Effective Health Care

Mental health treatments in pregnancy

Results of Topic Selection Process & Next Steps

The nominators, American College of Obstetrics and Gynecology (ACOG) and the American Psychiatric Association (APA), are interested in a new evidence review on Mental health treatments in pregnancy to inform clinical practice.

This topic will go forward for refinement as a new systematic review. The scope of this topic, including populations, interventions, comparators, and outcomes, will be further developed in the refinement phase. When key questions have been drafted, they will be posted on the AHRQ Web site and open for public comment. To sign up for notification when this and other Effective Health Care (EHC) Program topics are posted for public comment, please go to https://effectivehealthcare.ahrq.gov/email-updates.

Topic Brief

Topic Name: Mental health treatments in pregnancy, #0776, #0778

Nomination Date: 03/01/2018

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Summary

- This nomination meets all selection criteria.
- The topic is nominated by two partners who are committed to use the evidence to update clinical guidelines.
- The scope of a new review would likely be large.

Table of Contents

Background

Mental illness can complicate pregnancy and the postpartum period. The most common disorders affecting pregnant and postpartum women include depression (20%), anxiety (15%), substance abuse (5%) and bipolar disorder (1.5%). Among women who are pregnant, post-partum or breastfeeding, decisions about treatment for mental health conditions can be challenging. Women and their treating clinicians need to consider the comparative effectiveness and potential harms of different pharmacologic treatments on the mother and fetus/infant. The literature is complex, and difficult to interpret without substantial methodological expertise. A well-done systematic review that synthesizes the best available evidence on this topic would be of major benefit.

Nominator and Stakeholder Engagement: This topic brief addresses two separate nominations from ACOG and APA. ACOG and APA agreed to provide input on a single topic brief with the understanding that a single systematic review for each of their guideline efforts would be developed, if this were selected to go forward. ACOG and APA plan to develop separate clinical practice guidelines for their constituencies. ACOG and APA are engaged and committed to the topic. They worked together to prioritize KQs, to narrow the specific conditions, and to limit comparators.

The key questions for this nomination are:

1. Among reproductive age women with **any** mental health disorder, what are the **harms** associated with **pharmacologic** interventions during preconception, pregnancy and postpartum?

2. Among reproductive aged women with **any** mental health disorder, what are the **comparative harms** of pharmacologic interventions during preconception, pregnancy and postpartum?

3. Among pregnant or breastfeeding women, what is the **effectiveness** of interventions on **maternal** outcomes
    a. Among those with anxiety?
    b. Among those with depression?
    c. Among those with bipolar disorder?
    d. Among those with substance use disorder?

4. Among pregnant, or breastfeeding women, what is the is the **comparative effectiveness** of different treatments on **maternal** outcomes
    a. Among those with anxiety?
    b. Among those with depression?
    c. Among those with bipolar disorder?
    d. Among those with substance use disorder?

Contextual questions:

- Within a given disorder, what are the harms of NOT treating, of stopping a treatment, or of switching medications?
- Which of these harms are most important to patients and providers?

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, outcomes, and timing (PICOT) of interest (Table 1).

Table 1. Key Questions and PICOTs

PICOT			
Population:	KQ 1-2	• Reproductive age women (15-44 years old) with any mental health disorder (new or pre-existing)	
	KQ 3-4	• Women who are pregnant, postpartum, or breastfeeding, with new or pre-existing anxiety, depression, bipolar or substance use disorder	Other mental health conditions
Intervention(s):	KQ 1-4	• Pharmacologic intervention (eg antipsychotics, SSRI, lithium, anticonvulsants, substance abuse disorder treatments)	• Other Somatic treatments • Complementary and alternative medications • Non-pharmacologic intervention (eg psychotherapy, yoga, mindfulness, self-care)
Comparator(s):	KQ 1, KQ 3	• Placebo/no treatment	
	KQ 2, KQ 4	• Other pharmacologic intervention • Psychotherapy	• Yoga, Mindfulness, Self-care
Outcome(s):	KQ 3, KQ 4 benefits	<u>Maternal</u>: • Symptoms (response/remission) • Functional capacity • Quality of Life • Peripartum events (delivery mode, breastfeeding, weight gain) • Adherence to treatment/care	
	KQ 1, KQ 2 harms	*Maternal:* • Infertility • Miscarriage • Danger to self or infant • Substance use • All adverse events, related to treatment or discontinuation • Death *Fetal/Infant* • Death • Preterm birth/low birthweight • Congenital anomalies • Perinatal complications (low APGAR, withdrawal, respiratory distress, NICU time) • Poor infant attachment/bonding • Delayed social, emotional and cognitive development	
Timing:	KQ 1-2	All	
	KQ 3-4	From conception up to 1 year postpartum, or duration of breastfeeding	

