



## Evidence-based Practice Center Systematic Review Protocol

### **Project Title: *A Systematic Review of Postpartum Home Blood Pressure Monitoring, Postpartum Treatment of Hypertensive Disorders of Pregnancy, and Peripartum Magnesium Sulfate Regimens for Preeclampsia With Severe Features***

#### **I. Background and Purpose of the Systematic Review**

##### **Background**

Hypertensive disorders of pregnancy (HDP) affect up to 10 percent of pregnancies, and encompass a spectrum of disorders that include preexisting chronic hypertension (HTN), gestational HTN, preeclampsia with and without severe features, eclampsia (seizure), and the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome.<sup>1</sup> Rates of HDP are rising in the U.S.,<sup>2</sup> likely due to increased prevalence of pre-existing HTN, obesity, diabetes, older maternal age at delivery, and use of artificial reproductive technologies with an associated increased likelihood of multifetal gestation.<sup>3</sup> Historically, it was believed that HDP was cured by delivery of the placenta, but it is now understood that HDP can persist, worsen, or develop *de novo* after discharge from hospitalization for the delivery, and may result in severe morbidity or mortality due to eclampsia and stroke.<sup>4, 5</sup>

Diagnoses of HDP have important implications for healthcare utilization, patient experience, and long-term health outcomes in pregnant and postpartum individuals and their children. Over the past 20 years, pregnancy-related deaths have increased in the U.S., from 7.2 deaths per 100,000 live births in 1987 to 20.1 per 100,000 live births in 2019.<sup>6, 7</sup> More than half of pregnancy-related deaths in the U.S. occur in the postpartum period.<sup>8</sup> The Centers for Disease Control and Prevention (CDC) reports that 6.6 percent of the pregnancy-related deaths between 2014 and 2017 were attributable to HDP.<sup>6</sup> Beyond the postpartum period, data suggest that individuals with pregnancies complicated by HDP have a higher risk of chronic HTN and a higher lifelong risk of cardiovascular complications.<sup>9-11</sup>

In terms of healthcare utilization, patients with HDP require increased monitoring during and after pregnancy and have potentially prolonged hospitalization at delivery for blood pressure (BP) control and management of acute sequelae. In addition to the increased risks of death and serious complications, postpartum HDP can have important implications for the mother's and baby's wellbeing. For example, hospital readmission and medicalization of the postpartum period due to HDP may complicate the family's adjustment to parenting. Postpartum HDP may also affect breastfeeding and postpartum mental health, with important implications for mother-child bonding.

HDP and its sequelae disproportionately affect minority and marginalized communities.<sup>8, 12</sup> There are substantial disparities across income and racial/ethnic minority groups in terms of who is affected and their outcomes. Overall, Black individuals are three times more likely to die than non-Hispanic White individuals while pregnant, both around the time of delivery and up to 1 year postpartum.<sup>12</sup> A higher percentage of these deaths are attributable to HDP (8.2% in Black

individuals versus 6.7% in White, non-Hispanic individuals).<sup>12</sup> Some of the hypothesized reasons for the disparities relate to differential incidence of risk factors (e.g., diabetes and obesity). But these differences do not fully explain the wide disparity in deaths. In addition, the disparities may also reflect differential access to care (e.g., differences in preconception insurance coverage and duration of postpartum insurance coverage), unequal treatment of different subgroups of pregnant individuals by providers and the healthcare system, differential ability to take time off work, different levels of social support, and other structural effects of systemic racism (such as chronic stress).<sup>12, 13</sup>

Recent innovations in healthcare delivery—specifically, remote monitoring—show promise in improving early detection of postpartum HTN while also improving the patient experience by increasing the convenience of care and decreasing the need for clinical encounters. Key missing information includes whether postpartum BP home- or tele-monitoring is effective, whether the form of home monitoring (e.g., monitoring regimen, communication method) impacts effectiveness, and whether home monitoring may affect observed disparities in outcomes.

Some individuals with HDP begin the postpartum period receiving large doses of antihypertensive medications. Others may develop HTN after discharge and require treatment. In the postpartum period, BP can change rapidly and unpredictably, with shifting medication requirements, before returning to normal in most patients. More evidence is needed regarding which medication(s) are most effective for outpatient postpartum BP management, have the fewest side effects, do not interfere with breastfeeding, and have dosing intervals that support adherence. The evidence is also emerging regarding the use of home BP monitoring accompanied by self-titration of antihypertensive medications.<sup>14, 15</sup>

