A Meta-analysis of Depression During Pregnancy and the Risk of Preterm Birth, Low Birth Weight, and Intrauterine Growth Restriction

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Context: Maternal depressive symptoms during pregnancy have been reported in some, but not all, studies to be associated with an increased risk of preterm birth (PTB), low birth weight (LBW), and intrauterine growth restriction (IUGR).

Objective: To estimate the risk of PTB, LBW, and IUGR associated with antenatal depression.

Data Sources and Study Selection: We searched for English-language and non–English-language articles via the MEDLINE, PsycINFO, CINAHL, Social Work Abstracts, Social Services Abstracts, and Dissertation Abstracts International databases (January 1980 through December 2009). We aimed to include prospective studies reporting data on antenatal depression and at least 1 adverse birth outcome: PTB (<37 weeks' gestation), LBW (<2500 g), or IUGR (<10th percentile for gestational age). Of 862 reviewed studies, 29 US-published and non–US-published studies met the selection criteria.

Data Extraction: Information was extracted on study characteristics, antenatal depression measurement, and other biopsychosocial risk factors and was reviewed twice to minimize error.

Data Synthesis: Pooled relative risks (RRs) for the effect of antenatal depression on each birth outcome were calculated using random-effects methods. In studies of PTB, LBW, and IUGR that used a categorical depression measure, pooled effect sizes were significantly larger (pooled RR [95% confidence interval] = 1.39 [1.19-1.61], 1.49 [1.25-1.77], and 1.45 [1.05-2.02], respectively) compared with studies that used a continuous depression measure (1.03 [1.00-1.06], 1.04 [0.99-1.09], and 1.02 [1.00-1.04], respectively). The estimates of risk for categorically defined antenatal depression and PTB and LBW remained significant when the trim-and-fill procedure was used to correct for publication bias. The risk of LBW associated with antenatal depression was significantly larger in developing countries (RR = 2.05; 95% confidence interval, 1.43-2.93) compared with the United States (RR = 1.10; 95% confidence interval, 1.01-1.21) or European social democracies (RR = 1.16; 95% confidence interval, 0.92-1.47). Categorically defined antenatal depression tended to be associated with an increased risk of PTB among women of lower socioeconomic status in the United States.

Conclusions: Women with depression during pregnancy are at increased risk for PTB and LBW, although the magnitude of the effect varies as a function of depression measurement, country location, and US socioeconomic status. An important implication of these findings is that antenatal depression should be identified through universal screening and treated.

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PRETERM BIRTH (PTB), LOW birth weight (LBW), and intrauterine growth restriction (IUGR) are the leading causes of neonatal, infant, and childhood morbidity, mortality, and neurodevelopmental impairments and disabilities worldwide.[1-5] Maternal depression during pregnancy has begun to be recognized as a factor that may adversely alter pregnancy outcomes.[6-8] Depression also has been linked to known risk factors for adverse pregnancy outcomes such as smoking,[9,10] substance abuse,[11] hypertension,[12,13] preeclampsia,[14,15] and gestational diabetes.[16,17] Recent estimates of the prevalence of major depression during pregnancy show that from 8.3%[18] to 12.7%[19] of US women experience this condition. Moreover, many community-based studies have indicated that poor urban women from minority backgrounds[20-22] are at least twice as likely as middle-class women[23-25] to meet diagnostic criteria for major and minor depression during pregnancy and the postpartum period (20%-25% vs 9%-13%, respectively). These findings are congruent with epidemiological data showing higher rates of depression in poor young women[26] and with data on prevalence rates of perinatal depression for women in developing countries.[27-29]

Research findings during the last decades on the links between antenatal depression and PTB, LBW, and IUGR have

revealed a relatively inconsistent and inconclusive picture.[30] Some evidence indicates that depression during pregnancy may be significantly related to PTB,[31,32] LBW,[33,34] and IUGR,[35] whereas other studies have reported no direct association.[36-38] Reasons for these contradictory results are most likely related to differences in (1) study design, methods, sample sizes, and the timing, frequency, and type of antenatal depression measurement; (2) misclassification bias with respect to depression or birth outcomes; (3) the populations studied; and (4) the extent to which studies control for confounding factors of PTB, LBW, or IUGR such as socioeconomic status (SES), race/ethnicity, antidepressant use during pregnancy, smoking, substance abuse, previous preterm birth, or obstetric/medical complications.

We therefore conducted a meta-analysis of all available studies to quantify the strength of the relationships between depression during pregnancy and PTB, LBW, and IUGR and examined potential moderators of negative birth outcomes, such as categorical vs continuous measurement of antenatal depression, race or SES of the sample, and country location of the study (ie, whether the study was from the United States, a developing country, or a European social democracy). A social democracy was defined broadly as a democratic welfare state that incorporates both capitalist and socialist practices and provides universal access to health care.[39,40] We expected that women with antenatal depression who lived in developing countries, relative to their peers in the United States or social democracies, would show greater disparities in the likelihood of PTB, LBW, and IUGR because of their more limited access to adequate prenatal, health, and mental health care.[41] Similarly, we expected that socioeconomically disadvantaged, depressed, pregnant women within the United States would show a higher probability of negative birth outcomes compared with their middle- or upper-class counterparts because they have less access to ongoing adequate health and mental health services.[42-44] Finally, given that categorical measures of antenatal depression more closely approximate clinical diagnoses of major depression than do continuous measures, we hypothesized that the former would show a stronger association with adverse birth outcomes.

