

Draft Systematic Review

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Treatment of Depression During Pregnancy and the Postpartum Period

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.
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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In designing the review questions and methodology at the outset of this report, the EPC with consulted several technical and content experts, reflecting a variety of viewpoints relevant to this topic. Technical experts consulted are expected to have divergent and possibly conflicting opinions. This diversity is helpful in achieving a well-rounded report. The study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

Treatment of Depression During Pregnancy and the Postpartum Period

Structured Abstract

Objectives. To evaluate the benefits and harms of pharmacological therapy for depression in women during pregnancy or the postpartum period.

Data sources. Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Cumulative Index to Nursing and Allied Health Literature (CINAHL®), MEDLINE®, Scopus, ClinicalTrials.gov, and Scientific Information Packets from pharmaceutical manufacturers.

Review methods. We included studies comparing pharmacological treatments for depression during or after pregnancy with each other, with nonpharmacological treatments or with usual care/no treatment. Outcomes included both maternal and infant or child benefits and harms. Dual review was used for study inclusion, data abstraction and quality assessment. We assessed study quality using methods of the Drug Effectiveness Review Project. We graded the strength of the body of evidence according to the methods of the Effective Healthcare Program.

Results. We included 6 RCTs and 13 observational studies that provide direct evidence on benefits and harms of pharmacologic treatment in pregnant women with depression. This evidence was insufficient for the outcomes of maternal depression symptoms, functional capacity, breastfeeding, infant and child development and preterm birth. Low strength evidence suggests that neonates of women with depression taking selective serotonin reuptake inhibitors (SSRIs) had higher risk of respiratory distress than neonates of untreated women but that there is no difference in risk of neonatal convulsions. Direct evidence on the risk of major malformations was insufficient to draw conclusions. To address gaps, we included indirect evidence from an additional 104 observational studies of pregnant women receiving antidepressants for mixed or unreported reasons compared with pregnant women not taking antidepressants whose depression status was unknown. Signals from this evidence suggest that future research should focus on the risk of congenital anomalies and the diagnosis of autism spectrum disorder or attention deficit disorder in the child associated with antidepressant use for depression in pregnancy and, making comparisons across the available treatments as well as with untreated depression. Evidence is insufficient for treatment in the postpartum period, comparisons with nonpharmacological treatments, the impact of dose, severity of depression, timing of diagnosis, or prior depressive episodes.

Conclusions. Evidence about the comparative benefits and harms of pharmacologic treatment of depression in pregnant and postpartum women is largely inadequate to allow well-informed decisions about treatment, mainly because comparison groups were not exclusively depressed women. This is a serious limitation as depression is known to be associated with serious adverse outcomes. Given the prevalence of depression and impact on the lives of pregnant women, new mothers, and children, filling this informational gap is important.

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Executive Summary

Background

Depression is a potentially life-threatening condition. With an incidence during pregnancy and the postpartum period estimated to be anywhere from 5.5 to 33.1 percent, the American Academy of Pediatrics estimates that more than 400,000 infants are born each year to mothers who are depressed.¹

Depression during pregnancy is known to lead to harmful prenatal health behaviors such as poor nutrition, poor prenatal medical care, smoking, alcohol or other substance misuse, and risk of suicide; each of these compromises the health of both the woman and her fetus.^{2,3} Several adverse obstetric complications have been reported with untreated prenatal stress and depression, including pre-eclampsia, preterm delivery, low birth weight, miscarriage, small-for-gestational-age babies, low Apgar scores, and neonatal complications.^{4,5} In addition to being debilitating for the mother, postpartum depression affects maternal-infant interactions and some measures of infant development. In extreme cases it may increase the risk of infant mortality through neglect, abuse, or homicide.⁶ It also negatively affects interactions within other members of the family unit and is associated with intimate partner violence.⁷

A 2013 Agency for Healthcare Research and Quality (AHRQ) report found that screening can significantly reduce postpartum depressive symptoms when systems are in place to ensure adequate followup of women with positive results. Management of depression in pregnancy or the postpartum period varies case by case; providers and patients are often concerned about the safety of pharmacological treatment during pregnancy and the postpartum period.⁸

Clinicians can use interventions such as pharmacological treatments, nonpharmacological treatments, and watchful waiting for patients with depression both during pregnancy and in the postpartum period; they may also elect not to provide any intervention at all. Pharmacological treatments approved by the U.S. Food and Drug Administration (FDA) for treating depression are listed in Table A. Antidepressant medications have been shown to be effective at reducing the symptoms of depression in nonpregnant adults.^{9,10} In general, medications that are effective in treating conditions outside of pregnancy are often presumed to remain effective in pregnancy, but the developing fetus and changes in maternal physiology raise questions about safety and dosing of various agents. For safety of the fetus, the FDA Pregnancy Category of antidepressant medications taken during pregnancy is category C (“animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks”), with the exception of paroxetine, which is category D (“there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks”). However, evidence on how the risk of one antidepressant compares with another when taken during pregnancy is not well understood. Antidepressant medications are used to treat a variety of other indications, including anxiety disorders such as generalized anxiety disorder, panic attacks, obsessive compulsive disorder, depressed phase of bipolar disorder, and neuropathic pain.

A wide array of nonpharmacological interventions can be used to treat depression, including various psychotherapies, electroconvulsive therapy, repetitive transcranial magnetic

stimulation, and acupuncture.¹¹ Some of these may be used during pregnancy, whereas others may be reserved for use in the postpartum period (e.g., electroconvulsive therapy). Decisionmaking surrounding treatment of depression in pregnancy is complex because the harms of treatments must be balanced against the potential harms to mother and fetus of untreated depression.

Objectives

The objective of this systematic review is to evaluate the benefits and harms of various pharmacological treatment options for depression during pregnancy and the postpartum period, compared with each other, nonpharmacological treatments, and with usual care/no treatment.

Key Question 1

What are the comparative benefits of pharmacological and nonpharmacological treatments for women with depression during pregnancy and in the postpartum period?

- a. How do pharmacological treatments affect maternal and child* outcomes when compared with placebo or no active treatment or usual care?
- b. How do pharmacological treatments affect maternal and child outcomes when compared with each other (drug A vs. drug B)?
- c. How do pharmacological treatments affect maternal and child outcomes when compared with active nonpharmacological treatments?
- d. How does combination therapy affect maternal and child outcomes? The combinations include:
 - i. Using a second drug to augment the effects of the primary drug and comparing this treatment with monotherapy with a single drug
 - ii. Combining pharmacological treatments with nonpharmacological treatments and comparing them with nonpharmacological treatments alone
 - iii. Comparing pharmacological treatments alone with pharmacological treatments used in combination with nonpharmacological treatments

*A child is defined as a fetus, infant, or a child up to age 18.

Key Question 2

- a. What are the comparative harms of pharmacological and nonpharmacological treatments for women with depression during pregnancy and in the postpartum period?
 - i. How do pharmacological treatments affect maternal and child* outcomes when compared with placebo or no active treatment or usual care?
 - ii. How do pharmacological treatments affect maternal and child outcomes when compared with each other (drug A vs. drug B)?
 - iii. How do pharmacological treatments affect maternal and child outcomes when compared with active nonpharmacological treatments?
 - iv. How does combination therapy affect maternal and child outcomes? The combination include:
 - (a) Using a second drug to augment the effects of the primary drug and comparing this treatment with monotherapy with pharmacological treatment
 - (b) Combining pharmacological treatments with nonpharmacological treatments and comparing them with nonpharmacological treatments alone

- (c) Comparing pharmacological treatments alone with pharmacological treatments used in combination with nonpharmacological treatments
- b. In babies born to women who become pregnant while taking medications to treat depression, what is the comparative risk of teratogenicity?

*A child is defined as a fetus, infant, or a child up to age 18.

Key Question 3

Is there evidence that the comparative effectiveness (benefits or harms) of pharmacological and nonpharmacological treatments for women with depression during pregnancy and in the postpartum period varies based on characteristics** such as:

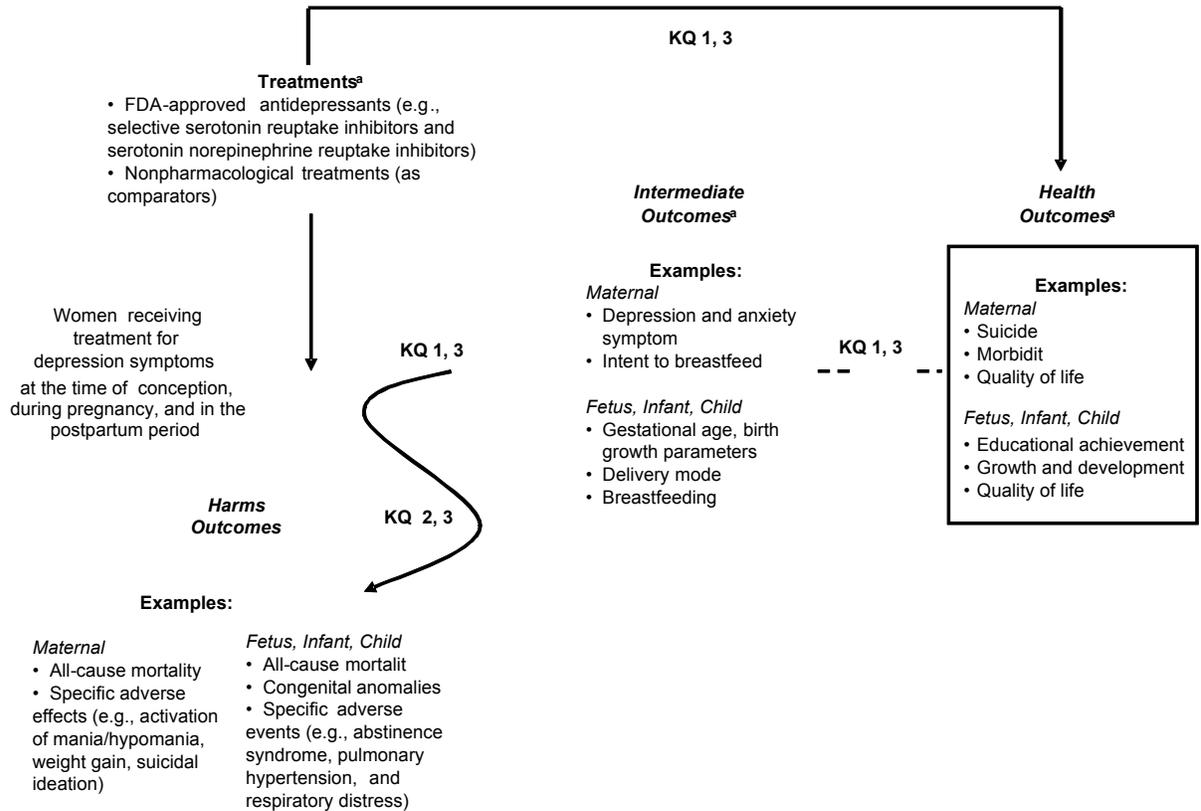
- a. Patient characteristics—race, age, socioeconomic status, family history of depressive/mood disorders, prior use of antidepressive drugs (for treatment or prevention), severity of symptoms, situation at home, unplanned pregnancy, and marital/partner status?
- b. Patient comorbidities (e.g., anxiety diagnoses)?
- c. Intervention characteristics—dosing regimens and duration of treatments?
- d. Coadministration of other psychoactive drugs, specifically, antipsychotics, antianxiety agents (e.g., benzodiazepines), and drugs for insomnia?
- e. Medical provider characteristics (primary care physician, obstetrician, pediatrician, psychiatrist, nurse, midwife, or community worker)?
- f. Medical care environment (community/private/public clinic or hospital)?
- g. Characteristics of diagnosis—whether depression was detected during screening or not, time of diagnosis, method of diagnosis, and when treatment commenced relative to the onset of symptoms?

**Other factors will be considered as they are identified within the comparative studies.

Analytic Framework

The analytic framework (Figure A) illustrates the population, interventions, outcomes, and adverse effects that guided the literature search and synthesis. We classified outcomes into benefits (intermediate and health outcomes) and harms; some outcomes classified as benefits could be viewed as harms (and vice versa) depending on whether an increase or decrease in risk is expected. For example, because a decrease in suicidality is a goal of treatment, we classified maternal suicide as a benefit; by contrast, because treatment is not typically anticipated to affect risk of all-cause mortality, we classified it as a harm. The placement of such outcomes in the framework is based on input from experts.

Figure A. Analytic framework for evaluating treatment of depression in pregnancy and the postpartum period



^a Complete lists of interventions and outcomes are too extensive to illustrate in their entirety in this diagram; see the inclusion criteria below for details.

FDA=U.S. Food and Drug Administration; KQ=Key Question.

Methods

The methods for this comparative effectiveness review follow the methods suggested in the *ARHQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (available at <http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm>).¹² The methods reported here reflect the elements of the protocol established for the comparative effectiveness review and methods mapping to the PRISMA checklist.¹³ All methods and analyses were determined a priori; we registered the protocol in the systematic review registry, PROSPERO (http://www.crd.york.ac.uk/NIHR_PROSPERO/).

Literature Search Strategy

To identify studies relevant to each Key Question, the librarian searched Cochrane Database of Systematic Reviews (CDSR) from 2005 to November 2012, the Cochrane Central Register of Controlled Trials (CCRCT) December 2012, the Cumulative Index to Nursing and Allied Health Literature (CINAHL[®]) from 1941 to December 2012, Ovid MEDLINE[®] and Ovid OLDMEDLINE[®] (1946 to November Week 3, 2012), PsychINFO[®] (1996 to December Week 2

2012), and Scopus (1974 to December 2012). Grey literature was identified by searching clinical trial registries (ClinicalTrials.gov). The AHRQ Scientific Resource Center solicited Scientific Information Packets from industry stakeholders.

Inclusion and Exclusion Criteria

Populations

We defined the populations of interest as pregnant women and women during the first 12 months after delivery, who are receiving treatment for a depressive episode. They included:

- Women with diagnosis for major depressive disorder according to the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*.
- Women with subthreshold depressive symptoms.

Based on input from experts, we also included studies with populations of pregnant women receiving antidepressant drugs for unknown or mixed reasons. We used these studies to provide evidence where no evidence was available in women with known depression or depressive symptoms (gaps in the evidence). To differentiate these populations, in this report we refer to studies of women with known depression as “treated” or “untreated” populations. We refer to studies of women with mixed or unknown diagnoses as “maternal exposure” when receiving antidepressants (at typically unknown doses) and “maternal nonexposure” when not receiving antidepressants.

This report focuses on women diagnosed with depression during pregnancy or the postpartum period, rather than those with a continuing episode, except for Key Question 2b regarding teratogenicity of antidepressant drugs taken at the time of conception or in early pregnancy.

Interventions

Interventions include commonly used antidepressant drugs listed in Table A. Drugs not listed below were not included (e.g., monoamine oxidase inhibitors). We used the following therapeutic classifications used in previous AHRQ Comparative Effectiveness Reviews,^{9, 10} selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), selective serotonin norepinephrine reuptake inhibitor (SSNRI), and tricyclic antidepressants (TCA), except that we classified trazodone and nefazodone as norepinephrine reuptake inhibitors (NRI) for this report.

Table A. Pharmacologic interventions: Antidepressant agents

Drug Category	Generic Name	Trade Name ^a
Selective serotonin reuptake inhibitor	Citalopram	Celexa [®] , various generics
	Escitalopram	Lexapro [®]
	Fluoxetine	Prozac [®] , various generics Prozac Weekly [®] Sarafem [®]
	Fluvoxamine	Luvox [®] , various generics Luvox CR [®]
	Sertraline	Zoloft [®] , various generics
	Paroxetine	Paxil [®] , various generics Paxil CR [®]
	Vilazodone	Viibryd [®]
Serotonin norepinephrine reuptake inhibitor	Desvenlafaxine	Pristiq [®]
	Venlafaxine	Effexor XR [®]
	Mirtazapine	Remeron [®] , various generics Remeron Soltab [®]
Selective serotonin norepinephrine reuptake inhibitor	Duloxetine	Cymbalta [®]
Tricyclic antidepressants	Amitriptyline	Various generics
	Desipramine	Norpramin [®] , various generics
	Imipramine	Tofranil [®] , various generics
	Nortriptyline	Aventyl hydrochloride [®] Pamelor [™] Various generics
Norepinephrine reuptake inhibitors	Nefazodone	Various generics (previously available as Serzone [®])
	Trazodone	Desyrel [®] , various generics
Other	Bupropion	Wellbutrin [®] Wellbutrin SR [®] Wellbutrin XL [®] Forfivo XL [®] Aplenzin [®]

Footnotes: a=CR, SR, XL abbreviations all refer to extended release formulations.

Comparators

- Placebo or no treatment
- Usual care: defined as receiving pregnancy and postpartum care similar to that received by those with normal risk pregnancies
- The drugs listed above in Table A when compared with each other
- Other active pharmacological treatments used to augment drugs in Table A
- Any nonpharmacological treatment, including but not limited to osteopathic or naturopathic treatments, all forms of psychotherapy, repetitive transcranial magnetic stimulation, vagal nerve stimulation, exercise, meditation, and touch therapies.

Benefits Outcomes

Maternal

- Danger to self or child
- Depression symptomatology (e.g., response, remission, relapse, recurrence, and change in core depressive symptoms)
- Anxiety symptoms

- Functional capacity (e.g., quality of life, caring for self, infant and family, mother-father dyad interaction, and work productivity)
- Delivery and postpartum parameters (e.g., breastfeeding, delivery mode, mother-infant dyad interaction, pregnancy weight gain, use of social services and health care resources).

Fetus, Infant, Child

- Parameters at birth and up to 12 months of age:
 - Preterm birth (e.g., < 32 weeks, < 37 weeks)
 - Appropriate growth (e.g., small for gestational age, taking race and ethnicity into consideration, gestational age, height, weight, and head circumference)
 - Birth hospitalization length of stay
 - Infant attachment
 - Developmental screening—Ages and Stages Questionnaire, Denver Developmental Screening Test, Modified Checklist for Autism in Toddlers, Bayley Scales of Infant Development
- Growth and development after 1 year of age:
 - Developmental screening and diagnoses
 - Growth parameters (height, weight, and body mass index percentile according to sex and age)
- Learning (e.g., linguistic, cognitive, and social-emotional skills) and educational achievement
 - Kindergarten readiness
 - Age at kindergarten entry
 - Third grade testing outcomes
 - Other standard testing outcomes (eighth grade, etc.)
 - Intelligence tests (any)
 - Individualized education plans or use of school services
 - School failure or dropout rate
 - High school graduation rate
 - Missed school days
- Stress-related chronic disease
 - Mental illness
 - Chronic illness
- Infant health system utilization (e.g., well baby visits, primary care, emergency department, and hospitalization)
- Social services utilization (e.g., Women, Infants, and Children Program [WIC], community health nurse, social worker, State Department of Health and Human Services, free and reduced lunch, and food stamps)
 - Community resource utilization (community engagement measures)
- Social and emotional development
 - Quality of life
- Contact with juvenile justice system.

Harms Outcomes

Maternal

- Death (including suicide, all-cause mortality and cause-specific [e.g., cardiac] death)
- Specific adverse effects or withdrawals due to specific adverse events related to treatment (e.g., suicidal ideation, hepatotoxicity, and loss of libido)
- Overall adverse-event reports
- Withdrawals from study due to adverse events
- Adverse events associated with discontinuation of treatment
- Serious adverse events reported.

Fetus, Infant, and Child

- All-cause mortality
- Congenital anomalies stratified into major and cardiovascular
- Other specific adverse events.

Study Designs

- For effectiveness, we used a “best evidence” approach. Top-tier evidence included randomized controlled trials (RCTs) and systematic reviews comparing pregnant women receiving pharmacologic treatments for depression during pregnancy with control groups of pregnant women with depression who were treated with nonpharmacologic or untreated. If no or very few RCTs were found, observational study evidence and studies comparing with control groups of nonexposed pregnant women were included.
- For harms, in addition to RCTs and systematic reviews, observational studies comparing pharmacologic treatments for depression during pregnancy with control groups of pregnant women with depression who were treated with nonpharmacologic treatments or no treatment were included. If insufficient evidence was found, studies comparing to control groups of nonexposed pregnant women were included.
- Exclusions: case reports, case series, and single-group studies.

Study Selection

Two reviewers independently assessed publications identified through literature searches for inclusion using the criteria described above. Potentially relevant full-text articles were retrieved and assessed for inclusion by two reviewers. Disagreements were resolved by consensus or a third-party arbitrator.

Data Extraction

Key study characteristics were abstracted from included studies into evidence tables. One reviewer abstracted study data and a second reviewer did random checking. Intention-to-treat results were recorded if available.

Risk of Bias Assessment of Individual Studies

We assessed the internal validity (quality) based on predefined criteria established by the Drug Effectiveness Review Project.¹⁴ We rated the internal validity of observational studies

based on the adequacy of the patient selection process; whether important differential loss to followup or overall high loss to followup occurred; the adequacy of exposure and event ascertainment; whether acceptable statistical techniques were used to minimize potential confounding factors; and whether the duration of followup was reasonable to capture investigated events.

All assessments resulted in a rating of high, medium, or low risk of bias, primarily at the study level. In some cases, however, the reviewers determined that validity varied by outcome and rated risk of bias for different outcomes separately. Studies that have serious flaws were rated high risk of bias, studies that met all criteria were low risk of bias, and the remainder were medium risk of bias. All studies were rated by one reviewer and checked by another reviewer. All disagreements were resolved through consensus.

Based on input from experts, we selected four potential confounding factors that we considered key for all outcomes and that should be adjusted for in analyses of observational studies: age, race, parity, and other exposures (e.g., alcohol, smoking, and other potential teratogens). In some cases, additional confounders were considered based on their particular relevancy to specific outcomes. Low or moderate risk of bias studies adjusting for these confounders were considered the best evidence if no RCTs were available.

Data Synthesis

We used a hierarchy-of-evidence approach, in which the best evidence was the focus of our synthesis for each question, population, intervention, and outcome addressed. Studies that evaluated one treatment for depression against another in pregnant or postpartum women with depression provided direct evidence of comparative effectiveness and adverse event rates. Where possible, these data are the primary focus.

Direct comparisons were preferred over indirect comparisons. Direct evidence would include studies (trials or observational studies) that compared pregnant or postpartum women with depression who receive antidepressant treatment with pregnant or postpartum women with depression who were not treated.

Indirect evidence would include studies (trials or observational studies) of pregnant or postpartum women treated with antidepressants without specifying that the women have depression. Similarly, studies that compare pregnant or postpartum women taking an antidepressant drug with pregnant or postpartum women who are not taking such medications but also are not known to have a diagnosis of depression (a general population) are considered indirect. Indirect comparisons can be difficult to interpret for several reasons; in the latter case the issue is primarily heterogeneity of underlying risk of the populations. The underlying risk of untreated depression during pregnancy or the postpartum period is an important factor in assessing the relative benefits and harms of potential treatments. We use data from indirect comparisons when no other directly applicable evidence exists, but findings should be interpreted with caution because comparisons with a generally healthy population without depression rather than with a depressed population may underestimate the benefits and overestimate the harms of treatment.

Data from high risk of bias studies were generally not used in the main analysis, except to undertake sensitivity analyses for meta-analyses or where high risk of bias studies constitute the only evidence for an important outcome. To determine the appropriateness of meta-analysis, we considered the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. We generally used random-effects models to estimate

pooled effects; when only two studies were being pooled we applied a fixed effect model.^{15, 16} We calculated the Q statistic and the I² statistic to assess heterogeneity in effects between studies.^{17, 18} When we found statistical heterogeneity, we explored reasons for this by using subgroup analysis. When we could not perform meta-analysis, we summarized the data qualitatively, grouping studies by similarity of population and/or intervention characteristics, or both.

Strength of the Body of Evidence

We used the methods outlined in Chapter 10 of the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*^{12, 19} to grade strength of evidence. Domains considered in grading the strength of evidence were risk of bias, consistency, directness, and precision. Based on this assessment, reviewers assigned the body of evidence a strength-of-evidence grade of high, moderate, or low. A rating of High, for example, means that we have high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect while a rating of Low means that we have low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.^{2, 19} In cases in which evidence did not exist, was sparse, or contained irreconcilable inconsistency, we assigned a grade of insufficient evidence. A rating of Insufficient means that the evidence either is unavailable or does not permit estimation of an effect.

We consulted our technical experts to help inform prioritization of the outcomes for grading. Specific outcomes selected for rating included the following for any comparison with at least moderate risk-of-bias evidence, for maternal outcomes, danger to self or infant, depression symptomatology (response and remission), breastfeeding intention and duration, number with adverse events, discontinuation due to adverse events, and weight gain; for infant outcomes, preterm birth, small for gestational age, neonatal mortality, congenital malformations, persistent pulmonary hypertension, infant and child neurodevelopment, intellectual function, educational outcome and school performance, mental health, and healthcare/social service utilization.

Applicability

We assessed applicability by examining the characteristics of the enrolled populations compared with target populations, characteristics interventions, and comparators. Technical experts identified items of particular interest that may affect applicability, which are reflected in the subgroups specified in Key Question 3.

Results

Results of Literature Searches

Based on electronic searches (3,144 citations), manual searches (18 citations), and scientific information packets (Forest Pharmaceuticals, Inc, Jazz Pharmaceuticals, and Sanofi Aventis, U.S.), we identified a total of 3,162 potentially relevant citations. From these, we included 124 eligible unique studies in this report. The majority of the evidence was from observational studies (117 unique studies); and only seven RCTs.

Only six RCTs and 13 observational studies provided direct evidence, comparing treatments in groups of pregnant or postpartum women with depression. This is the primary evidence for

this report. We included indirect evidence from 104 observational studies that included pregnant or postpartum women receiving an antidepressant drug for any reason and making comparisons to women who were not receiving an antidepressant drug during pregnancy or the postpartum period. The depression status of women in the intervention or control groups was generally not noted, although a few of these studies included depression as a confounder that was controlled for in analyses. This evidence is indirect for this report. Findings from these studies were reported only for important outcomes for which evidence in pregnant women with depression did not exist or was sparse, particularly for serious harms where even such indirect evidence may have been useful in guiding clinical decisions. No studies compared an antidepressant drug with a nonpharmacological treatment, and in only a few did the intervention involve use of a nonpharmacological treatment as an add-on to drug therapy.

Key Question 1

The overarching finding for Key Question 1 is that little evidence exists on the maternal benefits of antidepressant therapy during pregnancy or the postpartum period. Studies were generally not designed to measure benefits (e.g., effect on depressive symptoms) when women are treated during pregnancy, and evidence did not allow comparisons among either the specific classes or individual drugs. Evidence on key outcomes and comparisons are lacking. Similarly, we have no information on the most effective dose of antidepressant drugs in pregnant women, based on severity of symptoms or on either pharmacokinetic or pharmacodynamic alterations during pregnancy.

Maternal Benefits

Comparative evidence on depressive symptom response, anxiety, functional capacity, healthy maternal weight gain, and breastfeeding outcomes is insufficient to draw conclusions about the effects of antidepressant drugs in women with depression during pregnancy. Based on direct evidence from two very small observational studies, we found inconsistent results on the benefit of SSRI treatment on depressive symptoms during pregnancy and no evidence for other drug classes. A small observational study reported that depressed women treated with SSRIs continuously during pregnancy had higher scores on the SF-12 mental component scale than did untreated women with depression throughout pregnancy (scores of 45 and 35), but the timing of measurement was not clear. We found no direct evidence of the effects of antidepressant drugs on other important depression outcomes such as anxiety symptoms in women with depression during pregnancy. No direct evidence was available regarding pregnancy weight gain, intention to breastfeed, uptake of breastfeeding, or duration of breastfeeding.