There is robust evidence supporting use of magnesium sulfate ( $MgSO_4$ ) to prevent eclamptic seizures for individuals with peripartum preeclampsia with severe features.<sup>16</sup> Severe features of preeclampsia include a severe-range BP (defined by the American College of Obstetricians and Gynecologists [ACOG] as persistent systolic BP of 160 mm Hg or higher, or diastolic BP of 110 mm Hg or higher<sup>17</sup>), low platelet count, abnormal liver function, acute abnormal kidney function, pulmonary edema, new-onset headache, visual disturbance, and seizures (eclampsia).<sup>17, 18</sup> However, there is uncertainty regarding the optimal  $MgSO_4$  regimen pertaining to dose (loading and total), route of administration, and treatment duration.<sup>19</sup> There is also limited evidence regarding the indications for and duration of use of  $MgSO_4$  for preeclampsia with severe features arising or worsening after delivery.<sup>4, 20</sup>

Despite some evidence to the contrary,<sup>21</sup> concerns persist<sup>22</sup> regarding the potential for adverse interactions between  $MgSO_4$  and specific antihypertensive agents, such as hypotension, neuromuscular blockade, or pulmonary edema with concurrent use of calcium channel blockers.

A thorough review of the literature is critical to improving the early detection and management of postpartum HDP and of  $MgSO_4$  use for peripartum preeclampsia with severe features.

## **Purpose of the Review**

ACOG nominated this topic to the Patient-Centered Outcomes Research Institute (PCORI), which contracted with the Agency for Healthcare Research and Quality (AHRQ) to conduct the review.

Specifically, the systematic review will summarize the findings from (1) studies of home BP monitoring in the postpartum period, (2) studies of pharmacological treatment of HDP in the postpartum period, and (3) studies comparing the effectiveness and harms of different  $MgSO_4$

regimens in patients with preeclampsia with severe features to prevent eclampsia during the peripartum period. For the third topic, the peripartum period is operationally defined as the time interval prior to, during, or after delivery when individuals may be diagnosed with preeclampsia with severe features. For all topics, the review will summarize findings related to differences in treatment effectiveness (and harms) in different populations, with an emphasis, as feasible, on factors related to healthcare disparities and pregnancy-related risk factors.

The intended audience includes guideline developers, clinicians, other providers of peripartum and postpartum care, healthcare policy makers, and patients.

## II. Key Questions and Eligibility Criteria

### Key Questions (KQ)

**KQ 1:** What are the effectiveness, comparative effectiveness, and harms of home blood pressure monitoring/telemonitoring in postpartum individuals?

**KQ 2:** What are the effectiveness, comparative effectiveness, and harms of pharmacological treatments for hypertensive disorders of pregnancy in postpartum individuals?

**KQ 3:** What are the comparative effectiveness and harms of alternative magnesium sulfate (MgSO<sub>4</sub>) treatment regimens to treat preeclampsia with severe features during the peripartum period?

**3.a.** Are there harms associated with the concomitant use of particular antihypertensive medications during treatment with MgSO<sub>4</sub>?

For **all Key Questions**, how do the findings vary by race, ethnicity, HDP subgroup, maternal age, parity, singleton/multiple pregnancies, mode of delivery, co-occurring conditions (e.g., obesity), and social determinants of health (e.g., postpartum insurance coverage, English proficiency, income, educational attainment)?

### Contextual Question (CQ)

**CQ 1:** How are race, ethnicity, and social determinants of health related to disparities associated with incidence of HDP, detection, access to care, management, followup care, and clinical outcomes in individuals with postpartum hypertensive disorders of pregnancy?

## Study Eligibility Criteria

### Key Question 1 (Home BP Monitoring)

#### Population

- Postpartum individuals (with or without a prior HDP diagnosis)

#### Modifiers/Subgroups of interest

- Subgroups defined by ACOG HDP classification (some of which may arise *de novo* in the postpartum period)

- chronic HTN
- gestational HTN
- preeclampsia (may be superimposed on chronic HTN)
- preeclampsia with severe features (as defined by study authors)
- *de novo* HTN postpartum
- Subgroups defined by BP diagnostic threshold(s)
- Race, ethnicity
- Maternal age, parity, singleton/multiple pregnancy, delivery (e.g., cesarean versus vaginal delivery, preterm versus term)
- Co-occurring disorders (e.g., obesity, diabetes)
- Subgroups defined by potential indicators of social determinants of health (e.g., insurance coverage, English proficiency, income, educational attainment)
- Access to technology (e.g., broadband internet, smartphone)

### Interventions and intervention components

- Postpartum home BP monitoring interventions
  - Electronic, digital monitors, any
  - With or without web-based connectivity and communication
  - With or without education or training in use of monitor
  - With or without validation of accuracy of patient's monitor
- Exclude: Ambulatory BP monitoring (e.g., 24- or 48-hour continuous monitoring)
- Exclude: Monitors with manual inflation and auscultation
- Exclude: BP monitoring only by third parties, such as home health aides, visiting nurses
- Exclude: Very limited use of monitoring (e.g., single reading or single day)
- Exclude: Use of device only in laboratory or clinic setting