METHODS

The methods for conducting and reporting the meta-analysis followed state-of-the-art guidelines.[45-47]

SEARCH STRATEGY AND STUDY SELECTION

Study investigators (N.K.G., A.R.G., J.L.M., and W.J.K.) retrieved potential studies based on a literature search of English-language and non–English-language articles from January 1980 through December 2009 using the MEDLINE, PsycINFO, CINAHL, Social Work Abstracts, Social Services Abstracts, and Dissertation Abstracts International databases. The time frame ensured that the applied standards for the categorical measures of depression were consistent with the *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition)[48] or later criteria. We used the following keywords and their combinations: *depression*, *depressive symptoms*, *pregnancy*, *prematurity*, *antenatal*, *prenatal*, *birthweight*, *birth weight*, *preterm birth*, *gestational age*, *fetal growth restriction*, *intrauterine growth restriction,* and *small-for-gestational age*. Relevant articles were also identified through references of retrieved articles and contact with prominent investigators in the field.

Published and unpublished English-language and non–English-language observational studies were included in the meta-analysis if they assessed depressive symptoms or unipolar depression diagnoses by means of a depression-screening questionnaire or structured psychiatric interview at 1 or more times during pregnancy. Studies were included if they reported sufficient data to calculate an effect size between depressive symptoms/diagnoses and at least 1 adverse birth outcome: PTB, LBW, or IUGR. Studies were excluded if they used a retrospective design to measure antenatal depression, did not use a prospective or longitudinal design, combined unipolar and bipolar depression diagnoses to measure antenatal depression,[49] or reported the same data on antenatal depression and PTB, LBW, or IUGR from a previous article. Of 862 reviewed studies, 29 published studies met the inclusion criteria.

DATA EXTRACTION

Adverse Birth Outcomes

Two investigators (one of whom was N.K.G.) reviewed all the studies. Standardized data collection forms were developed a priori for data extraction.[47] In cases of disagreement in coding, we reached agreement through consensus. The mean percentage of disagreement in coding across all 29 studies included in the meta-analysis was 2.1% (95% confidence interval [CI], 1.6%-2.6%). When a report did not contain sufficient data to calculate an effect size, we contacted the primary author up to 3 times to obtain this information. Six of 9 authors contacted provided the requested data. The following types of studies[31-38,50-70](**Table 1**) were included in the meta-analysis: PTB (n=20), LBW (n=11), and IUGR (n=12). The latter included studies examining the keyword topics *fetal growth restriction* or *small-for-gestational age*. We extracted information from each study pertinent to each adverse outcome using the authors' definition of clinical significance. Typically, PTB was defined as less than 37 weeks' gestation, LBW was defined as less than 2500 g, and IUGR was defined as a fetal weight lower than the 10th percentile for gestational age as determined through an ultrasound.[80,81] Alternatively, IUGR was defined in some studies as LBW controlling for gestational age,[56,60,64] a fetal weight lower than the 15th percentile for gestational age,[70] or a fetal weight lower than the 10th customized percentile.[63]

Study Characteristics and Antenatal Depression Measures

Information extracted from each study included year of publication, mean maternal age, mean gestational age at first depression assessment, timing and frequency of antenatal depression measurement, country location, country rating of inequality of income distribution (ie, Gini coefficient[82]), sample size, and the predominant (ie, >60% of the participants) race/ethnicity, SES, parity, marital status, educational level, and work status of the sample. We also recorded the type of antenatal depression measure used (ie, depression-screening questionnaire or structured psychiatric interview).

Other Biopsychosocial Risk Factors for Adverse Birth Outcomes

We coded the extent to which each study controlled for a group of variables observed in the literature to be risk factors for each

Table 1. Characteristics of Studies Included in the Meta-analysis[a]

