event* or outcome* or incident*)))

Search 3 – pharmacodynamics

PubMed

((“Breast Feeding”[Mesh] OR “Fertilization”[Mesh] OR “Gestational age”[Mesh] OR “Lactation”[Mesh] OR “Maternal Behavior”[Mesh] OR “Maternal exposure”[Mesh] OR “Maternal-Fetal Exchange”[Mesh] OR “Perinatal Care”[Mesh] OR “Pregnancy”[Mesh] OR “pregnancy complications”[Mesh] OR “pregnancy trimesters”[Mesh] OR breastfeeding OR “fetal growth” OR “gestational age” OR postpartum OR pregnancy OR pregnant OR trimester OR lactation)

AND

(“Antidepressive agents, Tricyclic”[Mesh] OR “Adrenergic beta-Antagonists”[Mesh] OR “Calcium Channel Blockers”[Mesh] OR “Anticonvulsants”[Mesh] OR “Serotonin Uptake Inhibitors”[Mesh] OR “Benzodiazepines”[Mesh] OR “Anti-Inflammatory Agents, Non-Steroidal”[Mesh] OR “Neuromuscular Blocking Agents”[Mesh] OR “Histamine Antagonists”[Mesh] OR “Central Nervous System Stimulants”[Mesh] OR “Tryptamines”[Mesh] OR “narcotics”[Mesh] OR “Analgesics, Opioid”[Mesh] OR “Antimanic Agents”[Mesh] OR “Antipsychotic Agents”[Mesh] OR “Antiemetics”[Mesh] OR “Anesthetics, Local”[Mesh] OR “Analgesics”[Mesh] OR “Tricyclic antidepressants” OR amitriptyline OR nortriptyline OR imipramine OR “Beta blockers” OR metoprolol OR propranolol OR nadolol OR atenolol OR timolol OR nebivolol OR “Calcium channel blockers” OR verapamil OR nimodipine OR nifedipine OR nicardipine OR lisinopril OR candesartan OR Antiepileptic* OR “divalproex sodium” OR “valproic acid” OR “sodium valproate” OR topiramate OR carbamazepine OR lamotrigine OR gabapentin OR ((Serotonin OR norepinephrine) AND “reuptake inhibitor”) OR venlafaxine OR duloxetine OR benzodiazepines OR clonazepam OR (NMDA AND receptor AND (inhibitor OR antagonist)) OR memantine OR (CGRP AND (inhibitor OR antagonist)) OR erenumab OR fremanezumab OR galcanezumab OR riboflavin OR “coenzyme Q10” OR melatonin OR feverfew OR “herbal supplement” OR feverfew OR butterbur OR frankincense OR cannabidiol OR cyproheptadine OR acetaminophen OR paracetamol OR (Nonsteroidal AND (antiinflammatory OR anti-inflammatory)) OR NSAID OR Excedrin OR ibuprofen OR naproxen OR aspirin OR celecoxib OR ketorolac OR indomethacin OR ketoprofen OR diclofenac OR “mefenamic acid” OR Midrin OR isometheptene OR dichloralphenazone OR Antiemetics OR metoclopramide OR Antihistamines OR meclizine OR dimenhydrinate OR diphenhydramine OR promethazine OR prochlorperazine OR ((“Central Nervous System” OR “CNS”) AND “Stimulant”) OR caffeine OR “muscle relaxant” OR baclofen OR cyclobenzaprine OR tizanidine OR metaxolone OR carisoprodol OR “neuromuscular block” OR OnabotulinumtoxinA OR botox OR AbobotulinumtoxinA OR dysport OR magnesium OR corticosteroids OR methylprednisolone OR triamcinolone OR prednisolone OR prednisone OR triptans OR sumatriptan OR frovatriptan OR naratriptan OR rizatriptan OR almotriptan OR eletriptan OR zolmitriptan OR narcotics OR opioids OR codeine OR nalbuphine OR butorphanol OR

hydrocodone OR oxycodone OR morphine OR meperidine OR tramadol OR Fioricet OR Fiorinal OR butalbital OR dihydroergotamine OR ergotamine OR (“5HT3” AND (“inhibitor” OR “antagonist”)) OR ondansetron OR “Sympathomimetic Amine” OR isometheptene OR “topical anesthetics” OR lidocaine OR bupivacaine OR Antipsychotics OR chlorpromazine OR droperidol OR olanzapine OR antimanic OR lithium OR “Tetracyclic antidepressant” OR mirtazapine OR “Somatostatin analog” OR octreotide)