### Comparators

- No home BP monitoring (e.g., usual care with clinic-only BP monitoring)
- Alternative non-clinic-based BP monitoring approaches (e.g., kiosks, pharmacy-based BP monitoring, home health aide visits)
- Alternative education modalities about self-monitoring BP (e.g., demonstration of correct use, confirmation of appropriate cuff size)
- Alternative home BP monitor characteristics (e.g., direct transmission of results, prompts for communication of symptoms)
- Alternative home BP monitoring regimen (e.g., BP measurement frequency, duration)
- Alternative instructions for when to communicate results immediately (e.g., different BP threshold alerts)
- Alternative mode of communicating results (e.g., during clinic visit, automatic web-based, via text/email/portal/phone)
- Alternative clinician feedback processes
- No use of validation of accuracy of patient's monitor

### Outcomes (prioritized outcomes have an asterisk and are in bold font)

- Blood pressure
  - **Ascertainment of elevated BP or new onset HDP\***
    - Time to clinical recognition of elevated BP

- **Treatment\***
  - Initiation or discontinuation of antihypertensive medications
  - Increase or decrease in dose (or number) of antihypertensive medications
  - BP control (e.g., BP normalization)
- Documentation of BP after discharge
- Recognition of white coat HTN
- Severe maternal outcomes
  - **Maternal mortality, including pregnancy-related mortality\***
  - **Severe maternal morbidity\*** (e.g., **stroke\***, eclampsia, pulmonary edema)
- Patient reported outcomes
  - Patient reported experience measures (PREMs) for example
    - **Satisfaction with postpartum care\***
    - Ease of access to care
    - Quality of communication
    - Support to manage HTN
    - Patient Reported Experience Measure of Obstetric racism (PREM-OB Scale)
  - Patient reported outcome measures (PROMs), for example
    - **Global Quality of life\***, e.g., SF-36
    - Psychosocial distress
      - **Anxiety\***, e.g., State-Trait Anxiety Inventory (STAI)
      - **Depression\***, e.g., Edinburgh Postnatal Depression Score (EPDS)
- Healthcare utilization
  - **Length of postpartum hospital stay\***
  - **Unplanned obstetrical triage area or clinic visits\***
  - **Emergency department visits\***
  - **Re-hospitalization after discharge\***
- **Reduction of health disparities\*** (increase in disparities included under *Harms*)
- Other Harms
  - **Generation or exacerbation of health disparities\***
  - Anxiety associated with use of monitoring technology

## Study Design

- Comparative studies (comparisons of different interventions or regimens)
  - Randomized controlled trials ( $N \geq 10$  per group)
  - Nonrandomized comparative studies (prospective or retrospective) that use statistical techniques (e.g., regression adjustment, propensity score matching, inverse probability weighting) to reduce bias due to confounding)
- Any publication language (unless cannot be translated)
- Exclude
  - Single group (noncomparative) studies
  - Case-control studies
  - Claims database analyses
  - Feasibility studies
  - Device validation studies (not including validation of patients' monitors in the clinic)

- Qualitative studies
- Conference abstracts prior to 2020 (without subsequent, eligible peer-reviewed publication)

### Timing

- Intervention: Day of birth through 1 year postpartum
  - Self-monitoring may start antenatal, in hospital, or postpartum, but must continue postpartum
- Outcomes: Any (postpartum)

### Setting

- Outpatient postpartum management (although training and initiation may start in hospital or at clinic)
- Any publication date
- Any country

## Key Question 2 (Treatment of HDP)

### Population

- Postpartum individuals with diagnosed HDP (whether diagnosed antenatal, peripartum, or postpartum)

### Modifiers/Subgroups of interest

- Subgroups defined by ACOG HDP classification (these may arise *de novo* in the postpartum period)
  - chronic HTN
  - gestational HTN
  - preeclampsia (may be superimposed on chronic HTN)
  - preeclampsia with severe features (as defined by study authors)
  - *de novo* HTN postpartum
- Subgroups defined by BP thresholds/categories
- Race, ethnicity
- Maternal age, parity, singleton/multiple pregnancy, mode of delivery (e.g., cesarean versus vaginal delivery, preterm versus term)
- Co-occurring disorders (e.g., obesity, diabetes)
- Subgroups defined by potential indicators of social determinants of health (e.g., insurance coverage, English proficiency, income, educational attainment)
- Use of home monitoring

### Interventions

- Pharmacological treatments for HTN or HDP administered postpartum
  - Antihypertensive medications (single or combination therapies)
  - Loop diuretics (alone or in combination with antihypertensive medications)
- Exclude:
  - Medication not available for use in the U.S.
  - Nonpharmacological treatments (e.g., uterine curettage)
  - Corticosteroids (e.g., for HELLP)

- *Interventions to prevent preeclampsia (e.g., low-dose aspirin)*
- *Treatments not used to treat HDP (e.g., NSAIDs)*
- *Behavioral modification (e.g., diet, exercise)*
- *Non-medical interventions (e.g., traditional medicine, complementary and alternative medicine, meditation, mindfulness)*

