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Neonatal Outcomes in Women With Untreated Antenatal Depression Compared With Women Without Depression
A Systematic Review and Meta-analysis

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IMPORTANCE Despite the prevalence of antenatal depression and the fact that only one-third of pregnant women with depression consider it acceptable to take antidepressants, the effect of untreated depression on neonatal outcomes remains to be addressed thoroughly.

OBJECTIVE To undertake a systematic review and meta-analysis to understand the effect of untreated depression on neonatal outcomes.

DATA SOURCES We executed our search strategy, with emphasis on its exhaustiveness, in MEDLINE, EMBASE, PsycINFO, Cumulative Index to Nursing and Allied Health, Cochrane Central Register of Controlled Trials, and Web of Science. The search was conducted in July, 2015.

STUDY SELECTION We included randomized and nonrandomized studies that examined neonatal outcomes in women with depression receiving neither pharmacological nor nonpharmacological treatment compared with women without depression.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently screened titles and abstracts, assessed full-text articles, extracted data, and assessed their quality using a modified version of the Newcastle-Ottawa Scale. We pooled data using random-effects meta-analyses, quantified heterogeneity using the I^2 statistic, and explored it with subgroup analyses by type of assessment of depression, severity, reported conflicts of interest, and study quality.

MAIN OUTCOMES AND MEASURES Primary outcomes were preterm birth before 37 weeks and before 32 weeks, small and large for gestational age, low birth weight, and neonatal intensive care unit admission.

RESULTS Of the 6646 titles initially identified, 23 studies met inclusion criteria, all observational, with a total of 25 663 women. Untreated depression was associated with significantly increased risks of preterm birth (odds ratio [OR], 1.56; 95% CI, 1.25-1.94; 14 studies; I^2, 39%) and low birth weight (OR, 1.96; 95% CI, 1.24-3.10; 8 studies; I^2, 48%), with a trend toward higher risks for exposure to more severe depression. While the odds of preterm birth more than doubled in studies reporting conflicts of interest (OR, 2.50; 95% CI, 1.70-3.67; 5 studies; I^2, 0%), studies not reporting such conflicts showed more moderate results (OR, 1.34; 95% CI, 1.08-1.66; 9 studies; I^2, 30%).

CONCLUSIONS AND RELEVANCE Our results contrast with what is, to our knowledge, the only previous systematic review that examined the question of untreated depression because we found significant risks of 2 key perinatal outcomes, preterm birth and low birth weight. These are important results for pregnant women and clinicians to take into account in the decision-making process around depression treatment.

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Because only one-third of pregnant women with depression would consider taking antidepressants as an acceptable treatment option,[1] it is critical to understand pregnancy outcomes with untreated depression for clinicians to be able to adequately counsel and support women who choose this course. Antenatal depression is a prevalent problem, affecting 5% to 15% of pregnant women.[2] It also has high public health significance because depression has been associated with an increased risk of preterm birth and low birth weight,[3,4] which are 2 leading causes of mortality and morbidity in infants.[5,6]

The use of antidepressant medications during pregnancy has been increasing in the last few decades both in Europe and in the United States, with 3% to 8% of women being prescribed or having used antidepressants during pregnancy.[7-10] However, since 2010, several meta-analyses examining antidepressant use during pregnancy found significantly higher risks of preterm birth and low birth weight in women with depression taking antidepressants compared with either women without depression or women with untreated depression.[11-13] Moreover, in a meta-analysis by Huang et al,[11] the risks associated with antidepressant use were higher when the comparison group was women with untreated depression (odds ratio [OR], 2.85; 95% CI, 2.00-4.07) than when the comparison group was women who were not depressed (OR, 1.88; 95% CI. 1.50-2.27). These results highlight the complexity of this topic and the need to better understand the risks in untreated women.

In previous systematic reviews of risks of neonatal outcomes associated with antenatal depression,[3,4] most of the included studies did not control for the potential confounding effect of antidepressant use[3]; as such, the estimations of the risks of untreated depression might be biased, resulting in an overestimation of adverse perinatal outcomes such as preterm birth and low birth weight. Therefore, we hypothesized that the risk of adverse infant outcomes would be lower after rigorously excluding the potential confounding effect of antidepressants. The results of a subgroup analysis[3] partially support this hypothesis because the odds of preterm birth were not only lower but also not statistically significant in the studies of women with short or no exposure to antidepressants. Additionally, it is surprising that the influence of financial conflicts of interest with direct or indirect funding by pharmacological companies has not been explored in previous reviews, given that a statistically significant association between industry sponsorship and proindustry conclusions is well known.[14-16]

Our objective was to address the limitations of existing reviews by undertaking a meta-analysis of randomized and nonrandomized studies to determine neonatal risks associated with untreated antenatal depression, using strict inclusion criteria to remove any potential effect of antidepressant medication.

Key Points

Question Do women with untreated antenatal depression have worse neonatal outcomes than women without depression?

Findings In this meta-analysis, pregnant women not receiving any treatment for their depression were associated with significantly increased risks of preterm birth and low birth weight when compared with women without depression, with a trend towards higher risks for exposure to more severe depression. Studies reporting conflicts of interest reported significantly higher odds of preterm birth.

Meaning Untreated depression during pregnancy is associated with adverse effects not only for the mother but also for the fetus through worse neonatal outcomes.

Methods

We published our protocol in the Prospective Register of Systematic Reviews database (registration number: CRD42015007455).

Search Strategy

We executed our search strategy in 6 electronic databases (MEDLINE, EMBASE, and PsycINFO [all through OVID] and Cumulative Index to Nursing and Allied Health, Cochrane Central Register of Controlled Trials, and Web of Science) using both controlled vocabulary and free text terms, developed in consultation with an experienced research librarian, with no restriction by publication date. The full electronic search strategy for all databases can be accessed online (http://www.crd.york.ac.uk/PROSPEROFILES/16038_STRATEGY_20150016.pdf).