Studies of pregnant women with unknown depression status provided indirect evidence on weight gain and breastfeeding outcomes. Such evidence is insufficient to draw conclusions about these outcomes in pregnant women with depression, but it may provide insight into directions for future research. Among pregnant women with unknown depression status who received SSRIs, weight gain was slightly above recommended limits compared with weight gain among women who did not receive SSRIs. Indirect evidence also suggested that, in pregnant women with unknown depression status, SSRI treatment during pregnancy was associated with fewer women intending to or initiating breastfeeding than among pregnant women not receiving such treatment; this probably reflects concerns or uncertainty about potential harms to the breastfed child. No evidence is available for comparative benefits of other pharmacological treatments in pregnant women with depression.

Evidence on maternal benefits from pharmacologic treatments for depression during the postpartum period was insufficient. Direct evidence was limited to one small placebo-controlled trial that we rated as high risk of bias; indirect evidence came from a small observational study in pregnant women with unknown depression status rated medium risk of bias.

Evidence on the combination of antidepressant therapy with nonpharmacologic interventions was insufficient to draw conclusions due to inconsistency and imprecision and generally suffered from lack of adequate sample sizes.

Child Benefits

The potential benefits of treatment of depressed women during pregnancy to their children include parameters at birth (e.g., birth weight), child development, diagnosis of chronic diseases, and health care utilization. Direct evidence is only available for preterm birth and some developmental outcomes. For preterm birth following use of SSRIs for depression during pregnancy, evidence is insufficient to draw conclusions. Only one observational study was found, and the EPC-calculated unadjusted odds of preterm birth was not statistically significant (1.73, 965% CI 0.63 to 4.42) but the confidence interval is wide and consistency of these findings is unknown. Indirect evidence suggests that infants of mothers exposed to SSRIs, TCAs, SNRIs, or NRIs during pregnancy are at increased risk of preterm birth compared to women not treated with antidepressants during pregnancy and with unknown depression status. For SSRIs, this finding is consistent across studies but the magnitude of risk associated with specific timing of maternal exposure during pregnancy was unclear. Risk may be higher with citalopram/escitalopram than fluoxetine, paroxetine and sertraline, but direct comparisons of the drugs in women with depression are needed to confirm these findings. Evidence on fetal growth was limited to indirect evidence; we found no apparent increased risk associated with exposure to SSRIs or TCAs.

Direct evidence on infant and child development is limited to two very small studies, providing evidence that is insufficient to draw conclusions about the risk of delayed development in children of mothers taking SSRIs for depression during pregnancy compared to those of mothers whose depression was not treated with antidepressants. Indirect evidence did not indicate increased risk of motor, language or cognitive development that is outside of the normal range for age.

Comparative evidence on the risk of diagnosis of attention deficit hyperactivity disorder (ADHD) in children of mothers treated for depression during pregnancy is insufficient as there is no direct evidence. Indirect evidence suggests that compared with children not exposed during pregnancy, diagnosis by the age of 5 years is associated with bupropion use (OR 3.63, $P < 0.02$), particularly in the second trimester, but not associated with use of SSRIs or other antidepressants during pregnancy. Filling a prescription for an SSRI after pregnancy (timing not defined) was statistically significantly associated with increased risk of ADHD diagnosis by age 5 (OR 2.04, $P < 0.001$). These analyses controlled for parental mental health diagnoses; a diagnosis of depression in the mother during pregnancy was statistically significantly associated with the diagnosis of ADHD in the child (OR 2.58, $P < 0.001$).

Whether autism spectrum disorder (ASD) is associated with depression during pregnancy, antidepressant treatment, or an interaction of the two is not clear. We found no direct evidence on the risk of different treatments for depression during pregnancy on development of ASD in the child. We found indirect evidence, based on two large population-based case-control studies with low and medium risk of bias, that suggested that maternal use of SSRIs is statistically

significantly associated with diagnosis of ASD in the child after controlling for maternal depression diagnosis during pregnancy (pooled odds ratio 1.82; 95% CI 1.14 to 2.91).^{20, 21} Both studies examined other antidepressant drugs, one found an increased risk with TCAs and the other found no increased risk with TCAs combined with SNRIs/NRIs. Although these results control for depression, the comparison groups were children of women who did not receive an antidepressant during pregnancy, rather than women with untreated known depression, and the proportion of women with a diagnosis of depression was not reported for either group.

In one of these studies, results of subgroup analyses suggest that depression itself may contribute ASD diagnosis. Compared with pregnant women without depression or antidepressant use, the risk for ASD in the children of pregnant women with depression and antidepressant use was statistically significantly elevated, (OR 3.34; 95% CI 1.50 to 7.47). In contrast, the risk in pregnant women taking an antidepressant for another indication was lower and not statistically significant (OR 1.61; 95% CI 0.85 to 3.06).

We found no evidence comparing drug therapy to nondrug therapy. Evidence for other outcomes or comparisons either for exposure during pregnancy or in the postpartum period was either not found or insufficient.

Key Question 2

Maternal Harms

We found no direct evidence on maternal harms of pharmacologic treatments for depression during pregnancy. This is primarily because for this population there is only observational evidence and the harms outcomes for this report, for example, rates of specific adverse effects (e.g., suicidal ideation, hepatotoxicity, and loss of libido) are not reported. The risk of mortality may have been reported sporadically, but most of these retrospective observational studies would have excluded women who died during pregnancy, and the remaining studies did not have explicit methodology to ascertain this and other serious harms.

Child Harms

Evidence for Key Question 2, comparative harms, was also limited by the comparison groups selected by most studies (pregnant women who did not take an antidepressant, and with unknown depression status in compared groups). As with comparative benefits, the direct evidence is very limited, leading to mostly insufficient evidence for drawing conclusions. Indirect evidence may be more valuable for harms such as mortality and congenital anomalies where signals for increased risk of harm may be used to direct future studies. The findings for maternal treatment with antidepressants during pregnancy reflected evidence of greater risk for some serious infant harms associated primarily with exposure to SSRIs, but the contributory role of depression in these outcomes is mostly unstudied.

There was no direct evidence for the risk of infant mortality with maternal use of antidepressant drugs to treat depression during pregnancy. Indirect evidence, based on large population-based cohort studies is inconsistent with an increased risk of infant death over the first year of life is associated with exposure to SSRIs (OR 1.81; 95% CI, 1.26, 2.60), but not when early and late death are evaluated separately. A single cohort study reported no increased risk of neonatal mortality with SNRI/NRI use during pregnancy.

Direct evidence on the association of major congenital malformations with use of SSRIs for depression during pregnancy is insufficient, based on two small studies (N = 282 total) that

reported only 1 or zero events. No comparative evidence on the risk of cardiac malformations in women treated for depression during pregnancy was found. A substantial amount of indirect evidence is available from fifteen cohort studies that reported the incidence of major congenital malformations associated with the use of any SSRI, or specific SSRIs, during pregnancy, compared with the children of women who did not receive an SSRI and were not known to be depressed. Although exposure to SSRIs as a group did not result in increased risk of major malformations in infants, evidence indicated small but statistically significant risk with exposure to fluoxetine (OR 1.14, 95% CI 1.01 to 1.30) or paroxetine (OR 1.17, 95% CI 1.02 to 1.35), but not the other SSRIs individually. Timing of exposure was primarily in the first trimester, although sensitivity analyses removing studies that may have included exposures at other timepoints did not alter these results. Results were similar for cardiac malformations, except that limiting our analysis to the highest-quality studies of fluoxetine yielded a nonsignificant increase in risk. The increased risk with paroxetine was 1.49 (95% CI 1.20 to 1.85). TCAs were also associated with increased risk for major (OR 1.31, 95% CI 1.04 to 1.65) and cardiac malformations (OR 1.58, 95% CI 1.10 to 2.29). Evidence for other antidepressants was not available.

No direct evidence on the risk of neonatal withdrawal symptoms or pulmonary hypertension with maternal use of antidepressant drugs to treat depression during pregnancy compared with depressed women who did not use an antidepressant during pregnancy was found. Indirect evidence suggests greater risk of neonatal withdrawal symptoms with fluoxetine use for any reason during the first trimester compared with women who did not use an antidepressant during pregnancy, but whose depression status was unknown (Relative Risk [RR] 8.7, 95% CI 2.9 to 26.6) and with SSRIs or venlafaxine (grouped) in late pregnancy, but suggested no difference in risk between SSRIs and SNRIs in neonatal withdrawal symptoms. Indirect evidence suggests that persistent pulmonary hypertension is statistically significantly associated with maternal SSRI use during late pregnancy (OR 2.72, 95% CI 1.63 to 4.54).

Based on three studies, there is low-strength evidence that, compared with untreated maternal depression during pregnancy, SSRI treatment is associated with a statistically significant increase in risk of respiratory distress in infants (pooled unadjusted OR 1.91; 95% CI, 1.63 to 2.24; $I^2 = 0\%$). Direct evidence was not available to assess the risk with TCAs, SNRI/NRIs but indirect evidence suggests an increase in risk with TCAs used late in pregnancy (adjusted odds ratio, 2.11; 95% CI, 1.57 to 2.83).

Low strength direct evidence suggests no statistically significant associations between maternal use of SSRIs during pregnancy and neonatal convulsions compared with infants of untreated, depressed pregnant women. Indirect evidence is in conflict with this finding, indicating an increased risk with use of SSRIs for any indication during pregnancy compared with women who did not take an SSRI during pregnancy and not known to have depression.

The risk for teratogenicity with exposure to antidepressants during the conception period was examined in few well-designed studies, with even fewer specifically isolating exposure during this period such that the evidence was insufficient.

Key Question 3

In Key Question 3, we attempted to examine a wide range of subgroups of patient and intervention characteristics. Given the difficulty we had in identifying evidence for the first two Key Questions with appropriate control and intervention groups, not surprisingly we found very little direct evidence to address these questions. Based on the direct evidence, with comparisons

between treated and untreated pregnant women with depression, the duration of treatment did not appear to influence the risk of preterm birth, stratifying into continuous use and use during only one trimester. In the postpartum period, we found that multiple sessions of cognitive behavioral therapy were not superior to a single session when both were combined with fluoxetine.

Depressive symptom response to dynamic psychotherapy, with or without sertraline, did not vary based on depression severity level. For all other subgroups (including coadministration of other drugs, medical provider characteristics, medical care environments, and characteristics of diagnosis) the evidence was limited. Studies that used a definite diagnosis of depression in all comparison groups and that had medium or low risk of bias provided insufficient evidence to draw conclusions about variation in treatment effects.

Discussion

Table B, below, highlights the findings based on studies that were designed to directly compare the benefits and harms of pharmacological treatments for depression in pregnant or postpartum women – direct evidence. We believe that this is the best evidence for the Key Questions posed for this review. Not shown are outcomes for which we only have indirect evidence; studies that made comparisons of outcomes for women who took an antidepressant during pregnancy for any reason, with women who did not take an antidepressant during pregnancy, with proportions of women with depression in either group rarely reported and not analyzed. The applicability of indirect evidence of findings from studies of pregnant women with unknown depression status is unclear. As reported in the table, evidence for virtually all outcomes provides insufficient strength of evidence; only the outcomes of neonatal convulsions and respiratory distress in infants of women who took SSRIs as a class during pregnancy compared to women with depression who did not take an antidepressant had low strength of evidence. The risk of convulsions was not higher with SSRIs, but the risk of respiratory distress was. The primary reason for the other direct evidence leading to insufficient strength of evidence, and a lack of ability to draw any meaningful conclusions from this evidence, is because these are small observational studies that may not have adequate statistical power to identify differences where they exist and are not as methodologically strong as is necessary to draw firm conclusions.

Table B. Key findings of direct comparison evidence for depression during pregnancy

Intervention	Comparison	Outcome	Strength of Evidence Results
Potential benefits			
SSRIs+psychotherapy	Psychotherapy alone	Depressive symptoms	Insufficient; no conclusions drawn
SSRIs: Fluoxetine	No treatment	Depressive symptoms	Insufficient; no conclusions drawn
SSRIs	No treatment	Functional capacity	Insufficient; no conclusions drawn
SSRIs+psychotherapy	Psychotherapy alone	Breastfeeding	Insufficient; no conclusions drawn
SSRIs	No treatment	Preterm birth	Insufficient; no conclusions drawn
SSRIs+psychotherapy	Psychotherapy alone	Infant/child development: Bayley Scales	Insufficient; no conclusions drawn
SSRIs	No treatment	Infant/child development: Brazelton Neonatal Behavioral Assessment Scale	Insufficient; no conclusions drawn
Potential harms			

SSRIs	No treatment	Major malformations	Insufficient; no conclusions drawn
SSRIs+psychotherapy	Psychotherapy alone	Major malformations	Insufficient; no conclusions drawn
SSRIs	No treatment	Neonatal convulsions	Low; Risk not different between groups
SSRIs	No treatment	Neonatal respiratory distress	Low; Risk higher with SSRIs
SSRIs	TCA (nortriptyline)	Neonatal respiratory distress	Insufficient; no conclusions drawn

SSRI=selective serotonin reuptake inhibitor

Findings in Relationship to What is Already Known

Putting these findings into the context of prior comparative effectiveness evidence reviews was difficult because we did not identify any such studies, in part because the scope of this report is so broad. A review by Bromley, et al.,²² assessed fetal and child outcomes and SSRIs only, but did not limit the comparison group to women with depression, such that our results are quite different. Additionally, we applied both formal assessment of the risk of bias to individual studies and strength of evidence to the body of evidence for each key outcome which the Bromley review did not, resulting in most outcomes in our review having insufficient strength of evidence.

Applicability

The evidence on the benefits and harms of pharmacological treatment during pregnancy was limited to observational studies that generally met criteria for effectiveness studies.²³ The evidence on benefits and harms of pharmacological treatment for postpartum depression came almost entirely from RCTs that met criteria for efficacy studies. These studies were limited by several factors: exclusion of patients with common comorbidities, such as drug and alcohol misuse or abuse, other Axis I disorders, and suicidal ideation; lack of health outcomes and comprehensive assessment of adverse events; short study durations; and small sample sizes.

Only a small group of studies included pregnant women known to be depressed and compared treated and untreated groups – direct evidence. In these studies, however, we did not have further information on the diagnosis timing, prior history, or the severity of symptoms. As maternal depression is widely recognized as a risk factor for poorer pregnancy outcomes, the findings from all the studies that do not account for maternal depression likely have very low applicability to our target population of pregnant women with depression.

With respect to other variables, the mean maternal age ranged from 26 years to 34 years. Few studies reported race or socioeconomic status. In the studies that reported race, the populations were predominantly white. When reported, a medium socioeconomic status level was most common. The data sources for these studies typically did not include access to information such as depressive symptom severity, comorbid anxiety diagnoses, and other mental health or medical conditions; family history of depressive or other mood disorders; prior use of antidepressive drugs; situation at home; unplanned pregnancy; and marital/partner status, therefore, we know very little about these important patient characteristics.

Very little evidence was available to assess the benefits and harms of nonpharmacological treatment modalities and it was limited to treatment during the postpartum period. The clinical relevance of the nonpharmacological treatment modalities was difficult to assess based on the

lack of detail about their characteristics. Likewise, the clinical relevance of the pharmacological treatment regimens was also difficult to assess because of a general lack of information about dose, duration, and cointerventions.

Only approximately 30 percent of included studies were conducted in the United States. Findings from many of the studies conducted in the United States and Canada may not be reflective of the general population because of their reliance on highly selected samples who voluntarily called teratogen information services, have specific health plan membership, or who attended specific community prenatal clinics.

Overall, the applicability of this evidence to programs such as the Federal Children's Health Insurance Program (CHIP) is somewhat limited because of the issues noted above. Of particular importance are the large number of studies conducted in non-US healthcare settings and the medium socioeconomic status of women studied.

Implications for Clinical and Policy Decisionmaking

Depression during pregnancy and postpartum can have adverse consequences for both mother and child. Knowing the best course of action when a woman is diagnosed with depression during these times is extremely important. The evidence base at present is extremely limited in the specific guidance it can provide, for multiple reasons. The overall findings of this review are based on insufficient or low strength of evidence, meaning that future studies are very likely to alter the findings in a meaningful way. The implications for decision-making for women with depression during pregnancy are unclear. Without better evidence, specific to this population, the balance of benefit and harm are uncertain.

Based on the best evidence available today, the benefits to mothers are unclear. For pregnant women, treatment with drugs may offer benefits, although the specific benefits, particularly in terms of tangible benefits (health outcomes), and how benefits compare across potential treatments are still very unclear. Although we believe that treatment with SSRIs is likely to improve some symptoms based on indirect evidence in nonpregnant patients, direct evidence comparing the interventions of interest in the population of interest is currently insufficient. Similarly, the evidence on functional outcomes for the mother are unfortunately insufficient, although they lean towards better outcomes in women treated with an SSRI compared with untreated pregnant women.

While there is a suggestion that women taking antidepressants are less likely to breastfeed or breastfeed for shorter durations than are women who are not taking an antidepressant in the postpartum period, and that there is no evidence of harm to the infant of breastfeeding while the mother is taking an antidepressant, this evidence is also insufficient to draw specific conclusions. This evidence suggests room for education of pregnant women and possibly providers that women taking antidepressants should not necessarily be discouraged from breastfeeding. Clinicians can know in advance that, for women treated with antidepressants, decisions around breastfeeding can be problematic; thus, early discussion and support for maternal intention to breastfeed is warranted. Women who receive antenatal education and professional encouragement, or who report that their health care provider encouraged them to breastfeed are more likely to initiate and sustain breastfeeding.²⁴⁻²⁶ Antidepressants are widely used in postpartum women. For most antidepressants, no or only negligible amounts are passed from mother to baby through breast milk (fluoxetine and citalopram may be exceptions, but the amount varies with dose and frequency of dosing), and no evidence exists of adverse events in babies.²⁷⁻²⁹

Evidence on the comparative benefits of treating depression during pregnancy (compared with not treating) is expected to include benefits in developmental achievement in the child. Our evidence indicates that SSRIs results in no differences on most measures, but may result in slightly worse motor development than no treatment at all, but again this evidence is insufficient to guide clinical decisions. When making direct comparisons, while the evidence does not indicate higher rates of preterm birth with use of SSRIs during pregnancy, unadjusted odds ratio of 1.73 (95% CI 0.63 to 4.42), it is insufficient to guide clinical decisions.

Numerous potentially serious harms have been suggested to be associated with use of antidepressants during pregnancy; but in the comparison of depressed women treated and untreated, we found only the risk for respiratory distress to be associated with SSRIs (as a drug class). The fact that different conclusions may be drawn for some outcomes based on a large body of evidence we consider indirect for our questions highlights the importance of making clinically relevant comparisons.

An example is the risk of ASD in children of women treated for depression during pregnancy. The increasing prevalence of ASD diagnosis, likely in part attributable to increased detection, temporally parallels an increasing tendency to prescribe antidepressants in pregnancy. Based on indirect evidence, whether ASD in the child is associated with maternal depression during pregnancy, treatment with antidepressants, or a combination of the two remains unclear. Although we found that ASD was associated with maternal exposure to antidepressants, particularly SSRIs, compared with the maternal nonexposure (depression status unknown), we did not find clear evidence on the risk when untreated depressed women were the comparison group. Any suggestion of increased risk for ASD is very concerning. In studies comparing with maternal nonexposure, although researchers controlled for depression, the relationship between depression, antidepressant use, and risk of ASD remains unclear. The small, but statistically significant risk of ASD diagnosis with antidepressant use or depression or both is important to understand better, because treatment could mitigate this risk if severe depression underlies the association with ASD. One study examined the risk of having depression during pregnancy and a diagnosis of ASD in the child, finding statistically significant increased odds in depressed mothers (with and without known treatment), and a nonsignificant increase in mothers without depression. An interaction between depression and antidepressant treatment is possible, but has not been fully elucidated. Nevertheless, women should be informed about the risk of ASD if antidepressants are found more conclusively to increase this risk. Because the fraction of cases of ASD that could potentially be attributed to antidepressants in these studies is exceedingly small (0.6 to 2.5 percent of the study populations), prenatal antidepressant use is not a major risk factor for ASD and does not explain the increasing prevalence of autism.

Evidence on the benefits or harms of treatment of depression in the postpartum is insufficient to draw conclusions. Women and clinicians are currently left with only evidence in nonpregnant populations and evidence on intermediate outcomes (e.g., which drugs are passed into breast milk) to guide treatment choices.

Limitations of the Comparative Effectiveness Review Process

Methodological limitations of the review within the defined scope included the exclusion of studies published in languages other than English and lack of a specific search for unpublished studies. The review process and results could have benefited from further refinement of the scope to limit inclusion of studies of pregnant or postpartum women with depression, in both the intervention and control groups.

Limitations of the Evidence Base and Gaps in the Evidence

A major caveat to interpreting the findings of the majority of studies of exposure during pregnancy is the role of depression itself. Most of the studies specified that women were taking an antidepressant for any reason; few reported the proportions of women with depression and even fewer used this information in their analyses. Studies of women taking an antidepressant during or after pregnancy but not known to be depressed are problematic in part because we do not know what the differential baseline risk of various outcomes are for the various indications for which antidepressants can be used. We do know that there are baseline risks associated with depression during pregnancy, however, making it important to limit the treated group to women with depression.^{2,3}

Although RCTs may not be feasible in pregnant women, the assumption that the clinical efficacy of interventions in nonpregnant populations is directly applicable to pregnant women may not be valid for many reasons. Making these types of comparisons requires well-designed prospective studies, with measurement of depression severity at baseline and during followup. Comparisons of specific treatments in these more appropriate populations are needed. Ascertainment of exposure, including both timing and dose, must be done in a way that insures accuracy and reliability. Outcomes should be determined by blinded evaluators, which is possible for nearly all outcomes considered here. Evidence on the relative benefits and harms of nonpharmacological treatments is almost entirely lacking, as is the effectiveness of combinations of drug and nondrug treatments. Studies of women in the postpartum period are both small and methodologically weak, leaving a gap in knowledge about a group of patients in whom RCTs could be undertaken. Specifically-designed research that addresses the problems identified in this report is badly needed.

The current evidence base is insufficient to support clinical decisionmaking fully, because it requires knowing both benefits and harms and being able to determine the tradeoffs of individual choices. For example, if a medication has a lower adverse event profile but is also less effective for a given condition, prescribing it for a patient who needs therapy for that particular condition just because of a lower adverse event profile is not a reasonable therapeutic strategy. We know that depression during pregnancy and the postpartum period can lead to serious adverse outcomes for both mother and child, such that treatment is important. Research in this area needs to measure both benefits and harms simultaneously in the same study, so that results can better inform the tradeoffs that women and clinicians need to weigh.

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Introduction

Background

Condition

Depression is a potentially life-threatening condition. With an incidence during pregnancy and the postpartum period estimated to be anywhere from 5.5 to 33.1 percent, the American Academy of Pediatrics estimates that more than 400,000 infants are born each year to mothers who are depressed.^{30, 31} During the postpartum period, up to 85 percent of women experience some type of mood disturbance.¹

Depression during pregnancy is known to lead to harmful prenatal health behaviors such as poor nutrition, poor prenatal medical care, smoking, alcohol or other substance misuse, and risk of suicide, each of which compromises the health of both the woman and her fetus.^{2, 3} Several adverse obstetric complications have been reported with untreated prenatal stress and depression, including pre-eclampsia, preterm delivery, low birth weight, miscarriage, small-for-gestational-age babies, low Apgar scores, and neonatal complications.^{4, 5} In addition to being debilitating for the mother, postpartum depression affects maternal-infant interactions and some measures of infant development; in extreme cases it may increase the risk of infant mortality through neglect, abuse, or homicide.⁶ It also negatively affects interactions within other members of the family unit and is associated with intimate partner violence.⁷

Depression during pregnancy and the postpartum period has a range of presentations including continuation or relapse of a pre-existing mood disorder, the development of changes in mood during pregnancy and the postpartum period, and the postpartum “baby blues.” Differentiating the correct diagnosis can be complex. Problems with mood are often accompanied by comorbid anxiety and occasionally by potentially life-threatening psychosis.³²

General risk factors for depression include female sex, previous depression, family history of depression, poor social support, and substance abuse. Additional factors associated with depression in pregnant women include younger age, non-Latino ethnicity, being without a partner, traumatic events within the previous 12 months, and pregnancy complications.^{31, 33} A 2013 Agency for Healthcare Research and Quality (AHRQ) report found that screening can significantly reduce postpartum depressive symptoms when there are systems in place to ensure adequate followup of women with positive results.³⁴

Treatment Strategies

Management of mood disorders in pregnancy or the postpartum period varies case by case. In women with existing depression, the tactic may be to stabilize symptoms before attempting pregnancy. But providers and patients are often concerned about the safety of continued pharmacological treatment to the fetus during pregnancy and the postpartum period, particularly if considering breastfeeding.⁸ This makes information about the comparative effectiveness of nonpharmacological treatments during pregnancy of high interest. Treatment choice, or dosing, may vary by the severity of depression, for example whether the symptoms meet criteria for a diagnosis of major depressive disorder according to the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM IV), are subclinical (symptoms are present but not

meeting these criteria), or whether there are other coexisting psychiatric symptoms (most typically anxiety). Thus clear and accurate diagnosis, and reporting of diagnosis, is important to understanding the benefits and harms of treatment.

Interventions for depression both during pregnancy and in the postpartum period can include pharmacological treatments, nonpharmacological treatments, and watchful waiting or no intervention. Pharmacological treatments approved by the U.S. Food and Drug Administration (FDA) for treating depression are listed in Table 1. Antidepressant medications have been shown to be effective at reducing the symptoms of depression in nonpregnant adults.^{9, 35} In general, medications that are effective in treating conditions outside of pregnancy are often presumed to remain effective in pregnancy, but the developing fetus and changes in maternal physiology raise questions about safety and dosing of various agents. The FDA Pregnancy Category for safety to the fetus of antidepressant medications taken during pregnancy is category C (“animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks”), with the exception of paroxetine which is category D (“there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks”). However, evidence on how the risk of one antidepressant compares to another when taken during pregnancy is not well understood. Antidepressant medications are used to treat a variety of other indications, including anxiety disorders (e.g., generalized anxiety disorder, panic attacks, obsessive compulsive disorder, depressed phase of bipolar disorder, and neuropathic pain).

In the postpartum period, depressed mothers often have concerns regarding the use of antidepressants while breastfeeding. Providers can offer encouragement by educating women as to the well-documented benefits of breastfeeding and guide their choice of an individual antidepressant by considering the degree to which each antidepressant is known to pass into breast milk.^{27, 28, 36} There are also a wide array of nonpharmacological interventions that can be used to treat depression including various psychotherapies, electroconvulsive therapy, transcranial magnetic stimulation, and acupuncture, among others.¹¹ Some of these may be used during pregnancy, while others may be reserved for use in the postpartum period (e.g., electroconvulsive therapy). Decisionmaking surrounding treatment of depression in pregnancy is complex because the harms of treatments must be balanced against the potential harms to mother and fetus of untreated depression.