## Comparators

- Alternative specific treatments (e.g., alternative antihypertensive medication(s) or combinations of medications, alternative diuretic)
- Alternative treatment regimen (e.g., alternative dose, duration of treatment)
- Alternative blood pressure targets
- No treatment (or placebo)
- Exclude: *Excluded interventions*

## Outcomes (prioritized outcomes have an asterisk and are in bold font)

- Intermediate outcomes
  - **Blood pressure control\***
  - Measures of end-organ function
    - Cardiovascular measures (e.g., echocardiographic measurements of diastolic function and hypertrophy)
    - Kidney function (e.g., estimated glomerular filtration rate)
- Severe maternal outcomes
  - **Maternal mortality, including pregnancy-related mortality\***
  - **Severe maternal morbidity\*** (e.g., **stroke\***, eclampsia, pulmonary edema)
- Patient reported outcomes
  - Patient reported experience measures (PREMs), for example
    - **Satisfaction with postpartum care\***
    - Ease of access to care
    - Quality of communication
    - Support to manage HTN
  - Patient reported outcome measures (PROMs), for example
    - **Global Quality of life\***, e.g., SF-36
    - Maternal-neonatal bonding, e.g., Postpartum Bonding Questionnaire
    - Psychosocial distress
      - **Anxiety\***, e.g., State-Trait Anxiety Inventory (STAI)
      - **Depression\***, e.g., Edinburgh Postnatal Depression Score (EPDS)
- Healthcare utilization
  - **Length of postpartum hospital stay\***
  - **Unplanned obstetrical triage area or clinic visits\***
  - **Emergency department visits\***
  - **Re-hospitalization after discharge\***
- Infant health outcomes
  - **Breastfeeding outcomes (e.g., initiation, success, duration)\***
- **Reduction of health disparities\*** (increase in disparities included under *Harms*)
- **Harms**
  - **Severe adverse events\*** (e.g., electrolyte abnormalities, severe hypotension)

- **Infant morbidities\*** (e.g., hypotension, other symptoms attributed to medication exposure via breast milk)
- **Generation or exacerbation of health disparities\***
- Adverse interactions with other medications

### Study Design

- Comparative studies (comparisons of different interventions or regimens)
  - Randomized controlled trials ( $N \geq 10$  per group)
  - Nonrandomized comparative studies (prospective or retrospective) that use statistical techniques (e.g., regression adjustment, propensity score matching, inverse probability weighting) to reduce bias due to confounding
- Any publication language (unless cannot be translated)
- Exclude
  - Single group (noncomparative) studies
  - Case-control studies
  - Claims database analyses
  - Feasibility studies
  - Qualitative studies
  - Conference abstracts prior to 2020 (without subsequent, eligible peer-reviewed publication)

### Timing

- Intervention: Day of birth up to 1 year postpartum
  - Intervention may start antenatal, in hospital, or postpartum, but must continue postpartum
- Outcomes: Any (postpartum)

### Setting

- Outpatient, non-acute management (treatment may start inpatient)
- Any publication date
- Any country

## Key Question 3 (MgSO<sub>4</sub> for Preeclampsia with Severe Features)

### Population

- Individuals who have preeclampsia with severe features (as defined by study authors) during the peripartum period (prior to and/or after delivery)
- Exclude: *Pregnant patients who are treated with MgSO<sub>4</sub> with the goal of suppressing premature labor, for fetal neuroprotection, or for other reasons*

### Modifiers/Subgroups of interest

- Race, ethnicity
- Maternal age, parity, singleton/multiple pregnancy, mode of delivery (e.g., cesarean versus vaginal delivery, preterm versus term)
- Co-occurring disorders (e.g., obesity, diabetes)
- Subgroups defined by potential indicators of social determinants of health (e.g., insurance coverage, English proficiency, income, educational attainment)



- Timing of MgSO<sub>4</sub> administration or onset of preeclampsia with severe features with respect to delivery
  - Antepartum
  - Intrapartum
  - Postpartum
- Individuals with reduced kidney function

### Interventions

- Peripartum MgSO<sub>4</sub> administration
  - Any dose, route (except oral), timing, duration of treatment, concomitant treatment, or regimen
- Exclude: Oral magnesium supplementation

### Comparators

- Alternative MgSO<sub>4</sub> regimens
  - Different criteria for initiation of treatment
  - Different criteria for stopping (or continuing) treatment
  - Different criteria for altering dosing during treatment
  - Different loading dose
  - Different planned total dose
  - Different route
  - Different planned duration of treatment
  - Tailored interventions based on pharmacokinetic monitoring (i.e., based on serum Mg levels)
  - Combined treatment with antihypertensive medications (including regimens with alternative antihypertensive medications)
  - Other variations in regimens
- Exclude: No MgSO<sub>4</sub> treatment (either placebo, no treatment, or non-MgSO<sub>4</sub> comparators)
  - Except retain RCTs with placebo, no treatment, or non-MgSO<sub>4</sub> comparators and NRCSs comparing MgSO<sub>4</sub> with no MgSO<sub>4</sub> for postpartum preeclampsia with severe features  
These may be included in network meta-analyses to indirectly compare alternative MgSO<sub>4</sub> regimens.