We performed several complementary steps to overcome challenges in identifying studies assessing untreated depression, ie, women with untreated depression are usually a comparison group in intervention studies and not always clearly described in the abstracts. To be confident in the exhaustiveness of our literature search: first, besides keywords for untreated depression, we also included terms for pharmacological and nonpharmacological therapies in our main search strategy. Second, in an effort to capture studies assessing the risks of antenatal depression that did not state the presence or absence of any treatment in the title or abstract, we complemented the main search strategy with a broader, less specific one not including any intervention term. Using this search strategy, we considered only studies published in 2010 or later, the date of the literature searches of the 2 most recent systematic reviews,[3,4] owing to the very large number of results obtained without time limits in such a nonspecific search. Third, we identified studies and reviews closely related to the topic under study during the titles and abstracts screening stage. We read their full text and examined all potentially relevant references. Finally, we screened the full text of primary studies in systematic reviews of antidepressant effects because 2 control groups (pregnant women with untreated depression and pregnant women without depression) were sometimes used but not explicitly stated in the abstract.

Selection Criteria

We included randomized and nonrandomized studies reporting the risk of adverse neonatal outcomes in pregnant women with untreated depression compared with pregnant women without depression. We excluded case reports, case series,

reviews, conference abstracts, non-peer-reviewed literature, and non-English language studies (owing to potential bias of a single translator not familiar with the area).

We included studies that assessed depression using either a clinical interview/diagnosis or a screening tool or scale at any time during pregnancy. We excluded studies including and not stratifying outcomes by multiple pregnancies owing to worse outcomes in twins and higher-order multiples, women experiencing domestic violence, or with other reported comorbid psychiatric diseases (eg, anxiety or bipolar disorders).

The absence of any pharmacological treatment for depression had to be explicitly stated in the article or its effects adjusted for in the analyses. Studies that reported no changes in the results after redoing the analyses without antidepressant users were included (and their effect also assessed in a sensitivity analysis). However, we did not include studies that reported only that the conclusions did not change (in terms of accepting or rejecting the null hypothesis) after redoing the analyses because this could still be the case even with considerable differences in the effect estimates. We also excluded studies in which participants received nonpharmacological treatments.

Primary outcomes were preterm birth before 37 weeks and before 32 weeks, small for gestational age (birth weight <10th percentile for sex and gestation), large for gestational age (birth weight >90th percentile for sex and gestation), low birth weight (<2500 g), and neonatal intensive care unit admission. Secondary outcomes were birth weight less than the third and fifth percentiles and greater than the 95th and 97th percentiles for sex and gestation; high birth weight (macrosomia, >4000 g and >4500 g); and gestational age and birth weight (continuous data).

Study Selection and Data Collection

Two reviewers, 1 of them always being the first author, screened the titles and abstracts, assessed the full text of the potentially eligible studies, and extracted data of included studies using a piloted data extraction form. A third reviewer was available as an adjudicator if disagreements could not be settled by discussion. When additional information regarding the inclusion and exclusion criteria were required, we contacted the authors, all of whom replied to our inquiries. Data extracted included information regarding the authors' affiliations and conflicts of interest (direct or indirect funding by or links to pharmacological companies), study characteristics (design, sample, and assessment of depression), and outcomes of interest (both crude and adjusted). The same reviewers assessed the methodological quality (risk of bias) using the Cochrane Risk of Bias Tool for randomized trials and a modified version of the Newcastle-Ottawa Scale[17] for observational studies.

Statistical Analyses

We pooled ORs (for binary outcomes) and mean differences (for continuous outcomes) using random-effects meta-analyses. Adjusted and nonadjusted effect estimates were pooled separately. Heterogeneity was quantified using the I^2 statistic.[18] Publication bias was assessed using Duval and Tweedie's trim and fill method.[19]

To explore heterogeneity, we had planned to do a number of subgroup analyses, but owing to the relatively small number of studies located, we decided to limit them to assessment of depression (clinical diagnosis or interview vs self-administered questionnaire), depression severity (moderate vs severe), declared conflicts of interest (reported direct or indirect funding by or links to pharmacological companies vs not reported or stated none), and study quality (high or acceptable, defined as 5 or more points in the Newcastle-Ottawa Scale vs low, defined as 4 or less points). We did a post hoc subgroup analysis of term gestation (sample limited vs not limited to term infants) because 2500 g, the approximate average at 35 weeks' gestation, is appropriate for many preterm infants but is the equivalent of small for gestational age at 37 weeks and older, which is term. To explore the effect of newer studies in our pooled effects, we did further post hoc subgroup analyses by publication year (before and after 2010, which was the year the previous systematic reviews executed their search strategy). The effect of including studies that reported only "no changes after excluding antidepressant users from their analyses" was assessed in sensitivity analyses.

Results

Of the 6646 studies initially identified, 2367 duplicates were deleted, leaving 4279 for titles and abstracts screening, resulting in 347 full-text articles for assessment. Of these, 23[20-42] met our inclusion criteria (**Figure 1**), involving 25 440 women. All but 1 study (which assessed depression retrospectively) were prospective observational studies.

Nine studies (40%) defined depression using a clinical diagnosis or interview. Although half of these studies (5) used a *DSM-IV* diagnosis of major depression disorder, other *DSM-IV* criteria, such as dysthymia or both major and minor depression, were also used, and 1 study used the definition of moderate depression of the *International Classification of Diseases, Tenth Revision*. Among the 14 studies using a self-administered questionnaire to measure depression, the most commonly used scale was the Center for Epidemiologic Studies Depression Scale (6 studies), usually with a cutoff value of 16, followed by the Edinburgh Postnatal Depression Scale (3 studies) and the Beck Depression Inventory (2 studies; **Table 1**). Through inclusion and exclusion criteria, studies excluded some potential confounding variables, ie, illicit drug use in some studies and chronic diseases in others (Table 1).

