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

Supplemental Evidence and Data Request on Maternal and Fetal Effects of Mental Health Treatments in Pregnant and Breastfeeding Women: A Systematic Review of Pharmacological Interventions

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

ACTION: Request for Supplemental Evidence and Data Submissions

SUMMARY: The Agency for Healthcare Research and Quality (AHRQ) is seeking scientific information submissions from the public. Scientific information is being solicited to inform our review on *Maternal and Fetal Effects of Mental Health Treatments in Pregnant and Breastfeeding Women: A Systematic Review of Pharmacological Interventions,* which is currently being conducted by the AHRQ's Evidence-based Practice Centers (EPC) Program. Access to published and unpublished pertinent scientific information will improve the quality of this review.

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

ADDRESSES:

E-mail submissions: epc@ahrq.hhs.gov.

Print submissions:

Mailing Address:

Center for Evidence and Practice Improvement

Agency for Healthcare Research and Quality

ATTN: EPC SEADs Coordinator

5600 Fishers Lane

Mail Stop 06E53A
Rockville, MD 20857

Shipping Address (FedEx, UPS, etc.):
Center for Evidence and Practice Improvement
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ATTN: EPC SEADs Coordinator
5600 Fishers Lane
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FOR FURTHER INFORMATION CONTACT:
Jenae Benns, Telephone: 301-427-1496 or Email: epc@ahrq.hhs.gov.

SUPPLEMENTARY INFORMATION:
The Agency for Healthcare Research and Quality has commissioned the Evidence-based Practice Centers (EPC) Program to complete a review of the evidence for *Maternal and Fetal Effects of Mental Health Treatments in Pregnant and Breastfeeding Women: A Systematic Review of Pharmacological Interventions*. AHRQ is conducting this systematic review pursuant to Section 902(a) of the Public Health Service Act, 42 U.S.C. 299a(a).

The EPC Program is dedicated to identifying as many studies as possible that are relevant to the questions for each of its reviews. In order to do so, we are supplementing the usual manual and electronic database searches of the literature by requesting information from the public (e.g., details of studies conducted). We are looking for studies that report on *Maternal and Fetal Effects of Mental Health Treatments in Pregnant and Breastfeeding Women: A Systematic Review of Pharmacological Interventions*, including those that describe adverse events. The entire research protocol, including the key

questions, is also available online at: https://effectivehealthcare.ahrq.gov/topics/mental-health-pregnancy/protocol

This is to notify the public that the EPC Program would find the following information on Maternal and Fetal Effects of Mental Health Treatments in Pregnant and Breastfeeding Women: A Systematic Review of Pharmacological Interventions helpful:

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

Your contribution is very beneficial to the Program. Materials submitted must be publicly available or able to be made public. Materials that are considered confidential; marketing materials; study types not included in the review; or information on indications not included in the review cannot be used by the

EPC Program. This is a voluntary request for information, and all costs for complying with this request must be borne by the submitter.

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

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

The Key Questions

Key Question 1: Among pregnant and postpartum women, what is the effectiveness of pharmacologic interventions on maternal outcomes?

a. Among those with a new or preexisting anxiety disorder?
b. Among those with a new or preexisting depressive disorder?
c. Among those with a new or preexisting bipolar disorder?
d. Among those with new or preexisting schizophrenia?

Key Question 2: Among pregnant and postpartum women, what is the comparative effectiveness of pharmacologic interventions on maternal outcomes?

a. Among those with a new or preexisting anxiety disorder?
b. Among those with a new or preexisting depressive disorder?
c. Among those with a new or preexisting bipolar disorder?
d. Among those with new or preexisting schizophrenia?

Key Question 3: Among reproductive-aged women with any mental health disorder, what are the maternal and fetal harms associated with pharmacologic

interventions for a mental health disorder during preconception, pregnancy, and postpartum?

Key Question 4: Among reproductive-aged women with any mental health disorder, what are the comparative maternal and fetal harms of pharmacologic interventions for a mental health disorder during preconception, pregnancy, and postpartum?

Contextual Question 1: Among women who are preconceptional, pregnant, or postpartum, within a given disorder, what are the harms of NOT treating or stopping a pharmacological treatment, or of switching medications?