### Outcomes (prioritized outcomes have an asterisk and are in bold font)

- Severe maternal health outcomes
  - **Maternal mortality, including pregnancy-related mortality\***
  - **Severe maternal morbidity\* (e.g., eclampsia\*, stroke)**
- Newborn/child outcomes
  - **Infant morbidities\*** (e.g., respiratory depression, Apgar score)
  - **Breastfeeding outcomes\* (e.g., initiation, success, duration)**
  - Fetal/neonatal mortality
  - Cognitive function
- Healthcare utilization and functional status
  - Length of postpartum hospital stay
  - Time to ambulation

- Patient reported outcomes
  - Patient reported experience measures (PREMs) , for example
    - **Satisfaction with care\***
    - Quality of communication
    - Support to manage preeclampsia treatment
  - Patient reported outcome measures (PROMs), for example
    - **Global Quality of life\***, e.g., SF-36
    - **Specific to postpartum population\***, e.g., Mother-Generated Index, Functional Status After Childbirth scales
    - Psychosocial distress
      - **Anxiety\***, e.g., State-Trait Anxiety Inventory (STAI)
      - **Depression\***, e.g., Edinburgh Postnatal Depression Score (EPDS)
      - **Stress\***, e.g., Impact of Event Scale
    - **Maternal-neonatal bonding\***, e.g., Postpartum Bonding Questionnaire
- **Reduction of health disparities\*** (increase in disparities included under *Harms*)
- Maternal harms/adverse events
  - **Magnesium-related toxicity\*** (respiratory depression, loss of reflexes, reduced urine output, need for calcium infusion)\*
  - **Other clinically important adverse events\*** (e.g., hypotension, neuromuscular blockade)
  - **Adverse drug interactions\*** (e.g., with antihypertensive medications)
  - **Generation or exacerbation of health disparities\***
  - Other serious (e.g., severe flushing)

## Study Design

- Comparative studies (comparisons of different interventions)
  - Randomized controlled trials  $N \geq 10$  per group
    - Comparisons between  $MgSO_4$  and placebo/no treatment or non- $MgSO_4$  treatments must be randomized (for potential network meta-analyses)
  - Nonrandomized comparative studies (prospective or retrospective) that use statistical techniques (e.g., regression adjustment, propensity score matching, inverse probability weighting) to reduce bias due to confounding
- Any publication language (unless cannot be translated)
- Exclude
  - Single group (noncomparative) studies
  - Case-control studies
  - Claims database analyses
  - Feasibility studies
  - Qualitative studies
  - Conference abstracts prior to 2020 (without subsequent, eligible peer-reviewed publication)

## Timing

- Intervention: Peripartum (antenatal, during delivery hospitalization, postpartum)
- Outcomes: Any

**Setting**

- Inpatient management
- Any publication date
- Any country

**Contextual Question**

The Contextual Question will not be addressed by a formal systematic review. However, articles meeting the following criteria will be reviewed for potential inclusion.

**Population**

- Same as for KQs 1, 2, and 3

**Interventions/Comparators**

- Same as for KQs 1, 2, and 3

**Outcomes**

- Health disparities across populations defined by race, ethnicity, or social determinants of health (as discussed or described by authors)