Seven studies (30%) reported conflicts of interest (direct or indirect funding by or links to pharmacological companies), 8 studies (35%) stated that there were no conflicts of interest, and conflicts of interest were not reported in the rest of the studies (8 studies, 35%). Sixteen studies (70%) had a quality score equal to or above our cutoff value of 5, indicating an acceptable or high methodological quality. The mean (SD) intraclass correlation coefficient between raters was 0.64 (0.30), which is considered good agreement.[43] Three studies reported our outcomes of interest in a metric that could not be pooled with the rest of the studies and were therefore not included in the meta-analyses[38,40,41] (Table 1). Two more stud-

ies could not be pooled in any meta-analysis because only gestational age and birth weight of term infants (continuous data) were reported.[39,42]

Syntheses of Results

Pregnant women with untreated depression had a significantly increased risk of both preterm birth (<37 weeks; OR, 1.56; 95% CI, 1.25-1.94; 14 studies; I^2, 39%) and low birth weight (<2500 g; OR, 1.96; 95% CI, 1.24-3.10; 8 studies; I^2, 48%) compared with women without depression. Only 1 study reported small for gestational age (birth weight <10%; OR, 1.37; 95% CI, 1.10-1.70), 2 studies reported neonatal intensive care unit admission (OR, 1.12; 95% CI, 0.40-3.15; I^2, 0%), and none reported either preterm birth before 32 weeks or large for gestational age (birth weight >90%, **Table 2**; eFigures 1-3 in the Supplement).

Only 1 study reported birth weight greater than 4500 g without finding significant differences between the groups. There were no statistically significant differences between women with depression and women without depression in gestational age (continuous data, 10 studies) and no clinically significant differences in birth weight (mean difference, -84 g; 95% CI, -153 g to -15 g; 11 studies; I^2, 77%; Table 2; eFigures 4 and 5 in the Supplement).

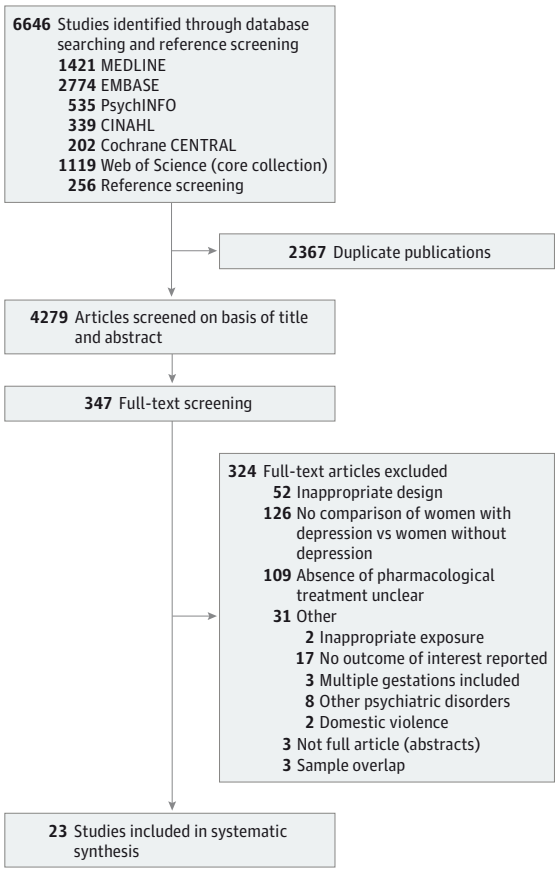
Although the funnel plot suggested potential publication bias for preterm birth before 37 weeks, the results did not change significantly after 3 studies were inputted using the trim and fill method (adjusted OR, 1.47; 95% CI, 1.17-1.85). None of the other outcomes were suspicious for publication bias.

Subgroup Analyses

For preterm birth before 37 weeks, results were not statistically different among subgroups based on assessment of depression by a clinical diagnosis/interview vs self-administered questionnaire or quality of the study (**Figure 2**). There appeared to be a trend toward an increased risk of preterm birth in women with more severe depression, although the differences were not statistically significant (Figure 2). There were significant differences between the results of studies reporting conflicts of interest (OR, 2.50; 95% CI, 1.70-3.67; 5 studies; I^2, 0%) and those that did not (OR, 1.34; 95% CI, 1.08-1.66; 9 studies; I^2, 30%). This difference remained after redoing the analyses without low-quality studies and does not seem to be explained by severity of depression.

For low birth weight (<2500 g), our subgroup analyses found a significant increased risk in term infants, which would be approximately the equivalent of being small for gestational age (<10th percentile). Our results also suggested that there are significant differences (P = .06) between the results of high- or acceptable-quality studies (OR, 2.39; 95% CI, 1.72-3.30; 5 studies; I^2, 0%) and low-quality studies (OR, 0.89; 95% CI, 0.33-2.35; 3 studies; I^2, 36%). There was also a trend toward significant differences between the studies reporting conflicts of interest (OR, 1.66; 95% CI, 0.98-2.79; 6 studies; I^2, 53%) and those that did not (OR, 3.76; 95% CI, 1.69-8.37; 2 studies; I^2, 0%) (P = .09), although it disappeared when removing low-quality studies (Figure 2).

Figure 1. Flow Diagram of Study Identification and Selection, Including Reasons for Exclusion in Systematic Review



A study could be excluded for more than 1 reason. CENTRAL indicates Central Register of Controlled Trials; CINHAL, Cumulative Index to Nursing and Allied Health.

Sensitivity Analyses

Few studies reported adjusted effect estimates, although each study excluded a number of potential confounding variables through their population inclusion and exclusion criteria. Although pooling these adjusted effect estimates yielded different results than pooling the nonadjusted effect sizes of all the studies, pooling the nonadjusted effect sizes of the same subset of studies resulted in almost identical adjusted and crude results. For example, 3 studies[22,23,32] reported both adjusted and nonadjusted effect estimates for preterm birth before 37 weeks. Pooling these 3 adjusted effect estimates resulted in an adjusted OR of 1.03 (95% CI, 0.64-1.64), which is significantly different from pooling the nonadjusted effect estimates of all 14 studies reporting this outcome. However, if the nonadjusted effect estimates of only those 3 studies were pooled together, the results were almost identical (nonadjusted OR, 1.08; 95% CI, 0.74-1.57) to the pooled adjusted estimates. Therefore, the differences in the results of the meta-analyses of adjusted values (not shown) are mostly owing to the differences in the subset of studies pooled instead of the use of adjusted data.

