

Maternal, Fetal, and Child Outcomes of Mental Health Treatments in Women: A Systematic Review of Perinatal Pharmacologic Interventions

Evidence Summary



Main Points

- Few studies have been conducted in pregnant and postpartum women on the benefits of pharmacotherapy; many studies report on harms but are of low quality.
- Brexanolone probably improves depressive symptoms; it may increase the risk of sedation or somnolence, leading to dose interruption or reduction.
- Sertraline may improve response, remission, and depression and anxiety symptoms.
- Mood stabilizers may reduce recurrence and increase time to recurrence.
- Although associations may exist between psychotropic medications and adverse events, causality cannot be inferred.
- First-trimester exposure to lithium is more likely to be associated with overall congenital and cardiac anomalies than first trimester exposure to lamotrigine, which can inform the decision to switch a medication in a successfully treated individual.
- We did not find eligible evidence on congenital anomalies for triazolam, alprazolam, valproate, carbamazepine, clonazepam, and topiramate, although evidence is available from studies of other populations ineligible for this review.
- The paucity of evidence does not mean that pharmacotherapy is not beneficial, nor that harms do not exist; rather, it underscores the absence of high-quality research.



Background and Purpose

Untreated mental health disorders in perinatal (pregnant and postpartum, including breastfeeding) women can have devastating sequelae. Pregnancy-associated suicide kills more women than hemorrhage or preeclampsia. Depressive symptoms are associated with reduced safety for the child, increased harsh punishment, impaired development of infant emotional regulation and attachment, and greater risk of psychiatric disease in the

child. Treatment choices for mental health disorders include pharmacotherapy, psychotherapy, and other approaches (e.g., yoga, mindfulness, self-care, nutritional or herbal supplements). For women who are currently or planning to become pregnant, a critical question is whether the benefits for mother and fetus of treating psychiatric illness with pharmacologic interventions outweigh the harms; a systematic review will help clarify the balance of benefits and harms.



Methods

We employed methods consistent with those outlined in the Agency for Healthcare Quality and Research Evidence-based Practice Center Program Methods Guidance (<https://effectivehealthcare.ahrq.gov/topics/ebp-methods-guide/overview>), and we describe these in the full report. Our searches covered publication dates in PubMed®, the Cochrane Library, Embase®, and PsycINFO® from inception through June 5, 2020. We surveilled key journals and PubMed through March 2, 2021.



Results

A total of 164 studies (168 articles) met eligibility criteria. Most studies were observational in design and had high risk of bias; they cannot fully address confounding. The associations between psychotropic medications and outcomes reported in observational studies cannot be inferred to be causal and varied by exposure and outcome.

Key Question (KQ) 1: Benefits of Pharmacologic Treatments Versus No Treatment or Placebo for Pregnant and Postpartum Women With Anxiety, Depression, Bipolar Disorder, or Schizophrenia. Substantial evidence exists on the effectiveness of medications in the general population, but evidence in pregnant and postpartum women is sparse (9 randomized controlled trials [RCTs] and 10 observational studies). When evidence was available, we found low to moderate strength of evidence of benefit. Specifically, for depression, three RCTs offered evidence that brexanolone for depression onset in the third trimester or postpartum is associated with improved depressive symptoms shortly after infusion (60 hours) and at 30 days after treatment (moderate strength of evidence); two RCTs reported that sertraline in the postpartum period achieves response, remission, and improvements in depressive symptoms (low strength of evidence). For bipolar disorders, two cohort studies found that discontinuing mood stabilizers during pregnancy may increase recurrence and reduce time to recurrence (low strength of evidence).

KQ 2: Comparative Benefits of Pharmacologic Treatments for Pregnant and Postpartum Women With Anxiety, Depression, Bipolar Disorder, or Schizophrenia. For depression and bipolar disorder, we found insufficient evidence to judge the comparative effectiveness of a very limited number of outcomes and interventions from one RCT and four observational studies of exposure during pregnancy. For anxiety and schizophrenia, we found no evidence on comparative effectiveness.

KQ 3: Harms of Pharmacologic Treatments Versus No Treatment or Placebo for Pregnant and Postpartum Women With Mental Health Disorders. We found 5

RCTs and 70 observational studies. As a result, most studies could not assert a causal relationship between exposure and resultant harms. We found low strength of evidence for several outcomes. Regarding maternal harms, benzodiazepine before conception may be associated with an increased risk of ectopic pregnancy. During pregnancy, exposure to several antidepressants may be associated with a higher risk of postpartum hemorrhage; serotonin-norepinephrine reuptake inhibitor (SNRIs) and tricyclic antidepressants may be associated with an increased risk of preeclampsia; SNRIs may be associated with spontaneous abortion; and quetiapine and olanzapine may be associated with an increased risk of gestational diabetes. For depression onset in the third trimester or within 4 weeks of birth, brexanolone may be associated with the risk of sedation or somnolence leading to dose interruption or reduction. For child adverse outcomes, we found an association between benzodiazepine and neonatal intensive care unit admissions; between selective serotonin reuptake inhibitors and respiratory issues, low Apgar scores, persistent pulmonary hypertension of the newborn, and depression in children; and between citalopram and autism spectrum disorder. Signals of harms that we identified above may be partially or wholly attributable to residual confounding. Importantly, we found insufficient evidence on congenital anomalies and cardiac defects from studies included our review. We note, however, that we did not find eligible evidence on congenital anomalies for triazolam, alprazolam, valproate, carbamazepine, clonazepam, and topiramate, although evidence is available from studies of other populations ineligible for this review.