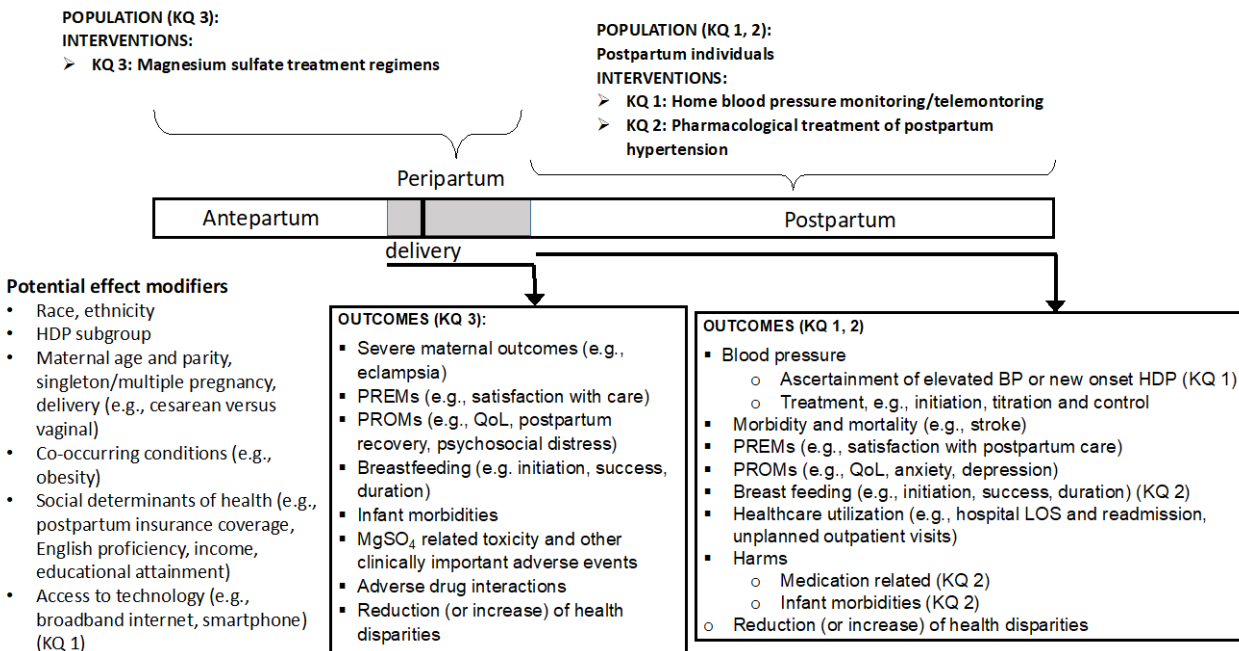
**Study Design**

- Any, including comparative, noncomparative (single group), qualitative studies, surveys, claims or other database analyses, narrative reviews

**Setting**

- Focus on evidence pertinent to the U.S.

### III. Analytic Framework



Abbreviations: BP = blood pressure, ED = Emergency Department, HDP = hypertensive disorders of pregnancy, HTN = hypertension, KQ = Key Question, LOS = length of stay, PREM = patient reported experience measure, PROM = patient reported outcome measure, QoL = quality of life

### IV. Methods

The systematic review for KQs 1, 2, and 3 will follow the Evidence-based Practice Center Program methodology, as described in its Methods Guide, particularly as it pertains to reviews of comparative effectiveness.<sup>23</sup> The Contextual Question will be addressed as a narrative review

**Criteria for Inclusion/Exclusion of Studies in the Systematic Review:** See detailed eligibility criteria in Section II.

In brief, for Key Question 1, we will include studies that compared home BP monitoring during the postpartum period (up to 1 year after delivery) with usual clinic-based BP monitoring or other non-clinic approaches (e.g., kiosks, pharmacy-based) or alternative home BP monitoring interventions (including alternative training, education, or alert triggering protocols). The ACOG classification for HDP subgroups will be used to categorize risk groups. We will evaluate outcomes as listed in the *Study Eligibility Criteria* section, focusing on the prioritized outcomes related to BP management, severe maternal health outcomes, PROMs,<sup>24</sup> PREMs<sup>25</sup>, healthcare utilization, disparities, and harms (see below).

For Key Question 2, we will include comparative studies of postpartum pharmacological treatments for HDP (specifically, antihypertensive medications and diuretics). We will evaluate outcomes as listed in the *Study Eligibility Criteria* section, focusing on listed prioritized outcomes related to BP management, severe maternal health outcomes, PROMs, PREMs, healthcare utilization, infant outcomes, disparities, and harms (see below).

For Key Question 3 we will evaluate the comparative effectiveness of alternative MgSO<sub>4</sub> treatment regimens in individuals who have preeclampsia with severe features (during the

peripartum period, including after hospital discharge). We will primarily evaluate studies that directly compare alternative regimens but will also attempt to conduct network meta-analysis that would include effectiveness RCTs (e.g., placebo-controlled) to include indirect comparisons of alternative MgSO<sub>4</sub> regimens. We will evaluate outcomes as listed in the *Study Eligibility Criteria* section, focusing on the prioritized outcomes related to severe maternal health outcomes, newborn/child outcomes, patient-reported outcome and experience measures, disparities, and harms (see below).

For all Key Questions, we will attempt to describe differential effects of interventions in different subgroups, including by race/ethnicity, maternal and pregnancy characteristics, co-occurring conditions, and potential indicators of social determinants of health. For KQ 3, we will also evaluate, timing with respect to delivery and subgroups with obesity or reduced kidney function.

With input from the TEP, we have prioritized the following list of outcomes. As described below, we will evaluate the strength of evidence (SoE) for these outcomes. We may also evaluate SoE for other included outcomes. The prioritized outcomes include:

#### **KQ 1**

- Ascertainment of elevated BP or new onset HDP
- Treatment initiation/discontinuation/adjustment and BP control
- Maternal morbidity and mortality
- Satisfaction with postpartum care
- Quality of life
- Psychosocial distress (anxiety, depression)
- Length of postpartum hospital stay
- Unplanned healthcare utilization (re-hospitalization, obstetrical triage area or clinic visits, emergency department visits)
- Reduction (or generation) of health disparities