Table 1. Characteristics of Studies Included

Source (Country)	Inclusion and Exclusion Criteria	Measure of Depression (Criterion)	Sample Size (Depressed/ Nondepressed), No.	Outcomes: OR/MD (95%CI)[a]	QAT	Conflicts of Interest
Field et al,[37] 2004 (United States)	Inclusion: women in their second trimester and scored ≥16 or ≤12 on the CES-D. Exclusion: recreational drug use during pregnancy.	CES-D (≥16 or ≤12)[b]	119 (58/61)	PTB: 4.97 (1.54-16.05); LBW: 3.49 (1.39-8.75)[f]	5	Yes
Suri et al,[27] 2004 (United States)	Inclusion: outpatient women aged 18-45 y in the first trimester of pregnancy with either a history of major depressive disorder or no psychiatric history. Exclusion: presence of psychotic symptoms; use of medications known to adversely affect the fetus; the use of other psychotropic medications; presence of suicidality; use of alcohol, cigarettes, or substances while pregnant; and twin pregnancy.	*DSM-IV* (major or minor depression)[c]	34 (18/16)	NICU: 0.54 (0.08 to 3.74); GA: 0.80 weeks (−0.38 to 1.98); and BW: 400 g (45 to 754)	5	Yes
Field et al,[33] 2006 (United States)	Exclusion: illicit drug use during pregnancy.	*DSM-IV* (dysthymia)[c]	810 (340/470)	PTB: 2.34 (1.31-4.16)	3	Yes
Rahman et al,[36] 2007 (Pakistan)	Inclusion: did not have a physical illness for which they were undergoing treatment and had an uneventful pregnancy. Exclusion: women with severe depression or other mental disorder; stillbirths; infants who died before reaching their first birthday or born with a congenital abnormality; and mothers who gave birth prematurely (<37 wk).	*ICD-10* (moderate depression)[c,d]	290 (143/147)	PTB: 1.00 (0.25-4.07)[g]; LBW: 2.43 (1.40-4.19)[h]; and LBW (adj.): 2.20 (1.21-4.02)	7	NR
Diego et al,[34] 2009 (United States)	Inclusion: did not report any pregnancy complication at study entry including hypertensive disorders, anemia, vaginal bleeding or intrauterine growth restriction; did not exhibit any pregnancy complication at study entry or any pregnancy or delivery complication during previous pregnancies including hypertensive disorders, anemia, vaginal bleeding, or intrauterine growth restriction; were not diagnosed as having HIV or any other infectious disease; had normal pregnancy body mass indices as defined by Institute of Medicine criteria (BMI, 19.8-26.0); did not report any metabolic or eating disorder (diabetes, obesity, bulimia, and/or anorexia) or any psychiatric condition other than depression; and did not report smoking cigarettes, drinking alcohol or using recreational drugs during pregnancy, or taking antidepressants or other psychotropic medications during pregnancy. Only mothers who were able to accurately recall their last menstrual period date were included.	*DSM-IV* (MDD)[c,e]	79 (39/40)	PTB: 2.61 (0.73-9.33); LBW: 4.75 (0.94-23.98)[f]; GA: −0.44 wks (−1.07 to 0.19); and BW: −332 g (−535 to −129)	6	Yes
Field et al,[35] 2009 (United States)	Inclusion: older than 18 y; singleton pregnancy; and uncomplicated pregnancy. Exclusion: medical illness (diabetes, HIV); other psychiatric conditions (eg, bipolar disorder); self-reported drug use or medications that might affect cortisol levels including antidepressants and steroids; and positive screen for illicit drugs.	*DSM-IV* (MDD)[c,e]	336 (131/205)	PTB: 2.05 (0.95-4.43)	6	Yes
Gavin et al,[23] 2009 (United States)	Inclusion: women older than 15 y; competency in English; singleton pregnancy with no known congenital or chromosomal abnormalities; no history of diabetes; and gestational age at recruitment: 15-27 wk of pregnancy.	CES-D (≥24)[b,e]	2815 (432/2383)	PTB: 0.79 (0.52-1.20)[i]; PTB (adj): 0.71 (0.47-1.07)[i]	7	NR
Li et al,[25] 2009 (United States)	Inclusion: living in San Francisco and South San Francisco area; positive pregnancy test; speak English; and intent to carry pregnancy to term. Exclusion: miscarriages and preterm births (<33 wk).	CES-D (≥16, ≥22)[b,d,e]	791 (326/465)	PTB: 1.95 (1.05-3.60)[j]; PTB (CES−D, 16-21): 1.46 (0.64-3.29)[j]; and PTB (CES−D ≥22): 2.41 (1.21-4.80)[j]	6	NR
Wisner et al,[28] 2009 (United States)	Exclusion: women with active substance use disorder or with gestational exposure to benzodiazepines or prescription drugs in the US FDA category of D or X; and women with psychosis or bipolar disorder. Those with multiple gestations or chronic diseases were also excluded.	*DSM-IV* (MDD)[c,e]	167 (36/131)	PTB: 2.48 (0.76-8.11)[k]; NICU: 1.50 (0.44-5.10)[k]; and BW: −220 g (−434 to −6)[k]	4	Yes
Benute et al,[20] 2010 (Brazil)	Inclusion: singleton pregnancy, intact chorioamniotic membrane, absence of fetal congenital and chromosomal abnormalities, and absence of pregnancy complications owing to medical disorders (all women enrolled had medical disorders). Exclusion: Fetal malformations and lack of postnatal data.	PRIME-MD (MDD)[c]	326 (29/297)	PTB: 1.08 (0.50 to 2.33); LBW: 0.55 (0.22-1.39)[f]; GA: 0.10 weeks (−0.62 to 0.82); and BW: −64 g (−307 to 180)	2	NR
Hodgkinson et al,[24] 2010 (United States)	Inclusion: adolescents enrolled in Teen Alliance for Prepared Parenting.	5 Questions[b]	294 (81/213)	BW (adj): 42 g (−69 to 153)	3	NR