KQ 4: Comparative Harms of Pharmacologic Treatments for Pregnant and Postpartum Women With Mental Health Disorders. We found 1 RCT and 55 observational studies; limiting causal inference regarding exposures and resultant harms. Evidence from one study suggested that the association between first trimester exposure to lithium and overall congenital anomalies and cardiac anomalies may be greater than the association between first trimester exposure to lamotrigine and the same outcomes (low strength of evidence) during pregnancy, which can inform the decision to switch a medication in a successfully treated individual. The evidence is insufficient for all other comparisons and outcomes.



Limitations

We identified few randomized controlled RCTs of pharmacotherapy for mental health disorders during pregnancy or lactation; therefore we relied on observational studies for the bulk of this review. A significant constraint to interpreting the evidence is the widespread risk of confounding. Underlying mental health disorders result in the use of psychotropic medications. Underlying mental health disorders may also result in some of the harms investigated in this review regardless of exposure to medications. Studies varied greatly in the extent to which they were able to address underlying severity of mental health disorders. The majority were unable to address confounding, often because of a lack of the necessary variables in registry datasets. A small subset of studies attempted various approaches to address confounding (e.g., propensity score adjustment, stratification by number of disorders). In many instances, controls for confounding reduced the effect size and, in some instances, reversed the direction of effect. Most studies were unable to identify dose and duration of exposure. For the benefits question

(KQ 1), eligible studies had comparator arms of women with the same disorder as in the treatment arm. For the harms question (KQ 3), however, we were more inclusive and included studies with comparator arms comprising women with prior exposure to the drug, even if the disorder status was not specified. As a result, our KQ 1 evidence base controls for underlying severity as a confounder better than the KQ 3 evidence base.

We elected to restrict the evidence to women with mental health disorders as a means of reducing the potential for confounding in the evidence base. However, this criterion excluded studies of well-conducted negative controls that might bolster the evidence on the association between the exposure and the outcome. Also, this criterion resulted in the exclusion of studies reporting on relevant outcomes for exposures to the intervention for other clinical conditions. Studies of multiple drug exposures presented results for each exposure but did not always present results separately for the women with multiple drug exposures. In these studies with overlapping arms, we were not able to attribute the effect of the intervention to a single drug. As a result, we excluded these studies. The exclusion of studies with overlapping arms also restricted the comprehensiveness of our review. These limitations of the evidence and of our review criteria mean that the signals of harms that we identified above may be partially or wholly attributable to residual confounding. We may also have missed eligible studies because of our restriction to English language studies.



Implications and Conclusions

The central decisional dilemma facing pregnant and postpartum women with mental health disorders and their healthcare providers is how to balance benefits and harms of psychotropic drugs for both themselves and their children. One such critical trade-off is whether improved symptoms in the mother outweigh the harms from potential congenital anomalies in the fetus. Given long-standing restrictions on including pregnant and lactating women in clinical trials, few clinical trials have evaluated the effectiveness of pharmacotherapy. By contrast, evidence is voluminous but of low quality on the harms of pharmacotherapy. Our findings indicate the need for clear communication to patients on four primary points: (1) evidence exists that medication works in the general populations; (2) few studies have measured effectiveness in pregnant women; (3) the limited evidence available is consistent with some benefit; and (4) some studies suggested some increased adverse events, many of which are rare or transient. However, because these studies could not rule out the severity of the underlying mental health disorder as the cause of the association, the causal link between the exposure and adverse events is unclear. The patient and her provider are uniquely qualified to determine whether the mother's medical need for treatment exceeds any potential harms.

Full Report

Viswanathan M, Middleton JC, Stuebe A., Berkman N., Goulding AN, McLaurin-Jiang S, Dotson AB, Coker-Schwimmer M, Baker C, Voisin C, Bann C, Gaynes BN. Maternal, Fetal, and Child Outcomes of Mental Health Treatments in Women: A Systematic Review of Perinatal Pharmacologic Interventions. Comparative Effectiveness Review No. 236. (Prepared by the RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center under Contract No. 290-2015-00011-I.) AHRQ Publication No. 21-EHC001. Rockville, MD: Agency for Healthcare Research and Quality; April 2021. DOI: <https://doi.org/10.23970/AHRQEPCCER236>. Posted final reports are located on the Effective Health Care Program [search page](#).