Source	Country/ Gini Coefficient	Sample Size	Sample SES	Race/ Ethnicity	Depression Measure	Assessment Times/ Trimesters	RR (95% CI)			Control Variables	Quality Rating
							PTB	LBW	IUGR		
Andersson et al,[36] 2004	Sweden/25.0	1465	Mixed	White	PRIME-MD[71]	Once/second	1.19 (0.59-2.40)	1.19 (0.40-3.56)	. . .	Yes	12
Berle et al,[50] 2005	Norway/25.8	680	Mixed	White	HADS-D[72]	Once/third	. . .	1.78 (0.23-13.89)	. . .	No	8
Chung et al,[51] 2001	Hong Kong/43.4	642	Mixed	Chinese	BDI[73]	Twice/first, second, and third	. . .	. . .	1.60 (0.69-3.72)	Yes	8
Copper et al,[37] 1996	United States/40.8	2593	Lower	Black	CES-D[74]	Once/second and third	1.03 (0.99-1.06)	1.02 (1.00-1.04)	100 (0.97-1.03)	Yes	10
Dayan et al,[52] 1999	France/32.7	392	Mixed	White	EPDS[75]	Once/second	2.10 (1.10-4.10)[b]	. . .	. . .	No	4
Dayan et al,[31] 2006	France/32.7	641	Mixed	White	EPDS[75]	Once/second	4.90 (1.60-14.90)[c]	. . .	. . .	Yes	10
Diego et al,[53] 2009	United States/40.8	79	Mixed	Mixed	SCID[76]	Once/second	2.61 (0.73-9.33)	4.75 (0.94-24.00)	11.28 (0.64-197.35)	No	4
Dole et al,[54] 2003	United States/40.8	1962	Mixed	Black/white	CES-D[74]	Once/second and third	1.12 (0.91-1.38)	. . .	. . .	Yes	11
Elsenbruch et al,[55] 2007	Germany/28.3	896	Mixed	White	CES-D[74]	Once/first	. . .	1.16 (0.91-1.47)	. . .	No	8
Evans et al,[56] 2007	England/30.0	10 967	Mixed	White	EPDS[75]	Twice/second and third	. . .	. . .	1.29 (0.87-1.91)	Yes	9
Gavin et al,[57] 2009	United States/40.8	3019	Mixed	White	CES-D[74]	Once/second	1.26 (0.61-2.61)	. . .	. . .	Yes	10
Goldenberg et al,[70] 1991	United States/40.8	1545	Lower	Black	CES-D[74]	Once/second	. . .	. . .	2.00 (0.94-4.26)	Yes	8
Haas et al,[58] 2005	United States/40.8	1619	Mixed	Mixed	CES-D[74]	Twice/second and third	1.05 (0.66-1.67)	. . .	. . .	Yes	11
Hedegaard et al,[59] 1993	Denmark/24.7	5872	Mixed	White	GHQ[77]	Twice/second and third	1.33 (1.10-1.60)[c]	. . .	. . .	Yes	11
Hoffman and Hatch,[60] 2000	United States/40.8	666	Mixed	White	CES-D[74]	3/Second and third	1.07 (0.87-1.31)	. . .	0.69 (0.23-2.07)	Yes	10
Jesse et al,[61] 2003	United States/40.8	119	Lower	White	2-Item validated screening tool	Once/second	3.19 (1.08-9.44)[b]	. . .	. . .	Yes	5
Li et al,[62] 2009	United States/40.8	791	Mixed	Mixed	CES-D[74]	Once/first and second	1.60 (0.71-3.63)	. . .	. . .	Yes	8
Neggers et al,[33] 2006	United States/40.8	3149	Lower	Black	CES-D[74]	Once/second	1.30 (1.03-1.64)[b]	1.40 (1.09-1.79)[c]	0.99 (0.75-1.31)	Yes	10
Nordentoft et al,[38] 1996	Denmark/24.7	2432	Mixed	White	GHQ[77]	Once/second	1.01 (0.98-1.05)	. . .	1.01 (0.97-1.05)	No	9
Orr et al,[32] 2002	United States/40.8	1399	Lower	Black	CES-D[74]	Once/first and second	1.96 (1.04-3.71)[b]	. . .	. . .	Yes	10
Paarlberg et al,[63] 1999	The Netherlands/ 30.9	396	Mixed	White	HSCL[78]	3/First, second, and third	. . .	. . .	1.03 (0.98-1.08)	Yes	9
Patel and Prince,[64] 2006	India/32.5	245	Lower	Indian	GHQ[77]	Once/third	. . .	. . .	3.49 (1.48-8.23)[c]	Yes	8
Perkin et al,[65] 1993	United States/40.8	1515	Lower	White	GHQ[77]	3/First, second, and third	1.28 (0.95-1.73)	. . .	. . .	Yes	10
Rahman et al,[34] 2004	Pakistan/30.6	265	Lower	Pakistani	SCAN[79]	Once/third	. . .	2.10 (1.32-3.35)[c]	. . .	Yes	9
Rondó et al,[66] 2003	Brazil/54.0	865	Lower	Brazilian	GHQ[77]	3/Second and third	2.32 (1.18-4.58)[b]	1.97 (1.12-3.47)[b]	1.58 (0.84-2.96)	Yes	9
Steer et al,[35] 1992	United States/40.8	389[d]	Lower	Black	BDI[73]	Once/third	1.06 (1.01-1.11)[b]	1.07 (1.02-1.12)[c]	1.05 (1.00-1.11)[b]	Yes	5
Suri et al,[67] 2007	United States/40.8	90	Mixed	. . .	SCID[76]	Once/first, second, and third	1.41 (0.26-7.73)	1.86 (0.18-19.45)	. . .	No	6
Wisner et al,[68] 2009	United States/40.8	238	Mixed	Mixed	SCID[76]	Continuous/first, second, and third	2.62 (1.09-6.29)[b]	. . .	. . .	Yes	7
Zimmer-Gembeck and Helfand,[69] 1996	United States/40.8	3073	Lower	Mixed	Nonvalidated	Once/first and second	. . .	1.65 (1.12-2.42)[b]	. . .	Yes	8

Abbreviations: BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression scale; CI, confidence interval; ellipses, not available; EPDS, Edinburgh Depression Scale; GHQ, General Health Questionnaire; HADS-D, Hospital Anxiety and Depression Scale–Depression; HSCL, Hopkins Symptom Checklist; IUGR, intrauterine growth restriction; LBW, low birth weight; PRIME-MD, Primary Care Evaluation of Mental Disorders; PTB, preterm birth; RR, relative risk; SCAN, Schedules for Clinical Assessment in Neuropsychiatry; SCID, Structured Clinical Interview for *DSM-IV*; SES, socioeconomic status (as defined by income level, educational level, or type of insurance).

[a] Each row in this table describes an independent study of antenatal depression and adverse birth outcomes. Gini coefficient refers to the numerical coefficient indicating the degree of income inequality in each country (0 = perfect equality; 100 = perfect inequality). Effect sizes are represented by RRs and 95% CIs. Control variables include (1) demographic (age, SES, parity, race/ethnicity, educational level, marital status, work status, and sex of infant); (2) psychiatric (anxiety, stress, alcohol and substance abuse, selective serotonin reuptake inhibitor use, smoking, and previous depression or psychiatric illness); and (3) obstetric/medical (gestational age; prepregnancy body mass index; previous PTB, LBW, or IUGR; previous or current hypertension, diabetes, or preeclampsia; or other obstetric complications). Study quality ratings range from 0 to 12.

[b] $P < .05$.

[c] $P < .01$.