#### **KQ 2**

- Blood pressure control
- Maternal morbidity and mortality
- Satisfaction with care
- Quality of life
- Psychosocial distress (anxiety, depression)
- Length of postpartum hospital stay
- Unplanned healthcare utilization (re-hospitalization, obstetrical triage area or clinic visits, emergency department visits)
- Breastfeeding
- Reduction (or generation) of health disparities
- Severe adverse events
- Severe infant morbidities

#### **KQ 3**

- Maternal morbidity and mortality
- Infant morbidities
- Breastfeeding
- Satisfaction with care

- Quality of life
- Postpartum recovery
- Maternal-neonatal bonding
- Psychosocial distress (anxiety, depression)
- Reduction (or generation) of health disparities
- Magnesium related toxicity
- Other clinically important adverse events
- Adverse drug interactions

### **Literature Search Strategies to Identify Relevant Studies to Answer the Key Questions:**

We will search for studies and existing systematic reviews in MEDLINE (via PubMed), the Cochrane Register of Clinical Trials, the Cochrane Database of Systematic Reviews, Embase, and CINAHL. Duplicate citations will be removed prior to screening. We will not apply language, date, or country restrictions. Search strategies will include filters to remove nonhuman studies and articles that are not primary studies, systematic reviews, or clinical practice guidelines.

The searches include MeSH or Emtree terms, along with free-text words, for concepts related to postpartum and peripartum care crossed with terms for hypertension, high blood pressure, preeclampsia, and eclampsia. The PubMed, Embase, Cochrane and CINAHL search strategies are detailed in Appendix A.

During screening of abstracts, we will also flag articles that may pertain to the Contextual Question. These may include single group (including registry) studies, qualitative and mixed-methods studies, and narrative reviews that specifically evaluate how race, ethnicity, and social determinants of health influence health disparities in individuals with HDP.

Additional 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 and guidelines will be screened for additional eligible studies.

As per our EPC's standard processes to conduct systematic reviews, we will take advantage of the machine learning capacities of Abstrackr (<http://abstrackr.cebm.brown.edu/>) to limit resources spent on abstract screening. We will train the machine learning algorithm as follows: (1) We will review the reference lists from known existing systematic reviews and clinical practice guidelines to identify potentially relevant studies for each KQ. (2) We will confirm this set of potentially relevant citations was successfully captured by our PubMed search. (3) Based on recently published work by Sampson et. Al.,<sup>26</sup> we will select the top 500 articles from our search using PubMed's best-match algorithm. (4) The articles from steps (1) and (3) will be entered into Abstrackr and screened by all team members, with resolution of all conflicts in conference. (5) Subsequently, citations found by the full literature searches will be added to the already-screened citations in Abstrackr, and abstract screening will continue in duplicate, with conflicts adjudicated in conference or by a third screener. (6) As screening progresses, the pretrained Abstrackr machine learning algorithm will continue to adapt and will sort the list of unscreened abstracts such that the most potentially relevant articles are presented first. This process will make screening more efficient and will enable us to capture the preponderance of relevant articles relatively early in the abstract screening process. (7) We will stop double screening when the predicted likelihood of the remaining unscreened papers being relevant is very low. We typically use a threshold for the prediction score of the unscreened citations of 0.40 (this threshold is based on experience with several dozen screening projects and an analysis in

preparation for publication but may be lowered depending on whether we continue to find eligible abstracts near the threshold). To confirm that the selected prediction score threshold is appropriate for this literature base, when the maximum prediction score is  $<0.40$ , we will screen at least 400 additional consecutive citations (this sample size is chosen because the upper 97.5% confidence interval bound for a proportion of  $0/400$  is less than 1%). If any of the 400 citations are screened in (at the abstract level), we will repeat the process (restart counting an additional 400 citations) until we have rejected at least 400 consecutive citations.

A Supplemental Evidence And Data for Systematic review (SEADS) portal will be available for this review. Additional articles suggested to us from any source, including peer and public review, will be screened applying identical eligibility criteria.

Potentially relevant citations will be retrieved in full text. Non-English language articles will be screened, and data extracted from full text, either by readers of the relevant languages or after translation via Google Translate (<https://translate.google.com/>), if possible. Searches will be updated during the draft report's public posting period.

### **Data Extraction and Data Management:**

Data from eligible studies will be extracted into the Systematic Review Data Repository Plus (SRDR+) software. Each article will be extracted by one researcher and entered data will be confirmed by a second researcher. Individual studies with multiple publications will be extracted as a single study (with a single entry in SRDR+). Articles that report multiple studies will be entered into SRDR+ separately for each study.

For each study, we will extract publication data, study design features, population characteristics, intervention and comparator names and descriptions, relevant outcomes and their definitions, and funding source. All subgroup analyses or other evaluations of heterogeneity of treatment effect will be extracted.

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

For randomized controlled trials (RCTs), including cluster randomized trials, we will complete the Cochrane Risk of Bias tool,<sup>27</sup> which addresses issues related to randomization and allocation concealment; blinding; deviations from intended intervention; missing data; outcome measurement; and reporting biases. We will also evaluate the adequacy of descriptions of study participants, interventions, outcomes, and study designs. In addition, we will assess the adequacy of analyses. Questions related to outcome assessor blinding, missing data, outcome measurement reporting adequacy, and analytic adequacy will be assessed for each outcome.