Scope and Key Questions

Previous reviews have broadly evaluated infant and child outcomes following all-purpose maternal use of antidepressants during pregnancy,²² but have generally not focused on specific populations of women with depression. The objective of this systematic review is to compare the benefits and harms of various pharmacological treatment options, to each other and to nonpharmacological treatments, for depression during pregnancy or the postpartum period. The focus is on women who develop depression during pregnancy or the postpartum period, rather than those with a continuing episode. Factors that might impact maternal and child outcomes are assessed (patient, provider, or environmental) including a prior history of depression. Negative effects of untreated disease and exposure to antidepressive drugs are evaluated, highlighting the treatment dilemmas confronting women with depression during pregnancy or the postpartum period. Finally, we identified issues that future studies should address so that women, health care

providers, and other stakeholders can make optimally informed decisions based on balancing benefits and harms.

The Agency for Healthcare Research and Quality wrote preliminary Key Questions based on input from the topic nominator. The Pacific Northwest Evidence-based Practice Center (PNW EPC) revised the Key Questions and developed eligibility criteria to identify the populations, interventions, comparators, outcomes, timing, and study designs of interest. The PNW EPC solicited additional input from the Technical Expert Panel (TEP).

Key Question 1

What are the comparative benefits of pharmacological and nonpharmacological treatments for women with depression during pregnancy and in the postpartum period?

- a. How do pharmacological treatments affect maternal and child* outcomes when compared with placebo or no active treatment or usual care?
- b. How do pharmacological treatments affect maternal and child outcomes when compared with each other (drug A vs. drug B)?
- c. How do pharmacological treatments affect maternal and child outcomes when compared with active nonpharmacological treatments?
- d. How does combination therapy affect maternal and child outcomes? The combinations include:
 - i. Using a second drug to augment the effects of the primary drug and comparing this treatment with monotherapy with a single drug
 - ii. Combining pharmacological treatments with nonpharmacological treatments and comparing them with nonpharmacological treatments alone
 - iii. Comparing pharmacological treatments alone with pharmacological treatments used in combination with nonpharmacological treatments

*A child is defined as a fetus, infant, or a child up to age 18.

Key Question 2

- a. What are the comparative harms of pharmacological and nonpharmacological treatments for women with depression during pregnancy and in the postpartum period?
 - i. How do pharmacological treatments affect maternal and child* outcomes when compared with placebo or no active treatment or usual care?
 - ii. How do pharmacological treatments affect maternal and child outcomes when compared with each other (drug A vs. drug B)?
 - iii. How do pharmacological treatments affect maternal and child outcomes when compared with active nonpharmacological treatments?
 - iv. How does combination therapy affect maternal and child outcomes? The combination include:
 - (a) Using a second drug to augment the effects of the primary drug and comparing this treatment with monotherapy with pharmacological treatment
 - (b) Combining pharmacological treatments with nonpharmacological treatments and comparing them with nonpharmacological treatments alone

- (c) Comparing pharmacological treatments alone with pharmacological treatments used in combination with nonpharmacological treatments
 - b. In babies born to women who become pregnant while taking medications to treat depression, what is the comparative risk of teratogenicity?
- *A child is defined as a fetus, infant, or a child up to age 18.

Key Question 3

Is there evidence that the comparative effectiveness (benefits or harms) of pharmacological and nonpharmacological treatments for women with depression during pregnancy and in the postpartum period varies based on characteristics** such as:

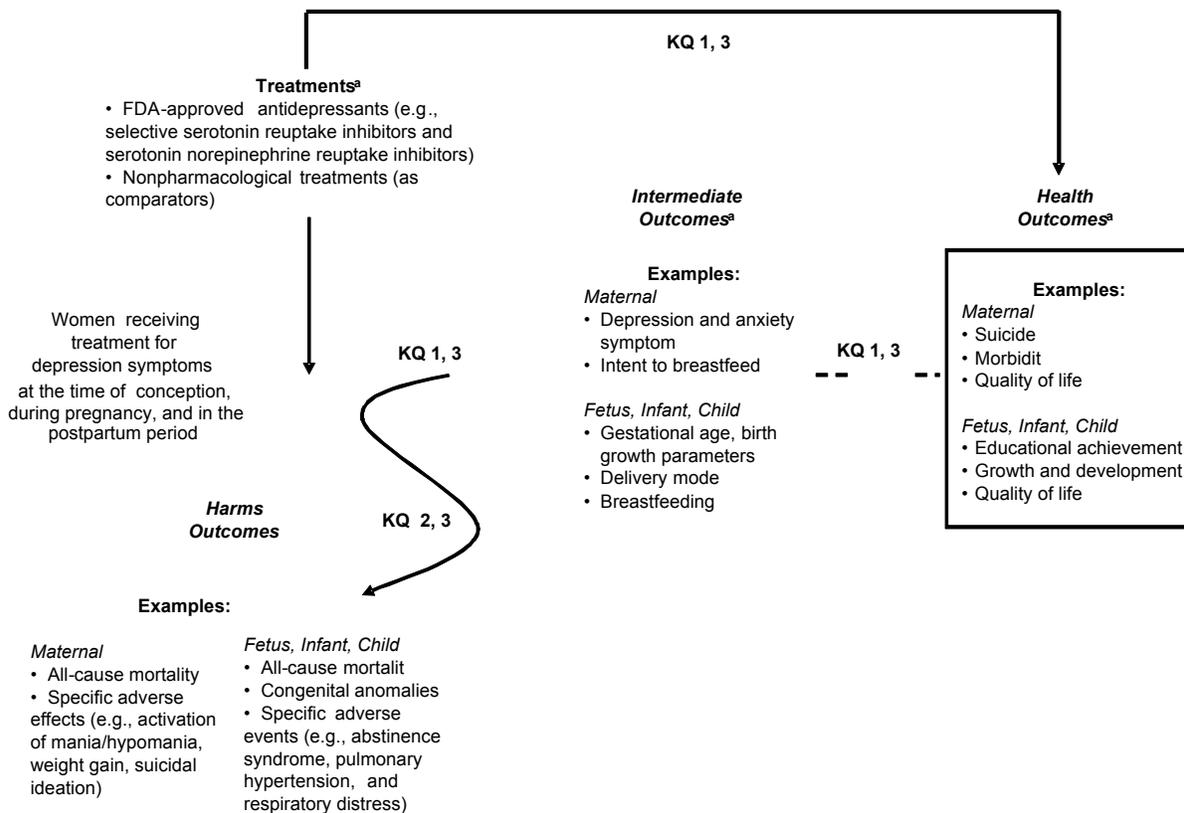
- a. Patient characteristics—race, age, socioeconomic status, family history of depressive/mood disorders, prior use of antidepressive drugs (for treatment or prevention), severity of symptoms, situation at home, unplanned pregnancy, and marital/partner status?
- b. Patient comorbidities (e.g., anxiety diagnoses)?
- c. Intervention characteristics—dosing regimens and duration of treatments?
- d. Coadministration of other psychoactive drugs, specifically, antipsychotics, antianxiety agents (e.g., benzodiazepines), and drugs for insomnia?
- e. Medical provider characteristics (primary care physician, obstetrician, pediatrician, psychiatrist, nurse, midwife, or community worker)?
- f. Medical care environment (community/private/public clinic or hospital)?
- g. Characteristics of diagnosis—whether depression was detected during screening or not, time of diagnosis, method of diagnosis, and when treatment commenced relative to the onset of symptoms?

**Other factors will be considered as they are identified within the comparative studies.

Analytic Framework

The analytic framework below illustrates the population, interventions, outcomes, and adverse effects that guided the literature search and synthesis. Outcomes are classified into benefits (intermediate and health outcomes) and harms. Some classified as benefits could be viewed as harms (and vice versa) depending on whether an increase or decrease in risk is expected, their placement in the framework was determined based on input from experts. For example, as a decrease in suicidality is a goal of treatment, maternal suicide was classified as a benefit, whereas since treatment is not typically anticipated to affect risk of all-cause mortality, it was classified as a harm.

Figure 1. Analytic framework



^aThe full lists of interventions and outcomes are too extensive to illustrate in their entirety in this diagram. See the inclusion criteria for the full list of interventions and outcomes.
 FDA = U.S. Food and Drug Administration; KQ = Key Question.

Organization of This Report

The evidence below is organized first by Key Question, then by the subquestions of the Key Questions, then by pregnancy status at the time of exposure – during pregnancy or postpartum. Within those categories the evidence is presented by pharmacological class with all outcomes for a given class presented together, then by comparisons of pharmacological and nonpharmacological or combination therapy. Under each intervention individual outcomes are assessed; outcomes listed in the inclusions criteria (above) for which *no* evidence was found are not itemized below.

Methods

The methods for this comparative effectiveness review follow the methods suggested in the ARHQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (available at <http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm>). The main sections in this chapter reflect the elements of the protocol established for the comparative effectiveness review; certain methods map to the PRISMA checklist.¹³ All methods and analyses were determined a priori.

Search Strategy

To identify articles relevant to each Key Question, the librarian searched Cochrane Database of Systematic Reviews (CDSR) from 2005 to November 2012, the Cochrane Central Register of Controlled Trials (CCRCT) December 2012, the Cumulative Index to Nursing and Allied Health Literature (CINAHL[®]) from 1941-December 2012, Ovid MEDLINE[®] and Ovid OLDMEDLINE[®] (1946 to November Week 3, 2012, PsychINFO[®] (1996 to December Week 2 2012), and Scopus (1974 to December 2012). Search dates and exact search strings are provided in Appendix A. Date restrictions are not placed on database searches. Grey literature is identified by searching clinical trial registries (ClinicalTrials.gov). Scientific Information Packets were solicited from industry stakeholders through the Scientific Resource Center.

Inclusion and Exclusion Criteria

Populations

Pregnant women and women during the first 12 months after delivery, who are receiving treatment for a depressive episode, including:

- Those who meet the diagnosis for major depressive disorder as described in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).
- Subthreshold depressive symptoms which have become the subject of clinical attention.
- Exclusions: Those who meet DSM-IV diagnosis for bipolar depression, psychotic depression, a mood disorder secondary to a general medical condition, or a mood disorder secondary substance abuse.

Based on input from experts, we also included studies with populations of pregnant women receiving antidepressant drugs for unknown or mixed reasons. These studies were used to provide evidence where no evidence was available in women with known depression or depressive symptoms (gaps in the evidence). To differentiate these populations, in this report we refer to studies of women with known depression as “treated” or “untreated” populations, and studies of women with mixed or unknown diagnoses as “exposed” populations when receiving antidepressants (typically at unknown doses) or “nonexposed” populations when not receiving antidepressants. The focus of the report is on women diagnosed with depression during pregnancy or the postpartum period, rather than those with a continuing episode, except for Key Question 2b regarding teratogenicity of antidepressant drugs taken at the time of conception or in early pregnancy.

Interventions

Interventions included commonly used antidepressant drugs. Drugs not listed below were not included (e.g., monoamine oxidase inhibitors). We used the therapeutic classifications used in previous AHRQ Comparative Effectiveness Reviews,^{9, 35} except that trazodone and nefazodone were classified as norepinephrine reuptake inhibitors for this report.

Table 1. Pharmacologic interventions: Antidepressant agents

Drug Category	Generic Name	Trade Name
Selective serotonin reuptake inhibitor (SSRI)	Citalopram	Celexa [®] , various generics
	Escitalopram	Lexapro [®]
	Fluoxetine	Prozac [®] , various generics Prozac Weekly [®] Sarafem [®]
	Fluvoxamine	Luvox [®] , various generics Luvox CR [®]
	Sertraline	Zoloft [®] , various generics
	Paroxetine	Paxil [®] , various generics Paxil CR [®]
	Vilazodone	Viibryd [®]
Serotonin norepinephrine reuptake inhibitor (SNRI)	Desvenlafaxine	Pristiq [®]
	Venlafaxine	Effexor XR [®]
	Mirtazapine	Remeron [®] , various generics Remeron Soltab [®]
Selective serotonin norepinephrine reuptake (SSNRI)	Duloxetine	Cymbalta [®]
Tricyclic antidepressants (TCAs)	Amitriptyline	Various generics
	Desipramine	Norpramin [®] , various generics
	Imipramine	Tofranil [®] , various generics
	Nortriptyline	Aventyl hydrochloride [®] Pamelor [™] Various generics
Norepinephrine reuptake inhibitors (NRIs)	Nefazodone	Various generics (previously available as Serzone [®])
	Trazodone	Desyrel [®] , various generics
Other	Bupropion	Wellbutrin [®] Wellbutrin SR [®] Wellbutrin XL [®] Forfivo XL [®] Aplenzin [®]

Comparators

- Placebo or no treatment
- Usual care: We defined usual care as receiving pregnancy and postpartum care similar to those with normal risk pregnancies. When “usual care” was the comparator, two reviewers with experience in delivering postpartum health care (JR and JMG) separately determined if it is “usual,” and if they believed it not to be usual it was included as a separate “greater than usual care” comparator.
- The drugs listed above in Table 1 when compared with each other.

- Other active pharmacological treatments used to augment drugs with a U.S. Food and Drug Administration indication for unipolar or bipolar depression.
- Any nonpharmacological treatment, including but not limited to over-the-counter treatments, osteopathic or naturopathic treatments, herbal remedies and vitamins, all forms of psychotherapy, case management, electroconvulsive therapy, nonrepetitive and repetitive transcranial magnetic stimulation, vagal nerve stimulation, exercise, meditation, and touch therapies.

Benefits Outcomes

Maternal

- Danger to self (suicidal and nonsuicidal behaviors)
- Danger to infant (infanticidal behavior, abuse, or neglect)
- Depression symptomatology as scored using validated scales measuring depression
 - Response
 - Remission
 - Speed and duration of response/remission
 - Relapse
 - Recurrence
 - Change in core depressive symptoms
- Anxiety symptoms as scored as a subscale item using validated scales measuring depression, or validated scales used to measure anxiety symptoms
- Functional capacity
 - Quality of life using validated scales, for example, Medical Outcomes Survey 36-item Short Form (SF-36)
 - Caring for self, infant and family
 - Mother-father dyad interaction success, including reduced violence among intimate partners
 - Work productivity
- Delivery and postpartum parameters
 - Breastfeeding
 - Shared decision making around delivery choices (e.g., cesarean)
 - Delivery mode
 - Mother-infant dyad interaction patterns
 - Pregnancy weight gain within or outside of 1990 Institute of Medicine Guidelines
- Social services utilization
 - Prevention of child protective service involvement.
- Maternal health system resource utilization including emergency department use, hospitalizations, and office visits
- Adherence or persistence with treatment regimen.

Fetus, Infant, Child

- Parameters at birth and up to 12 months of age:
 - Preterm birth (e.g., < 32 weeks, < 37 weeks)
 - Appropriate growth (height, weight, and head circumference)

- Gestational age (e.g., small for gestational age), race/ethnicity taken into consideration
 - Birth hospitalization length of stay
 - Infant attachment
 - Developmental screening—Ages and Stages Questionnaire; Denver; Modified Checklist for Autism in Toddlers; Bayley Scales of Infant Development.
- Growth and development after 1 year of age:
 - Developmental screening and diagnoses
 - Growth parameters (height, weight, and body mass index percentile according to sex and age)
- Learning (e.g., linguistic, cognitive, and social-emotional skills) and educational achievement
 - Kindergarten readiness
 - Age at Kindergarten entry
 - Third grade testing outcomes
 - Other standard testing outcomes (Eighth grade, etc)
 - Intelligence tests (any)
 - Individualized education plans/use of school services
 - School failure/dropout rate
 - High school graduation rate
 - Missed school days
- Stress-related chronic disease
 - Mental illness
 - Chronic illness
- Infant health system visits (e.g., well baby visits)
 - Health care utilization (primary care, emergency department, hospitalization)
- Social services utilization (Women, Infants, and Children Program [WIC], community health nurse, social worker, State Department of Health and Human Services, free and reduced lunch, and food stamps)
 - Community resource utilization (community engagement measures)
- Social and emotional development
 - Quality of life
- Contact with juvenile justice system.

Harms Outcomes

Maternal

- Death (including suicide, all-cause mortality and cause-specific [e.g., cardiac] death)
- Specific adverse effects or withdrawals due to specific adverse events related to treatment (e.g., hyponatremia, activation of mania/hypomania, seizures, suicidal ideation, hepatotoxicity, weight gain, metabolic syndrome, gastrointestinal symptoms, and loss of libido)
- Overall adverse-event reports
- Withdrawals from study and discontinuation of treatment due to adverse events
- Adverse events associated with discontinuation of treatment
- Serious adverse events reported

Fetus, Infant, and Child

- All-cause mortality
- Congenital anomalies (any)
 - Stratified into major and minor with further grouping by organ system or type of anomaly
- Other specific adverse events (e.g., withdrawal symptoms [neonatal abstinence symptoms], pulmonary hypertension, respiratory distress, neonatal convulsions, and heart defects)

Timing

- All followup periods were eligible.

Setting

- Studies conducted in economically advanced countries were included (www.imf.org/external). These countries are: Australia, Austria, Belgium, Canada, Cyprus, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Iceland, Ireland, Israel, Italy, Japan, South Korea, Luxembourg, Malta, The Netherlands, New Zealand, Norway, Portugal, Singapore, the Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Taiwan, the United Kingdom, and the United States of America.

Study Designs

- For efficacy or effectiveness, a “best evidence” approach was used. Randomized controlled clinical trials and systematic reviews comparing pharmacologic treatments for depression during pregnancy to control groups of pregnant women with depression who were treated with nonpharmacologic or no treatment were included as the top-tier evidence. If insufficient evidence was found with these study designs, observational study evidence (defined as cohort studies comparing at least two concurrent treatment groups, case-control studies, and time-series studies) and studies comparing to control groups of nonexposed pregnant women were included.
- For harms, in addition to randomized controlled clinical trials and systematic reviews, observational studies (defined as cohort studies comparing at least two concurrent treatment groups, case-control studies, and time-series studies) comparing pharmacologic treatments for depression during pregnancy to control groups of pregnant women with depression who were treated with nonpharmacologic or no treatment were included. If insufficient evidence was found with these designs, studies comparing to control groups of nonexposed pregnant women were included.
- For systematic reviews, only included reviews that (1) searched at least two databases and (2) discussed methodology of quality assessment and data abstraction. In accordance with established methodologies, systematic reviews were used in place of de novo analysis and synthesis of the included studies wherever possible, depending on the details of how closely the review matched our report scope and how recent the review was.^{14, 37} Exclusions: case reports, case series, and single-group studies.

Study Selection

Two reviewers independently assessed titles and abstracts of citations identified through literature searches for inclusion using the criteria described above. Full-text articles of potentially

relevant citations were retrieved and again were assessed for inclusion by both reviewers. Disagreements were resolved by consensus or a third-party arbitrator. Results published *only* in abstract form were not included because inadequate details were available for quality assessment. At full-text level, studies were excluded if they met one or more of the following reasons for exclusion: published in language other than English, the intervention, outcome, population and study design did not meet inclusion criteria, or they were letters, editorials and nonsystematic reviews. All studies excluded at full text are listed in Appendix B. All citations and screening decisions for each citation were entered in an electronic database (Endnote[®] X3, Thomson Reuters). Appendix C lists all studies included at full text.

Data Extraction

The following data were abstracted from included studies: design; setting (community/private/public clinic, hospital); population characteristics (race, age, socioeconomic status, family history of depressive/mood disorders, prior use of antidepressive drugs, severity of symptoms, situation at home, unplanned pregnancy, marital/partner status, comorbidities); eligibility and exclusion criteria; characteristics of diagnosis (whether depression was detected during screening or not, time of diagnosis, method of diagnosis, and when treatment commenced relative to the onset of symptoms); intervention characteristics (dose, duration, and cointerventions); comparisons; medical provider characteristics (primary care physician, obstetrician, psychiatrist, nurse, midwife, community worker, and pediatrician visits); numbers of patients, enrolled; and results for each outcome. One reviewer abstracted study data, and the second reviewer did random checking of data abstractions. Intention-to-treat results were recorded if available. Appendix F contains evidence tables for data abstraction of trials and observational studies. Studies that were considered high risk if bias are not abstracted as they are not included in the evidence synthesis.

Quality (Risk of Bias) Assessment of Individual Studies

We assessed the internal validity (quality) of randomized trials, and cohort and case control studies abased on predefined criteria established by the Drug Effectiveness Review Project.¹⁴ For trials, these criteria were based initially on the criteria used by the U.S. Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom).^{38,39} In rating the internal validity of trials, we evaluated methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; and the use of intention-to-treat analysis.

We rated the internal validity of observational studies based on the adequacy of the patient selection process; whether there was important differential loss to followup or overall high loss to followup; the adequacy of exposure and event ascertainment; whether acceptable statistical techniques were used to minimize potential confounding factors; and whether the duration of followup was reasonable to capture investigated events. Based on input from experts, we selected four potential confounding factors that were considered key and should be adjusted for in analyses: age, race, parity, and other exposures (e.g., alcohol, smoking, and other potential teratogens). Low or moderate risk of bias studies adjusting for these were considered best evidence if no randomized controlled trials (RCTs) were available.

All assessments resulted in a rating of high, medium or low risk of bias, primarily at the study-level. In some cases, however, the reviewers determined that validity varied by outcome

and rated risk of bias for different outcomes separately. Studies that have a fatal flaw were rated high risk of bias; studies that meet all criteria are rated low risk of bias; the remainder are rated medium risk of bias. As the medium risk of bias category is broad, studies with this rating vary in their strengths and weaknesses: The results of some medium risk of bias studies are *likely* to be valid, while others are only *possibly* valid. A high risk of bias study is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared interventions. A fatal flaw is reflected by failure to meet combinations of items of the risk of bias checklist.

All studies were first rated by one reviewer and then checked by another reviewer. All disagreements were resolved using a consensus process.

Data Synthesis

Evidence tables were constructed to show the study characteristics, quality ratings, and results for all included studies. A hierarchy-of-evidence approach was used, where the best evidence is the focus of our synthesis for each question, population, intervention, and outcome addressed. Based on input from experts, we stratified our assessment of congenital anomalies into major and cardiovascular categories. Most cardiovascular malformations are considered to be major malformations in congenital anomaly classification systems and were included in our evaluation of major congenital anomalies as a whole. But, due to our experts' particular concern for cardiovascular malformations with depression and/or pharmacologic therapy for depression, we also separately evaluated subsets of cardiovascular anomalies as reported in the studies. Data from high risk of bias studies were generally excluded from the synthesis, except to undertake sensitivity analyses or to note where high risk of bias studies constitute the only evidence for an important outcome.

Direct comparisons were preferred over indirect comparisons. Direct evidence would include studies (trials or observational studies) that compared pregnant or postpartum women with depression who receive antidepressant treatment with pregnant or postpartum women with depression who were not treated.

Indirect evidence would include studies (trials or observational studies) of pregnant or postpartum women treated with antidepressants without specifying that the women have depression. Similarly, studies that compare pregnant or postpartum women taking an antidepressant drug with pregnant or postpartum women who are not taking such medications but also are not known to have a diagnosis of depression (a general population) are considered indirect. Indirect comparisons can be difficult to interpret for several reasons; in the latter case the issue is primarily heterogeneity of underlying risk of the populations. The underlying risk of untreated depression during pregnancy or the postpartum period is an important factor in assessing the relative benefits and harms of potential treatments. We use data from indirect comparisons when no other directly applicable evidence exists, but findings should be interpreted with caution because comparisons with a generally healthy population without depression rather than with a depressed population may underestimate the benefits and overestimate the harms of treatment.

High risk of bias studies are not presented in the data evidence tables, but they were included in the quality assessment evidence tables. To determine the appropriateness of meta-analysis, the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes were considered. Appropriate measures are chosen based on the type of data for meta-analysis, according to the guidance for the EPC program.³⁵ Random-effects

models were used to estimate pooled effects, except when only two studies were being pooled where a fixed effect model was used.^{15, 16} The Q statistic and the I² statistic (the proportion of variation in study estimates due to heterogeneity) were calculated to assess heterogeneity in effects between studies.^{17, 18} Where statistical heterogeneity was found, reasons were explored by using subgroup analysis. For rare events, such as congenital malformations, relative risks would be similar to odds ratios. In meta-analysis, we combined relative risks and odds ratios for such outcomes. Where adjusted summary measures (e.g., odds ratios) were reported by individual studies, we combined summary measures using the 95% confidence intervals to estimate variance.

When meta-analysis could not be performed, the data was summarized qualitatively, grouping studies by similarity of population and/or intervention characteristics.

Strength of the Body of Evidence

We used the methods outlined in chapter 10 of the *AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews*¹² (an edited version of the chapter has also been published in the *Journal of Clinical Epidemiology*¹⁹) to grade strength of evidence. Domains considered in grading the strength of evidence include consistency, directness, precision, and risk of bias. Based on this assessment, the body of evidence was assigned a strength-of-evidence grade of high, moderate, or low. In cases where evidence does not exist, is sparse, or contains irreconcilable inconsistency, a grade of insufficient evidence was assigned. Technical experts were consulted to help inform prioritization of the outcomes for grading. Specific outcomes selected for rating included the following for any comparison with at least moderate risk of bias evidence: maternal outcomes; danger to self or infant, depression symptomatology (response and remission), breastfeeding intention and duration, number with adverse events, discontinuing due to adverse events, weight gain and infant outcomes; preterm birth, small for gestational age, neonatal mortality, congenital malformations, persistent pulmonary hypertension, infant and child neurodevelopment, intellectual function, educational outcome/school performance, mental health and healthcare/social service utilization.

Applicability

The applicability of the bodies of evidence addressing each Key Question was examined by paying special attention to study eligibility criteria, characteristics of the enrolled population in comparison to the target population, characteristics of the intervention and comparator used in comparison with care models currently in use, and clinical relevance and timing of the outcome measures. Technical experts identified items of particular interest that contributed to heterogeneity and impact applicability. In general, these included the subgroups specified in Key Question 3: population characteristics (race, age, socioeconomic status, family history of depressive/mood disorders, prior use of antidepressive drugs, severity of symptoms, situation at home, unplanned pregnancy, and marital/partner status), comorbid anxiety diagnoses and other comorbidities, characteristics of diagnosis (whether depression was detected during screening or not, time of diagnosis, method of diagnosis, and when treatment commenced relative to the onset of symptoms), intervention characteristics (dose, duration, and cointerventions), comparisons, and medical provider characteristics (primary care physician, obstetrician, pediatrician, psychiatrist, nurse, midwife, or community worker), and how the evidence may be used to inform the development of quality measures to be used by healthcare funders such as the Federal Children's Health Insurance Program (CHIP).