(continued)

Table 1. Characteristics of Studies Included (continued)

Source (Country)	Inclusion and Exclusion Criteria	Measure of Depression (Criterion)	Sample Size (Depressed/ Nondepressed), No.	Outcomes: OR/MD (95%CI)[a]	QAT	Conflicts of Interest
Van Dijk et al,[31] 2010 (Netherlands)	Inclusion: participant in the ABCD biomarker study; singleton live births; gestational age more than 22 wk; and data on prenatal depression status and birth weight available.	CES-D (≥16, ≥23)[b,d,e]	4044 (1119/2925)	PTB: 1.56 (1.17-2.09)[l]; PTB (CES−D 16-22): 1.30 (0.89-1.89)[l]; PTB (CES−D≥23): 1.93 (1.33-2.78)[l]; SGA: 1.37 (1.10-1.70)[l]; SGA(CES−D 16-22): 1.46 (1.12-1.89)[l]; SGA (CES−D≥23): 1.25 (0.92-1.70)[l]; GA: −0.29 weeks (−0.49 to −0.09)[l]; and BW: −96 g (−136 to −56)[l]	5	NR
Fransson et al,[29] 2011 (Sweden)	Exclusion: inability to understand Swedish.	EPDS (≥12)[b]	2891 (443/2448)	PTB: 1.59 (1.07-2.37)	5	NR
El Marroun et al,[22] 2012 (Netherlands)	Exclusion: fetal death; twin pregnancies; and SSRI use before pregnancy.	BSI (>0.75)[b]	7597 (570/7027)	PTB: 1.27 (0.89-1.81); PTB (adj): 1.10 (0.77-1.58); LBW (adj): 0.96 (0.65-1.42); GA: 0.10 weeks (−0.05 to 0.25); GA (adj): 0.18 weeks (0.02-0.34); BW: −91 g (−137 to −45); and BW (adj): −28 g (−66 to 9)	6	No
Liu et al,[26] 2012 (United States)	Inclusion: women aged ≥18 y and women intending to use the obstetric facilities for delivery. Exclusion: women planning to relinquish custody of the child; planning to move from the area in the next 3 y; and infection with HIV.	CES-D (≥16)[b]	973 (272/701)	LBW: 1.79 (1.05-3.06)[f,m]; LBW (adj): 1.67 (0.78-3.58)[m]; LBW (moderate depression): 1.58 (0.88-2.83)[n,m]; LBW (severe depression): 3.00 (1.19-7.56)[o,m]; BW >4,5 kg: 0.64 (0.18-2.29)[m]	5	No
Bindt et al,[32] 2013 (Ghana and Côte d'Ivoire)	Inclusion: women in third trimester of pregnancy and residing within a distance of 5 km around the hospitals. Exclusion: women younger than 18 y; multiple pregnancies; and chronic physical disease or other risk factors such as severe complications during pregnancy owing to diabetes, hemorrhage, hypertension, and preeclampsia.	PHQ-9 (≥10)[b]	717 (207/510)	PTB: 1.54 (0.63-3.76); PTB (adj): 2.10 (0.79-5.58); LBW: 0.82 (0.22-3.05)[f]; GA: −0.10 wks (−0.40 to 0.20); BW: 48 g (−24 to 121); BW (adj): 52 g (−18 to 123)	4	No

(continued)

Table 1. Characteristics of Studies Included (continued)

Source (Country)	Inclusion and Exclusion Criteria	Measure of Depression (Criterion)	Sample Size (Depressed/ Nondepressed), No.	Outcomes: OR/MD (95%CI)[a]	QAT	Conflicts of Interest
Chang et al,[21] 2014 (Korea)	Inclusion: women in third trimester with depression data and who delivered at term. Exclusion: twin births and women with missing data on confounders.	CES-D (≥10)[b]	691 (152/539)	LBW: 2.94 (1.14-7.58)[g]; LBW (adj.):1.66 (0.55-5.02); GA: −0.20 wks (−0.40 to −0.00)[p]; GA: −35 (−104 to 33)[p]	7	No
Sahingoz et al,[30] 2014 (Turkey)	(*DSM-IV* criteria were applied retrospectively after delivery). Inclusion: at least 18 y ; no history of medical illness (eg, endocrine, cardiovascular, pulmonary, neurological, and metabolic disease) or pregnancy-related complications (eg, gestational hypertension, imminent abortion, placenta previa and other placental abnormalities, vaginal bleeding, and gestational diabetes); absence of any fetal malformation; absence of maternal infection that can negatively affect fetal growth (eg, toxoplasma, rubella, cytomegalovirus, herpes simplex, mycoplasma, and chlamydia); no history of bipolar affective disorder, schizophrenia, or related psychotic disorders; no reported smoking or alcohol consumption; and no mental retardation.	*DSM-IV* (MDD)[c,e]	66 (36/30)	PTB: 8.45 (0.44-163.53); LBW: 4.68 (0.52-42.46)[f]; GA: −1.03 wks (−1.78 to −0.28); BW: −409 g (−605 to −213)	4	No
Studies not included in any of our meta-analyses						
Steer et al,[40] 1992 (United States)	Inclusion: adolescent gravidas included if they were primigravidas, age 12-15 y, or multi-gravidas <17 y, with a first pregnancy between ages 12 and 15 y; adult gravidas were ages 18-29 at first pregnancy, and thus unexposed to an early adolescent pregnancy. Exclusion: history of nonobstetric, chronic disease (eg, insulin-dependent diabetes or systemic lupus erythematosus); drug or alcohol abuse; and history of psychiatric illness.	BDI (none)	712 (NR/NR)	PTB: 1.06 (1.01-1.10)[q]; PTB (adj): 1.06 (1.01-1.11)[q]; LBW: 1.07 (1.02-1.11)[q]; LBW (adj): 1.07 (1.02-1.12)[q]; SGA: 1.05 (1.01-1.11)[q]; SGA (adj): 1.05 (1.01-1.11)[q]	6	NR
Chung et al,[41] 2001 (China)	Exclusion: women were not ethnically Chinese or were leaving Hong Kong within 12 mo of delivery; participants with no labor (eg, elective cesarean section) because their obstetric outcomes were substantially confounded by the conditions that led to no labor; and lack of informed consent.	BDI (≥15)	642 (103/539)	PTB (adj RR): 0.23 (0.03 to 1.90); LBW (adj RR): 1.60 (0.69-3.72); NICU (adj RR): 2.18 (1.02 to 4.66)	6	No
Salisbury et al,[39] 2011 (United States)	Inclusion: Women aged 18-40 y; 23-36 wk gestation; singleton pregnancy; no prenatal illicit drug use; no hypertension or diabetes; alcohol use <0.5 drinks/d; and <10 cigarettes/d during pregnancy. Exclusion: Women taking US FDA class D or X medications; women who took benzodiazepines in the third trimester; infants born before 37 wk; infants with abnormalities or serious health conditions; and infants unable to be examined within 21 d of birth.	*DSM-IV-R* (MDD)	76 (20/56)	GA: 0.18 weeks (−0.40 to 0.76)[p]; BW: −86.87 g (−329.16 to 155.42)[p]	4	Yes
Broekman et al,[38] 2013 (Singapore)	Inclusion: Chinese, Malay, or Indian ethnicity with homogeneous parental ethnic background; Singaporean citizens or permanent residents intending to deliver in the study hospitals and reside in Singapore for the next 5 y; and women who delivered term infants with gestational age 37- 40 wk. Exclusion: women with major medical complications and complicated obstetric complications (stillbirths, IVF treatment, multiple births) and women taking psychotropic medications.	EPDS (none)	946 (NR)	BW (adjusted linear regression): For each SD increase in the EPDS score (4.47) to birth weight was reduced by 0.55 g (95% CI −27.1 to 28.2)	6	No