Abbreviations: NICU: neonatal intensive care unit, SSRI: selective serotonin reuptake inhibitor

Methods

We assessed nomination Mental health treatments in pregnancy (#0776, #0778) for priority for a systematic review or other AHRQ EHC report with a hierarchical process using established selection criteria (Appendix A). Assessment of each criterion determined the need for evaluation of the next one.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years on the key questions of the nomination. See Appendix B for sources searched.

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a literature search in PubMed from 4/18/2013 to 4/18/2018. (Appendix C). We added primary research articles that we identified during the duplication search. We reviewed all identified titles and abstracts for inclusion and classified them by study design, to assess the size and scope of a potential evidence review. See Appendix C for the PubMed search strategy and links to the ClinicalTrials.gov search.

Value

We assessed the nomination for value. We considered whether or not the clinical, consumer, or policymaking context had the potential to respond with evidence-based change; and if a partner organization would use this evidence review to influence practice.

Compilation of Findings

We constructed a table with the selection criteria and our assessments (Appendix A).

Results

Appropriateness and Importance

This is an appropriate and important topic. Perinatal mental illness is a significant complication of pregnancy and the postpartum period. Common disorders include depression, anxiety, substance abuse and bipolar disorder. These disorders impair a woman's function and are associated with suboptimal development of her offspring.

The prevalence of depression is almost 20% during pregnancy and the first 3 months postpartum.[1] With about 4 million births per year in the USA[1], this corresponds to about 800,000 women affected by perinatal depression each year. For anxiety, the worldwide prevalence of any clinically diagnosed anxiety disorder was 15% in pregnant women. [2] According to Medicaid claims data, as of 2010, about 1.4% of pregnant women were taking an anti-psychotic (treatment for bipolar disorder) during pregnancy. [3]

In a 2012 national survey, 5.9% of pregnant women use illicit drugs and 8.5% drink alcohol, resulting in over 380,000 offspring exposed to illicit substances, over 550,000 exposed to alcohol. Between 2000 and 2009, the United States saw a five-fold increase in opiate use in pregnancy, coincident with the general epidemic of prescription opiate misuse.

For women who are pregnant, planning to become pregnant, post-partum or breastfeeding, decisions about treatment for mental health conditions can be challenging. Women and their treating clinicians need to consider the comparative effectiveness and potential harms of different pharmacologic treatments on the mother and fetus/infant.

Desirability of New Review/Duplication

A new evidence review on Mental health treatments in pregnancy would not be duplicative of an existing product.

We initially found 17 systematic reviews (SR). We excluded an EPC review of treatment of depression in pregnancy (2014)[4], and Cochrane review of postpartum depression (2014)[5] as both were outdated. We focus on those that are the most recent and with the most complete reporting of methods and results. We describe eight reviews below as they relate to each KQ.

KQ1: harms of medications: Although we identified six reviews they do not address the spectrum of medications and harms of interest to the nominators.

- Antidepressants
    - Prady et al assessed only two harms (low birth weight and neurodevelopmental outcomes) among children of pregnant women with depression, comparing those exposed to antidepressants to those not exposed, but the search date ended January 2015, so this is likely outdated. [7] Also, the specific type of antidepressant is not delineated.
    - Another good quality review assessed autism spectrum disorders among children of women exposed to antidepressants from preconception through delivery, compared to women with depression but without drug exposure. (10 studies, search end May 2016). [8]
    - One review assessed fertility outcomes for women exposed to antidepressants. (4 studies, search end November 2015). [9]
    - We found no reviews on any other maternal or fetal harms.