Results

Introduction

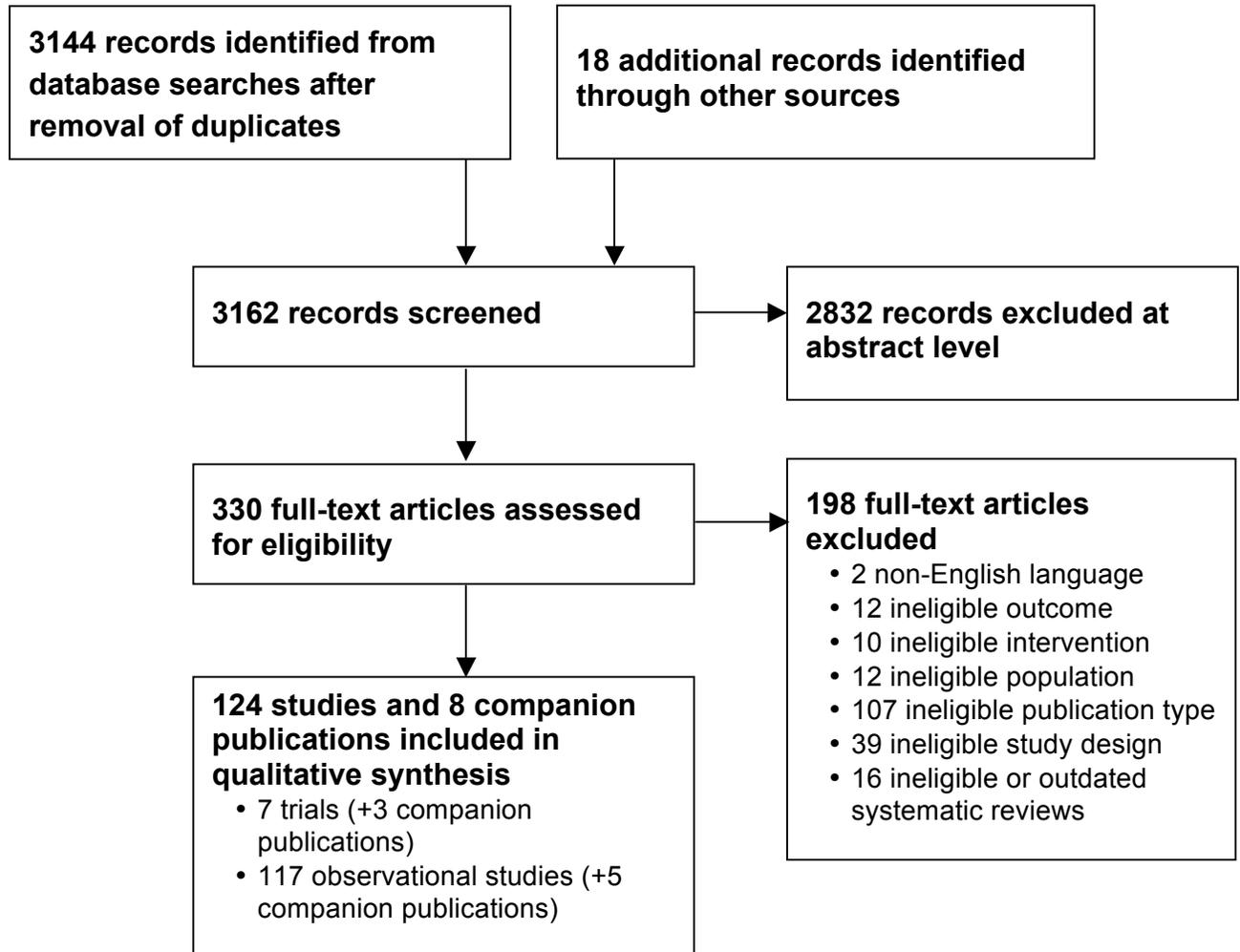
We begin by describing the results of our literature searches. We then provide a brief description of the included studies. The remainder of the chapter is organized by Key Question. A list of abbreviations and acronyms is provided at the end of the report.

Results of Literature Searches

Figure 2 depicts the flow of articles through the literature search and screening process.¹³ Searches of Ovid MEDLINE[®], CDSR[®], CCRCT[®], CINAHL[®], SCOPUS[®] and PsycINFO[®] yielded 3144 citations. Manual searching identified 18 additional citations. We received scientific information packets from Jazz Pharmaceuticals, Forest Pharmaceuticals, Inc, and Sanofi Aventis, U.S. Based on these sources, a total of 3,162 abstracts were screened of which 330 articles were retrieved and assessed for eligibility. Of those, 124 unique studies and 8 companion publications met inclusion criteria and are included in this report.^{20, 21, 40-135, 136, 137-169} No systematic reviews were found to be eligible for evidence synthesis. The majority of the evidence is from observational studies with 122 articles describing 117 unique studies. Very few trials met inclusion criteria for this report with 10 articles describing 7 unique trials. Appendix B provides a listing of all included studies and Appendix C provides a complete list of articles excluded at full text with the reasons for exclusion.

Few studies included only pregnant women with depression – most included pregnant women receiving an antidepressant drug for any reason (i.e., maternal exposure) with comparisons to pregnant women who were not receiving an antidepressant drug during pregnancy (i.e., maternal nonexposure). There were no studies comparing an antidepressant drug to a nonpharmacological treatment, and only a few where nonpharmacological treatment was used as an add-on to drug therapy. Using a “best evidence” approach, we focus our findings and conclusions on evidence in pregnant women with depression. We included 6 RCTs and 13 observational studies that focused on women with depression. To address gaps, we included indirect evidence from an additional 104 observational studies of women receiving antidepressant drugs for mixed or unknown reasons compared with pregnant women not taking an antidepressant. Findings from these studies are reported only for important outcomes where there is no better evidence, particularly for serious harms where even such indirect evidence may be useful in guiding clinical decisions.

Figure 2. Results of literature search^a



^a This is a modified PRISMA flow diagram.¹³

Description of Included Studies

Of the 124 unique studies that were included, most (67 percent) were conducted in non-US countries while 30 percent were conducted in the US. The remaining studies were conducted in multiple countries, but included sites in the US and Canada. Of the 122 included observational studies, 37 (30 percent) were rated high risk of bias,^{48, 53, 55, 58, 67, 73-75, 82-84, 88, 89, 91, 95, 101-103, 115, 117, 118, 127, 130, 131, 134, 136-140, 143, 144, 148, 151, 153, 157, 161} 12 were rated low risk of bias (10 percent),^{21, 40, 42, 60, 62, 92, 104, 119, 124, 125, 135, 145} and the rest of the observational studies were rated medium risk of bias.^{20, 41, 44, 45, 47, 49, 51, 52, 54, 56, 57, 59, 63-66, 68-72, 76-81, 85-87, 90, 93, 96, 98-100, 105-107, 109-112, 114, 116, 120-123, 126, 128, 129, 132, 133, 141, 142, 146, 147, 149, 150, 152, 154-156, 158, 159, 162-165, 167-169} Appendix F, Evidence Table 2 lists all the observational studies rated High Risk of bias. Observational studies were rated high risk of bias here due primarily to potentially biased selection of patients, lack of assessment of comparability of subjects at baseline, uncertain accuracy of exposure or outcome ascertainment, and lack of appropriate statistical analysis, including controlling for potential confounding. See Appendix F, Evidence Table 1 for details on individual study assessments. These observational studies largely examined outcomes and associations of exposures during pregnancy, with limited evaluation of exposure in the postpartum period. The designs of the studies included cohort and case control, with large, linked databases providing data for most of the larger studies – including several population-based cohort studies from Nordic countries. Prospective cohort studies, including data collected by teratology information services around the world, constituted a smaller set of studies with smaller sample sizes. The control groups in most of these observational studies were pregnant women without exposure to an antidepressant drug. The indication for treatment with an antidepressant drug was reported infrequently, and depression in either intervention or control groups was controlled for in few studies, particularly in a way to allow comparison of treatment groups or examination of the effect on outcomes of treatment. All seven of the randomized controlled trials (RCTs) included examined women in the postpartum period, and four were rated medium risk of bias while three were considered high risk of bias due to problems with uncertain randomization, allocation concealment, or blinding methods combined with lack of an intention to treat analysis and/or a high rate of missing data. None of the trials were rated as having a low risk of bias. Further details on studies are provided below.

Key Question 1. What are the comparative benefits of pharmacological and nonpharmacological treatments for women with depression during pregnancy and in the postpartum period?

Summary

There were no clinical trials of antidepressant drugs used to treat depression in pregnancy to provide direct evidence on the comparative benefit or harms. Direct evidence is limited to 16 observational studies of pharmacological treatments given at unknown dosages. Indirect evidence consists of studies of women taking an antidepressant during pregnancy for any reason compared with women who did not take an antidepressant during pregnancy, with unknown depression status in either group.

- Direct evidence was sparse on the maternal and infant/child benefits associated with pharmacological and nonpharmacological treatment for depression during pregnancy and the postpartum period, and it was insufficient to support conclusions due to methodological limitations, unknown consistency and imprecision. Types of direct evidence available are:
 - Maternal depression symptomatology
 - One small observational study with high risk of bias (N=46) compared mean CES-D scores between depressed pregnant women treated with fluoxetine and untreated depressed pregnant women.
 - One small RCT with high risk of bias (N=109) compared response and remission rates between sertraline and nortriptyline in postpartum women with depression.
 - Two small medium risk of bias RCTs and one small, high risk of bias observational study (N=150) compared the effects of combining pharmacologic treatments with nonpharmacological treatments versus nonpharmacological treatments alone on depression symptomatology when used to treat depression in postpartum women.
 - One small medium risk of bias RCTs and one small, high risk of bias observational study (N=58) compared the effects of combining pharmacologic treatments with nonpharmacological treatments versus pharmacological treatments alone on depression symptomatology when used to treat depression in postpartum women.
 - Maternal functional capacity:
 - One small observational study with medium risk of bias (N=62) compared mean SF-12 mental components scores between depressed pregnant women treated with SSRIs and untreated depressed pregnant women.
 - Breastfeeding
 - One small observational study with medium risk of bias compared the effects of SSRI treatment during pregnancy on the proportions of women breastfeeding 6 weeks after birth
 - One small RCT with high risk of bias (N=70) compared the effects of taking sertraline versus nortriptyline for depression during the postpartum period on breastfeeding rates.
 - Pre-term birth
 - One observational study with medium risk of bias (N=200) compared the effects of SSRIs to no treatment of depression during pregnancy.
 - Infant/child development
 - One small observational study with medium risk of bias (N=49) compared mean scores on the Brazelton Neonatal Behavioral Assessment Scale between depressed pregnant women treated with SSRIs and untreated depressed pregnant women.
 - One small observational study with medium risk of bias (N=44) compared the effects of SSRIs plus psychotherapy versus psychotherapy alone during pregnancy on the Bayley Mental Development Index and Psychomotor Development Index and Behavioral Rating Scale.

Detailed Assessment of the Evidence

Key Question 1. What are the comparative benefits of pharmacological and nonpharmacological treatments for women with

depression during pregnancy and in the postpartum period?

There were no clinical trials of pharmacologic treatment during pregnancy to inform the question of the comparative benefits of treatment. Evidence was limited to observational studies (cohort and case control designs). Most of these studies provide only indirect evidence, comparing women treated with antidepressants during pregnancy for any reason to pregnant women who were not treated. The diagnosis for treatment in the treated group was most often not reported, or reported as a baseline characteristic but with no subgroup analysis based on diagnosis. The rates of depression in the control groups were rarely reported. However, some studies controlled for depression in statistical analyses. Both RCTs and observational studies were found for treatment in the postpartum period.

The evidence below is organized first by the subquestions of Key Question 1, then by pregnancy status at the time of exposure – during pregnancy or postpartum. Within those categories the evidence is presented by pharmacological class with all outcomes for a given class presented together. Direct evidence is the primary focus, with indirect evidence reported only for important outcomes for which evidence in pregnant women with depression did not exist or was sparse, particularly for serious harms where even such indirect evidence may have been useful in guiding clinical decisions. Outcomes for which no evidence was found are not itemized below.

Key Question 1a. How do pharmacological treatments affect maternal and child outcomes when compared with placebo or no active treatment or usual care?

Antidepressant Exposure During Pregnancy

Selective Serotonin Reuptake Inhibitors

Maternal Outcomes

Twenty-five observational studies reported maternal health outcomes for active SSRI treatment (as a class or as an individual drug),^{45, 49, 52, 55, 62, 65, 66, 76, 78, 82, 83, 85, 98, 100, 107, 114, 129, 145, 147, 149, 150, 154, 156, 159} with only three^{40, 55, 156} explicitly including women with depression during pregnancy in both the intervention and control groups (i.e. direct evidence). Two were methodologically weak with high risk of bias, due primarily to potentially biased selection of patients, unclear completeness of data, and lack of appropriate statistical analysis, including controlling for potential confounding.^{55, 83}

Depression symptomatology. Associations of treatment effect require study populations that include depressed pregnant women with and without treatment and ideally would include an assessment prior to initiation of treatment in the treated group. Six reports of five observational studies^{55, 78, 82, 83, 98, 156} reported some feature of mood or depression symptoms with SSRI use; but only two^{55, 156} provide direct comparative evidence on depression symptomatology among depressed pregnant women with and without pharmacological treatment. These studies are small, totaling 106 women between them (59 treated, 31 depressed without pharmacologic treatment, and 16 without depression and no treatment). The smallest, totaling 44 depressed pregnant women,¹⁵⁶ 31 of whom were taking SSRIs showed no significant difference between treated and untreated in change in symptoms across pregnancy. The larger study of 62 women⁵⁵ focused

exclusively on fluoxetine treatment and found significant improvement in depression symptoms as measured by CES-D score with treatment, also improving with each trimester. By the third trimester the mean CES-D score for depressed women on fluoxetine was 14.33 ± 12.02 compared with 25.93 ± 4.91 for those not treated with fluoxetine ($P=0.0010$). It is important to note however, that these two studies differ in the scales they use to measure depression and all differ from measures commonly used outside of pregnancy. The four other studies provide only indirect evidence because the untreated group includes a mixture of women with and without depression and or other mood disorders.

Anxiety symptoms. No direct evidence was found in that no studies examined anxiety symptom change in depressed pregnant women with and without treatment or comparing treatments. Indirect evidence comes from two studies with medium⁹⁸ and high risk of bias⁸³ that monitored anxiety and depression symptoms in depressed women taking SSRIs or SNRIs, but made comparisons to women with and without mood disorders not taking antidepressants. Both studies used the HAM-A, as well as additional scales to measure anxiety. Anxiety scores were higher among women taking antidepressants compared with women not taking antidepressants. While there was a trend toward declining anxiety scores postpartum, it is unclear whether the declines were statistically significant.

Functional capacity. Only one medium risk of bias study^{45, 107} provided direct evidence on functional capacity in pregnant women with depression with and without SSRI use. Women who were depressed continually throughout pregnancy and treated with an SSRI continuously throughout pregnancy had better functional capacity as measured by the mental component of the SF-12 compared to those that were depressed throughout pregnancy but untreated (45.2 ± 13.7 compared with 35.3 ± 11.4).⁴⁵ Women treated with SSRIs for only part of their pregnancy had a mean score of 44.6, and those with depression in only part of their pregnancy but who received no SSRI had a mean score of 40.5. A control group with no depression and no SSRI treatment had a mean score of 55.7. While the P-value across all groups was statistically significant ($P < 0.001$), pairwise comparisons were not undertaken. Additionally, the specific timing of the SF-12 scores is not clear from the study report.

Pregnancy weight gain. No direct evidence on the effect of different treatments for depression on weight gain in pregnant women with depression was found. In a 1990 report,¹⁷⁰ the Institute of Medicine recommended a maternal weight gain of 25 to 35 pounds for women with normal weight for height. Despite the fact that weight gain is associated with both the use of antidepressant drugs and with some forms of depression and can have a significant effect on maternal health, there were only two medium risk of bias studies that addressed this topic, both of which were indirect evidence because they include women treated with an SSRI for any reason and make comparisons to women who did not receive an SSRI (unknown depression status). Therefore the strength of evidence is considered insufficient (See Appendix E, Table 2). A study of 5961 women reported mean weight gain during pregnancy, which was 33.4 pounds for non-SSRI users, 34.0 pounds for women who discontinued SSRIs two months before pregnancy and 37.0 pounds for women who continued SSRIs through the first trimester. Although the group who continued SSRIs through the first trimester is the only group to have a mean weight gain in excess of the 1990 IOM guidelines, the statistical significance of this difference is unknown.⁵² Another small study found that women in treated with fluoxetine gained

an average of 37 +/- 15.4 pounds, which exceeds recommendations but no data were available for the control group.¹⁵⁴

Breastfeeding. No direct evidence was found on the effect of SSRIs used to treat depression during pregnancy compared with untreated depression during pregnancy.

Indirect evidence consists of four prospective observational studies ranging in size from 44 to 466 women reported on breastfeeding rates among women taking SSRIs compared with women not taking SSRIs (depression status unknown in either group).^{65, 114, 129, 156, 159} All had medium risk of bias due to potentially biased selection of patients and lack of controlling for potential confounding (e.g., not controlling for parity or prior experience breastfeeding). The best indirect evidence on breastfeeding comes from a study of 168 pregnant women enrolled by 20 weeks gestation and assessed for breastfeeding intention, initiation, and breastfeeding up to 12 weeks postpartum.¹⁵⁹ This study assessed depression symptoms at weeks 20, 30 and 36. The analysis controlled for depression symptoms and presence of a diagnosis of major depressive disorder, as well as parity and prior experience breastfeeding (factors known to be strongly associated with future breastfeeding). Intention to exclusively breastfeed was the most significant factor associated with breastfeeding initiation and duration. Neither depression symptoms nor symptom severity was associated with intention to breastfeed however there was a significant and negative association between SSRI use (for any reason) and intention to breastfeed compared with no antidepressant use in women with and without depression (RRR 12.31 (95% CI 2.50-60.66) for intention to formula feed). There was also no association between diagnosis of major depressive disorder or depressive symptoms and initiation of breastfeeding. Furthermore, even though SSRI use at 2 weeks postpartum was associated with lower depression symptom scores, women taking SSRIs at 2 weeks postpartum were more likely to stop breastfeeding by 12 weeks (RRR 12.0, 95% CI 1.64-88.3) compared with women not taking SSRIs. This evidence is insufficient strength to draw conclusions for the questions posed in this report.

Infant/Child Outcomes: Birth Parameters

Preterm birth. Direct evidence on the risk of preterm birth is limited to one observational study providing insufficient evidence.⁴² This medium risk of bias study reported preterm birth rates for depressed women treated with an SSRI during pregnancy compared with those who were depressed but did not receive an SSRI.⁴² Preterm birth for the main analysis was defined as delivery prior to the 37th week of gestation, and gestational age was based on ultrasound when available – the proportion with ultrasound validation available was not reported. While the study did not make statistical comparisons across the two groups of women with depression, we were able to calculate an unadjusted odds ratio of 1.73 (95% CI 0.63 to 4.42) based on numbers reported. We were unable to adjust for key factors, and because the confidence interval is wide and consistency of these findings is unknown the evidence is insufficient to draw conclusions. Subgroup analysis of those delivering prior to 34 weeks gestation was undertaken, but no births met this criterion for the group of women with depression and treated with an SSRI.

There is a large volume of indirect evidence on the risk of preterm birth with use of SSRIs during pregnancy in women with unknown depression status.^{42, 45, 49, 53, 64, 90, 111, 112, 122, 128, 133, 146} Based on eleven observational studies, there is evidence of an increased risk of preterm birth (< 37 weeks gestation) and that the magnitude of risk may vary by timing of exposure, but current evidence is inadequate to establish reliable estimates. The most relevant of these studies is a

medium risk of bias study that reported a statistically significant increased risk of preterm birth with SSRI use during pregnancy for any reason, compared with pregnant women with a documented psychiatric illness who did not receive an SSRI (or other antidepressant or antipsychotic drug) during pregnancy; adjusted OR 2.68 (95% CI, 1.83 to 3.93),¹²⁸ While this study did not limit the diagnoses to depression, gestational age was determined by ultrasound. This study adjusted for several key factors, including history of prior preterm birth, but did not adjust for severity or type of psychiatric illness.

Four other observational studies provide some information on the effect of timing of exposure to an SSRI during pregnancy.^{90, 111, 112, 128} These studies performed ultrasound verification of gestational age, defined preterm birth as delivery at less than 37 weeks gestation and found an increased risk of preterm birth. A single study found the risk with early exposure to be extremely increased, adjusted OR of 11.7 (95% CI, 2.20 to 60.70); and a second study found increased risk with late exposure, adjusted OR 2.48 (95% CI, 1.75 to 3.50). Pooling the two studies reporting exposure at any time during pregnancy also resulted in a statistically significant, but lower, increase in risk, pooled adjusted OR 1.24 (95% CI, 1.12 to 1.38).

Evidence on the risk of preterm birth with individual SSRIs is very limited, with few studies for each drug. None of these studies made comparisons of pregnant women with depression and therefore only provide indirect evidence for the risk in such women. The estimate of risk was highest with citalopram/escitalopram,^{58, 59, 118, 150} with non-statistically significant increase in risk with fluoxetine,^{75, 144, 150, 154} sertraline^{59, 150} and paroxetine^{58, 59, 75, 118, 122, 144, 150, 154} but all of the estimates are likely to shift with additional studies, particularly those that control for potential confounders.

Growth for gestational age. Evidence on the risk an infant to be small for gestational age at birth following maternal treatment for depression with an SSRI during pregnancy is insufficient because there is no direct evidence available. In order to determine whether SSRIs influence infant growth, it is necessary to understand whether depression in pregnancy itself influences infant growth parameters.

The best indirect evidence comes from two of the five studies using ultrasound confirmation of gestational age (above).^{128, 135} A study from Denmark identified three groups of women, those with depressive symptoms but receiving no pharmacological treatment, women taking SSRIs (indication for the SSRI not recorded), and a control group of pregnant women not depressed and not taking an SSRI.^{128, 135} This study did not report the outcome of small for gestational age for the group with depression but did report the outcome of head circumference at birth. This study found no statistically significant difference in head circumference between the depressed, untreated group and controls but did find a difference when comparing the group taking an SSRI for any reason to controls (-5.88 millimeters; 95% CI, -11.45 to -0.30). A study including women with a psychiatric illness who were not receiving an antidepressant or an antipsychotic treatment during pregnancy compared with a group of similar women who were taking an SSRI did not find an increased risk with use of SSRIs late in pregnancy (adjusted OR 1.13, 95% CI 0.65 to 1.94). This study did not adjust for severity or type of mental illness.

Eleven other medium- and high-risk of bias observational studies report on infants small for gestational age, comparing women taking an SSRI during pregnancy for unknown reasons to pregnant women not taking an SSRI (depression status unknown).^{41, 52, 69, 83, 86, 111, 119, 122, 128, 133, 135} Only five of these studies that used ultrasound to determine gestational age,^{111, 119, 128, 133, 135} four of which reported odds ratios adjusted for confounding factors. These studies did not find an

increased risk of an infant being small for gestational age (adjusted pooled OR of 1.04 , 95% CI, 0.64 to 1.69; $I^2=30\%$) with SSRI use during pregnancy.

Infant/Child Development

Direct evidence on the effect of maternal treatment with SSRIs for depression during pregnancy on infant and child development is insufficient to draw conclusions and is limited to two observational studies.^{54, 156}

Bayley development assessments. In a very small (N = 44) medium risk of bias study women with major depressive disorder (based on DSM-IV MDD criteria) were enrolled and two groups were identified; those taking an SSRI during pregnancy and those who were not taking a pharmacologic treatment. Both groups received what is described only as ‘supportive psychotherapy’ with no further details reported. No details on the psychotherapy received were reported. Bayley Scales for Infant Development, 2nd Edition, scores were assessed in children 6-40 months of age, with no statistically significant difference found between groups on the mental development index (MDI) or the behavioral rating scale (BRS) portions of the Bayley after adjusting for APGAR scores at birth and at 5 minutes. Ratings on the psychomotor development index (PDI) portion of the Bayley indicated lower scores in the SSRI-exposed group compared with the group whose mothers were depressed but not treated with an SSRI (90.0 versus 98.2, P = 0.02). Examining the BRS factor scales found the motor quality factor to be lower in the SSRI-exposed group (68.6 versus 88.8, P = 0.05).

Neurobehavioral assessments in infants <2 months. Neurobehavioral assessments for young infants exposed to antidepressants in utero (at least second and third trimester, n=33) were recorded at 1 week and again at 6-8 weeks by blinded trained raters using the Brazelton Neonatal Behavioral Assessment Scale (BNBAS).⁵⁴ The majority of mothers used SSRIs (fluoxetine 38 percent and sertraline 36 percent). Comparator groups included children of depressed mothers without antidepressant exposure (no antidepressants, discontinued antidepressants in first trimester, or <10 days, n=16) and children of healthy controls without DSM Axis 1 disorder (e.g. depression, anxiety; n=15). No differences were seen across the groups in infant BNBAS scores at either time point.

Eight other observational studies (in nine publications) provide only indirect evidence on the effect on developmental outcomes of children with prenatal antidepressant exposure for any reason compared with nonexposed children (depression status of mothers unknown).^{54, 60, 65, 71, 82, 87, 88, 131} The best indirect evidence on Bayley assessments comes from a small medium risk of bias study (N = 61) of children, 24 of who were exposed to SSRIs prenatally compared with 23 children born to mothers with unknown depression status who did not receive an SSRI during pregnancy and 14 whose mothers took an SSRI plus another psychoactive drug.⁶⁵ This study found no difference in the MDI or PDI scores across groups. The best indirect evidence on language development comes from a medium risk of bias study where children 15-71 months who were exposed prenatally to TCAs (n=45) or fluoxetine (n=38) were compared to children of a control nondepressed women (n=34) on the Reynell Verbal and Expressive Language Scales.⁸⁷ Scores for all three groups were within the normal range, but children in the TCA group scored higher than those in the fluoxetine or nonexposed group on Reynell Developmental Language Scales. This study measured McCarthy cognitive development scores but missing data make this outcome high risk of bias.

The best indirect evidence on achievement of developmental milestones at 6 months is available from a medium risk of bias study that compared children exposed in utero to antidepressants (n=415; 81% = SSRIs, 3% = TCAs) children of mothers with untreated depression during pregnancy (n=489) and children of women not receiving an antidepressant during pregnancy and not identified as being depressed by study methods.⁷¹ This study used maternal interviews at 6 months and 19 months after delivery to obtain assessments of milestone achievement and information about depression was obtained from two prenatal interviews. At 6 months, children with antidepressant exposure at any time during pregnancy had greater risk of not achieving milestones compared with children of mothers with untreated depression during pregnancy. (OR 95% CI, 1.5 (1.1-2.0)) A similar increase in risk was found for those with exposure in the 2nd or 2nd and 3rd trimester compared with untreated depression [OR 95% CI 2.6 (1.2-5.8)], while exposure only in the 1st trimester was not statistically significant [OR 95% CI 1.1 (0.6-2.1)]. At 19 months, there was no difference among the groups in the risk of not meeting one or more milestone. Analysis of the effect of specific types of antidepressants found no differences at 6 months, but on retrospective recall at 19 months the group exposed to SSRIs in utero were found to have longer days to sitting or walking unassisted but the reported days to sit and/or walk for all groups were within the normal range of development.

In a medium risk of bias retrospective study, motor and speech delays in children exposed to antidepressants in utero were compared to children of women who did not take antidepressants during pregnancy (depression status of mothers in either group unknown).⁶⁰ Delays were identified by blinded chart review and required physician diagnosis confirmed by a formal developmental evaluation in the course of routine clinical care. No statistically significant differences were found in motor delays or speech delays and SSRI exposure [OR 95% CI: 3.07 (0.61-15.40 and OR 95% CI: 1.0 (0.14-7.18)], respectively.

Autism spectrum disorders. No direct evidence on the risk of different treatments for depression during pregnancy on development of Autism spectrum disorders in the child was found.