(continued)

Table 1. Characteristics of Studies Included (continued)

Source (Country)	Inclusion and Exclusion Criteria	Measure of Depression (Criterion)	Sample Size (Depressed/ Nondepressed), No.	Outcomes: OR/MD (95%CI)[a]	QAT	Conflicts of Interest
Kaihola et al,[42] 2015 (Sweden)	Inclusion: women of Western European descent, normal pregnancies, normal deliveries, and healthy offspring (no diagnoses and no admittance to neonatal care). Exclusion: inability to adequately communicate in Swedish; women whose personal data were confidential; women with pathologic pregnancies as diagnosed by routine ultrasonography; women younger than 18 y; smoking or alcohol use during pregnancy; any daily use of prescribed drugs during pregnancy; any other chronic conditions or diseases; gestational age <35 wk; and maternal age <18 or >42 y.	EPDS (≥13)	24 (12/12)	GA: −0.50 weeks (−1.40 to 0.40)[p]; BW: 195 g (−124 to 514)[p]	7	No

Abbreviations: Adj, adjusted; BDI, Beck Depression Inventory; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BSI, Brief Symptom Inventory (6-item depression scale); BW, birth weight (g); CES-D, Center for Epidemiologic Studies Depression scale; EPDS, Edinburgh Postnatal Depression Scale; FDA, Food and Drug Administration; GA, gestational age (weeks); HIV, human immunodeficiency virus; *ICD-10, International Classification of Diseases, Tenth Revision*; LBW, low birth weight (<2500 g); MD, mean difference; MDD, major depressive disorder; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; PHQ-9, Patient Health Questionnaire-9; PRIME-MD, primary care evaluation of mental disorders; PTB, preterm birth (<37 weeks); QAT, Quality Assessment Tool score; RR, risk ratio; SGA, small for gestational age; SES, socioeconomic status; SSRI, selective serotonin reuptake inhibitor.

[a] Mean difference and the 95% CI are given for gestational age and birth weight.

[b] Included in the subgroup analysis by assessment of depression: self-administered questionnaire.

[c] Included in the subgroup analysis by assessment of depression: clinical diagnosis or interview.

[d] Included in the subgroup analysis by depression severity: moderate depression.

[e] Included in the subgroup analysis by depression severity: severe depression.

[f] Included in the subgroup analysis by infants: not limited to term infants.

[g] Although the study states that mothers who gave birth prematurely were excluded, the authors did report that 8 infants (3%) (4 of 160 from the depressed group and 4 of 160 from the nondepressed group) were born prematurely and excluded prior to assessment of LBW.

[h] Included in the subgroup analysis by infants: limited to term infants.

[i] Because evidence of psychiatric medication use was found in the subgroup with medically indicated preterm delivery, only the data reported for spontaneous PTB was used.

[j] Excluding antidepressant users (1.5%) or multiple pregnancies from their analysis "did not change the results" (personal communication, December 17, 2015). The effect of this study was assessed in sensitivity analyses.

[k] Continuous and partial depression were combined.

[l] Excluding women using antidepressants during pregnancy (1%) did not alter the associations. The effect of this study was assessed in sensitivity analyses.

[m] Results after excluding psychotropic medication users kindly facilitated by authors (personal communication, May 21, 2015).

[n] Moderate depression defined as women who did not self-identify as having a history of depression but scored 16 or more on the CES-D.

[o] Severe depression defined as women who self-reported a history of depression (checked yes when asked if they currently had depression) and also scored 16 or more points on the CES-D.

[p] These results were not pooled in a meta-analysis with the rest of the studies because the study was limited to term infants only.

[q] The ORs represent the increase for each point increase in BDI total score results for adults (data for adolescents also reported in original article).