AND

(Pharmacokinetic* OR pharmacodynamic* OR "Pharmacokinetics"[Mesh] OR “Breast milk” OR “Milk, Human”[Mesh] OR “human milk” OR “Fetal blood”[Mesh] OR “fetal blood” OR “cord blood” OR “amniotic fluid” OR “Amniotic Fluid”[Mesh]))

AND

(systematic[sb] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy* OR metanaly* OR metaanaly* OR met analy* OR (systematic AND (review* OR overview*)) OR "Review Literature as Topic"[Mesh] OR cochrane[tiab] OR embase[tiab] OR (psyclit[tiab] OR psyclit[tiab]) OR (psychinfo[tiab] OR psycinfo[tiab]) OR (cinahl[tiab] OR cinhal[tiab] OR “cumulative index to nursing and allied health”) OR science citation index[tiab] OR ibids[tiab] OR “international bibliographic information on dietary supplements” OR cancerlit[tiab] OR reference list*[tiab] OR bibliograph*[tiab] OR hand-search*[tiab] OR relevant journals[tiab] OR manual search*[tiab] OR ((selection OR inclusion OR exclusion) AND criteria[tiab]) OR data extraction[tiab] OR relevant journals OR "Systematic Review" [Publication Type])

Cochrane and CINAHL

(breastfeeding OR “fetal growth” OR “gestational age” OR postpartum OR pregnancy OR pregnant OR trimester OR lactation)

AND

(Tricyclic antidepressants” OR amitriptyline OR nortriptyline OR imipramine OR “Beta blockers” OR metoprolol OR propranolol OR nadolol OR atenolol OR timolol OR nebivolol OR “Calcium channel blockers” OR verapamil OR nimodipine OR nifedipine OR nicardipine OR lisinopril OR candesartan OR Antiepileptic* OR “divalproex sodium” OR “valproic acid” OR “sodium valproate” OR topiramate OR carbamazepine OR lamotrigine OR gabapentin OR ((Serotonin OR norepinephrine) AND “reuptake inhibitor”) OR venlafaxine OR duloxetine OR benzodiazepines OR clonazepam OR (NMDA AND receptor AND (inhibitor OR antagonist)) OR memantine OR (CGRP AND (inhibitor OR antagonist)) OR erenumab OR fremanezumab OR galcanezumab OR riboflavin OR “coenzyme Q10” OR melatonin OR feverfew OR “herbal supplement” OR feverfew OR butterbur OR frankincense OR cannabidiol OR cyproheptadine OR acetaminophen OR paracetamol OR (Nonsteroidal AND (antiinflammatory OR anti-inflammatory)) OR NSAID OR Excedrin OR ibuprofen OR naproxen OR aspirin OR celecoxib OR ketorolac OR indomethacin OR ketoprofen OR diclofenac OR “mefenamic acid” OR Midrin OR isometheptene OR dichloralphenazone OR Antiemetics OR metoclopramide OR Antihistamines OR meclizine OR dimenhydrinate OR diphenhydramine OR promethazine OR prochlorperazine OR (“Central Nervous System” OR “CNS”) AND “Stimulant”) OR caffeine OR “muscle relaxant” OR baclofen OR cyclobenzaprine OR tizanidine OR metaxalone OR carisoprodol OR “neuromuscular block” OR OnabotulinumtoxinA OR botox OR AbobotulinumtoxinA OR dysport OR magnesium OR corticosteroids OR methylprednisolone OR triamcinolone OR prednisolone OR prednisone OR triptans OR sumatriptan OR frovatriptan

OR naratriptan OR rizatriptan OR almotriptan OR eletriptan OR zolmitriptan OR narcotics OR opioids OR codeine OR nalbuphine OR butorphanol OR hydrocodone OR oxycodone OR morphine OR meperidine OR tramadol OR Fioricet OR Fiorinal OR butalbital OR dihydroergotamine OR ergotamine OR (“5HT3” AND (“inhibitor” OR “antagonist”)) OR ondansetron OR “Sympathomimetic Amine” OR isometheptene OR “topical anesthetics” OR lidocaine OR bupivacaine OR Antipsychotics OR chlorpromazine OR droperidol OR olanzapine OR antimanic OR lithium OR “Tetracyclic antidepressant” OR mirtazapine OR “Somatostatin analog” OR octreotide)