Indirect evidence is found in two large case-control studies (n=1,805; n=47,656, respectively) reported the risk of ASD in offspring of mothers who used SSRIs during pregnancy.^{20, 21} Both utilized health system databases, one in the United States²⁰ and the other in Sweden.²¹ The Swedish study²¹ was rated low risk of bias and the US study²⁰ was rated moderate risk of bias. Both studies adjusted for maternal age and mental health disorders and the Swedish study additionally adjusted for paternal age.²¹ Only the US study adjusted for child's sex.²⁰ Neither adjusted for family history of ASD or prematurity, both factors known to be strongly associated with ASD. These studies find that maternal SSRI use at any time during pregnancy is statistically significantly associated with an increased risk of autism spectrum disorder in offspring (pooled adjusted odds ratio 1.82; 95% CI, 1.14 to 2.91). The US study additionally evaluated whether risk of ASD varied based on exposure period and found that the risk only reached statistical significance during the first trimester (adjusted OR, 3.5; 95% CI, 1.5 to 7.9), and not during the preconception period (adjusted OR, 1.9; 95% CI, 0.9 to 4.2), the second trimester (adjusted OR, 1.5; 95% CI, 0.5 to 5.0) or the third trimester (adjusted OR, 2.2; 95% CI, 0.7 to 6.9).²⁰

In one of these studies, the study investigators examined the contribution of depression itself by conducting an analysis that compared groups of pregnant women with and without a

diagnosis of depression who were using or not using any antidepressants. Compared with pregnant women without depression or antidepressant use, the risk for ASD in the children of pregnant women with depression and antidepressant use was statistically significantly elevated, with a greater OR than the OR from our analysis that combined data from both studies (OR 3.34; 95% CI 1.50 to 7.47); by contrast, the risk in pregnant women taking an antidepressant for another indication was lower and not statistically significant (OR 1.61; 95% CI 0.85 to 3.06).

Education and Learning

No evidence on school performance or educational outcomes was found. Observational studies were found comparing maternal antidepressant exposure compared with nonexposure and risk of lowered intelligence testing results (IQ) in their children. Indirect evidence on SSRIs and IQ testing is based on two observational studies that assessed childhood intelligence by performance on standardized testing and compared exposure to antidepressants compared with nonexposure.^{82, 89} Both were high risk of bias observational studies.

Illness Outcomes

We did not find evidence on the risk of stress related chronic disease in children associated with maternal SSRI use during pregnancy. We found evidence on the risk of developing ADHD or having internalizing or externalizing behaviors, reported below.

Attention deficit hyperactivity disorder (ADHD). No direct evidence on the risk of different treatments for depression during pregnancy on development of ADHD in the child was found. One retrospective cohort study with medium risk of bias assessed ADHD diagnoses by age 5 years utilizing a large national claims-based dataset from self-insured employers.¹³² This provides indirect evidence as a mental health diagnosis was identified in only 33 percent of women, including 10 percent with a depressive disorder and 5 percent with an anxiety disorder. After multiple logistic regression analysis, risk of diagnosis with ADHD in children born to women who used bupropion, SSRIs, or any other antidepressant during or after pregnancy was compared to women not exposed during pregnancy. SSRI use at any time during pregnancy was not associated with increased risk of ADHD in offspring (OR 0.91; 95% CI, 0.51 to 1.60), but use after pregnancy (up to four years post-delivery) was associated with increased risk of ADHD diagnosis (OR 2.04; 95% CI, 1.43 to 2.91). No breastfeeding data were provided to determine whether direct exposure may have occurred. Children of mothers with depressive disorders had statistically significantly higher risk of ADHD at age 5 than those without (OR, 2.58; 95% CI, 2.02 to 3.29).

Two additional high risk of bias studies were identified which reported on ADHD symptoms.^{82, 89} Neither study found an association between exposure to SSRIs in utero (n=22) and ADHD symptoms in offspring compared with nonexposed, presumed nondepressed groups.

Internalizing behaviors. No direct evidence on the risk of internalizing behaviors in the child with different treatments for depression during pregnancy was found. Internalizing behaviors are described as behaviors directed internally or “within the self”. They include emotional reactivity, depression, anxiety, irritability and withdrawal.

Three observational studies provide indirect evidence. One of medium risk of bias⁹⁶ and two of high risk of bias,^{83, 89} reported on outcomes of children exposed to SSRIs and venlafaxine in utero. Levels of internalizing behaviors were assessed by maternal and teacher/caregiver reports in 36 children aged 4 to 5 years exposed to SSRIs and/or clonazepam prenatally.⁹⁶ Mothers rated

their children on the Child Behavior Checklist (CBCL) and teachers/caregivers rated children using the Child-Teacher Report Form (C-TRF). Maternal mood and anxiety was assessed by the Hamilton Rating Scale for Depression (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A). No statistically significant differences in internalizing behaviors were found in maternal or caregiver/teacher ratings of children at 4-5 years exposed to SSRIs during pregnancy compared to nonexposed controls [OR (95% CI) 1.53 (0.24-9.85); 2.89 (0.29-28.90)]. This remained true when controlled for maternal depression [OR (95% CI) 0.99 (0.13-7.88); 2.85 (0.26-31.20)]. However, increased maternal but not teacher reports of internalizing behaviors were associated with maternal depression ($P < 0.05$) and anxiety ($P < 0.05$).

Both high risk of bias studies found increased risk of internalizing behaviors associated with SSRI use during pregnancy compared with general nonexposed populations, but both also found that the increase was correlated with maternal depression.^{83, 89}

Externalizing behaviors. No direct evidence on the risk of externalizing behaviors in the child with different treatments for depression during pregnancy was found. Externalizing behaviors (noncompliance, verbal/physical aggression, disruptive acts, and emotional outbursts) are described as behaviors which are “directed outward”. The presence of these behaviors may herald a diagnosis of externalizing disorders such as ADHD, oppositional defiant disorder (ODD) and/or conduct disorder (CD). Indirect evidence comes from three observational studies, but all are high risk of bias, and are not described further.^{82, 83, 89}

Healthcare Utilization

No direct evidence on healthcare utilization among children born to mothers with depression during pregnancy, comparing those treated with antidepressants to those not treated, or comparing antidepressants, was found. Indirect evidence, based on one medium risk of bias observational study (N=38,602), suggests that antidepressant use (primarily SSRIs, 71 percent) is associated with increased healthcare utilization among children born to women who were prescribed SSRIs during pregnancy compared with nonexposed children (Table 3).⁵¹ The depression status of mothers was not reported. For continuous SSRIs exposure during pregnancy the risk was increased for several markers of resource utilization both during the first two weeks and the first year of life, including a two-fold increase in the utilization of physiotherapy. Intermittent use of SSRIs during pregnancy was also associated with increased risk for some measures, primarily in the first year of life and the risk for those who discontinued an antidepressant during pregnancy; only risks for increased risk during the first two weeks of life were statistically significant.

Table 2. Association between antidepressant use during pregnancy and general practitioner visits and hospital admissions; unadjusted relative risk (95% confidence interval)

	First 2 Weeks After Birth			First Year After Birth	
	Continuous	Intermittent	Discontinued	Continuous	Irregular
≥ 1 GP visits	NS	NS	1.3 (1.2-1.5)	--	--
>2 GP visits	--	--	--	1.5 (1.3-1.8)	1.2 (1.1-1.4)
1 hospital admission	NS	NS	1.3 (1.1-1.7)	NS	NS
≥ 2 Hospitalizations	2.4 (1.8-3.1)	1.4 (1.1-1.8)	1.4 (1.1-1.9)	NS	1.5 (1.1-2.1)
1 specialist visit	1.3 (1.1 - 1.5)	1.2 (1.0- 1.3)		1.4 (1.1-1.8)	NS
>2 specialist visits	2.4 (1.7 - 3.3)	NS	1.2 (1.1-1.4)	1.5 (1.2-1.9)	1.4 (1.2-1.6)
1 specialist	1.5 (1.2 - 1.8)	1.1 (1.0-1.3)		1.6 (1.3 to 2.0)	NS

procedure					
>2 specialist procedure	1.7 (1.1 - 2.6)	NS		NS	1.3 (1.1-1.5)
2 diagnostic tests	1.9 (1.4 - 2.5)	NS		NS	NS
Physiotherapy	--	--	--	2.0 (1.5-2.6)	1.3 (1.1-1.7)

GP=general practitioner, NS=not significant.

Tricyclic Antidepressants

Antidepressant Exposure During Pregnancy

Maternal Outcomes

No evidence was found for maternal outcomes with the use of TCAs during pregnancy.

Infant/Child Outcomes

Preterm birth. No direct evidence on the effect of different treatments for depression on preterm birth in women with depression during pregnancy was found.

Indirect evidence based on two observational studies indicates an increased risk of preterm birth with exposure to TCAs during pregnancy for any reason, compared with pregnant women who were not treated with TCAs (depression status unknown for both groups).^{64, 146}

Growth for gestational age. No direct evidence on the effect of different treatments for depression on fetal growth in women with depression during pregnancy was found.

Indirect evidence indicated no increased risk for the infant to be small for gestational age at birth with exposure to TCAs for any reason compared with pregnant women who were not treated with TCAs (depression status unknown for both groups), based on two medium risk of bias studies.^{69, 122} The pooled adjusted OR for exposure at any time point during pregnancy is 0.97 (95% CI, 0.64 to 1.46), with no statistical heterogeneity. One of the studies reported the rates of a depression diagnosis in the treated and untreated group (46 percent and 36 percent, respectively). This study also evaluated the result by timing of exposure (1st, 2nd or 3rd trimester) and found no statistically significant increase in risk for any of these time points.

Child Development

Direct evidence on the effect of maternal treatment with TCAs for depression during pregnancy on infant and child development was not found. Indirect evidence is limited to three observational studies reporting on comparisons of children whose mothers took TCAs during pregnancy for any reason, compared with children whose mothers did not take TCAs; depression status unknown for both groups.^{60, 71, 87}

The best indirect evidence on developmental milestones comes from a medium risk of bias study (described above regarding SSRI use).⁷¹ Adjusted OR (days) were calculated for maternal report of sitting without support (at 6 months interview) for TCA exposure at any point during pregnancy. No statistically significant differences were found for exposure to TCAs (OR 2.9; 95% CI 0.89-9.51) at any point in pregnancy, nor were there differences with 1st, or 2nd/3rd trimester exposure. On retrospective recall at 19 months statistically significant delays with TCA exposure were also not found. The best evidence on motor and speech delays comes from a medium risk of bias retrospective study of children exposed to antidepressants in utero were compared to children of women who did not take antidepressants during pregnancy (depression

status of mothers in either group unknown).⁶⁰ Delays were identified by blinded chart review and required physician diagnosis confirmed by a formal developmental evaluation in the course of routine clinical care. No statistically significant differences were found with motor delays and TCA exposure [OR 95% CI: 1.0 (0.14-7.17)]. TCA exposure was also not associated with speech delays [OR 95% CI: 1.0 (0.14-7.17)]. Another study of language development used the Reynell Verbal and Expressive Language Scales.⁸⁷ Scores for children 15-71 months exposed prenatally to TCAs (n=45) or fluoxetine (n=38) were compared to children of nondepressed comparison women (n=34). All three groups scored within the normal range. Children in the TCA group scored higher than those in the fluoxetine or nonexposed group on Reynell Developmental Language Scales.

Autism spectrum disorder. No direct evidence on the risk of different treatments for depression during pregnancy on development of Autism spectrum disorders in the child was found.

Indirect evidence is found in two large case-control studies (n=1,805; n=47,656, respectively) reported the risk of ASD in offspring of mothers who used antidepressants, including TCAs, described in detail in the section on SSRIs, above.^{20, 21} These studies included subgroups of women exposed to either TCAs or TCAs/SNRIs (as a group). In the study examining TCAs as a group, (N=6 cases, N=20 controls there is indirect evidence that maternal use of TCAs during pregnancy is statistically significantly associated with an increased risk of autism spectrum disorder in offspring (adjusted odds ratio 2.69; 95% CI, 1.04 to 6.96).²¹ This study was rated low risk of bias and adjusted for any maternal psychiatric disorder, maternal age, paternal age, parental income, education, occupation, maternal country of birth, and birth parity. It did not adjust for family history of ASD or prematurity, both factors known to be strongly associated with ASD.

The other study included SNRIs with their analysis of TCAs (N=5 cases, N=16 controls).²⁰ Adding SNRIs to the group resulted in a nonstatistically significant associated increase in risk of ASD (adjusted odds ratio 1.6; 95% CI, 0.5 to 4.5). This study was rated moderate risk of bias and provides indirect evidence for this outcome, adjusting for maternal age, race/ethnicity, maternal education, birth weight, sex, birth year of child and birth facility, but not family history of ASD or prematurity, both factors known to be strongly associated with ASD.

Selective Norepinephrine Reuptake Inhibitors and Norepinephrine Reuptake Inhibitors

Maternal Outcomes

No evidence was found for maternal outcomes with the use of SNRIs/NRIs during pregnancy.

Child Outcomes

Preterm birth. No direct evidence on the effect of different treatments for depression on preterm birth in women with depression during pregnancy was found.

Indirect evidence, based on two medium-risk of bias observational studies, indicates an increased risk of preterm birth associated with use of an SNRI/NRI (including bupropion for one study) during pregnancy for any reason (adjusted OR 1.79, 95% CI 1.46 - 2.19).^{64, 111} These studies compared birth outcomes of women treated with an SNRI/NRI during pregnancy to pregnant women who were not treated with an SNRI /NRI; depression status of either group was not analyzed.

Growth for gestational age. No direct evidence on the effect of SNRI/NRIs for depression on having an infant that is small for gestational age in women with depression during pregnancy was found. Indirect evidence is limited to two studies, one of venlafaxine⁶⁹ and the other including any SNRI/NRI, both with comparison to infants of mothers not receiving an SNRI/NRI during pregnancy but with no known depression.¹¹¹ These studies had results in opposite directions. The reason for the discrepancy may simply be inadequate sample sizes – the larger study, the analysis of SNRI/NRI included only 27 exposures,¹¹¹ and the smaller study included only five exposures to venlafaxine.⁶⁹

Education and learning. No direct evidence on the effect of SNRI/NRIs for depression on education or learning outcomes in children of women with depression during pregnancy was found. Indirect evidence regarding prenatal SNRI exposure and subsequent intelligence testing in offspring is limited to one high risk of bias observational study, described in detail above (under SSRIs).⁸⁹

Illness Outcomes

We did not find evidence on the risk of stress related chronic disease in children associated with maternal SNRI use during pregnancy. We found evidence on the risk of developing ADHD, internalizing or externalizing behaviors, or mental illness, reported below.

Internalizing behaviors. No direct evidence was found on the risk of internalizing behaviors and exposure to an SNRI/NRI during pregnancy. Indirect evidence was found to determine an effect of SNRI exposure during pregnancy on internalizing or externalizing behaviors in offspring compared with nonexposed children. Increased internalizing behaviors reported by mothers using the CBCL (n=178) correlated with severity of maternal depression during pregnancy and at time of testing, not maternal venlafaxine treatment in pregnancy. Depression in pregnancy and at time of testing, not exposure to venlafaxine, predicted externalizing behaviors as reported by mothers on the CBCL.⁸⁹

Other Antidepressants: Bupropion

Attention deficit hyperactivity disorder. No direct evidence on the effect of bupropion for depression on the risk of children of women with depression during pregnancy developing ADHD in was found. One retrospective cohort study with medium risk of bias provides indirect evidence on the risk of ADHD in children of women exposed to bupropion during pregnancy. This study assessed ADHD diagnoses by age 5 years utilizing a large national claims-based dataset.¹³² A mental health diagnosis was identified in only 33 percent of women, including 10 percent with a depressive disorder. After multiple logistic regression analysis, risk of diagnosis with ADHD in children born to women who used bupropion, SSRIs, or any other antidepressant during or after pregnancy was compared to children of women who did not take any antidepressant during pregnancy. Exposure to bupropion at any time during pregnancy was associated with increased risk of ADHD diagnosis in children (OR, 3.63; 95% CI, 1.20 to 11.04), in particular for exposure during the second trimester (OR, 14.66; 95% CI, 3.27 to 65.73), but not first or third trimesters (OR, 2.06; 95% CI, 0.35 to 12.16; OR=<0.01, <0.01 to >99.9, respectively).

Postpartum Exposure

Selective Serotonin Reuptake Inhibitors

Maternal Outcomes

We found one high risk of bias placebo-controlled RCT of paroxetine in women who were depressed in the postpartum period.⁴³ The trial was small, 70 women enrolled and 31 completed) and short-term (8 weeks). This is the only direct evidence for maternal outcomes of treatment for depression in the postpartum period. Additionally there was indirect evidence from a medium risk of bias observational study that compared treatment with citalopram during pregnancy and up to 2 months postpartum with pregnant and postpartum women who did not receive an SSRI (depression status unknown).¹²⁶

Danger to Self or Infant. Evidence on the risk of danger to self or infant while being treated for depression with an SSRI is insufficient. The small, high risk of bias, RCT reported zero such events.⁴³

Depression Symptomatology. Evidence on the effect of SSRIs on depressive symptoms in the postpartum period is insufficient to draw conclusions. Only one RCT with high risk of bias compared depression symptom improvement during the postpartum period, between paroxetine and placebo.⁴³ Response at week 8 was defined as a Clinical Global Impression-Improvement (CGI-I) of 1 or 2 with 43 percent (n=15/35) of the paroxetine group achieving response as compared with 32 percent (n=11/35) of the placebo group (OR, 1.31; 95% CI, 0.50 to 3.41). Remission by week 8 as defined as a rating of <8 on the 17 Item Hamilton rating Scale for Depression (HAM-D-17) was significantly improved for women taking paroxetine with 37 percent achieving remission in the paroxetine group and 14 percent in the placebo group (OR, 3.54; 95% CI, 1.10 to 11.41).

Delivery and Postpartum Parameters

Breastfeeding. Evidence on the effect of SSRI treatment for depression during the postpartum period on breastfeeding outcomes is insufficient as there is no direct evidence available. Indirect evidence from one very small observational study (n=21) comparing women who took citalopram to during pregnancy and in the postpartum period (for any reason) to women who did not (depression status not reported) reported equal numbers of mothers breastfeeding in both groups (n=9) and so no significant difference between groups (OR, 0.91; 95% CI, 0.26 to 3.20).¹²⁶

Key Question 1b. How do pharmacological treatments affect maternal and child outcomes when compared with each other (drug A vs. drug B)?

Pregnancy Exposure

Maternal Outcomes

No evidence was found for maternal outcomes comparing antidepressants to each other for depression during pregnancy.

Child Outcomes

Preterm birth. No direct evidence is available comparing one antidepressant to another in women with depression during pregnancy. Three studies provide indirect evidence for risk of preterm birth in women taking specific SSRIs to other SSRIs in women taking the drugs during pregnancy. A single high risk of bias study (N = 809) provides opportunity to compare paroxetine and fluoxetine, where no difference between the drugs was found.¹⁴⁴ Additionally, two studies compared citalopram or escitalopram to “other SSRIs”; the unadjusted pooled estimate from these studies is 1.26 (95% CI, 0.54 to 2.96).^{58, 59} These are small studies, one high risk of bias and one medium.

Growth for gestational age. No direct evidence is available comparing one antidepressant to another in women with depression during pregnancy. Indirect evidence is limited to one medium risk of bias study reporting the risk of having an infant that is small for gestational age at birth for any specific drug compared with other drugs.¹²² The risk with paroxetine treatment during pregnancy compared to other SSRIs was an adjusted OR of 0.9 (95% CI, 0.09 to 4.34).

Postpartum Exposure

Maternal Outcomes

The evidence comparing one antidepressant to another in women with depression during the postpartum period is insufficient to draw conclusions for maternal outcomes. We found one small RCT (n=109) that compared sertraline with nortriptyline in treating depression in postpartum women.⁴⁶ Additionally, there are two publications of post-hoc analyses using data from this trial.^{108, 113} The study was high risk of bias, due to unclear allocation concealment, dissimilarity of groups at baseline, and high levels of overall attrition. See Appendix E for strength of evidence ratings for selected outcomes. There was also no difference between the groups in response or remission rates; by week 8 the proportions with either response or remission were 69 percent in the sertraline group, and 73 percent in the nortriptyline group. In a post-hoc analysis using a subset of the data (N=70), no difference in breastfeeding rates between the sertraline and nortriptyline was found (OR 2.78 95% CI 0.86-8.94).¹¹³ No information in intention to breastfeed or baseline breastfeeding status is presented.

Key Question 1c. How do pharmacological treatments affect outcomes when compared with active nonpharmacological treatments?

No evidence meeting inclusion criteria was found for this question for either exposure during pregnancy or during the postpartum period.

Key Question 1d. How does combination therapy affect maternal and child outcomes?

1. Using a Second Drug to Augment the Effects of the Primary Drug and Comparing This Treatment with Monotherapy with a Single Drug

Pregnancy Exposure

Maternal Outcomes

No evidence was found for maternal outcomes for this question.

Child Outcomes

No direct comparative evidence on the benefits to children of combination pharmacological treatment for maternal depression during pregnancy was found. Indirect evidence from observational studies comparing results for children of women taking combination antidepressant therapy during pregnancy for any reason to women who did not take an antidepressant during pregnancy, but with unknown depression status was found.

The best indirect evidence on the risk of preterm birth with combination therapy with an antidepressant during pregnancy comes from a single observational study that reported a non-statistically significant unadjusted odds ratio of 1.3 (95% CI, 0.5 to 3.33) for comparison of using two drugs (one SSRI and a second antidepressant from a different class) with use of a single SSRI.¹³⁶

Indirect evidence on combination antidepressant therapy during pregnancy and having an infant that is small for gestational age is limited to a single observational study.⁶⁹ Although this study was medium risk of bias, it is important for this outcome that the method used to determine gestational age was not reported. Seventy percent were taking an SSRI in combination with a non-SSRI drug. In women who took two antidepressants in the second trimester there was an increased risk of having a small for gestational age infant compared with women who did not take an antidepressant during pregnancy (ARR = 3.48; 95% CI 1.56 to 7.75).

2. Combining Pharmacological Treatments with Nonpharmacological Treatments and Comparing Them with Nonpharmacological Treatments Alone

Postpartum Exposure

Maternal Outcomes

Direct evidence on maternal outcomes with combination pharmacological and nonpharmacological treatments for depression during the postpartum period compared with nonpharmacological treatments alone is insufficient to draw conclusions due to limited, inconsistent evidence. We found three small medium risk of bias RCTs^{156, 160, 166} and one small, high risk of bias observational study⁷³ that compared combining pharmacologic treatments with nonpharmacological treatments and comparing them with nonpharmacological treatments alone. All of the studies focused on the postpartum period only and reported on depression symptoms. See Appendix E for strength of evidence ratings.

Depression symptomatology. A medium risk of bias RCT¹⁶⁰ compared sertraline and brief psychodynamic psychotherapy with psychotherapy alone, finding no statistical differences in the rate of response or remission over 12 weeks of treatment. The study included 40 women. They defined response to treatment as >50 percent reduction in either the MADRS or EPDS scores. By the end of week 8 there was no statistically significant difference in response rates between groups (70 percent in the combination group and 50 percent psychotherapy only group, OR, 1.91; 95% CI, 0.52 to 7.00). Similarly, there was no statistically significant difference in remission (defined as final score on the MADRS of <10 or the EPDS <7) at week 8; the combination group had a rate of 65 percent and the psychotherapy only group had a rate of 50 percent (OR, 3.09; 95% CI, 0.78 to 12.14). At week 12, the combination group had a remission rate of 94 percent and the psychotherapy only group had a rate of 82 percent (OR, 3.64; 95% CI, 0.34 to 39.02).

A second trial¹⁶⁶ randomized 87 women with depression six to eight weeks after delivery to fluoxetine plus cognitive behavioral counseling (one or six sessions) compared to counseling alone (one or six sessions). Outcomes measured were changes in the Revised Clinical Interview Scale (CIS-R), the EPDS, and the HAM-D at weeks 4 and 12. Clinically important morbidity was defined as > the CIS-R and the EPDS, and ‘mild depression’ was defined as a score of 8-17 on the HAM-D. Based on study completers, mean CIS-R scores were less than 12 at weeks 4 and 12 for fluoxetine plus 1 counseling session, fluoxetine plus 6 counseling sessions, and 6 sessions of counseling alone. The group assigned to one session of counseling alone never had scores below 12. On the EPDS, mean scores were below 12 starting in week 4 for all groups. At week 12, mean scores were less than 8 for all groups. The drop-out rate for this study was very high, 30%, however, and the results based on intention to treat analysis are different. In this analysis, only the fluoxetine plus 6 counseling sessions had CIS-R scores at week 4, and at week 12 this group and e fluoxetine plus 1 counseling session had scores less than 12. Two counseling alone groups did not have scores less than 12 at any timepoint. This pattern held true for the analysis of EPDS scores. For the HAM-D at week 12, only the single session of counseling did not have a mean score less than 8.

Breastfeeding. Direct evidence on the effect of different treatments for depression used in combination with nonpharmacological treatments compared to nonpharmacological treatments alone on breastfeeding outcomes in women with depression during pregnancy comes from a single observational study and is insufficient to draw conclusions.¹⁵⁶ In this very small (N = 44) medium risk of bias study women with major depressive disorder (based on DSM-IV MDD criteria) were enrolled and two groups were identified; those taking an SSRI during pregnancy and those who were not taking a pharmacologic treatment. Both groups received what is described only as ‘supportive psychotherapy’ with no further details reported. No details on the psychotherapy received were reported. The duration of breastfeeding was two months longer in the untreated group (8.5 months) compared with the group treated with an SSRI (6.4 months, P = 0.4) but the difference was not statistically significant.

A high risk of bias observational study⁷³ compared sertraline plus interpersonal psychotherapy (IPT) to IPT alone in postpartum women, which also included a third sertraline only group. This was a small observational study (n=23) with high loss to followup and high risk of bias.

3. Comparing Pharmacological Treatments Alone with Pharmacological Treatments Used in Combination with Nonpharmacological Treatments

Postpartum Exposure

Maternal Outcomes

Direct evidence is insufficient to draw conclusions, based only on one small medium risk of bias RCT⁹⁷ and one small high risk of bias observational study⁷³ that compared SSRI treatment (as a class or as an individual drug) with pharmacological treatments used in combination with nonpharmacological treatments. The observational study was high risk of bias due to high overall and differential loss to followup and potentially inadequate handling of confounders.⁷³ Both of the studies focused on the postpartum period only and both concluded that all treatment groups produced reduction in depression symptomatology compared to baseline. Please see Appendix E for strength of evidence ratings for selected outcomes. The RCT⁹⁷ compared 16 postpartum women on paroxetine to 19 on paroxetine plus cognitive behavioral therapy. It was a small study with high loss to followup. There was no difference in response between the two groups on either the HAM-D (OR, 1.87; 95% CI, 0.29 to 11.84) or on the EPDS (OR, 1.71; 95% CI, 0.36 to 8.16). The response rate at the last visit on the HAM-D was 87.5 percent in the paroxetine only group versus 78.9 percent in the combination group and on the EPDS it was 50 percent compared with 58.3 percent. With anxiety symptoms, there was no difference in response between the two groups on either the HAM-A (OR, 1.12; 95% CI, 0.16 to 7.82) or on the YBOCS (OR, 0.72; 95% CI, 0.19 to 2.77).

The high risk of bias observational study⁷³ comparing sertraline to sertraline plus interpersonal psychotherapy (IPT) in postpartum women. This was a small observational study (n=23) with high loss to followup and high risk of bias. Those who completed the study experienced significant overall improvement and in an analysis of covariance comparing outcomes on the HAM-D, BDI and EPDS, controlling for pretreatment depression, no differences in outcome were identified between the IPT and IPT plus sertraline

Key Question 2a. What are the comparative harms of pharmacological and nonpharmacological treatments for women with depression during pregnancy and in the postpartum period?