Bindt, 2013, adjusted for SES, maternal age, country, and child sex. Broekman, 2013, adjusted for smoking, pregnancy complications (hypertension history during pregnancy and diabetes history during pregnancy), household income, maternal age, ethnicity, alcohol, and maternal height. Chang, 2014, adjusted for smoking, prepregnancy BMI, alcohol, gestational age, neonate sex, and delivery by caesarean section. Chung, 2001, adjusted for pregnancy complications, maternal age, parity, gestation, past psychiatric history, male fetus, and actual birth weight, low birth weight, induced labor, labor augmentation, fetal presentation, and previous caesarean section. Gavin, 2009, adjusted for smoking, BMI, maternal age (modeled as a dichotomous variable), parity (no previous live births, 1 or more births), ethnicity, and Medicaid status. Hodjkinson, 2010, adjusted for maternal age, completed prenatal appointments, and gestational age. Liu, 2012, adjusted for smoking, education, parity, delivery mode, PTB, and folic acid use. Marroun, 2012, adjusted for smoking, BMI, maternal age, parity, ethnicity, alcohol, sex of the child, maternal education, maternal benzodiazepine use, and gestational age. Rahman, 2007, adjusted for relative poverty, parity, low BMI at 8 weeks postnatal, living in a nuclear family, maternal empowerment, and at least 1 antenatal consultation. Steer, 1992, adjusted for smoking, prepregnancy BMI, parity, race/ethnicity, previous PTB/LBW/intrauterine growth restriction, and inadequate weight gain.

Table 2. Results of the Meta-analyses of Our Primary and Secondary Outcomes

Outcomes	No. of Studies	No. of Women Included	Crude OR/MD (95% CI)	*P* Value	I^2, %
Primary outcomes					
PTB, wk					
<37	14	21 048	1.56 (1.25 to 1.94)[a]	<.001[a]	39
<32	No study reported data				
LBW (<2500 g)	8	3262	1.96 (1.24 to 3.10)[a]	.004[a]	48
SGA (<10%)	1	4044	1.37 (1.10 to 1.70)[a]	.005[a]	NA
LGA (>90%)	No study reported data				
NICU admission	2	200	1.12 (0.40 to 3.15)	.83	0
Secondary outcomes					
Birth weight					
<3%	No study reported data				
<5%	No study reported data				
>95%	No study reported data				
>97%	No study reported data				
>4000 g	No study reported data				
>4500 g	1	973	0.64 (0.18 to 2.29)	.49	NA
Gestational age, wk	7	12 863	−0.15 (−0.41 to 0.11)	.25	70
Birth weight, g	8	13 030	−109 (−195 to -23)[a]	.01	77

Abbreviations: LBW, low birth weight; LGA, large for gestational age (above the 90th percentile for the gestational age); MD, mean difference; NA, not applicable; NICU, neonatal intensive care unit; OR, odds ratio; PTB, preterm birth; SGA , small for gestational age (below the 10th percentile for gestational age).

[a] Statistically significant result.

One study[30] applied the *DSM-IV* criteria for depression retrospectively after delivery. Repeating the analyses excluding this study yielded almost identical results for almost all outcomes and subgroup analyses. The only outcome where the results were not almost identical was in the subgroup analysis for low birth weight by study quality, in which the pooled effect size of subgroup with low quality changed to an OR of 0.63 (95% CI, 0.29-1.34), a statistically significant difference (*P* = .001) from the high or acceptable quality group (OR, 2.39; 95% CI, 1.72-3.30).

Two studies[25,31] included a small proportion of antidepressant users (and multiple gestations in 1 of them[25]), although their authors reported no changes after excluding these cases. Excluding these studies from our analyses yielded similar results (not shown).

Discussion

Summary of the Findings

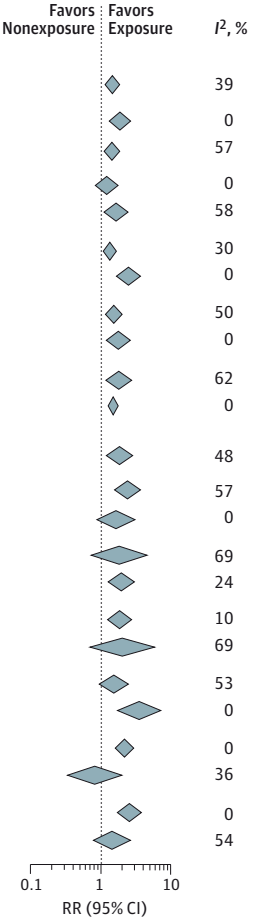
In our systematic review, we found that pregnant women with depression who were not receiving any treatment for their depression had significantly increased infant risks compared with pregnant women without depression, specifically with regard to preterm birth and small infant size (whether defined as low birth weight overall or restricted to term infants or birth weight <10%). We also found a trend toward higher risks with more severe depression. The odds of preterm birth in studies with authors reporting conflicts of interest (ie, received pharmaceutical support) were significantly higher than in studies not reporting such conflicts. This difference was not explained by either differences in depression severity or study quality and remains to be fully understood.

We had hypothesized that we would find lower risks of preterm birth and small infant size than existing systematic reviews, but this generally was not the case (OR, 1.56; 95% CI, 1.25-1.94 and OR, 1.96; 95% CI, 1.24-3.11; respectively). Previous systematic reviews found that depression treated with antidepressants was associated with significantly increased risks of preterm birth (ORs ranging from 1.44; 95% CI, 1.34-1.56 to 1.69; 95% CI, 1.52-1.88)[11-13] and low birth weight (OR, 1.44; 95% CI, 1.34-1.56).[11] The 2 other existing systematic reviews on depression,[3,4] which included studies potentially confounded by antidepressant use (because in these primary studies, women taking antidepressants were not excluded), found ORs ranging from 1.13 to 1.37 for preterm birth and from 1.18 to 1.21 for low birth weight. However, despite rigorously excluding the potential confounding effect of antidepressant use, we did not find lower risks of either preterm birth or low birth weight. This stands in direct contrast to what is, to our knowledge, the only previous systematic review attempting to examine this in a subgroup analysis of studies of women with no or short exposures to antidepressants and that found no significant increase in either preterm birth or low birth weight.[3] This might have inadvertently conveyed a message that not using antidepressant medications could remove these risks. We explored this contradiction, and it could not be attributed to the newer studies published after the search dates of the previous systematic reviews[3,4] (2010) because a lower pooled effect was seen in the more recent studies.