[d] Only the adult (≥18 years) sample was included in the meta-analysis.

adverse birth outcome, including demographic variables such as maternal age, SES, parity, race/ethnicity, educational level, marital status, work status, and sex of the infant; psychiatric variables such as antenatal anxiety, stress, drug/alcohol use, antidepressant medication use, and smoking; and obstetric/medical variables such as history of PTB or LBW, current gestational diabetes or preeclampsia, prepregnancy maternal weight or body mass index, and gestational age. We designated the following as key control variables because they have shown the strongest and most consistent associations with adverse birth outcomes in the literature: (1) smoking or substance abuse,[10,11,83-85] (2) race/ethnicity or SES,[42,60,86] (3) previous PTB,[87-89] and (4) selective serotonin reuptake inhibitor (SSRI) antidepressant use.[90-94]

Methodologic Quality Assessment

Two of the investigators (one of whom was N.K.G.) rated each study on 6 components of methodologic quality, which we developed by modifying the instrument by Downs and Black[95] for randomized controlled trials and observational studies. We used a consensus approach in which any differences were resolved before assigning a final rating (intraclass correlation coefficient, 0.97; 95% CI, 0.93-0.98). The 6 components evaluated (1) the size of the sample, (2) the representativeness of the sample, (3) whether the sample was clearly described, (4) the reliability and validity of the measure used to assess antenatal depression, (5) whether the statistical tests were appropriate and controlled for the key variables described previously, and (6) whether the study response rate (ie, those who declined to enter the study) and attrition rate (ie, those who entered the study but dropped out) were reported and taken into account statistically. The 3 levels of quality for each component (not adequate, somewhat adequate, and adequate) received equal weights in scoring. A composite quality score was created for each study (Table 1), which was a sum of the number of the 6 components rated (total score range, 0-12).

DATA ANALYSIS

The association of antenatal depressive symptoms or diagnoses with each adverse birth outcome was examined using relative risks (RRs). To do this, we considered odds ratios (ORs) as surrogates for RRs because when outcomes undergoing study are relatively uncommon, the relative odds approximate RRs. One study[55] used the correlation coefficient as the measure of effect size between antenatal depression and LBW; in this case, we computed the RR by means of transformation from the Pearson correlation to the standardized mean difference and then from this difference to the log OR.[96] Two studies of PTB[60,62] reported hazard ratios as a measure of association between antenatal depression and time to delivery. Because hazard ratios provide a control for calendar time, we consider an effect size derived from Cox regression as a measure of RR.[97] For each birth outcome, there were a sufficient number of studies to calculate an effect size with a corresponding 95% CI.[98] We weighted the study-specific RR by the inverse of its variance to compute a pooled RR using random-effects models. A 2-tailed $P < .05$ was used to determine statistical significance. Statistical analyses were performed with Comprehensive Meta-analysis version 2.2 (Biostat, Englewood, New Jersey) and SPSS version 17.0 (SPSS Inc, Chicago, Illinois) statistical software.

Heterogeneity of effect size was assessed using the Cochran Q χ^2 statistic ($P \leq .10$) and the I^2 statistic (a transformation of the Cochran Q that indicates the percentage of variation in the effect size estimate attributable to heterogeneity rather than sampling error).[99] A nonsignificant χ^2 statistic suggests that the obtained pooled RR represents a unitary effect and that any variability in effect sizes is caused by random error rather than the influence of other potential moderator variables. For outcomes in which the test of homogeneity of effect sizes was significant, random-effects meta-regression analyses and moderator analyses were conducted to determine whether 6 study characteristics could explain variability across studies: (1) country location: United States, developing country, or social democracy; (2) the country rating of inequality of income distribution (ie, Gini coefficient); (3) sample SES; (4) sample race (eg, black or white), controlling for SES; (5) study methodologic quality; and (6) categorical vs continuous antenatal depression measurement. Sensitivity analyses[100] (known as "leave-one-out") were conducted by iteratively deleting each study and calculating the resulting effect sizes.

We followed a group of a priori decision rules for pooling data from each study. First, we used the most typical cutoff value for the validated depression scale in each study. Second, when the cutoff score was trichotomized, we used the typical cutoff value to determine the mean of the scores for the medium- and high-risk groups to comprise the group with depression. Third, when a study examined a depression-only group and a depression plus antidepressant medication group, we pooled the effect sizes for the 2 groups in the primary analysis. We then conducted sensitivity analyses[100] for the studies that stratified for antidepressant medication use during pregnancy to compare the birth outcomes for depressed women treated and not treated with antidepressants. Fourth, for studies that measured depression more than once at different times or trimesters during pregnancy, we used the mean of the effect sizes in the primary analyses. Fifth, we used both categorical and continuous measures of antenatal depression in the primary analyses and then conducted moderator analyses based on the categorical-continuous distinction. Sixth, in the primary analyses we included 28 studies that used a validated measure of antenatal depression and an additional study that did not report validity or reliability data for its antenatal depression measure.[69] We also conducted sensitivity analyses comparing the birth outcomes for the 28 studies using validated measures with the outcomes for the 29 studies used in the primary analyses.

Publication bias was assessed visually using a funnel plot and quantitatively using an adjusted rank correlation test[101] and a regression procedure to measure funnel plot asymmetry.[102] The trim-and-fill method by Duval and Tweedie[103,104] was used to adjust for potential publication bias. The trim-and-fill method assesses asymmetry in the funnel plot, imputes the number of suspected missing studies, and recalculates the adjusted effect size estimate. The adjusted result can be used as a sensitivity analysis to indicate the extent to which publication bias may affect the pooled estimate.[105]

RESULTS

The study retrieval and selection strategy is illustrated in **Figure 1**. Of 862 citations meeting initial search criteria, 54 articles were retrieved and 3 were identified from the references of the retrieved articles, making a total of 57. Of these, 28 studies were excluded (23 studies met at least 1 of the exclusion criteria, and 5 studies represented duplicate studies in which the same data were reported in a previous article), leaving a total of 29 articles included in the meta-analysis. Table 1 gives the characteristics of the studies included in the meta-analysis.