Summary

- Direct evidence was also sparse on the maternal and infant/child harms associated with pharmacological and nonpharmacological treatment for depression during pregnancy and the postpartum period.
 - Direct evidence provided sufficient data to draw the following low-strength conclusions:
 - Results from one observational study with medium risk of bias (N=107,877) suggest that infants of depressed mothers treated with SSRIs during pregnancy do not have a statistically significantly higher risk of convulsions than those of depressed mothers not treated with medication (0.14% compared with 0.11%; risk difference 0.0005; 95% CI, -0.0015 to 0.0025).

- Consistent results from three medium risk of bias observational studies (N=15,793) suggest that, compared with untreated maternal depression during pregnancy, SSRI treatment is associated with a statistically significant increase in risk of respiratory distress in infants (pooled unadjusted OR 1.91; 95% CI, 1.63 to 2.24; $I^2 = 0\%$).
 - Direct evidence provided insufficient data to support conclusions on the following additional harms due to methodological limitations, unknown consistency and imprecision:
 - Major malformations:
 - One small medium risk of bias observational study (N=62) compared the effects of SSRIs to no treatment of depression during pregnancy.
 - One small medium risk of bias observational study (N=44) compared the effects of SSRIs plus psychotherapy to psychotherapy alone for depression during pregnancy.
 - Respiratory distress: One small medium risk of bias observational study (N=21) compared the effects of SSRIs to TCAs when used to treat depression during pregnancy.
 - Overall adverse events and withdrawals due to adverse events in babies of breastfeeding mothers:
 - One RCT with high risk of bias (N=109) compared risk between women taking either sertraline or nortriptyline for postpartum depression
 - One small observational study with high risk of bias (n=23) compared risk between women treated with either sertraline or interpersonal psychotherapy for postpartum depression

Detailed Assessment of the Evidence

Key Question 2. What are the comparative harms of pharmacological and nonpharmacological treatments for women with depression during pregnancy and in the postpartum period?

There were no clinical trials of antidepressant drugs used to treat depression in pregnancy to provide direct evidence on the comparative harms. Direct evidence is limited to 16 observational studies of pharmacological treatments given at unknown dosages. Indirect evidence consists of studies of women taking an antidepressant during pregnancy for any reason compared with women who did not take an antidepressant during pregnancy, with unknown depression status in either group. Both RCTs and observational studies were found for comparative harms of pharmacologic treatment in the postpartum period.

We found no direct evidence on maternal harms of pharmacologic treatments for depression during pregnancy. This is primarily because for this population there is only observational evidence and the harms outcomes for this report, for example, rates of specific adverse effects (e.g., suicidal ideation, hepatotoxicity, and loss of libido) are not reported. The risk of mortality may have been reported sporadically, but most of these retrospective observational studies would have excluded women who died during pregnancy, and the remaining studies did not have explicit methodology to ascertain this and other serious harms.

i. How do pharmacological treatments affect child outcomes when compared with active nonpharmacological treatments?

Antidepressant Exposure During Pregnancy

Selective Serotonin Reuptake Inhibitors

Infant/Child Outcomes

All-cause mortality. No direct evidence is available assessing comparative harms of pharmacologic treatment for depression during pregnancy.

Indirect evidence for this important outcome is available from one Danish cohort study with low risk of bias¹²⁴ and four cohort studies with medium risk of bias.^{57, 111, 123, 149} This evidence suggests an increased risk of neonatal/postneonatal death over the first year following maternal use of SSRIs during pregnancy, but not when early and late deaths are examined separately. None accounted for depression in analysis and only one small retrospective cohort study (N=105) reported the proportions of women diagnosed with depression, with 65 percent in the SSRI group and 46 percent in the nonexposed group; there were no neonatal deaths in either group.¹²³

The remaining four studies did not have data on treatment indication or proportions of women with depression in groups.^{57, 111, 124, 149} A population-based cohort study (N=98,365) found a statistically significant increase in risk of neonatal death at any time during the first year of life for SSRIs as a group, paroxetine, escitalopram, and fluvoxamine, but not for other individual SSRIs (Table 4).¹⁴⁹ The remaining studies separately evaluated early and late death. Based on a study of all Nordic countries, maternal use of SSRIs as a group during pregnancy is not statistically significantly associated with a higher risk of early or late neonatal death (Table 4).⁵⁷ A Danish study additionally evaluated individual SSRIs and found that citalopram, but not fluoxetine, escitalopram, paroxetine, or sertraline was associated with a statistically significant increase in risk of early death.

Table 3. Risk of neonatal/postneonatal death for maternal use of a selective serotonin reuptake inhibitor in pregnancy

Author Year Country	Results
First year as a whole	
Colvin 2012 ¹⁴⁹ Western Australia	Adjusted OR for deaths during first year of life (95% CI): SSRIs grouped: 1.81 (1.26, 2.60) Citalopram: 1.28 (0.61, 2.72) Escitalopram: 3.52 (1.30, 9.49) Fluoxetine: 2.30 (0.85, 6.19) Fluvoxamine: 4.52 (1.44, 14.24) Paroxetine: 2.18 (1.03, 4.61) Sertraline: 1.40 (0.72, 2.72)
Early death	
Jimenez-Solem 2013 ¹²⁴ Denmark	Adjusted OR for death within 28 days of birth (95% CI): Any SSRI: 1.27 (0.82 to 1.99) Citalopram: 2.49 (1.33 to 4.65) Escitalopram: 2.07 (0.29 to 14.85) Fluoxetine: 0.63 (0.24 to 1.69) Paroxetine: 1.95 (0.73 to 5.23) Sertraline: 0.26 (0.04 to 1.81)
Stephansson 2013 ⁵⁷ Nordic countries	Adjusted OR (95% CI) for any SSRI Neonatal death (0-27 days): 1.23 (0.96 to 1.57)
Lenntal 2007 ¹¹¹ Sweden	Adjusted RR (95% CI) for any SSRI compared to expected: Early: 0.8 (0.6 to 1.2)
Jordan 2008 ¹²³	No neonatal deaths
Late Death	
Stephansson 2013 ⁵⁷ Nordic countries	Adjusted OR (95% CI) for any SSRI Postneonatal death (28-364 days): 1.34 (0.97 to 1.86)
Lenntal 2007 ¹¹¹ Sweden	Adjusted RR (95% CI) for any SSRI compared to expected: Late: 1.2 (0.7 to 2.0)

CI=confidence interval, OR=odds ratio, RR=relative risk, SSRI=selective serotonin reuptake inhibitor,

Congenital Anomalies

Major malformations. Only three studies provide direct evidence of the comparative risk of major malformations for the comparison of antidepressant-treated and untreated treated depressed pregnant women.^{45, 153, 156} The studies were small (N's = 44, 136 and 238) and reported 1 or zero major malformations.

In addition to these studies, indirect evidence is available from 26 other observational studies that report on the risk of major malformations in women taking an antidepressant during pregnancy for any reason compared with women who did not take an antidepressant during pregnancy – with depression status unknown for both groups.[Alwan, 2007 #6357;Bakker, 2010 #6393;Bérard, 2007 #3820;;Colvin, 2011 #6572;Costei, 2002 #8190;Diav-Citrin, 2008 #6627;Einarson, 2003 #4253;Ferreira, 2007 #6703;Jimenez-Solem, 2012 #4673;Kallen, 2007 #6980;Klieger-Grossmann, 2012 #7020;Kornum, 2010 #10547;Kulin, 1998 #7052;Laine, 2003 #7059;Louik, 2007 #7114;Malm, 2011 #8088;Manakova, 2011 #7139;Maschi, 2008 #7160;Merlob, 2009 #7196;Nulman, 1997 #7300;Oberlander, 2008 #7317;Pastuszak, 1993 #5304;Ramos, 2008 #7433;Sivojelezova, 2005 #7556;Wichman, 2009 #7747;Wogelius, 2006 #7779] Two of these studies reported that all included women in the antidepressant groups were depressed, with control groups of women who did not take an antidepressant during pregnancy but whose depression status was unknown.^{75, 140} Eight studies reported rates of depression in the exposed group reporting widely varying numbers, from 26 percent¹³³ to 77 percent.¹⁰² Unfortunately these studies did not report data in a way that allowed clear analysis of the effect

of depression on the outcomes in the exposed or nonexposed groups. Several studies explicitly used a comparison group exposed to drugs known to be nonteratogenic.^{58, 75, 88, 102, 114, 140, 144, 153}

Selective serotonin reuptake inhibitors as a group. Direct evidence on the risk of major congenital malformations associated with the use of any SSRI or specific SSRIs for depression during pregnancy is limited to only two small, medium risk of bias observational studies^{45, 156}. These studies were small, reporting no major malformations in one, and one in the group that were depressed but did not receive an SSRI in the other.

A substantial amount of indirect evidence is available from fifteen cohort studies that reported the incidence of major congenital malformations associated with the use of any SSRI, or specific SSRIs, during pregnancy, compared with the children of women who did not receive an SSRI and were not known to be depressed.^{49, 60, 64, 70, 86, 90, 103, 104, 114-116, 120, 125, 147, 150} Two of the studies were methodologically strong, with low risk of bias,^{104, 125} and two were methodologically weak, high risk of bias, due primarily to potentially biased selection of patients, lack of assessment of comparability of subjects at baseline, and lack of appropriate statistical analysis, including controlling for potential confounding.^{103, 115} Because major malformations are a fairly rare and serious adverse event, a signal from indirect evidence may be important.

Specific malformations that were classified as major varied across these studies, with most studies using ICD-9 codes to identify infants with malformations and some using additional methods to exclude more minor malformations. Other methods used to identify malformations were the EUROCAT classification system, and the approach identified by Holmes et al.^{171, 172} This variability in what was categorized as “major” may result in heterogeneity in the data set; based on information presented we were not able to refine this analysis further. As such, we focus our analysis on the best evidence – six studies that were methodologically stronger (medium or low risk of bias), used a formal system to identify and classify malformations (e.g., EUROCAT, Holmes, ICD), and controlled for at least three of the four types of potential confounders we had identified as critical, a priori (age, race, parity, and other relevant exposures such as smoking and drug use).^{49, 64, 90, 104, 120, 125} None of the studies adjusted for race and none of these studies reported on race characteristics of their study populations. None of these studies were conducted in the US; all were conducted in Nordic countries. This evidence, based six studies of over 2.4 million pregnancies, suggests no increased risk of major malformations with exposure during pregnancy to SSRIs (as a group) compared to not being exposed (pooled adjusted odds ratio 1.08; 95% CI, 0.95 to 1.22) (Table 5). However, the I^2 value of 67 percent suggests the presence of moderate heterogeneity. To explore potential sources of heterogeneity, we conducted exploratory subgroup analyses based on exposure timing, timing of diagnosis, and methods used to identify malformations. Exposure timing in these studies varied from first trimester to “any” timepoint in the ten studies that reported adjusted ORs; limiting the best evidence analysis to only exposures in the first trimester resulted in a similar estimate (pooled adjusted OR, 1.11; 95% CI, 0.97 to 1.28). The studies varied in the timing of diagnosis of the malformation in that two allowed diagnosis up to 1 year, one was unclear, and three included malformations diagnosed soon after birth (e.g., within 7 days or during the initial hospitalization). Limiting to these early diagnosis studies resulted in a pooled adjusted OR of 0.99 (95% CI, 0.85 to 1.16), again not changing the estimate in a meaningful way. Limiting the analysis to those studies that used ICD coding resulted in an OR of 0.99 (95% CI, 0.85 to 1.15) while limiting to studies that used EUROCAT coding resulted in a slightly higher risk estimate,

although still not statistically significant (OR, 1.19; 95% CI, 0.97 to 1.47). None of these sensitivity analyses reduced the heterogeneity to below 30 percent.

Compared with the results of our pooled analysis above the pooled estimate based on unadjusted rates from all studies, regardless of methods, shows a larger and statistically significant increased risk (OR, 1.19; 95% CI, 1.02 to 1.40). Heterogeneity was even higher in this analysis, with an inconsistency estimate (I^2) of 78 percent.

Table 4. Best Evidence Estimates of risk for major malformations with use of selective serotonin reuptake inhibitors during pregnancy

SSRI	Number of Studies Sample Size	Pooled Adjusted OR (95% CI)	Heterogeneity (I^2)
Any SSRI	6 ; 2,421,444	1.08 (0.95-1.22)	67%
Any SSRI during pregnancy vs. prior use of an SSRI	8	1.07 (0.78-1.47)	Not estimable Cochran Q 0.29, P = 0.59
Citalopram/escitalopram	8; 4,091,225	1.06 (0.97-1.16)	0%
Fluoxetine	7; 3,397,479	1.14 (1.01 – 1.30)	0%
Paroxetine	11; 4,192,613	1.17 (1.02-1.35)	0%
Sertraline	7; 4,020,791	0.98 (0.85 – 1.13)	23%
Fluvoxamine	2; 1,492,881	0.76 (0.38 – 1.50)	Not estimable (Cochran Q = 0.17; P = 0.68)

CI=confidence interval, OR=odds ratio, SSRI=selective serotonin reuptake inhibitor.

Citalopram/escitalopram. Twelve studies reported indirect evidence on the risk of malformations with citalopram and/or escitalopram for any reason.^{58, 64, 70, 79, 90, 104, 116, 118, 120, 138, 150, 168} One of the studies was methodologically strong, with low risk of bias,¹⁰⁴ and three were methodologically weak, high risk of bias, due primarily to potentially biased selection of patients, lack of assessment of comparability of subjects at baseline, and lack of appropriate statistical analysis, including controlling for potential confounding.^{58, 118, 138}

Based on eight medium and low risk of bias studies (seven cohort and one case control) reporting adjusted odds ratios, there is evidence that there is no increased risk of major malformations associated with use of either citalopram or escitalopram for any reason compared with women who did not take an antidepressant during pregnancy (depression status unknown) (Table 6). Using unadjusted rates for all 12 studies, regardless of methods, the pooled OR would be slightly greater, although not statistically significant (1.12; 95% CI, 0.91 to 1.38), but statistical heterogeneity was present ($I^2=64\%$). Because there was no heterogeneity in the adjusted analysis, we did not pursue subgroup analyses.

Fluoxetine. Thirteen observational studies provide indirect evidence on major malformations associated with fluoxetine use during pregnancy for any reason.^{64, 70, 75, 79, 88, 104, 116, 120, 138, 144, 150, 154, 168} Of these again one was low risk of bias¹⁰⁴ and five were high risk of bias.^{75, 88, 138, 144, 154}

We focused our analysis on the seven studies that were medium to low risk of bias and that reported adjusted odds ratios.^{64, 70, 104, 116, 120, 150, 168} Based on these studies, there was evidence that fluoxetine use during pregnancy for any reason is statistically significantly associated with an increased risk of major malformations compared with women who did not take an antidepressant (depression status unknown) (Table 6). Sensitivity analysis removing the only study that did not use a recognized classification system did not alter these results in a meaningful way (pooled adjusted OR, 1.15; 95% CI, 1.00 to 1.31; P=0.045).^{64, 70, 104, 116, 120, 150, 168}

Paroxetine. Eleven observational studies^{64, 70, 79, 90, 104, 116, 120, 138, 144, 150, 168} provide indirect evidence on major malformation rates associated with paroxetine use during pregnancy for any

reason compared with women who did not take an antidepressant during pregnancy (depression status unknown), of which two were high risk of bias.^{138, 144} Based on analysis of the eight medium and low risk of bias studies that adjusted for potential confounders and reported odds ratios,^{64, 70, 90, 104, 116, 120, 150, 168} an increased risk of major malformations was found (Table 6). Sensitivity analysis removing the two studies that did not adjust for at least three of four key confounding factors resulted in a similar estimate (pooled adjusted OR, 1.20; 95% CI, 1.03 to 1.41).

Sertraline. Nine medium and low risk of bias observational studies provide indirect evidence on rates of major malformations associated with sertraline use during pregnancy for any reason compared with women who did not use an antidepressant (depression status unknown).^{64, 70, 79, 104, 116, 120, 138, 150, 168} Analysis based on the seven studies that reported adjusted odds ratios indicates no increased risk for major malformations (Table 6).^{64, 70, 104, 116, 120, 150, 168} Sensitivity analysis removing studies that did not adjust for at least three of the four key confounding factors identified for this review left four studies and resulted in a more precise estimate (pooled adjusted OR, 0.92; 95% CI, 0.80 to 1.05).^{64, 104, 120, 168}

Fluvoxamine. Three medium and low risk of bias observational studies provide indirect evidence of the risk of major malformations with fluvoxamine use during pregnancy for any reason compared to women who did not use an antidepressant (depression status unknown), although the numbers of women using this SSRI were smaller than the others above.^{79, 104, 120} The pooled estimate from two studies reporting adjusted odds ratios indicated no increased risk (Table 6),^{104, 120} nor did the third study that reported adjusted mean differences.⁷⁹

Cardiac malformations. In addition to major malformations, we examined cardiac malformations as a separate category, in part because there is uncertainty in the ascertainment definitions and methods identifying major malformations, but also because although not all cardiac malformations are major, even those that are minor, if diagnosed, result in resource utilization and stress for families. No direct evidence is available on the risk of cardiac malformations following fetal exposure to SSRIs to treat maternal depression during pregnancy.

Ten observational studies provide indirect evidence on the risk of SSRIs as a group for cardiac malformations, compared with nonexposure.^{48, 64, 70, 86, 90, 104, 106, 116, 120, 125} Two of the studies were methodologically strong, with low risk of bias,^{104, 125} and one was methodologically weak, with high risk of bias, due primarily to potentially biased selection of patients, lack of assessment of comparability of subjects at baseline, and lack of appropriate statistical analysis, including controlling for potential confounding.⁴⁸ Similar to identification of major malformations, above, we have concerns over the accuracy of ascertainment of serious cardiovascular anomalies in these studies, as they depended on ICD coding to identify a defect, with some studies applying additional criteria to categorize the type of anomaly according to developmental groupings. As a result there may be heterogeneity in what is recorded as a major cardiac malformation across these studies. Because of this we focus our analysis on the best evidence – five studies that were methodologically stronger (medium or low risk of bias), used a formal system to identify and classify malformations (e.g., EUROCAT), and controlled for at least three of the four types of potential confounders we had identified as critical, a priori (age, race, parity, and other relevant exposures such as smoking and drug use).^{64, 90, 104, 106, 125} These studies provided evidence that there is no increased risk of cardiac malformations with SSRI use

during pregnancy for any reason, however there is statistically significant heterogeneity present in the analysis. In order to address this heterogeneity we conducted a sensitivity analysis removing the studies that did not use an additional method to classify the type of cardiovascular defect, leaving three studies with a pooled adjusted OR of 1.07 (95% CI, 0.94 to 1.2), with no heterogeneity present.^{64, 104, 106}

Table 5. Best evidence on risk of cardiac malformations with selective serotonin reuptake inhibitors compared with nonexposure

SSRI	Pooled Adjusted OR (95% CI)	Heterogeneity (I ²)
Any SSRI	1.29 (0.96 - 1.72)	84%
Sensitivity analysis	1.07 (0.94 - 1.20)	0%
Comparison to Prior SSRI use	Unadjusted OR 1.29 (0.77 - 2.18)	Cochran Q=0.71, P=0.40
Citalopram/escitalopram	1.05 (0.84 - 1.39)	5%
Fluoxetine	1.31 (1.08 - 1.58)	0%
Sensitivity analysis	1.2 (0.99 - 1.51)	0%
Paroxetine	1.49 (1.20 - 1.85)	0%
Sensitivity analysis	1.45 (1.13 - 1.85)	0%
Sertraline	1.08 (0.70 - 1.65)	68%
Sensitivity analysis	0.76 (0.57 - 1.00)	0%

CI=confidence interval, OR=odds ratio, SSRI=selective serotonin reuptake inhibitor.

Citalopram/escitalopram. Eight studies reported indirect evidence on the risk of malformations with citalopram and/or escitalopram.^{64, 70, 79, 90, 99, 104, 106, 116} One of the studies was methodologically strong, with low risk of bias,¹⁰⁴ and one was methodologically weak, high risk of bias, due primarily to potentially biased selection of patients, uncertain accuracy of outcome ascertainment, and lack of appropriate statistical analysis, including controlling for potential confounding.⁹⁹

Based on six medium and low risk of bias studies reporting adjusted odds ratios,^{64, 70, 90, 104, 106, 116} there was evidence that there is no increased risk of cardiac malformations associated with use of either citalopram or escitalopram for any reason during pregnancy compared with women who did not take an antidepressant during pregnancy (depression status unknown) (Table 7). Because there was very little heterogeneity in the adjusted analysis, we did not pursue subgroup analyses. Analysis of unadjusted risk of a cardiac malformation in women taking citalopram or escitalopram during pregnancy compared with those who discontinued an SSRI prior to pregnancy resulted in a nonstatistically significant difference (OR, 1.86; 95% CI, 0.31 to 8.21).⁹⁰

Fluoxetine. Eleven observational studies provide indirect evidence on the risk of major malformations associated with fluoxetine use during pregnancy for any reason, compared with women who did not take an antidepressant (depression status unknown).^{64, 70, 79, 104, 116, 120, 144, 150, 168} Of these one was low risk of bias¹⁰⁴ and one was high risk of bias.¹⁴⁴ We focused our analysis on the eight studies that were medium to low risk of bias and that reported adjusted odds ratios.^{64, 70, 104, 116, 120, 150, 168} Based on these studies, there is evidence that fluoxetine is associated with an increased risk of cardiac malformations (Table 7), with no statistical heterogeneity. Sensitivity analysis removing the three studies that did not adjust for at least three of four key confounders resulted in a nonstatistically significant finding (pooled adjusted OR, 1.2; 95% CI, 0.99 to 1.51).^{64, 104, 120, 168}

Paroxetine. Ten observational studies provide indirect evidence on the risk of cardiac malformation rates associated with paroxetine use during pregnancy for any reason compared with women who did not use an antidepressant during pregnancy (depression status unknown), of which one was high risk of bias.^{64, 70, 79, 104, 106, 116, 120, 144, 164, 168} Based on analysis of the six medium and low risk of bias studies that adjusted for potential confounders and reported odds ratios,^{64, 104, 106, 120, 164, 168} an increased risk of major malformations was found (Table 7). Sensitivity analysis removing one study that did not report additional methods of identifying serious cardiac malformations resulted in a similar estimate (pooled adjusted OR, 1.45; 95% CI, 1.13 to 1.85). Statistical heterogeneity was not present in any of these analyses.

Sertraline. Eight observational studies, all medium to low risk of bias, provide indirect evidence of the risk of cardiac malformations associated with sertraline use during pregnancy for any reason compared with women who did not use an antidepressant during pregnancy (depression status unknown),^{64, 70, 79, 104, 106, 116, 120, 168} Pooled analysis of the seven studies that reported adjusted odds ratios resulted no increased risk of cardiac malformations (Table 7) but with statistical heterogeneity. Sensitivity analysis, first removing two studies that did not adjust for at least three of the four potential confounding factors identified for this review resulted in a pooled estimate suggesting a reduced risk of cardiac anomalies with sertraline (pooled adjusted OR, 0.76; 95% CI, 0.59 to 0.97), but further limiting to the four studies that also indicated efforts to identify serious cardiac malformations resulted in a pooled estimate of 0.76 (95% CI, 0.57 to 1.00; P=0.51).

Fluvoxamine. Three observational studies provide indirect evidence on the risk of cardiac malformations associated with use of fluvoxamine use during pregnancy for any reason compared with women who did not use an antidepressant during pregnancy (depression status unknown),^{79, 88, 104} one being low risk of bias,¹⁰⁴ another being medium,⁷⁹ and the last being high risk of bias.⁸⁸ Collectively, these studies provided evidence of no increased risk of cardiac malformations with fluvoxamine. None reported adjusted results in a similar way across the studies, preventing a meta-analysis of adjusted odds. The best of these studies, which adjusted for three of four key confounding factors and used both ICD-9 and EUROCAT coding, reported an adjusted odds ratio of 0.56 (95% CI 0.14 to 2.25), and the medium risk of bias study reported an adjusted risk difference of -0.55 (95% CI -1.45 to 0.36). Pooling the crude rates from these studies resulted in an odds ratio of 0.67 (95% CI 0.19 to 2.34).

Other Specific Adverse Events

Withdrawal symptoms (neonatal abstinence symptoms). No direct evidence is available on the risk of withdrawal symptoms following fetal exposure to SSRIs to treat maternal depression during pregnancy. Five small cohort studies with medium risk of bias provide indirect evidence suggesting increased risk of neonatal withdrawal/abstinence syndrome symptoms following maternal use of SSRIs for any reason during pregnancy compared with infants of women who did not take an antidepressant (depression status unknown).^{66, 110, 123, 133, 154} Signs of neonatal withdrawal/abstinence syndrome were consistently more frequent in SSRI-exposed newborns (Table 7). In the largest studies that adjusted for multiple potential confounding factors, neonates exposed to fluoxetine during the first trimester had almost a nine-fold greater risk of poor neonatal adaptation¹⁵⁴ and those exposed to an SSRI or venlafaxine in late pregnancy had three-fold higher odds of neonatal behavioral signs.¹³³

Table 6. Risk of neonatal withdrawal/abstinence syndrome for maternal use of a selective serotonin reuptake inhibitor in pregnancy

Author Year Country Sample Size	Depression	Comparison	Results
<i>SSRIs grouped</i>			
Jordan 2008 ¹²³ US N=108	SRI: 65% Control: 46%	SSRI during pregnancy vs. nonexposed	NBS: Any component present: 28% vs. 17%; NSD
Levinson-Castiel, 2006 ¹¹⁰ Israel N=120	NR	SSRI during entire pregnancy or at least during the third trimester vs. nonexposed	Finnegan severe score of ≥ 8 : 13% vs. 0% Any symptoms: 30% vs. 0% P=NR
<i>Individual SSRIs</i>			
Chambers 1996 ¹⁵⁴ US N=482	Fluoxetine: 76.9% Control: NR	Fluoxetine during first trimester vs. nonexposed	Poor neonatal adaptation Adjusted RR, 8.7 (2.9 to 26.6)
<i>SSRIs or SNRIs</i>			
Ferreira 2007 ¹³³ USA N=166	Exposed: 41% Control: NR	SSRI or venlafaxine during third trimester or at least two weeks prior to delivery vs. nonexposed	Neonatal behavioral signs: Adjusted OR, 3.1 (1.3–7.1)
Rampono, 2009 ⁶⁶ Australia N=56	NR	SSRI/SNRI during pregnancy vs. nonexposed	Maximum median NAS on day 1: SSRI/SNRI=2 vs. nonexposed=0; P<0.05 No other differences in NAS scores (days 1 to 3) Percent infants with NAS > 12 or 3 scores > 8: SSRI=4% vs. SNRI=9%, NSD

NAS= Finnegan neonatal abstinence scoring system, NBS=neonatal behavioral syndrome, NR=not reported, NSD=no significant difference, OR=odds ratio, RR=risk ratio, SNRI= serotonin norepinephrine reuptake inhibitor, SSRI=selective serotonin reuptake inhibitor.