Our results highlight the risks of untreated depression during pregnancy, although they cannot be used as an argument in favor of antidepressant use because evidence shows that women treated with antidepressants have risks of similar magnitude. Nonpharmacological therapies might be more acceptable to women, but there is still a lack of evidence regarding

Figure 2. Results of Subgroup Analyses for Preterm Birth and Low Birth Weight

Variables	Groups	No. of Studies	No. of Women Included	Crude OR (95% CI)	*P* Value	I^2, %
Primary outcomes						
Preterm birth	All studies	14	21 048	1.56 (1.25-1.94)	–	39
Assessment of depression	Clinical diagnostic or interview	7	2104	1.91 (1.35-2.69)	.23	0
	Self-administered questionnaire	7	18 974	1.45 (1.09-1.92)		57
Depression severity	Moderate	3	4474	1.30 (0.94-1.82)	.36	0
	Severe	8	7830	1.66 (1.11-2.49)		58
Conflicts of interest	Not reported or stated none	9	19 537	1.34 (1.08-1.66)[a]	.006[c]	30
	Conflicts declared	5	1511	2.50 (1.70-3.67)[b]		0
Quality assessment	High or acceptable (≥5 points)	9	18 962	1.50 (1.15-1.95)	.40	50
	Low (≤4 points)	5	2086	1.83 (1.25-1.94)		0
Year of publication	Before 2010	8	5407	1.85 (1.17-2.93)	.35	62
	After 2010	6	15 641	1.46 (1.21-1.76)		0
Low birth weight (<2.5 kg)	All studies	8	3262	1.96 (1.24-3.10)	–	48
Infants included	Not limited to term infants	6	2305	1.72 (0.88-3.37)	.23	57
	Limited to term infants only	2	981	2.54 (1.59-4.09)		0
Assessment of depression	Clinical diagnostic or interview	4	762	1.94 (0.71-5.32)	.89	69
	Self-administered questionnaire	4	2524	2.09 (1.28-3.40)		24
Depression severity	Moderate	2	1220	1.98 (1.30-3.02)	.92	10
	Severe	4	1216	2.10 (0.67-6.63)		69
Conflicts of interest	Not reported or stated none	6	3087	1.66 (0.98-2.79)[d]	.09[e]	53
	Conflicts declared	2	199	3.76 (1.69-8.37)		0
Quality assessment	High or acceptable (≥5 points)	5	2177	2.39 (1.72-3.30)	.06	0
	Low (≤4 points)	3	1109	0.89 (0.33-2.35)		36
Year of publication	Before 2010	3	489	2.79 (1.78-4.38)	.11	0
	After 2010	5	2773	1.45 (0.74-2.83)		54



OR indicates odds ratio; RR, relative risk.

[a] After removing 3 low-quality studies: OR, 1.34; 95% CI, 1.04-1.72.

[b] After removing 2 low-quality studies: OR, 2.66; 95% CI, 1.50-4.73.

[c] After removing 5 low-quality studies: *P* = .03.

[d] After removing 3 low-quality studies: OR, 2.18; 95% CI, 1.53-3.11.

[e] After removing 3 low-quality studies: *P* = .22.

their effect on preterm birth and low birth weight.[44-46] However, these therapies might not be an effective option for treating more severe depression, which in turn appears to have higher risks than more moderate cases in our subgroup analyses.

Strengths and Limitations

The main strength of our systematic review was its strict inclusion criteria to make sure that we obtained results that were not confounded by the use of antidepressant medications. Further strengths include an exhaustive literature search, which allowed us to include several studies not included in previous systematic reviews; the assessment of the risk of low birth weight separately in studies limiting and not limiting their sample to term infants only, which is more clinically meaningful because this is approximately the equivalent of being small for gestational age; and a consideration of depression severity. Finally, we are not aware of any other systematic review on the topic that explored the effect of conflicts of interest. We are unable to explain why they seem to affect preterm birth but not low birth weight (after excluding low-quality studies). However, these are preliminary findings that need further exploration.

Our study has several limitations. First, the necessarily strict exclusion criteria might have filtered out studies with more detailed reporting or an assessment of certain exclusion variables that might be present but not measured or reported in other included studies. Second, more than half of the included studies lacked a rigorous diagnostic assessment of depression, using only screening tools instead. Although we found no significant differences between studies that used a clinical diagnosis and those that did not, it is not possible to know whether the symptoms measured constitute a major depressive episode or the trajectory of the symptoms. Third, there is no consensus on the best method to assess study quality in observational studies. We used a modified version of a previously validated and frequently used scale, the Newcastle-Ottawa Scale.[17] Fourth, journals' requirements for reporting conflicts of interest have changed over time and vary widely. Therefore, the definitions used in this review (which only took

into account the conflicts and affiliations reported in the publication) are likely to be of limited precision. Finally, there were several other important confounding variables whose effects could not be taken into account owing to a lack of reporting of adjusted data in most studies.

Conclusions

Taking a rigorous approach to understand the effect of untreated depression on pregnancy, we found increased risks of preterm birth and small infant size, in contrast to what is, to our knowledge, the only previous systematic review exploring untreated depression in a subgroup analysis, which found no increased risks. Moreover, we excluded the potential effect of comorbid anxiety and explored the potential effect of conflicts of interest. Our findings have important clinical implications for pregnant women and health care professionals because they suggest the need for more surveillance for preterm birth and small infant size, key perinatal outcomes in women with untreated depression. Our results also suggest methodological directions that future systematic reviews could take including examining the effect of reported conflicts of interest and potential confounding variables.

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