For nonrandomized comparative studies, we will add assessments of specific elements from ROBINS-I related to selection bias (comparability of groups) and relevant concepts addressed for RCTs (i.e., related to missing data, outcome measurement, analysis plan).<sup>28</sup> The questions will be assessed for each outcome (e.g., whether each outcome was adjusted for potential confounders).

### **Data Synthesis:**

We will summarize the evidence both narratively and, when feasible, quantitatively.

Each study 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. In text and tables, we will fully describe the characteristics of the

study participants (particularly including those related to subgroups of interest) and features of the interventions (particularly including those related to regimen details). In extraction and summary of NRCs, we will preferentially include adjusted over crude analyses.

Where appropriate and feasible, we will conduct random-effects meta-analyses of comparative studies if at least three studies are sufficiently similar in population, interventions, outcomes, and study design. Specific methods and metrics (summary measures) to be meta-analyzed will depend on available, reported study data, but we expect to summarize odds ratios of categorical outcomes and, if pertinent, standardized mean differences of net change of continuous outcomes (e.g., quality of life scores). For both KQ 2 and 3, we will explore the possibility of conducting network meta-analyses of RCTs of clinical outcomes to indirectly compare alternative treatment regimens (for HTN treatment and, separately, for MgSO<sub>4</sub> regimens) across studies. For KQ 3, RCTs that compare MgSO<sub>4</sub> with placebo, no treatment, or non-MgSO<sub>4</sub> treatments (which are not otherwise eligible) will be included in network meta-analyses to include indirect comparisons of alternative regimens. Separate network meta-analyses will be conducted for separate subpopulations (e.g., different HDP diagnoses, antenatal versus postpartum onset of preeclampsia with severe features).

As feasible, we will describe reporting of differences in effects and harms by different factors, subgroups, or predictors. We expect to primarily rely on reported within-study differences in effects (or harms). However, we will look for opportunities to qualitatively and/or quantitatively summarize and/or compare results across studies.

**Grading the Strength of Evidence for Prioritized Outcomes:** Following AHRQ Methods guidance<sup>33</sup> will evaluate the strength of evidence (SoE) addressing each prioritized outcome for each Key Question.

**Assessing Applicability:** For each Key Question, we will describe the applicability of the included studies primarily based on the studies' eligibility criteria and their included participants. We will describe the populations to which the evidence may be most applicable and will highlight populations for whom the evidence may be less applicable. We will assess such factors as prior history, age, and race/ethnicity. Other factors may include the age and geographic location of the study.

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## **VI. Definition of Terms and Abbreviations**

ACOG	American College of Obstetricians and Gynecologists
AHRQ	Agency for Healthcare Research and Quality
BP	Blood Pressure
CPG	Clinical practice guidelines
HELLP	Hemolysis, Elevated Liver enzymes and Low Platelets
HTN	Hypertension
KI	Key Informant
KQ	Key Question
QoL	Quality of Life
LOS	Length of Stay
MeSH	Medical Subject Heading
PICODTS	Population, Intervention, Comparator, Outcome, Design, Timing, and Setting details for systematic review search
PREM	Patient Reported Experience Measure that reflects the impact of the process of care on the patient's experience
PROM	Patient Reported Outcome Measure measuring patient perceptions of their health status
SEADS	Supplemental Evidence And Data for Systematic Review
SoE	Strength of Evidence
SRDR+	Systematic Review Data Repository Plus
TEP	Technical expert panel

## **VII. Summary of Protocol Amendments**

If we need to amend this protocol, we will give the date of each amendment, describe each 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 the public comments and seeking input from Key Informants (KIs).

## **IX. Key Informants (KIs)**

KIs are end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with a role in making health care decisions. Within the EPC program, the KIs' role is to provide input into refining the Key Questions for research that will inform healthcare decisions. The EPC solicits input from KIs when refining questions for systematic review. 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 \$5,000 and any other relevant business or professional conflicts of interest. Drawing upon their roles as end-users, diverse individuals are invited to serve as KIs. Those who present with potential conflicts can be retained although the TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## **X. Technical Expert Panel (TEP)**

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes. 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 the completion of a thoughtful, relevant systematic review. As such, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts.

Technical Experts provide further input to finalize the KQs, study eligibility criteria, and analysis plans. The Technical Experts provide feedback on the full protocol. They provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. They may help to identify particular studies or databases to search for studies to be included in the review. 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 although 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 \$5,000. 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 from participation in the review.

### **XIII. Role of the Funder**

This project is funded by the Patient-Centered Outcomes Research Institute (PCORI) and executed under AHRQ, U.S. Department of Health and Human Services through Contract Nos. 75Q80120D00001. 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 PCORI, AHRQ, 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).