- Antipsychotics
    - A large review examined maternal (miscarriage, stillbirth) and neonatal outcomes for pregnant women treated with lamotrigine for either bipolar disorder or epilepsy. Comparators were disease matched controls and healthy controls. search date ended June 2016. [10]

[1] https://www.statista.com/statistics/195908/number-of-births-in-the-united-states-since-1990/

- A review evaluated drug levels or neonatal harms among infants of breastfeeding women treated with antipsychotics. However, drug levels were not an outcome of interest, and it was unclear how many of the 56 included studies reported harms. The full text was not available, and the search end date was not specified. [11]

- We found no reviews of harms of other antipsychotics.

- Opioid use disorder treatment
  - Klaman et al performed a systematic review for SAMHSA on the use of medication assisted therapy (MAT) for pregnant women with opioid use disorder. This was a comprehensive but qualitative review, which used the Rand Appropriateness Method. [6]

  - We found no reviews for alcohol use disorders, and no quantification of opioid treatment harms.

KQ2: comparative harms:

- Only one review mentioned that the intervention (lamotrigine) was compared to another medication. [10] However, we were unable to access the full report to review in detail.

KQ3: effectiveness for specific disorders;

- No recent reviews were found for effectiveness in anxiety, depression, bipolar or substance use disorders.

KQ4: comparative effectiveness for specific disorders:

- Anxiety disorder:
  - One recent review examined symptom relief among women with anxiety disorders treated with an SSRI. Comparators were TCA or psychotherapy. They found 18 studies, with a search date ending January 2015. [12] This search strategy could be updated.
- We found no recent reviews for depression, bipolar or substance use disorders.

The limitations of existing reviews suggest that a new review is needed. The largest gaps seem to be in comparative effectiveness (KQ4), effectiveness (KQ3) and comparative harms (KQ2). The nominators are interested in a wide array of maternal and child outcomes that are not covered by the existing reviews. Additionally, the current reviews cover only a few of the pharmacotherapies of interest.

See Table 2, Duplication column.

Impact of a New Evidence Review

A new systematic review on the Mental health treatments in pregnancy may have a high level of impact. ACOG has a practice bulletin “Use of Psychiatric Medications during Pregnancy and Lactation” that was published in 2009, and reaffirmed in 2018. However, only 4 of 14 recommendations are based on good quality (“Level A”) evidence. The others are based on limited data and expert opinion. [13] The APA and ACOG jointly published a guide to management of depression in pregnant women. [14] Although it was reaffirmed in 2014, the guidance was based on expert opinion. Because of these limitations, each organization could only offer only weak clinical recommendations.

Feasibility of a New Evidence Review

A new evidence review examining mental health treatments in pregnancy is feasible. We found 106 primary studies published in the last five years. These are described as they relate to KQs:

For KQ1 (harms), we found 87 primary studies (80 cohort studies, six case control, one case series, and no RCTs). [15-101] Of the 80 cohort studies, one fourth were from large registries that linked maternal and infant outcomes. For example, five publications were based on the Norwegian Mother and Child Cohort Study that followed >50,000 pregnancies. [23,24,41,64,84]

Studies were distributed unevenly across medication classes: antidepressants (60); antipsychotics (27); anxiolytics (18); stimulants for attention deficit hyperactivity disorder (ADHD) (18); substance use disorder (SUD) (opioids- 12). Some studies evaluated more than one medication class. Thirty studies specifically address fetal/infant harms of SSRIs, such as congenital birth defects, perinatal outcomes, and neurologic development.

For KQ2 (comparative harms) we identified 11 studies (10 cohort studies, one case control).[28,55,71,74,76,78,98,99,102-104] In this group, only one cohort study was large (n>100,000 from Medicaid claims data), and the rest were much smaller studies. By medication class, we found studies covering antidepressants (6); antipsychotics (2); SUD (opioids -3).