Pulmonary hypertension. No direct evidence is available on the risk of withdrawal symptoms following fetal exposure to SSRIs to treat maternal depression during pregnancy. Indirect evidence indicates an increased risk of persistent pulmonary hypertension is associated with use of SSRIs for any reason during pregnancy compared with women who did not take an antidepressant (depression status unknown), based on eight observational studies.^{47, 48, 64, 119, 121, 123, 155, 167} All but one of these studies were medium risk of bias, but only four reported odds ratios adjusted for potential confounding factors.^{64, 119, 121, 155}

Using a broad “any exposure” category, the pooled adjusted OR is 2.41 (95% CI 1.47 to 3.95), with only 14 percent inconsistency.^{64, 121, 155} Exposure later in pregnancy (generally after week 20, excluding women who used SSRIs both early and late) was associated with a statistically significant increase in risk (pooled adjusted OR, 2.72; 95% CI, 1.63 to 4.54), based on three studies.^{64, 119, 155} However, this pooled analysis has moderate heterogeneity, $I^2=48\%$. While all three adjusted for multiple confounders, including three of the four key confounders identified for this review, the categorization of exposure timing (early) was described in a way that may not exclude overlap between the groups of early, late, or any exposure. Pooled analysis of “early” exposure, reported in four studies,^{64, 119, 121, 155} produced concerning statistical heterogeneity, $I^2=69\%$ (pooled adjusted OR 1.45, 95% CI 0.84 to 2.49), with three studies showing an increased risk and one showing a nonsignificant lower risk compared with nonexposure. In both analyses it appears to be the earliest study estimates are outliers.¹⁵⁵ This was a prospective study that identified infants with persistent pulmonary hypertension

prospectively using patient charts and blinded review by a pediatric cardiologist. The other three studies relied on ICD-9 coding to identify cases. However, the prospective study used mother's recall of medications used to identify exposure, while the other studies used combinations of medical and pharmacy records. Thus none of the studies is superior to the others and the heterogeneity cannot be fully explained.

Respiratory distress. Direct evidence is available from three medium risk of bias observational studies that directly compare the risk of respiratory distress in infants between SSRI-treatment of maternal depression during pregnancy and untreated maternal depression.^{45, 81, 156} Methods for measuring respiratory distress-related outcomes varied across studies, including use of ICD-9 codes,⁸¹ the Peripartum Events Scale (tachypnea, required oxygen, respiratory distress, acrocyanosis, and cyanosis),⁴⁵ and admission to the neonatal intensive care unit due to respiratory distress.¹⁵⁶ Based on these three studies, there is low-strength evidence that, compared with untreated maternal depression during pregnancy, SSRI treatment is associated with a statistically significant increase in risk of respiratory distress in infants (pooled unadjusted OR 1.91; 95% CI, 1.63 to 2.24; $I^2 = 0\%$).

Seven observational studies with medium risk of bias provide additional indirect evidence on the risk of respiratory distress among infants following maternal use of SSRIs for any reason during pregnancy compared with women who did not use SSRIs (depression status unknown).^{86, 111, 122, 123, 133, 146, 149} Four of the studies used ICD codes to identify infants with respiratory distress and used multivariate regression analyses to control for at least one of key confounders identified for this review (N=748,658).^{111, 122, 146, 149} Focusing our analysis on the best evidence from these studies, this indirect evidence supports the direct evidence that maternal exposure to SSRIs primarily in late pregnancy is associated with a statistically significant increased risk of respiratory distress in infants exposed to SSRIs during pregnancy compared with infants of nonexposed pregnant women (pooled adjusted odds ratio, 1.79; 95% CI, 1.64 to 1.97; $I^2 = 0\%$).^{111, 122, 146, 149}

Neonatal convulsions. Eight observational studies with low to moderate risk of bias reported risk of neonatal convulsions/seizures following maternal use of SSRIs during pregnancy.^{60, 81, 110, 114, 122, 123, 133, 147} Only one study (N=107,877) provides direct evidence by comparing outcomes from infants of depressed mothers treated with SSRIs to infants of depressed mothers not treated with medication and nondepressed mothers.⁸¹ Infants of depressed mothers treated with SSRIs (incidence 0.14%) did not have a statistically significantly higher risk of convulsions than those of depressed mothers not treated with medication (incidence=0.09%) or nondepressed mothers (Incidence =0.11%; risk difference 0.0005; 95% CI, -0.0015 to 0.0025).

Indirect evidence from the remaining studies suggests that maternal use of SSRIs during pregnancy for any indication is associated with a statistically significantly increased risk of convulsions compared with infants of nonexposed pregnant women (pooled unadjusted OR, 4.11 (95% CI, 1.78 to 9.48)). These findings are in conflict with the direct evidence.

Tricyclic Antidepressants

Infant/Child Outcomes

Congenital Anomalies

No direct evidence is available on the risk of congenital anomalies following fetal exposure to TCAs to treat maternal depression during pregnancy. We identified indirect evidence from five observational studies that reported rates of congenital malformations following exposure to TCAs for any indication during pregnancy compared with women not taking an antidepressant during pregnancy, who were not known to be depressed.^{60, 64, 75, 88, 157} Of these, one was methodologically strong, low risk of bias,⁶⁰ one was medium,⁶⁴ and three were methodologically weak, high risk of bias.^{75, 88, 157} These studies had less clear methods for obtaining an unbiased sample, ascertaining exposures and outcomes.

Major malformations. Limiting our analysis to two low and medium risk of bias studies,^{60, 64} both of which adjusted for at least three of four key confounding factors, there is indirect evidence of an increased risk of major malformations associated with TCAs as a group compared with non-use (pooled adjusted OR, 1.31; 95% CI, 1.04 to 1.65). Evidence was not reported in a way that allowed investigation of specific drugs in this class.

Cardiac malformations. Based on two low and medium risk of bias studies,^{60, 64} both of which adjusted for at least three of four key confounding factors, indirect evidence indicated a statistically significant increased risk of cardiovascular malformations associated with use of TCAs as a group for any indication during pregnancy compared with non-use (pooled adjusted OR, 1.58; 95% CI, 1.10 to 2.29). Evidence was not reported in a way that allowed investigation of specific drugs in this class.

Other Specific Adverse Events

Respiratory distress. No direct evidence is available on the risk of neonatal respiratory distress following fetal exposure to TCAs to treat maternal depression during pregnancy. Indirect evidence from two large observational studies with medium risk of bias reported risk of respiratory distress among infants exposed to TCAs during late pregnancy.^{122, 146} The first evaluated 16,299 cases and 566,497 controls using data from the Swedish Medical Birth Registry.¹²² The second was a cohort study of 76,093 women from five health maintenance organizations (HMOs) participating in the HMO Research Network's Center for Education and Research on Therapeutics (CERTs) project.¹⁴⁶ Neither study matched groups based on maternal depression and do not allow direct comparison of the risks of TCA-treated depression to untreated depression. Based on the results of these studies, there is evidence that exposure to TCAs during late pregnancy leads to a statistically significant increased risk of respiratory distress (pooled adjusted odds ratio, 2.11; 95% CI, 1.57 to 2.83; Cochran Q=0.08, df=1, P=0.78).

Neonatal convulsions. No direct evidence is available on the risk of neonatal convulsions following fetal exposure to TCAs to treat maternal depression during pregnancy. Indirect evidence indicates a statistically significant increase in risk of convulsions in infants of mothers exposed to TCAs during pregnancy. Two observational studies with moderate risk of bias evaluated risk of neonatal convulsions/seizures following maternal use of TCAs during pregnancy.^{60, 122} Neither accounted for depression exposure. The best evidence comes from the

large Swedish population-based case-control study (cases N=1009; controls N=581,787) that provided indirect evidence that infants exposed to TCAs during pregnancy have almost a seven-fold higher risk of convulsions (adjusted RR, 6.8; 95% CI, 2.2 to 16.0).¹²² A much smaller study (N=418) using data from a health plan also found that more infants of mothers treated with TCAs during pregnancy (1.9%) had seizure disorder than nonexposed infants (0.0%).⁶⁰ This study did not provide an adjusted odds ratio. When we combined data from both studies, the unadjusted pooled odds ratio indicated an even higher risk of convulsions/seizures than in the Swedish study alone (7.82; 95% CI, 2.81 to 21.76).

Selective Norepinephrine Reuptake Inhibitors and Norepinephrine Reuptake Inhibitors

Infant/Child Outcomes

All-Cause Mortality

There was no direct evidence to draw conclusions about the risk for infant death associated with use of SNRIs/NRIs during pregnancy to treat depression. One Swedish cohort study with medium risk of bias reported neonatal/postneonatal deaths following maternal use of SNRI/NRIs during pregnancy.¹¹¹ There was no statistically significant increased risk of either early (RR, 1.3; 95% CI, 0.5 to 2.8) or late (RR, 0.0; 95% CI, 0.0 to 4.4) neonatal death with SNRIs/NRIs as a group.

Congenital Anomalies

There was no direct evidence to draw conclusions about the risk for congenital anomalies associated with use of SNRIs/NRIs during pregnancy to treat depression. Indirect evidence on the risk of congenital malformations with an SNRI indicated no statically significant increase in risk compared with pregnant women who did not use an antidepressant and were not known to be depressed. Two studies reported on malformations with venlafaxine.^{79, 138} One was medium risk of bias and adjusted for depression and other diseases among other confounders, but did not control for the four key confounders identified for this review.⁷⁹ The other was high risk of bias and presented unadjusted rates.¹³⁸ There was no increased risk compared with a nonexposed group based on the adjusted risk difference presented in the medium risk of bias study (-1.18; 95% CI, -3.20 to 0.84) or the pooled unadjusted rates from both studies (OR, 0.68; 95% CI, 0.33 to 1.38). Evidence for NRIs (nefazodone or trazodone) was limited to two small high risk of bias studies.^{138, 140}

Other Specific Adverse Events

Respiratory distress. There was no direct evidence to draw conclusions about the risk for neonatal respiratory distress associated with use of SNRIs/NRIs during pregnancy to treat depression. Indirect evidence is limited with one very small cohort study with medium risk of bias reported risk of respiratory distress among infants exposed to SNRIs/NRIs during pregnancy.¹¹¹

Other Antidepressants: Bupropion

Congenital Malformations

Two observational studies reported on the risk of congenital malformations associated with use of bupropion during pregnancy.^{153, 169} One was high risk of bias, but was the only study to report provide direct evidence on major malformations.¹⁵³ There were few malformations in any group and the P value for comparison across the groups was 0.51. The second, medium risk of bias study¹⁶⁹ was a case control study (N=12,749) designed to examine the risk of cardiac malformations provides only indirect evidence. Compared with nonexposed controls, the adjusted OR for any cardiac malformation was 1.4 (95% CI 0.8 to 2.5).

Postpartum Exposure

Selective Serotonin Reuptake Inhibitors

Child Outcomes

Overall Adverse Events

One observational study with high risk of bias provided direct evidence on the comparative risk of overall adverse events in babies of 20 women taking an SSRI or venlafaxine for postpartum depression compared with 68 babies of breastfeeding mothers not treated with any medication and of unspecified depression status.¹⁶¹ Total adverse event symptom score was 5.9 in the treatment group and 7.6 in the control group (P not reported). The proportion of withdrawals from study drug due to adverse events was not reported. Due to high methodological limitations, unknown consistency and imprecision, however, this observational study provides insufficient evidence to draw strong conclusions about comparative risk of overall adverse events in babies.

ii. How do pharmacological treatments affect maternal outcomes when compared with each other (drug A compared with drug B)?

Antidepressant Exposure During Pregnancy

No direct evidence comparing antidepressants to each other in pregnant women with depression was found.

Class Compared With Class: Selective Serotonin Reuptake Inhibitors Compared With Tricyclic Antidepressants

Infant/Child Outcomes

Congenital malformations. Indirect evidence from two medium risk of bias studies reported major malformations and cardiac malformations associated with specific classes of antidepressant drugs.^{60, 64} Both of the studies adjusted for at least three of four key confounding factors. Both studies provide adjusted odds ratios for TCAs and SSRIs (and one includes SNRIs) compared with pregnant women who did not receive antidepressants during pregnancy but were not known to be depressed. These studies do not make direct comparisons across classes. The adjusted odds ratios are presented in the table below. Findings from these studies differ in that a statistically significant increase in risk of major and cardiac malformations was found with

TCA, but not SSRI in the larger study that used ICD-9 codes to identify malformations,⁶⁴ while the other smaller study that used an unblinded pediatric specialist review of patient records to identify malformations found a nonstatistically significant lower risk with TCAs, and a nonsignificant increase in risk with SSRIs.⁶⁰ Pooled the unadjusted rates from these two studies, we find SSRIs to have a statistically significantly lower risk of major or cardiac malformations compared with TCAs (Table 8). The comparison of SSRIs and SNRIs comes from a single medium risk of bias study (Table 8), where similar odds were found for both classes and neither was statistically significant.

Table 7. Class compared with class: Risk of congenital malformations

Study	SSRIs (Adjusted OR [95% CI] Compared With Nonexposure)	TCAs (Adjusted OR [95% CI] Compared With Nonexposure)	SNRIs (Adjusted OR [95% CI] Compared With Nonexposure)	SSRIs vs. TCAs (Unadjusted pooled odds ratio [fixed effect model])
Major malformations				
Reis 2010 Sweden N = 17,425 exposed	1.08 (0.97-1.21)	1.39 (1.07-1.72)	1.00 (0.73-1.37)	
Simon 2002 US N = 385 exposed	1.36 (0.56-3.30)	0.82 (0.35-1.95)	--	
				0.77 (0.60-0.98)
Cardiac malformations				
Reis 2010 Sweden N = 14, 821 exposed	0.99 (0.82-1.20)	1.63 (1.12-2.36)	1.33 (0.84-2.09)	
Simon 2002 US N = 385 exposed	Non-estimable (0 events in control group)	0.5 (0.05-5.53)	--	
				0.66 (0.44-0.99)

OR=odds ratio, SNRI=serotonin norepinephrine reuptake inhibitor, SSRI=selective serotonin reuptake inhibitor, TCA=tricyclic antidepressant.

Bupropion. One high risk of bias observational study reported no increase in risk of congenital malformations associated with the use of bupropion during pregnancy compared with other antidepressants as a group in women with depression during pregnancy.¹⁵³ Indirect evidence from a larger (N=7005), medium risk of bias study, also reported no statistically significant increase in risk with bupropion compared with other antidepressants reported an adjusted OR of 0.95 (95% CI, 0.62 to 1.45),⁴⁰ Depression status of women in either group was not known in this study.

Other Specific Adverse Events

Withdrawal symptoms (neonatal abstinence symptoms). Indirect evidence comparing the risk of neonatal abstinence symptoms in infants of women treated for depression with SSRIs compared with SNRIs during pregnancy comes from only one small (N=56) prospective cohort study with medium risk of bias evaluated the comparative risks of neonatal abstinence syndrome between maternal use of SSRIs as a group and SNRIs as a group during pregnancy.⁶⁶ Depression status of the women was not reported. Only one cohort study with medium risk of bias include both classes and made any comparison between them, finding no difference in the proportion of infants with neonatal abstinence symptoms scores greater than 12 (on the Finnegan scale, range of 0 to 21) or with 3 days of scores greater than 8 (SSRI=4%, SNRI=9%, P = NR).

Respiratory distress: SSRI compared with TCA. Indirect evidence comparing the risk of neonatal respiratory distress in infants of women treated for depression with SSRIs compared with TCAs during pregnancy comes from only one small study with medium risk of bias compared the risk of respiratory distress among infants between treatment of maternal depression during pregnancy with different SSRIs or nortriptyline.⁵⁹ The study included 21 women from the Women’s Behavioral HealthCARE Program at the University of Pittsburgh medical Center’s Western Psychiatric Institute and Clinic. Results from this study suggest that SSRIs and nortriptyline are associated with similar risks of respiratory distress in infants (10% vs. 0%; P=NR).

Within Class Comparisons: Selective Serotonin Reuptake Inhibitors Compared with Selective Serotonin Reuptake Inhibitors

Congenital Anomalies

Indirect evidence based on nine observational studies^{64, 70, 79, 90, 104, 120, 138, 144, 150} suggested that there is no difference in risk of major (unadjusted pooled OR, 1.14; 95% CI, 0.95 to 1.37) or cardiac (unadjusted pooled OR, 1.10; 95% CI, 0.85 to 1.43) malformations between paroxetine and fluoxetine used for any indication during pregnancy. The evidence is limited by a lack of adjusted analyses directly comparing the two drugs (these findings are based on unadjusted rates), and the methodological limitations of individual studies (range from high to low risk of bias), but is strengthened by the strong consistency across estimates.

Based on eight observational studies,^{64, 70, 79, 90, 104, 120, 138, 150} we compared the risk of citalopram/escitalopram with that of fluoxetine or paroxetine. Using unadjusted rates, we found that the pooled odds of a major malformations is 0.94 (95% CI, 0.82 to 1.07; $I^2=0\%$), suggesting no statistically significant difference between the drugs. Similarly, analysis of the unadjusted risk for cardiac malformations did not result in a statistically significant difference (OR 0.94, 95% CI 0.60 to 1.47). This analysis resulted in significant statistical heterogeneity ($I^2 = 49\%$), sensitivity analyses based on risk of bias did not reduce this heterogeneity. These findings compare to adjusted analyses reported for the individual drugs (above) where the confidence intervals overlap considerably.

These same eight studies indicated a lower risk of major malformations with sertraline compared with fluoxetine or paroxetine (pooled unadjusted OR, 0.59; 95% CI, 0.38 to 0.90; $I^2 = 0\%$). The risk for cardiac malformations is also lower, based on pooled unadjusted rates (OR, 0.59; 95% CI, 0.38 to 0.93) but statistically significant heterogeneity ($I^2 = 42\%$) suggested caution in interpreting these results. Sensitivity analysis removing a high risk of bias study did not alter these results.

Other Specific Adverse Events

Persistent pulmonary hypertension. Of the eight observational studies reporting persistent pulmonary hypertension rates with SSRIs, only one conducted an analysis by drug.¹¹⁹ Based on this medium risk of bias study, there was indirect evidence that only escitalopram did not have statistically significant increased risk when exposure occurs after 20 weeks gestation (Table 9). For early exposure (up to 8 weeks gestation), only citalopram was associated with a statistically significant increase in risk, while escitalopram had the lowest risk. No direct statistical comparisons across the drugs were made. While increased odds are similar for late exposure across the four drugs (citalopram, fluoxetine, paroxetine and sertraline), they are less similar for

the early exposure comparison, and a study designed to directly compare the drugs may result in differences being found.

Table 8. Risk of persistent pulmonary hypertension with individual selective serotonin reuptake inhibitors¹¹⁹

	Adjusted OR	Lower Bound (95% CI)	Upper Bound (95% CI)
Late exposure (20 weeks or after)			
Fluoxetine	2.0	1.0	3.8
Citalopram	2.3	1.2	4.1
Paroxetine	2.8	1.2	6.7
Sertraline	2.3	1.3	4.4
Escitalopram	1.3	0.2	9.5
Early exposure (up to 8 weeks)			
Fluoxetine	1.3	0.6	2.8
Citalopram	1.8	1.1	3.0
Paroxetine	1.3	0.5	3.5
Sertraline	1.9	1	3.6
Escitalopram	0.3	0	2.2

CI=confidence interval, OR=odds ratio.

Respiratory distress: Indirect evidence comparing the risk of neonatal abstinence symptoms in infants of women treated for depression with SSRIs compared with each other during pregnancy comes from only one small study with medium risk of bias compared the risk of respiratory distress among infants between treatments of maternal depression during pregnancy with different SSRIs.⁵⁹ The study included 20 women from the Women’s Behavioral HealthCARE Program at the University of Pittsburgh medical Center’s Western Psychiatric Institute and Clinic. Results from this study suggest that sertraline is not associated with a statistically significant increase in risk of respiratory distress compared with other SSRIs (22% vs. 0%; P=NR).

Postpartum Exposure

Class Compared With Class: Selective Serotonin Reuptake Inhibitors compared With Tricyclic Antidepressants

Child Outcomes

Overall adverse events and withdrawals due to adverse events.. One RCT with high risk of bias provided direct evidence on the comparative risk of overall adverse events in babies of 109 women taking either sertraline or nortriptyline for postpartum depression.⁴⁶ There were no adverse events or withdrawals due to adverse events in the babies of the breastfeeding mothers. Due to high methodological limitations, unknown consistency and imprecision, however, this trial provided insufficient evidence to draw strong conclusions about comparative risk of overall adverse events in babies.

iii. How do pharmacological treatments affect child outcomes when compared with active nonpharmacological treatments?

Antidepressant Exposure During Pregnancy

No evidence on the risk of serious adverse outcomes in the infant (e.g., mortality, malformations, and pulmonary hypertension) was found comparing pharmacologic and nonpharmacologic treatments.

Postpartum Exposure: Selective Serotonin Reuptake Inhibitors

Overall Adverse Events and Withdrawals Due To Adverse Events

One observational study with high risk of bias provided evidence on the comparative risk of overall adverse events and withdrawal due to adverse events in babies of 23 women treated with either sertraline or interpersonal psychotherapy for postpartum depression.⁷³ Breastfeeding women reported no adverse events in their babies and none withdrew from the study due to adverse events. Due to high methodological limitations, unknown consistency and imprecision, however, this study provides insufficient evidence to draw strong conclusions about comparative risk of overall adverse events in babies.

iv. How does combination therapy affect maternal and child outcomes?

Using a Second Drug to Augment the Effects of the Primary Drug and Comparing This Treatment with Single Drug Monotherapy

Congenital Anomalies

No direct evidence was found on the risk of congenital anomalies with multiple antidepressants taken during pregnancy for depression compared with monotherapy. Indirect evidence comes from only two small studies specifically addressed this question.^{70, 136} Both studies reported nonstatistically significant risks with wide confidence intervals for the comparison of multiple antidepressants to nonexposure, but the direction of the estimates were opposite. A medium risk of bias study that adjusted for age, calendar year, income, marriage and smoking status presented an adjusted OR of 1.62 (95% CI 0.83 to 3.16),⁷⁰ while a high risk of bias study that matched patients for age, smoking status, and alcohol use reported an odds ratio of 0.68 (0.11 to 4.16).¹³⁶ This study also reported the comparison to monotherapy, finding an OR of 1.03 (95% CI 0.14 to 7.48). Pooling these data results in an OR of 1.58 (95% CI 0.86 to 2.93), still an imprecise result.

A statistically significant increase in risk of cardiac malformations was found in the one study reporting this outcome, compared with nonexposure; adjusted OR of 3.42 (95% CI 1.40 to 8.34) compared to nonexposure. Because the use of multiple antidepressants may indicate more severe or resistant depression, and since this study did not control for depression or severity of depression, we cannot determine the role of the antidepressants compared with the role of the disease in these findings.

Combining Pharmacological Treatments With Nonpharmacological Treatments and Comparing Them With Nonpharmacological Treatments Alone

Antidepressant Exposure During Pregnancy

No evidence on the risk of serious adverse outcomes in the infant (e.g., mortality, malformations, pulmonary hypertension) was found comparing combination pharmacologic treatments with nonpharmacologic treatments.

Postpartum Exposure

Overall Adverse Events or Withdrawal due to Adverse Events

One RCT with high risk of bias provided direct evidence on the comparative risk of overall adverse events in babies of 23 women treated with either sertraline plus interpersonal psychotherapy or sertraline alone for postpartum depression.⁷³ Breastfeeding women reported no adverse events or withdrew from the study due to adverse events in their babies. Due to high methodological limitations, unknown consistency and imprecision, however, this trial provides insufficient evidence to draw strong conclusions about comparative risk of overall adverse events in babies.

Comparing Pharmacological Treatments Alone With Pharmacological Treatments Used in Combination With Nonpharmacological Treatments

Antidepressant Exposure During Pregnancy

No evidence on the risk of serious adverse outcomes in the infant (e.g., mortality, malformations, pulmonary hypertension) was found comparing pharmacologic treatments used alone with pharmacologic treatments combined with nonpharmacologic treatments.

Key Question 2b. In babies born to women who become pregnant while taking medications to treat depression, what is the comparative risk of teratogenicity?

The evidence on the risk of exposure to an antidepressant drug during the conception period in women with depression is extremely limited, and is insufficient to draw conclusions. The studies included in the sections above reporting on the risk of congenital malformations comprise the best evidence to answer this question, but even among those that specify exposure in the first trimester, there are few that specify exposure during conception and none that directly compare to a control group of untreated depression. For example, of the studies that reported specifically on first trimester exposure to SSRIs, and met our criteria for risk of bias, controlled for three of four of our key confounders and used a recognized categorization system to identify malformations, only one reported exposure timeframes that required exposure in the conception period,¹²⁵ Compared with the other three studies reporting major malformations following exposure in the first trimester, but without necessarily including the conception period, this study reported the highest odds (Figure 3). All of these studies made comparisons with nonexposed pregnant women, with unknown proportions in either group with depression, but the Jimenez-Salem study also reported on a small group of women who had taken an SSRI in the year prior to

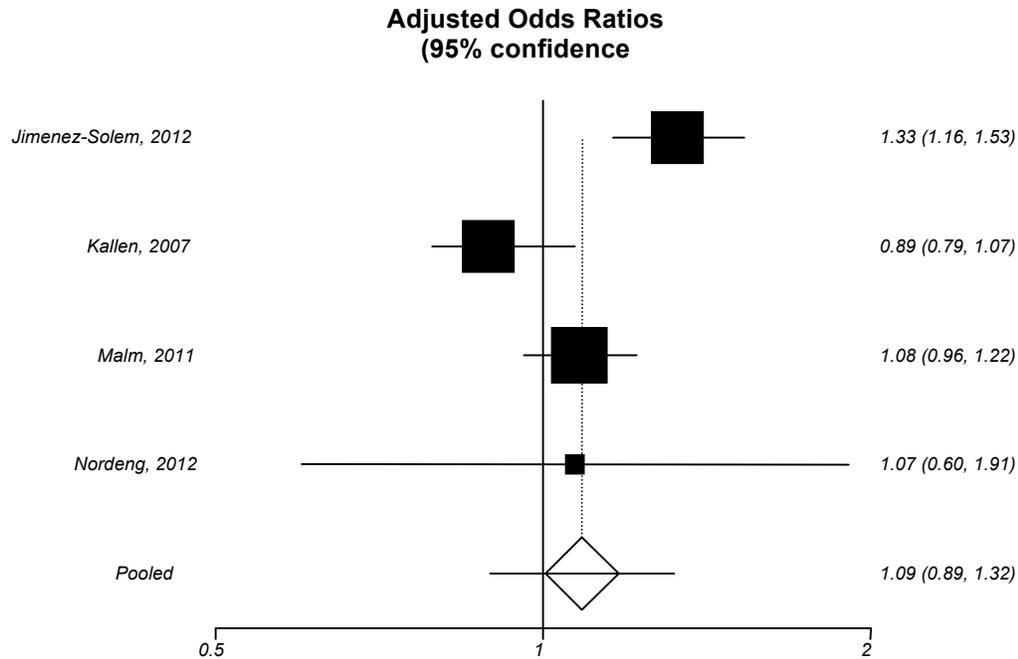
pregnancy, but had discontinued prior to conception. The risk in this group was similar to the exposed group, odds ratio 1.27 (0.91 to 0.78) but not statistically significant. This study also examined the effect of dose, with the risk associated with low dose SSRIs (e.g., ≤ 20 mg fluoxetine daily) was an OR of 1.26 (1.05 to 1.51) compared with 1.44 (1.15 to 1.79) for high doses. While the high dose risk is slightly higher, analysis comparing the odds ratios indicated no statistically significant difference, indicating no clear dose-response relationship. Because this is a single observational study using a control group of presumably mainly nondepressed women, with unknown consistency in findings, and the imprecise results, this evidence is insufficient to draw firm conclusions.