Table 1. PICOTS (Populations, Interventions, Comparators, Outcomes, Timing, Settings) and Inclusion/exclusion criteria

PICOTS	**Inclusion**	**Exclusion**
Population	KQ 1, KQ 2: Women who are pregnant or postpartum with new or preexisting diagnosis of anxiety, depression, bipolar disorder, or schizophrenia • Anxiety disorders include DSM 5 and DSM-IV diagnoses (including generalized anxiety disorder, panic disorder, social anxiety disorder [social phobia], obsessive compulsive disorder [OCD]; and posttraumatic stress disorder). • Depressive disorders include major depressive disorder KQ 3, KQ 4: Reproductive-aged women (15-44 years old during preconception [≤12 weeks before pregnancy], pregnancy, and postpartum [through 1 year]) with any mental health disorder (new or preexisting)	KQs 1, 2: Studies of women with disorders other than anxiety (including PTSD and OCD), depression, bipolar disorder, and schizophrenia KQs 3, 4: <90% of reproductive age (15-44) KQs 1-4: Studies with 100% substance use disorders
Intervention[†]	Pharmacologic interventions for a mental health disorder including: • Antipsychotics (haloperidol, chlorpromazine, aripiprazole, quetiapine, olanzapine, risperidone, clozapine, lurasidone, paliperidone, fluphenazine, perphenazine, iloperidone, asenapine, brexpiprazole, and ziprasidone) • SSRIs and serotonin modulators (citalopram, escitalopram, fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, trazodone, vilazodone, and vortioxetine) • SNRIs (venlafaxine, desvenlafaxine, milnacipran, and duloxetine) • Tricyclic antidepressants (amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, and trimipramine)	All other interventions

PICOTS	Inclusion	Exclusion
	• Other antidepressants (bupropion, mirtazapine) • Mood stabilizers (lithium) • Antianxiety agent (benzodiazepines [alprazolam, clobazam, clonazepam, clorazepate, clonidine, chlordiazepoxide, diazepam, lorazepam, temazepam, and triazolam] and buspirone) • Anticonvulsants (valproate, carbamazepine, oxcarbazepine, topiramate, and lamotrigine) • Other medications for a mental health disorder (gabapentin, zolpidem, eszopiclone, zaleplon, ramelteon, diphenhydramine, lisdexamfetamine, and hydroxyzine)	
Comparator	KQ 1, KQ 3: Placebo or no treatment KQ 2, KQ 4: Other pharmacologic interventions, any psychotherapy, combined pharmacotherapy, and psychotherapy	KQ 1, KQ 3: Active comparators, no comparators KQ 2, KQ 4: • Treatments other than pharmacologic interventions or psychotherapy (e.g., yoga, mindfulness, self-care, nutritional or herbal supplements) • No comparators • Placebo or no treatment comparators

Outcomes‡	KQ 1, KQ 2: Effectiveness
	• Final health outcomes (maternal benefits)
	• Symptoms (response/remission/relapse, suicidal ideation)
	• Functional capacity*
	• Quality of life*
	• Peripartum events (delivery mode, breastfeeding, weight change)
	• Adherence to treatment/care/discontinuation
	Suicidal events
	
	KQ 3, KQ 4: Harms
	• Maternal harms
	  ○ Harms specific to pregnancy and breastfeeding (infertility, miscarriage, abruption, preterm labor/preterm birth, preeclampsia, gestational hypertensive disorders, glucose intolerance/gestational diabetes mellitus, reduced milk production in breastfeeding/undesired weaning)
	  ○ Danger to self or infant
	  ○ Misuse of prescription medication
	  ○ Serious adverse events related to treatment
	  ○ Death
	• Fetal/infant/child harms
	  ○ Preterm birth/small for gestational age or large for gestational age
	  ○ Congenital anomalies
	  ○ Perinatal complications (low APGAR, withdrawal, respiratory distress, neonatal intensive care unit time, persistent pulmonary hypertension)
		All other outcomes

PICOTS	Inclusion	Exclusion
	○ Poor infant attachment/bonding*† ○ Delayed social, emotional, and cognitive development* ○ Death ○	
Time frame	Followup KQ 1, KQ 2: From conception up to 1 year postpartum for maternal outcomes KQ 3, KQ 4: All	Followup • KQ 1, KQ 2: more than 12 weeks preconception for maternal preconception outcomes, more than 1 year for maternal postpartum outcomes • KQ 3, KQ 4: None •
Settings§	Clinical setting All settings	Clinical setting None
Study design	• RCTs, CCTs, case-control studies, cohort studies with comparison arms • Reference lists of relevant systematic reviews published in 2013 or later will be used to ensure our search strategies captured all relevant studies.	All other designs and studies using included designs that do not meet the sample size criterion
Language	Studies published in English	Studies published in languages other than English

* We will limit included outcomes to those using validated measures. Another potential exclusion, depending on volume of yield, includes studies that fail to control for confounding.

† Drugs such as brexanolone that are awaiting FDA approval will be included in the review once they are approved ‡We will focus strength of evidence (SOE) grades on outcomes prioritized by the Technical Expert Panel (TEP).

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§ Depending on volume, we may limit the primary analysis to studies from geographic settings with resources comparable or applicable to the United States

Dated: 4 December 2019

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