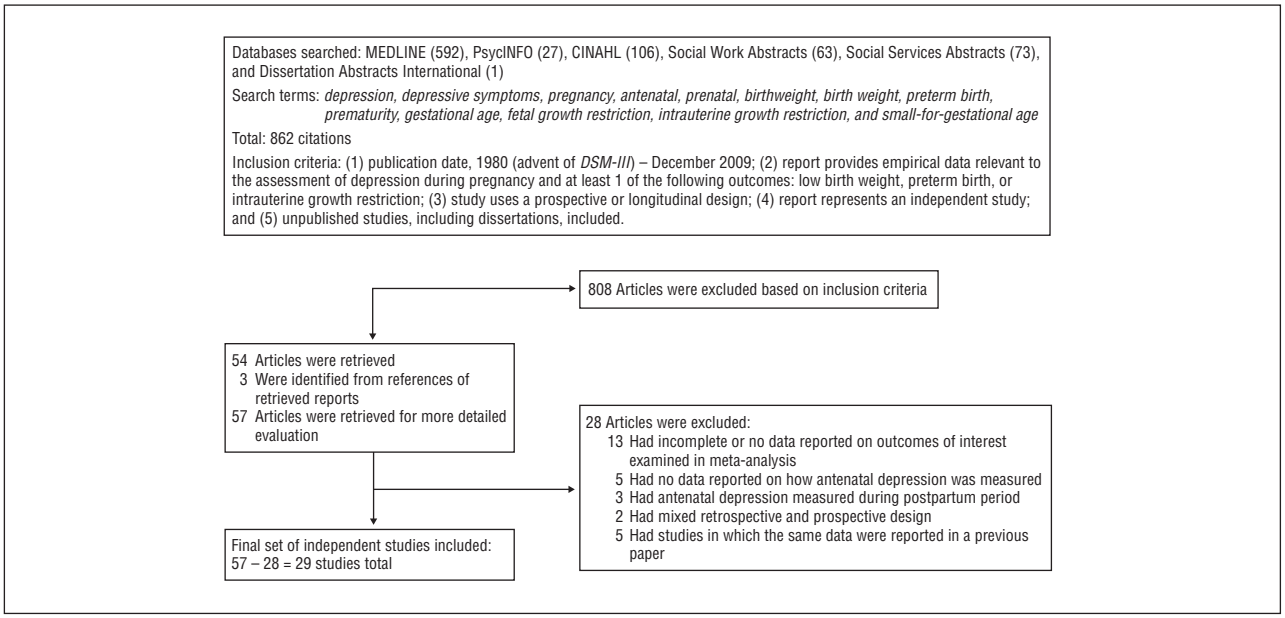

Figure 1. Identification of independent studies for inclusion in meta-analysis (adapted from QUOROM flowchart guidelines[46]).

Table 2. Effect of Antenatal Depression on Outcomes of PTB, LBW, and IUGR

Outcome	No. of Studies	Relative Risk (95% CI)[a]	*P* Value	Heterogeneity		
				Q_{df} Within	*P* Value	Variance Explained, %
PTB	20	1.13 (1.06-1.21)	<.001	49.0_{19}	<.001	61
LBW	11	1.18 (1.07-1.30)	.001	33.8_{10}	<.001	70
IUGR	12	1.03 (0.99-1.08)	.14	22.4_{11}	.02	51

Abbreviations: CI, confidence interval; IUGR, intrauterine growth restriction; LBW, low birth weight; PTB, preterm birth.
[a] Pooled effect size was estimated using the random-effects model.

ANTENATAL DEPRESSION AND RISK OF ADVERSE BIRTH OUTCOMES

Preterm Birth

Twenty studies evaluated the association between antenatal depression and PTB, with RRs ranging from 1.01 to 4.90 (**Table 2**). Eleven of the studies found no significant association. Using the random-effects model, depression during pregnancy was significantly associated with PTB (RR=1.13; 95% CI, 1.06-1.21). Significant heterogeneity across studies was noted (Q_{19}=49.0; $P<.001$; I^2=61%).

Low Birth Weight

Eleven studies evaluated the association between antenatal depression and LBW with RRs ranging from 1.02 to 4.75 (Table 2). Six of the studies found no significant association. The random-effects meta-analysis showed that antenatal depression was significantly associated with LBW (RR=1.18; 95% CI, 1.07-1.30). Significant heterogeneity across studies was found (Q_{10}=33.8; $P<.001$; I^2=70%).

Intrauterine Growth Restriction

Twelve studies evaluated the association between antenatal depression and IUGR, with RRs ranging from 0.69 to 11.28 (Table 2). Only 2 studies reported a significant association. The summary RR calculated from the random-effects model showed that antenatal depression was not significantly associated with IUGR (RR=1.03; 95% CI, 0.99-1.08). Significant heterogeneity across studies was noted (Q_{11}=22.4; P=.02; I^2=51%).

MODERATORS OF OUTCOME

Moderator analyses were conducted to explore sources of heterogeneity (**Table 3**). As expected, studies of PTB, LBW, and IUGR that used a categorical depression predictor yielded larger ($P<.05$ for all) pooled RRs (1.39 [95% CI, 1.19-1.61], 1.49 [1.25-1.77], and 1.45 [1.05-2.02], respectively) than studies that used a continuous depression predictor (1.03 [1.00-1.06], 1.04 [0.99-1.09], and 1.02 [1.00-1.04], respectively). In PTB trials, heterogeneity among studies was reduced by the addition of the depression predictor moderator (categorical: Q_{15}=24.6; P=.06; I^2=39%; continuous: Q_3=4.7; P=.20; I^2=36%).