Based on this single study, the risk of a cardiovascular malformation was also found to be significantly increased compared with nonexposed pregnant women, adjusted OR 2.01 (1.60 to 2.53). In this case, the risk in women who stopped taking an SSRI prior to conception was also statistically significantly elevated, adjusted OR 1.85 (1.07 to 3.20). Dose again showed a small increase in risk with greater dose, but comparison of the odds ratios resulted in a P value of 0.41, indicating no clear dose-response relationship. Analysis of other specific malformations did not result in any statistically significant increased risk estimates.

While there are a few other studies that report the risk of malformations after exposure during the conception period for individual or grouped SSRIs, SNRIs, and individual drugs,^{40, 49, 79, 152} none controlled for more than two of the key confounders, and suffered from inferior methods for ascertainment of exposure or outcomes.

Insufficient evidence is available to reasonably assess the risk of autism spectrum disorder in children of women taking an antidepressant at the time of conception. A single observational study examined this group and found no statistically significant increase in risk compared with nonexposed pregnant women.²⁰

Figure 3. Risk of major malformations with selective serotonin reuptake inhibitors compared with nonexposure



Key Question 3. Is there evidence that the comparative effectiveness of pharmacological and nonpharmacological treatments for women with depression during pregnancy and in the postpartum period varies based on characteristics such as interventions, populations, and providers?

Summary

- Evidence in subgroups based on characteristics such as interventions, populations, and providers is insufficient to draw conclusions. Direct evidence is limited.

Exposure During Pregnancy

Duration of Treatment

- Compared to partial SSRI exposure during pregnancy, there is not a statistically significantly greater risk of preterm birth (< 37 weeks) associated with continuous exposure (unadjusted pooled OR, 3.23; 95% CI, 0.74 to 14.17).
- Evidence on the influence of antidepressant dose on adverse effects was insufficient.

Postpartum Exposure

Depression Severity Level

- In women with postpartum depression, the difference between brief dynamic psychotherapy, with or without sertraline add-in, in treatment response rate, does not vary based on depression severity level.

Duration of Treatment

- In women with postpartum depression, symptom improvement does not differ when fluoxetine is used in combination with either one or six sessions of cognitive-behavioral counseling.

Depression History

- Evidence was insufficient to allow analysis of the impact of history of MDD prior to pregnancy versus those with a first episode during pregnancy or the postpartum period.

Other

- Studies with definite depression in all comparison groups and that had medium to low risk of bias provided insufficient evidence to draw conclusions about variation in treatment effects based on all other patient characteristics and comorbidities, intervention characteristics, coadministration of other drugs, medical provide characteristics, medical care environments, and characteristics of diagnosis.

Detailed Assessment

To answer this question about variation in the comparative effectiveness of pharmacological and nonpharmacological treatments in women with depression, we focused on the direct evidence from studies of women with definite depression in all comparison groups and that had medium to low risk of bias. There were six observational studies of treatment during pregnancy^{42, 45, 59, 76, 81, 156} and three RCTs of treatment during the postpartum period that met this best evidence criteria.^{97, 160, 166} Among those, only one randomized control of women with postpartum depression evaluated the effects of depression severity¹⁶⁰ and four studies evaluated the effects of treatment duration.^{42, 45, 76, 166}

Exposure During Pregnancy

Duration of Treatment

Preterm birth. Two prospective cohort studies conducted in the US (N=95) provide evidence that, compared to partial SSRI exposure, there is not a statistically significantly greater risk of preterm birth (< 37 weeks) associated with continuous exposure (unadjusted pooled OR, 3.23; 95% CI, 0.74 to 14.17).^{42, 45}

Postpartum Exposure

Severity of Symptoms

One RCT of 40 women treated for postpartum depression for 8 weeks with brief dynamic psychotherapy, with or without sertraline add-on, evaluated the effects of baseline depression

severity (above and below the median MADRS scores).¹⁶⁰ The main analysis of all patients provided evidence of no statistically significant difference between add-on sertraline (70%) and placebo (55%) in response rates (>50% reduction in either the MADRS or EPDS scores). The post-hoc analysis of the high depression severity subgroup also found no statistically significant difference in response rate ($t=1.05$; $P=0.31$).

Duration of Treatment

One 12-week RCT of 87 women treated for postpartum depression with fluoxetine, cognitive-behavioral counseling or their combination evaluated the effects of treatment duration.¹⁶⁶ Treatment groups that received fluoxetine plus either one or six session(s) had similar mean changes on the Edinburgh postnatal depression scale (-67% compared with -69%; $P=$ not reported) and on the Hamilton Depression Scale (-78% compared with -79%; $P=$ not reported).

Discussion

Key Findings and Strength of Evidence

The results of our review highlighted important concerns over the state of the evidence on benefits and harms of treating depression during and after pregnancy. The majority of the comparative evidence applies to selective serotonin reuptake inhibitors (SSRIs) taken during pregnancy, with little evidence for other types of antidepressant drugs, or nonpharmacological interventions. Additionally, the majority of the evidence is indirect for this report in that studies made comparisons of outcomes for women who took an antidepressant during pregnancy for any reason, with women who did not take an antidepressant during pregnancy, with proportions of women with depression in either group rarely reported and not analyzed. The applicability of indirect evidence of findings from studies of pregnant women with unknown depression status is unclear. We are left with a small body of direct evidence; studies that were designed to directly compare the benefits and harms of pharmacological treatments for depression in pregnant or postpartum women.

The overarching findings for Key Question 1, the benefits side of the equation, are that there is little direct evidence on the maternal benefits of antidepressants used to treat depression in pregnancy. Our questions were intended to cover the benefits of pharmacological treatments in comparison to “usual care” or no treatment, considering the drugs as classes, individual drugs, drug treatments compared with each other and when taken in various combinations (e.g., drug + drug, drug + nondrug treatment). The evidence was divided into treatment during pregnancy and treatment during the postpartum period. With exposure during pregnancy, the evidence we found was limited initially by the population comparisons made (the control groups) and also by the way outcomes were measured. In addition, the evidence is limited to observational studies, and these studies were generally not designed to measure benefits (e.g., effect on depressive symptoms) when women are treated during pregnancy. We are left with spotty evidence that does not allow comparisons among the specific classes or individual drugs. For example, while anxiety is a common feature of depression during pregnancy, direct evidence on the impact of treatment on this symptom is lacking. Where we do have evidence (Table 10), it is based on one or two small studies, with some methodological problems (none were low risk of bias), imprecise estimates of effect, and inconsistency where more than one study was found, leading to strength of evidence ratings of insufficient for the benefit of SSRI treatment on depressive symptoms during pregnancy, and no evidence for other drug classes. Similarly, the evidence on the effects of SSRI treatment during pregnancy on breastfeeding outcomes is insufficient to draw conclusions, as it is limited to a single study reporting the duration of breastfeeding. While the duration was two months longer in the group that received psychotherapy alone (8.5 months) compared with the group treated with an SSRI plus psychotherapy (6.4 months, $P = 0.4$) the difference was not statistically significant and the study was very small ($N = 44$). In contrast, women treated for depression with an SSRI throughout pregnancy were found to have better functional capacity than those with depression but not treated in a single small study. Again, this evidence is insufficient to draw conclusions for reasons noted above. Evidence for benefits in mothers is insufficient for other antidepressant drugs or for nonpharmacologic therapy, and for all other maternal benefit outcomes we studied.

The potential benefits we evaluated in children include outcomes related to parameters at birth, child development, diagnosis of chronic diseases and health care utilization. Here evidence was again very limited, with only the effect of SSRI treatment for depression compared with no

treatment on preterm birth and some child development scales studied in direct comparisons of these populations. Although no differences were found between groups on rates of preterm birth (defined as less than 37 weeks gestation), and most child development scales (SSRI-exposed infants may have lower scores on the Bayley Psychomotor Development Index), this evidence is insufficient to draw conclusions.

While we identified randomized controlled trials (RCTs) on treatment of postpartum depression, they were small and included limited comparisons and outcomes. For benefits to mothers, this direct evidence was insufficient to draw conclusions on the benefits of drug therapy compared with placebo or to other drug therapies, and we found no evidence comparing drug therapy to nondrug therapy. Evidence for other outcomes or comparisons either for exposure during pregnancy or in the postpartum period was either not found or insufficient.

Indirect evidence is available for several other benefits outcomes. Because it is difficult to make a case for applying the results of these studies directly to women with depression during pregnancy particularly for benefits outcomes only evidence on the risk of Autism spectrum disorder or attention deficit/hyperactivity disorder (ADHD). Diagnosis of attention deficit hyperactivity disorder (ADHD) in the children by the age of 5 was found to be associated with use of bupropion use (OR, 3.63; $P < 0.02$), particularly in the second trimester, but not associated with use of SSRIs or other antidepressants during pregnancy. Filling a prescription for an SSRI after pregnancy (timing not reported) was statistically significantly associated with increased risk of ADHD diagnosis by age five in the child (OR 2.04, $p < 0.001$). These analyses controlled for parental mental health diagnoses and found that a diagnosis of depression in the mother was statistically significantly associated with the diagnosis of ADHD in the child (OR, 2.58; $p < 0.001$).

Two studies, suggest that maternal use of SSRIs is statistically significantly associated with diagnosis of autism spectrum disorder (ASD) in the child (OR, 1.82; 95% CI, 1.14 to 2.91). Both studies examined other antidepressant drugs but grouped them differently, one finding an increased risk with TCAs and the other finding no increased risk with TCAs combined with SNRIs/NRIs. Although these results are controlled for depression, the comparison groups were women who did not receive an antidepressant during pregnancy, rather than women with untreated depression. The role of depression was studied in one study by conducting an analysis of exposure to any antidepressant in only women with depression compared to a population of nonexposed pregnant women; the risk for ASD was statistically significantly elevated with a greater odds ratio than the combined analysis (OR 3.34, 95% CI 1.50 to 7.47), while the risk in women taking an SSRI for another indication was lower and not statistically significant (OR, 1.61; 95% CI, 0.85 to 3.06).

Evidence on Key Question 2, comparative harms of pharmacological and nonpharmacological treatments for women with depression during pregnancy and in the postpartum period, is also limited by the comparison groups selected by most studies (pregnant women taking an antidepressant for any reason). The overarching findings for harms associated with exposure during pregnancy are that there is limited direct evidence about serious infant harms, with suggestion of increased risk of respiratory distress associated with exposure to SSRIs. The only outcomes for which we have direct evidence are major malformations, convulsions and respiratory distress in the neonate after exposure to SSRIs in utero (Table 10). This evidence is insufficient to draw conclusions for major malformations due to the limitations of the few small studies found. Low strength evidence suggests that there is no increased risk of neonatal convulsions, but a statistically significant increase in risk of neonatal respiratory

distress with use of SSRIs. The increase in risk for respiratory distress is a pooled unadjusted OR 1.91; 95% CI, 1.63 to 2.24. Because this is low strength evidence, the findings are likely to be altered by future studies.

Indirect evidence is available for several other harms outcomes. In cases where there is a signal of a serious harm this evidence may be useful both clinically and to direct future research. An increased risk of infant death in the first year of life was found with exposure to SSRIs (as a group and individually) during pregnancy, compared with nonexposed children (SSRIs OR 1.81; 95% CI, 1.26, 2.60). While exposure to SSRIs as a group did not result in increased risk of major malformations in infants, evidence indicates small but statistically significant risk with exposure to fluoxetine (OR 1.14, 95% CI 1.01 to 1.30) or paroxetine (OR 1.17, 95% CI 1.02 to 1.35), but not the other SSRIs individually. Timing of exposure was primarily in the first trimester, although sensitivity analyses removing studies that may have included exposures at other time points did not alter the results. Similar results were found for cardiac malformations, except that limiting our analysis to the highest quality studies of fluoxetine resulted in a nonsignificant increase in risk. The increased risk with paroxetine was 1.49 (95% CI 1.20 to 1.85). TCAs were also associated with increased risk for major (OR 1.31, 95% CI 1.04 to 1.65) and cardiac malformations (1.58, 95% CI 1.10 to 2.29). Evidence for other antidepressants was insufficient.

Persistent pulmonary hypertension is statistically significantly associated with maternal SSRI use during late pregnancy (OR, 2.72; 95% CI, 1.63 to 4.54). Indirect evidence suggests that neonatal withdrawal symptoms were more common with fluoxetine use during the first trimester (RR, 8.7; 95% CI, 2.9 to 26.6), and with SSRIs or venlafaxine (grouped) in late pregnancy, but suggests no difference in risk between SSRIs and SNRIs. The risk of respiratory distress in the neonate was statistically significantly elevated for SSRIs and TCAs, but not with SNRIs. The pooled OR was 2.11 (95% CI 1.57 to 2.83), comparing TCA exposure to nonexposed pregnant women. A single study indicates no difference in the risk of respiratory depression in the infant with maternal exposure to SSRIs compared with nortriptyline.

The risk for teratogenicity with exposure to antidepressants during the conception period was examined in few well designed studies, with even fewer specifically isolating exposure during this period such that the evidence is currently insufficient.

In Key Question 3, we attempted to examine a wide range of subgroups of patient and intervention characteristics. Given the difficulty we had in identifying direct evidence for the first two Key Questions with appropriate control and intervention groups, it is not surprising that we found very little evidence to address these questions. Based on the best evidence, with comparisons between pregnant women with depression who did and did not take an antidepressant during pregnancy, the duration of treatment did not appear to influence the risk of preterm birth, stratifying into continuous use and use during only one trimester. In the postpartum period, we found that multiple sessions of CBT were not superior to a single session, when both were combined with fluoxetine. Depressive symptom response to dynamic psychotherapy, with or without sertraline, did not vary based on depression severity level. For all other subgroups (including coadministration of other drugs, medical provider characteristics, medical care environments, and characteristics of diagnosis) the evidence is limited. Studies with definite diagnosis of depression in all comparison groups and that had medium or low risk of bias provided insufficient evidence to draw conclusions about variation in treatment effects.

Table 10, below, highlights the findings based on studies that were designed to take maternal depression in the treatment and/or control groups into account – direct evidence. We feel that this is the best evidence for the Key Questions posed for this review, as it is unclear how untreated or

nonpharmacologically treated depression in control groups, or indications other than depression in the treatment groups may have affected outcomes in the remainder of the evidence.

Table 9. Key findings of directly comparative evidence for depression during pregnancy

Intervention	Comparison	Outcome	Strength of Evidence Results
Potential benefits			
SSRIs+psychotherapy	Psychotherapy alone	Depressive symptoms	Insufficient; no conclusions drawn
SSRIs: Fluoxetine	No treatment	Depressive symptoms	Insufficient; no conclusions drawn
SSRIs	No treatment	Functional capacity	Insufficient; no conclusions drawn
SSRIs+psychotherapy	Psychotherapy alone	Breastfeeding	Insufficient; no conclusions drawn
SSRIs	No treatment	Preterm birth	Insufficient; no conclusions drawn
SSRIs+psychotherapy	Psychotherapy alone	Infant/child development: Bayley Scales	Insufficient; no conclusions drawn
SSRIs	No treatment	Infant/child development: Brazelton Neonatal Behavioral Assessment Scale	Insufficient; no conclusions drawn
Potential harms			
SSRIs	No treatment	Major malformations	Insufficient; no conclusions drawn
SSRIs+psychotherapy	Psychotherapy alone	Major malformations	Insufficient; no conclusions drawn
SSRIs	No treatment	Neonatal convulsions	Low; Risk not different between groups
SSRIs	No treatment	Neonatal respiratory distress	Low; Risk higher with SSRIs
SSRIs	TCA (nortriptyline)	Neonatal respiratory distress	Insufficient; no conclusions drawn

SSRI=selective serotonin reuptake inhibitor,

Findings in Relationship to What is Already Known

It is difficult to put these findings into the context of prior comparative effectiveness evidence reviews as we did not identify any such studies, in part because the scope of this report is so broad. A review by Bromley, et al.,²² assessed fetal and child outcomes and SSRIs only, but did not limit the comparison group to women with depression, such that our results are quite different. Additionally, we applied both formal assessment of the risk of bias to individual studies and strength of evidence to the body of evidence for each key outcome which the Bromley review did not, resulting in most outcomes in our review having insufficient strength of evidence.

Applicability

The evidence on exposure to pharmacological and nonpharmacological treatment during pregnancy was limited to observational studies that generally met criteria for effectiveness studies. The evidence on pharmacological and nonpharmacological treatment for postpartum depression came almost entirely from RCTs that met criteria for efficacy studies. These studies were limited by the exclusion of patients with common comorbidities, such as drug and alcohol

misuse/abuse, other Axis I disorders, and suicidal ideation, the lack of health outcomes and comprehensive assessment of adverse events, short study durations and small sample sizes.

The majority of studies were indirect, comparing women using antidepressants during pregnancy for any reason to nonexposed pregnant women – rates of depression not reported for either group. As maternal depression is widely recognized as a risk factor for poorer pregnancy outcomes, the findings from all the studies that don't account for maternal depression likely have very low applicability to our target population of pregnant women with depression. The mean maternal age ranged from 26 years to 34 years. Few studies reported race or socioeconomic status. In the studies that reported race, the populations were predominantly White. When reported, a medium socioeconomic status level was most common. The data sources for these studies typically did not include access to information about depressive symptom severity, comorbid anxiety diagnoses and other mental health or medical conditions, family history of depressive/mood disorders, prior use of antidepressive drugs, situation at home, unplanned pregnancy, marital/partner status, etc.; therefore, we know very little about these important patient characteristics.

There was very little evidence available to assess the benefits and harms of nonpharmacological treatment modalities and it was limited to treatment during the postpartum period. The clinical relevance of the nonpharmacological treatment modalities was difficult to assess based on the lack of detail about their characteristics. Likewise, the clinical relevance of the pharmacological treatment regimens was also difficult to assess due to a general lack of information about dose, duration and cointerventions.

Only approximately 30 percent of included studies were conducted in the US. Canada and Nordic countries each accounted for additional thirds of the studies, respectively. Findings from many of the studies conducted in the US and Canada may not be reflective of the general population due to their reliance on highly selected samples who voluntarily called teratogen information services, have specific health plan membership, or who attended specific community prenatal clinics. As they primarily relied on birth registry data, the studies from the Nordic countries are likely the most representative of the broad general populations. But, it is unclear how the differences in the health care systems and demographic characteristics between the US and the various Nordic countries impact the applicability of the findings from the Nordic country studies to the US context. Provider characteristics were generally not reported.

Overall, the applicability of this evidence to programs such as the federal Children's Health Insurance Program (CHIP) is somewhat limited due to the issues noted above, e.g. the large number of studies conducted in non-US healthcare settings and medium socioeconomic status of women studied.

Implications for Clinical and Policy Decisionmaking

Depression during pregnancy and postpartum can have adverse consequences for both mother and child. Knowing the best course of action when a woman is diagnosed with depression during these times is extremely important. The evidence base at present is extremely limited in the specific guidance it can provide, for multiple reasons. The overall findings of this review are based on insufficient or low strength of evidence, meaning that future studies are very likely to alter the findings in a meaningful way. The implications for decision-making for women with depression during pregnancy are unclear. Without better evidence, specific to this population, the balance of benefit and harm are uncertain.

Based on the best evidence available today, the benefits to mothers are unclear. For pregnant women, treatment with drugs may offer benefits, although the specific benefits, particularly in terms of tangible benefits (health outcomes), and how benefits compare across potential treatments are still very unclear. Although we believe that treatment with SSRIs is likely to improve some symptoms based on indirect evidence in nonpregnant patients, direct evidence comparing the interventions of interest in the population of interest is currently insufficient. Similarly, the evidence on functional outcomes for the mother are unfortunately insufficient, although they lean towards better outcomes in women treated with an SSRI compared with untreated pregnant women

While there is a suggestion that women taking antidepressants are less likely to breastfeed or breastfeed for shorter durations than are women who are not taking an antidepressant in the postpartum period, and we did not find evidence of harm to the infant of breastfeeding while the mother is taking an antidepressant, this evidence is also insufficient to draw specific conclusions. This evidence suggests room for education of pregnant women and possibly providers that women taking antidepressants should not necessarily be discouraged from breastfeeding. Clinicians can know in advance that, for women treated with antidepressants, decisions around breastfeeding can be problematic; thus, early discussion and support for maternal intention to breastfeed is warranted. Women who receive antenatal education and professional encouragement, or who report that their health care provider encouraged them to breastfeed are more likely to initiate and sustain breastfeeding.²⁴⁻²⁶ Antidepressants are widely used in postpartum women. For most antidepressants, no or only negligible amounts are passed from mother to baby through breast milk (fluoxetine and citalopram may be exceptions, but the amount varies with dose and frequency of dosing).²⁷⁻²⁹

Evidence on the comparative benefits of treating depression during pregnancy (compared with not treating) is expected to include benefits in developmental achievement in the child. Our evidence indicates that SSRIs results in no differences on most measures, but may result in slightly worse motor development than no treatment at all, but again this evidence is insufficient to guide clinical decisions. When making direct comparisons, while the evidence does not indicate higher rates of preterm birth with use of SSRIs during pregnancy, unadjusted odds ratio of 1.73 (95% CI 0.63 to 4.42), it is insufficient to guide clinical decisions.

Numerous potentially serious harms have been suggested to be associated with use of antidepressants during pregnancy; but in the comparison of depressed women treated and untreated, we found only the risk for respiratory distress to be associated with SSRIs (as a drug class). The fact that different conclusions may be drawn for some outcomes based on a large body of evidence we consider indirect for our questions highlights the importance of making clinically relevant comparisons.

An example is the risk of ASD in children of women treated for depression during pregnancy. The increasing prevalence of ASD diagnosis, likely in part attributable to increased detection, temporally parallels an increasing tendency to prescribe antidepressants in pregnancy. Based on indirect evidence, whether ASD in the child is associated with maternal depression during pregnancy, treatment with antidepressants, or a combination of the two remains unclear. Although we found that ASD was associated with maternal exposure to antidepressants, particularly SSRIs, compared with the maternal nonexposure (depression status unknown), we did not find clear evidence on the risk when untreated depressed women were the comparison group. Any suggestion of increased risk for ASD is very concerning. In studies comparing with maternal nonexposure, although researchers controlled for depression, the relationship between

depression, antidepressant use, and risk of ASD remains unclear. The small, but statistically significant risk of ASD diagnosis with antidepressant use or depression or both is important to understand better, because treatment could mitigate this risk if severe depression underlies the association with ASD. One study examined the risk of having depression during pregnancy and a diagnosis of ASD in the child, finding statistically significant increased odds in depressed mothers (with and without known treatment), and a nonsignificant increase in mothers without depression. An interaction between depression and antidepressant treatment is possible, but has not been fully elucidated. Nevertheless, women should be informed about the risk of ASD if antidepressants are found more conclusively to increase this risk. Because the fraction of cases of ASD that could potentially be attributed to antidepressants in these studies is exceedingly small (0.6 to 2.5 percent of the study populations), prenatal antidepressant use is not a major risk factor for ASD and does not explain the increasing prevalence of autism.

Evidence on the benefits or harms of treatment of depression in the postpartum is insufficient to draw conclusions. Women and clinicians are currently left with only evidence in nonpregnant populations and evidence on intermediate outcomes (e.g., which drugs are passed into breast milk) to guide treatment choices.

Limitations of the Comparative Effectiveness Review Process

Methodological limitations of the review within the defined scope included the exclusion of studies published in languages other than English and lack of a specific search for unpublished studies. The review process and results could have benefited from further refinement of the scope to limit inclusion of studies of pregnant or postpartum women with depression, both in the intervention and control groups.

Limitations of the Evidence Base and Gaps in the Evidence

A major caveat to interpreting the findings of the majority of observational studies of exposure during pregnancy is the potential confounding role of depression itself and its severity.⁷⁶ Most of the studies identified women taking an antidepressant for any reason, with few reporting the proportions with depression and even fewer using this information in their analyses. Studies of women taking an antidepressant during or after pregnancy but not known to be depressed are problematic in part because we do not know what the differential baseline risk of various outcomes are for the various indications for which antidepressants can be used. We do know that there are baseline risks associated with depression during pregnancy, however, making it important to limit the treated group to women with depression.^{2,3} Equally problematic is the control groups used in most of the studies, which were general populations of nonexposed pregnant women. These groups could have included a proportion of women with depression, but in general this characteristic is not reported. When it was reported, the range of depression in the control groups was large (as low as 6% to 36%). For much of the evidence, then, the comparison is mostly depressed-treated women compared with nondepressed, untreated women. This comparison is problematic because of known effects of untreated depression on both mother and child. A small number of studies set out to examine these questions by comparing to untreated, depressed, pregnant women, but these did not measure both benefits and harms (in both mother and baby) simultaneously.

While there is disagreement about whether RCTs are necessary or ethical to conduct in pregnant women,¹⁷³ the assumption that the clinical efficacy of interventions in nonpregnant populations is directly applicable to pregnant women may not be valid for many reasons. Making these types of comparisons requires well-designed prospective studies, with measurement of depression severity at baseline and during followup. Comparisons of specific treatments in these more appropriate populations are needed. For example, based on indirect evidence from comparisons with nondepressed controls, comparisons of specific drugs could uncover variation in risk across drugs even within a class. Ascertainment of exposure, including both timing and dose must be done in a way that insures accuracy and reliability. Outcomes should be determined by blinded evaluators, which is possible for nearly all outcomes considered here. Evidence on the relative benefits and harms of nonpharmacological treatments is almost entirely lacking, as is the effectiveness of combinations of drug and nondrug treatments. Studies of women in the postpartum period are both small and methodologically weak, leaving a gap in knowledge about a group of patients in whom RCTs could be undertaken. There is a real need for specifically-designed research that addresses the problems identified in this report.

It is important to recognize that the current evidence base is insufficient to fully support clinical decisionmaking, which requires knowing both benefits and harms and being able to determine the tradeoffs of individual choices. For example, if a medication has a lower adverse event profile but is also less effective for a given condition, it would not make sense to prescribe that for a patient who is needing to treat that particular condition just because of a lower adverse event profile. We know that depression during pregnancy and the postpartum period can lead to serious adverse outcomes for both mother and child, such that treatment is important. There is a real need for research in this area to simultaneously measure both benefits and harms in the same study so we will be able to inform the tradeoffs that women and clinicians need to weigh

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Abbreviations

Abbreviation Used	Term
ADHD	Attention deficit hyperactivity disorder
ASD	Autism spectrum disorder
BDI	Beck Depression Inventory
BNBAS	Brazelton Neonatal Behavioral Assessment Scale
CBT	Cognitive behavioral therapy
CES-D	Center for Epidemiologic Studies Depression Scale
CGI –I	Clinical Global Impressions Improvement Scale
CI	Confidence interval
CIS-R	Revised Clinical Interview Scale
DSM-IV	<i>Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition</i>
EPDS	Edinburgh Postnatal Depression Scale
GP	General practitioner
HAM – A	Hamilton Rating Scale for Anxiety
HAM – D	Hamilton Rating Scale for Depression
ICD	International Classification of Diseases
ICD-9	International Classification of Diseases, Ninth Revision
MADRS	Montgomery Asberg Depression Rating Scale
MDI	Mental Development Index
NR	Not reported
NRI	Norepinephrine reuptake inhibitor
NS	Not significant
NSD	No significant difference
OR	Odds ratio
RCT	Randomized controlled trial
RR	Relative risk
RRR	Relative risk reduction
SD	Standard deviation
SF-36	Medical Outcomes Survey 36-item Short Form
SNRI	Serotonin norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
Zung SDS	Zung Self-Rating Depression Scale