AND

(Pharmacokinetic* OR pharmacodynamic* OR “Breast milk” OR “human milk” OR “fetal blood” OR “cord blood” OR “amniotic fluid”)

Limited to Systematic Reviews and Meta-analyses

EMBASE

#32: #21 AND #29 AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)

#31: #21 AND #29 AND ([article]/lim OR [article in press]/lim) AND [humans]/lim

#30: #21 AND #29

#29: #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28

#28; hydrocodone OR oxycodone OR morphine OR meperidine OR tramadol OR fioricet OR fiorinal OR butalbital OR dihydroergotamine OR ergotamine OR '5ht3 inhibitor' OR '5ht3 antagonist' OR ondansetron OR 'sympathomimetic amine' OR isometheptene OR 'topical anesthetics' OR lidocaine OR bupivacaine OR antipsychotics OR chlorpromazine OR droperidol OR olanzapine OR antimanic OR lithium OR 'tetracyclic antidepressant' OR mirtazapine OR 'somatostatin analog' OR octreotide

#27; 'central nervous system stimulant' OR caffeine OR 'muscle relaxant' OR baclofen OR cyclobenzaprine OR tizanidine OR metaxolone OR carisoprodol OR 'neuromuscular block' OR onabotulinumtoxin OR botox OR abobotulinumtoxin OR dysport OR magnesium OR corticosteroids OR methylprednisolone OR triamcinolone OR prednisolone OR prednisone OR triptans OR sumatriptan OR frovatriptan OR naratriptan OR rizatriptan OR almotriptan OR eletriptan OR zolmitriptan OR narcotics OR opioids OR codeine OR nalbuphine OR butorphanol
#26; 'nonsteroidal anti-inflammatory' OR nsaid OR excedrin OR ibuprofen OR naproxen OR aspirin OR celecoxib OR ketorolac OR indomethacin OR ketoprofen OR diclofenac OR 'mefenamic acid' OR midrin OR isometheptene OR dichloralphenazone OR antiemetics OR metoclopramide OR antihistamines OR meclizine OR dimenhydrinate OR diphenhydramine OR promethazine OR prochlorperazine

#25: 'nmda receptor inhibitor' OR 'nmda receptor antagonist' OR memantine OR 'cgrp inhibitor' OR 'cgrp antagonist' OR erenumab OR fremanezumab OR galcanezumab OR riboflavin OR 'coenzyme q10' OR melatonin OR 'herbal supplement' OR feverfew OR butterbur OR frankincense OR cannabidiol OR cyproheptadine OR acetaminophen OR paracetamol

#24: antiepileptic OR 'divalproex sodium' OR 'valproic acid' OR 'sodium valproate' OR topiramate OR carbamazepine OR lamotrigine OR gabapentin OR 'serotonin reuptake inhibitor' OR 'norepinephrine reuptake inhibitor' OR venlafaxine OR duloxetine OR benzodiazepines OR clonazepam

#23: propranolol OR nadolol OR atenolol OR timolol OR nebivolol OR 'calcium channel blockers' OR verapamil OR nimodipine OR nifedipine OR nicardipine OR lisinopril OR candesartan
#22: 'tricyclic antidepressants' OR amitriptyline OR nortriptyline OR imipramine OR 'beta blockers' OR metoprolol
#21: #13 AND #20
#20: #14 OR #15 OR #16 OR #17 OR #18 OR #19
#19: 'amniotic fluid'/de
#18: 'umbilical cord blood'/de
#17: 'fetal blood'/de
#16: 'breast milk'/de
#15: 'pharmacokinetics'/de
#14: 'pharmacodynamics'/de
#13: #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#12: 'insemination'
#11: 'in vitro fertilization'/de
#10: 'ovary polycystic disease'/de
#9: 'lactation'/de
#8: trimester
#7: 'pregnant woman'/de
#6: 'pregnancy'/de
#5: postpartum
#4: 'puerperium'
#3: 'gestational age'/de
#2: 'fetal growth'/de
#1: 'breastfeeding'/exp OR 'breastfeeding'