Table 3. Moderators of Effect of Antenatal Depression on Outcomes of PTB, LBW, and IUGR

Moderator	No. of Studies	Within Group: Relative Risk (95% CI)[a]	Within Group: *P* Value	Within Group: Heterogeneity Q_{df} Within	Within Group: Heterogeneity *P* Value	Within Group: Heterogeneity Variance Explained, %	Effect of Moderator Q_{df} Between	Effect of Moderator *P* Value	Effect of Moderator Variance Explained, %
PTB									
Depression predictor							14.2_1	.001	29
Categorical	16	1.39 (1.19-1.61)	<.001	24.6_{15}	.06	39			
Continuous	4	1.03 (1.00-1.06)	.05	4.7_3	.20	36			
Study location[b]							1.8_1	.18	4
European social democracy	5	1.37 (1.01-1.85)	.04	20.0_4	<.001	80			
United States	14	1.10 (1.03-1.19)	.005	22.2_{13}	.05	41			
Study quality[c]							2.0_1	.15	4
≤6	5	1.70 (0.99-2.92)	.05	10.0_4	.04	60			
>6	15	1.14 (1.06-1.24)	.001	37.4_{14}	.001	63			
Effect size							0.6_1	.45	1
Adjusted	16	1.18 (1.08-1.28)	<.001	38.4_{15}	.001	61			
Unadjusted	4	1.46 (0.84-2.53)	.18	7.0_3	.07	57			
LBW									
Depression predictor							14.6_1	<.001	43
Categorical	9	1.49 (1.25-1.77)	<.001	9.8_8	.28	18			
Continuous	2	1.04 (0.99-1.09)	.10	3.3_1	.07	70			
Study location[d]							10.7_2	.005	32
Developing nation	2	2.05 (1.43-2.93)	<.001	0.0_1	.86	0			
European social democracy	3	1.16 (0.92-1.47)	.20	0.2_2	.92	0			
United States	6	1.10 (1.01-1.21)	.03	18.7_5	.002	73			
Study quality[c]							0.1_1	.78	0
≤6	3	1.59 (0.63-4.00)	.33	3.5_2	.18	42			
>6	8	1.39 (1.11-1.73)	.004	27.7_7	<.001	75			
Effect size							0.17_1	.68	0
Adjusted	7	1.17 (1.06-1.30)	.003	29.0_6	<.001	79			
Unadjusted	4	1.27 (0.88-1.82)	.20	3.1_3	.37	4			
IUGR									
Depression predictor							4.5_1	.04	20
Categorical	8	1.45 (1.05-2.02)	.03	14.0_7	.05	50			
Continuous	4	1.02 (1.00-1.04)	.12	3.7_3	.29	20			
Study location[e]							4.0_2	.14	19
Developing nation	2	2.22 (1.03-4.79)	.04	2.1_1	.14	53			
European social democracy	3	1.02 (0.99-1.05)	.21	1.8_2	.41	0			
United States	6	1.03 (0.96-1.10)	.41	9.6_5	.09	48			
Study quality[c]							0.5_1	.49	2
≤6	2	2.20 (0.26-18.80)	.47	2.6_1	.11	62			
>6	10	1.03 (0.98-1.08)	.30	17.3_9	.04	48			
Effect size							0.4_1	.52	2
Adjusted	10	1.04 (0.99-1.11)	.14	19.4_9	.20	54			
Unadjusted	2	2.17 (0.24-19.60)	.49	2.7_1	.10	63			

Abbreviations: CI, confidence interval; IUGR, intrauterine growth restriction; LBW, low birth weight; PTB, preterm birth.
[a] Pooled effect size was estimated using the random-effects model.
[b] Only 1 study was conducted in a developing nation.
[c] Study quality ratings range from 0 to 12.
[d] Pairwise effect of moderator for LBW: developing nation vs European social democracy, Q_1=7.0, *P*=.01; developing nation vs United States, Q_1=10.7, *P*=.001; European social democracy vs United States, Q_1=0.2, *P*=.68.
[e] Pairwise effect of moderator for IUGR: developing nation vs European social democracy, Q_1=3.9, *P*=.048; developing nation vs United States, Q_1=3.8, *P*=.05; European social democracy vs United States, Q_1=0.0, *P*=.84.

As expected, country location (developing nation, social democracy, or United States) was also a significant moderator of the association between antenatal depression and LBW (Table 3 and **Figure 2**). In developing nations, 2 studies of antenatal depression and LBW yielded a pooled RR of 2.05 (95% CI, 1.43-2.93).[34,66] In studies from social democracies[36,50,55] and the United States,[33,35,37,53,67,69] the resulting summary RRs were 1.16 (95% CI, 0.92-1.47) and 1.10 (95% CI, 1.01-1.21), respectively. Significant heterogeneity was still present in US studies (Q_5=18.7; *P*=.002; I^2=73%). A similar effect (Q_2=7.1; *P*=.03) was found after excluding 2 US studies[35,37] that used a continuous depression predictor, which yielded a pooled RR of 1.50 (95% CI, 1.22-1.84), and that eliminated heterogeneity across US trials (*P*>.45; I^2=0%). Table 3 reveals a similar pattern for studies evaluating the association between antenatal depression and IUGR, with a significant pairwise difference in RR between de-