For KQ3 (effectiveness), we found 16 studies (10 cohort studies, 2 feasibility and 4 RCTs).[31,78,97,105-117] All five RCT evaluated postpartum depression. Studies were distributed by medication class: antidepressants (11); antipsychotics (3); anxiolytics (1); SUD (opioids -1)

KQ4 (comparative effectiveness) included 6 studies (one RCT; five cohort).[71,78,111,118-120] The RCT examines postpartum depression. Studies were distributed by medication class: antidepressants (4); antipsychotics (1); SUD (opioids -1)

The search of clinicaltrials.gov yielded 11 results; four did not include outcomes of interest. Of the remaining seven, five are recruiting, two are not yet recruiting. Five pertain to postpartum depression. One RCT plans to compare a drug to a behavioral intervention for pregnant women with depression, and to evaluate both maternal and child outcomes (KQ4). Planned completion dates for these studies range from June 2018 to June 2021. Because of the timeframe it is unlikely these results could be included in a new review funded by AHRQ at this time.

These results show that the available literature has increased since the last systematic reviews that were used to develop clinical guidelines. This is especially true for harms of antidepressants, and specifically for SSRIs. This is encouraging, given that perinatal depression is common and often treated with SSRIs. There appears to be an overwhelming need to synthesize the literature to inform clinical decision making. As expected, we found few RCTs. We found few studies of medications for SUD, and none of these addressed more common alcohol abuse disorder.

We estimate that this will be a large review. The search strategies that we used were not exhaustive. The duplication search and the feasibility search results only showed a small overlap, which suggests that additional search strategies (targeting specific diagnoses and drug classes) might double the volume of study results.

See Table 2, Feasibility column.

Table 2. Key questions and Results for Duplication and Feasibility

Key Question	Duplication (04/2015 -04/2018)	Feasibility (04/2013 -04/2018)
KQ 1: Harms of any pharmacotherapy	Total number of identified systematic reviews: Six • Antidepressants (3) • Antipsychotics (2) • Opioid use disorder (1)	<u>Size/scope of review</u> Relevant Studies Identified: 87 o Type: 80 cohort studies, 6 case control, one case series and no RCTs <u>Clinicaltrials.gov</u>

Key Question	Duplication (04/2015 -04/2018)	Feasibility (04/2013 -04/2018)
		• Recruiting: 1 • Active: 0 • Complete: 0
KQ 2: Comparative harms of any pharmacotherapy	Total number of identified systematic reviews: One • Lamotrigine	Size/scope of review Relevant Studies Identified: 11 o 10 cohort studies, one case control Clinicaltrials.gov • Recruiting: 0 • Active: 0 • Complete: 0
KQ 3: Effectiveness of pharmacotherapy for: anxiety, depression, bipolar disorder, substance use disorder	Total number of identified systematic reviews: None •	Size/scope of review Relevant Studies Identified: 16 o 10 cohort studies, 4 RCTs, 2 feasibility Clinicaltrials.gov • Recruiting: 6 • Active: 0 • Complete: 0
KQ 4: Comparative Effectiveness of pharmacotherapy for: anxiety, depression, bipolar disorder, substance use disorder	Total number of identified systematic reviews: One • Anxiety disorder: SSRI compared to tricyclics	Size/scope of review Relevant Studies Identified: 6 o one RCT; 5 cohort Clinicaltrials.gov • Recruiting: 1 • Active: 0 • Complete: 0

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question;

Value

The potential for value is high given justification for value assessment. Both ACOG and APA intend to use the SR to update their guidelines. Each has an established process to use evidence wisely during guideline development. Both organizations are well-poised to influence practice, since they reach a large constituency.

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review would not be duplicative of an existing product. We identified six reviews, but the best of these (on depression) is outdated, and the others do not cover the breadth of the nominators topic.
- Impact: A new systematic review has high impact potential. Clinicians lack evidence-based recommendations.
- Feasibility: A new review is feasible. The evidence base is likely large, with several large registry studies contributing much needed data.
- Value: The potential for value is high. Both nominators intend to use the SR to update their guidelines.