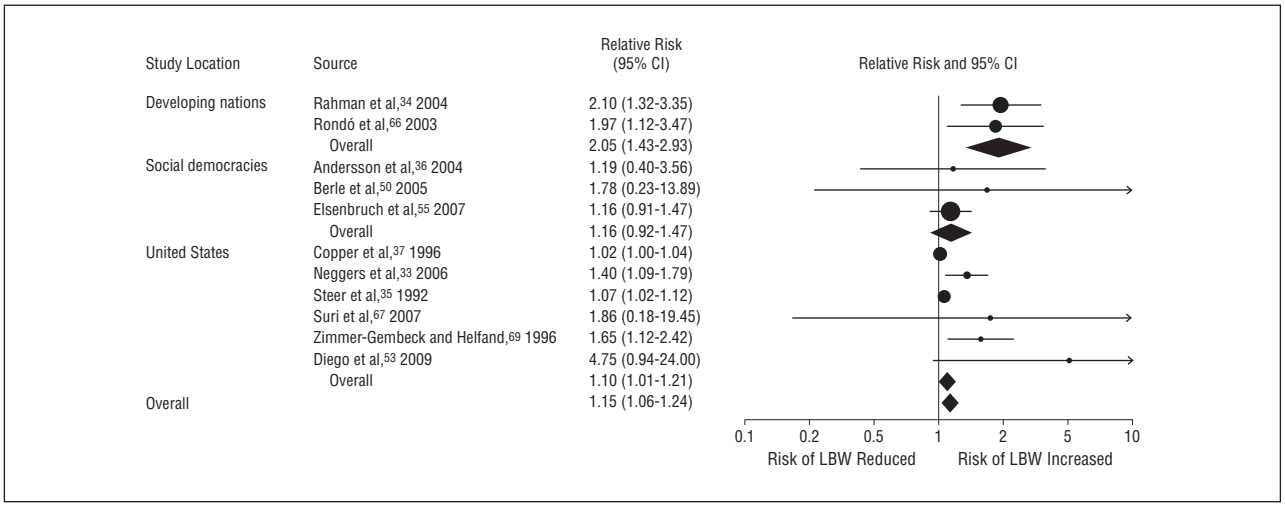

Figure 2. Effect of antenatal depression on the risk of low birth weight (LBW) in developing nations, European social democracies, and the United States. CI indicates confidence interval.

veloping countries and social democracies ($P=.048$) and a near significant pairwise difference in RR between developing countries and the United States ($P=.05$). These data indicate that depressed pregnant women in the developing world are twice as likely to experience IUGR as their European or US counterparts.

Limiting the analysis to the 10 US studies that used a categorically defined depression predictor showed a trend ($Q_1=3.54$; $P=.06$) for antenatal depression to be associated with an increased risk of PTB among women of lower SES (RR=1.69; 95% CI, 1.14-2.50) but not in women of middle- or upper-income status (RR=1.13; 95% CI, 0.99-1.29).

Inequality of income across countries, study quality, type of depression severity measurement, and use of adjusted vs unadjusted effect size estimates were not significant moderators of PTB, LBW, or IUGR. Race was not a significant moderator of PTB in US studies of predominantly low SES populations. Type of IUGR measurement was not a significant moderator of outcome in IUGR studies. In the 5 studies of PTB[31,57,62,67,68] for which stratification by antidepressant medication treatment during pregnancy was possible, the summary RR was comparable for depressed women treated and not treated with antidepressants.

Leave-One-Out Analyses

Sensitivity analyses revealed that no single study unduly influenced the pooled RR estimates of the association between antenatal depression and PTB, LBW, and IUGR (data available on request). In particular, leaving out the 1 study that did not report validity or reliability data for its measure of antenatal depression did not significantly alter the findings observed for LBW in the primary analyses.

Publication Bias

For all 3 outcome measures (PTB, LBW, and IUGR), visual inspection of funnel plots in which each study's effect size was plotted against the standard error showed marked asymmetry, suggesting that small studies with negative results may not have been published. Formal testing using the regression intercept approach[102] confirmed the possibility of publication bias for PTB ($P<.001$), LBW ($P=.001$), and IUGR ($P=.008$). As indicated in **Table 4**, the trim-and-fill adjusted RRs for each adverse birth outcome are generally lower than the unadjusted RRs. More important, however, the estimates of RR for categorically defined antenatal depression and PTB and LBW were robust to the effects of publication bias.

COMMENT

This meta-analysis showed that depression during pregnancy, regardless of the type of antenatal depression measurement (ie, categorical or continuous), is associated with modest but statistically significant risks of PTB and LBW. Furthermore, the estimates of risk for PTB and LBW from categorically defined antenatal depression appear resilient to the effects of publication bias. Sensitivity analyses showed that the magnitude of RR for these adverse birth outcomes was consistent within the set of 20 studies examining PTB and the set of 11 studies investigating LBW. Although the sizes of the significant RRs for PTB and LBW posed by antenatal depression are modest, the test of relevance in our study is not statistical significance but public health significance. That is, given the prevalence of antenatal depression in a population of pregnant women, what will be the likely burden of PTB or LBW for their infants? Thus, a relatively small effect size magnified by a large population base can have a considerable and noteworthy effect on public health.

We also found evidence that the type of depression measurement (categorical vs continuous) moderated the strength of the associations between antenatal depression and PTB, LBW, and IUGR, thereby eliminating or reducing the heterogeneity associated with these findings. Results for categorical measures of antenatal depression revealed that having major depression or clinically sig-

Table 4. Comparison of Unadjusted Pooled RRs and Trim-and-Fill Adjusted Pooled RRs

Depression Predictor	No. of Studies	Unadjusted Pooled RR (95% CI)[a]	No. of Missing Studies	Trim-and-Fill Adjusted Pooled RR (95% CI)[b]
PTB				
Overall	20	1.13 (1.06-1.21)	10	1.07 (0.99-1.15)
Categorical	16	1.39 (1.19-1.61)	6	1.24 (1.04-1.47)
Continuous	4	1.03 (1.00-1.06)	1	1.03 (1.00-1.07)
LBW[c]				
Overall	11	1.18 (1.07-1.30)	6	1.10 (1.00-1.22)
Categorical	9	1.49 (1.25-1.77)	4	1.34 (1.10-1.64)
IUGR				
Overall	12	1.03 (0.99-1.08)	4	1.03 (0.97-1.09)
Categorical	8	1.45 (1.05-2.02)	3	1.17 (0.82-1.68)
Continuous	4	1.02 (1.00-1.04)	2	1.00 (0.98-1.03)