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Appendix A. Selection Criteria Summary

Selection Criteria	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes
1b. Is the nomination a request for a systematic review?	Yes
1c. Is the focus on effectiveness or comparative effectiveness?	Yes
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes
2a. Represents a significant disease burden; large proportion of the population	Yes. Mental illness affects over 20% of pregnant/peripartum women, and the most common conditions are depression, anxiety, substance abuse and bipolar disorders.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes. Mental illness has significant effects on maternal and fetal health. Treatments vary in their effectiveness, and treatment may be discontinued due to perceived harms to the fetus/infant.
2c. Represents important uncertainty for decision makers	Yes. Decision-making requires up-to-date information on comparative effectiveness and harms, but the literature is complex and difficult to interpret.
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes. In addition to standard harms/benefits for the affected patient (maternal) the clinician must incorporate potential harms to the infant/fetus. These harms must be balanced with the harms of not treating the mother.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes.
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	Yes, it is not redundant. Existing SRs do not cover the breadth of KQs.
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes. ACOG and APA have published guidance that is based on expert opinion, and outdated literature. Neither organization can provide the evidence-based recommendations that clinicians need.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Unsure
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review	The volume is adequate for a new review. We found 106 primary studies, distributed as KQ1 (81), KQ2 (11), KQ3 (16), KQ4 (6). Many of these arise from large, well designed registries

- Newly available evidence (particularly for updates or new technologies)	that link maternal and infant outcomes. We estimate this would be a large review.
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes. Both ACOG and APA intend to use the SR to update their guidelines. Each has an established process to use evidence in their guidelines. Both organizations are well-poised to influence practice, since they reach a large constituency.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question;

Appendix B. Search for Evidence Reviews (Duplication)

Listed are the sources searched.

Search date: January 1, 2015 to April 6, 2018
AHRQ: Evidence reports and technology assessments, USPSTF recommendations
VA Products: HSR&D **(ESP)** publications, and VA/DoD EBCPG Program
Cochrane Systematic Reviews and Protocols http://www.cochranelibrary.com/
PubMed
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/

Appendix C. Search Strategy & Results (Feasibility)

Topic: Mental Health Treatments in Pregnancy April 18, 2018 Database Searched: MEDLINE(PubMed)	Dates: 4/18/2013 to 4/18/2018
Concept	Search String
Harms	**((harm[Title/Abstract] OR harms[Title/Abstract] OR safety[Title/Abstract] OR adverse[Title/Abstract] OR contraindication[Title/Abstract])) OR (("Patient Harm"[Mesh]) OR ("Long Term Adverse Effects"[Mesh] OR "adverse effects" [Subheading]))**
AND	
Pharmacologic Interventions	**((drug[Title/Abstract] OR pharmacologic[Title/Abstract] OR medicine[Title/Abstract] OR medication[Title/Abstract])) OR ("Drug Therapy"[Mesh] OR "drug therapy" [Subheading])**
AND	
Mental health disorders	**(((mental[Title/Abstract]) AND (health[Title/Abstract] OR illness[Title/Abstract] OR disorders[Title/Abstract]))) OR (("Mental Health"[Mesh]) OR "Mental Disorders"[Mesh])**
AND	
Preconception through Postpartum	**((preconception[Title/Abstract] OR pregnant[Title/Abstract] OR pregnancy[Title/Abstract] OR prenatal[Title/Abstract] OR postpartum[Title/Abstract] OR postnatal[Title/Abstract] OR perinatal[Title/Abstract] OR antenatal[Title/Abstract])) OR (("Maternal Health Services"[Mesh]) OR "Pregnant Women"[Mesh])**
NOT	
Not Editorials, etc.	((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type])) OR "Newspaper Article"[Publication Type]
AND	
Limit to last 5 years ; human ; English ; adult women	Filters activated: published in the last 5 years, Humans, English, Female, Adult: 19+ years
N=481	
Systematic Review N=26	PubMed subsection “Systematic [sb]”
https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/54780905/public/	
Randomized Controlled Trials N=85	Cochrane Sensitive Search Strategy for RCT’s “(((((((groups[tiab])) OR (trial[tiab]))

	OR (randomly[tiab])) OR (drug therapy[sh])) OR (placebo[tiab])) OR (randomized[tiab])) OR (controlled clinical trial[pt])) OR (randomized controlled trial[pt])”
https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/54780930/public/	
Other N=370	
https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/54780943/public/	

Clinical Trials.Gov search and yield:

24 Studies found for: **pregnancy | Recruiting, Active, not recruiting, Completed Studies | Mental Disorder | Drug Trial | Studies with Female Participants | Adult | Start date from 04/18/2013 to 04/18/2018**