Abbreviations: CI, confidence interval; IUGR, intrauterine growth restriction; LBW, low birth weight; PTB, preterm birth; RR, relative risk.
[a] Using random-effects models.
[b] Using random-random effects trim-and-fill models.
[c] Only 2 studies used a continuous depression predictor; the trim-and-fill algorithm requires 3 or more studies.

nificant depressive symptoms significantly increased the RR of PTB by 39%, the risk of LBW by 49%, and the risk of IUGR by 45%. As expected, continuous measures of antenatal depression showed a similar albeit weaker pattern, indicating that every 1-point increase in depression severity was associated with a 3% significantly increased risk of PTB and nonsignificantly increased risks of LBW (4%) and IUGR (2%). To place the categorical results for antenatal depression in context, we note that smoking was observed to have a dose-dependent relationship with PTB,[106,107] with smoking more than 10 cigarettes a day shown to increase the likelihood of PTB between 33 and 36 weeks by 40% and of PTB at 32 weeks or less by 60%. Furthermore, in a cohort analysis of a large, ethnically diverse population,[11] substance use disorders were associated with a 2.4-fold higher risk of PTB and a 3.7-fold higher risk of LBW, and black race increased the likelihood of PTB by 60% and of LBW by 2-fold. Thus, the magnitude of risk for PTB and LBW posed by antenatal depression is comparable to the risk of smoking 10 or more cigarettes a day for PTB but is relatively modest contrasted to the greater risks of black race and substance abuse associated with PTB and LBW.

Moderator analyses for country location revealed that the RR of delivering an infant with LBW or IUGR was higher among women from developing countries who experienced antenatal depression than their counterparts in the United States or social democracies. Moreover, in US studies, categorically defined antenatal depression tended to be associated with an elevated risk of PTB in women of predominantly lower SES but not in women of middle- or upper-income status. Pregnant women of lower SES in the United States are also twice as likely to experience antenatal major and minor depression as are women from middle- to upper-income strata.[20-22] Whereas cross-cultural variability in the prevalence of perinatal depression certainly exists,[29] estimates of the prevalence of perinatal depression in several developing countries[27,28] are similar to the higher depression rates in pregnant US women of lower SES. Thus, many socioeconomically disadvantaged childbearing women in developing countries and in the United States experience a double-barreled threat: an increased risk of becoming depressed during their pregnancies and an increased likelihood of experiencing adverse birth outcomes once they have antenatal depression. Depressed pregnant women living near or below poverty levels are subject to large amounts of acute and chronic stress, such as living in unsafe neighborhoods, experiencing racial/ethnic or economic discrimination, and confronting food inadequacy in their households.[22,108,109] At the same time, despite Medicaid or other public insurance coverage during pregnancy, their mental health problems are seldom accurately diagnosed and they often lack access to specialty mental health services.[110-112]

Several potential direct and indirect causal pathways through which antenatal depression leads to adverse pregnancy outcomes have been proposed. One possibility is that prenatal stress or depression during pregnancy might promote adverse birth outcomes through the dysregulation of the hypothalamic-pituitary-adrenocortical axis, stimulating the release of stress hormones, such as cortisol and catecholamines. These biological changes may result in placental hypofusion and consequent restriction of oxygen and nutrients to the fetus, leading to fetal growth restriction and/or precipitation of PTB.[113-117] Other mechanisms include the possibility that antenatal depression might compromise immune system functioning,[118] which in turn may lead to a reproductive tract infection triggering PTB.[117] The harmful public health effect of antenatal depression on birth outcomes is further heightened by evidence that depression during pregnancy is associated with risky but modifiable health practices, such as poor nutrition and hygiene, lack of motivation to obtain prenatal care or to follow medical recommendations, and smoking and/or alcohol and substance abuse, all of which adversely affect pregnancy outcomes.[11,33,85,119]

Clearly, pregnancy is an important time to universally screen women for depression, especially those who are socioeconomically disadvantaged, and to improve their timely access to evidence-based prenatal and mental health services.[120] Improved accuracy of diagnosis and treatment of antenatal depression combined with education about harmful but potentially modifiable lifestyle practices could lead to decreased rates of PTB and LBW.

Reducing the rates of these adverse birth outcomes is a critically important public health issue. During childhood, PTB is associated with an increased risk of mortality[3]; adverse medical outcomes[4,121-123] including respiratory distress syndrome, cerebral palsy, chronic lung disease, vision and hearing loss, and neurodevelopmental disabilities; cognitive difficulties[124]; and psychiatric problems,[124] such as internalizing and externalizing behaviors and attention-deficit/hyperactivity disorder. Long-term consequences of PTB in adulthood include diminished rates of reproduction and, for women born preterm, an increased risk of next-generation PTB, fetal stillbirth, and infant mortality.[3] Pernicious child and adult outcomes related to LBW[125-133] and IUGR[134-139] reflect patterns similar to that of PTB. Furthermore, in the United States, the annual economic costs of medically managing the consequences of these adverse birth outcomes are enormous.[140,141] For example, approximately 75% of admissions to the neonatal intensive care unit are related to prematurity.[142] Daily neonatal intensive care unit costs in the United States exceed $3500 per infant, and it is not unusual for costs to reach $1 million for a prolonged stay.[142]

A strength of our meta-analysis is that our search included US and non-US English-language studies, as well as a study in French that was translated into English by an expert. Thus, the 29 studies included in our meta-analysis came from 12 non-US countries, indicating significant international representation. Our meta-analysis also included studies that varied in the extent to which they controlled for confounding factors related to PTB, LBW, and IUGR. For example, one-third of the studies (n=10) controlled for SSRI use[31,57,62,67,68] or reported that SSRI use was unlikely in their sample.[34,36,51,64,66] An increasing number of women with depression are prescribed antidepressant medications during pregnancy.[143] These medications, especially SSRIs, have been significantly linked with LBW in some[49,92,93,144] but not all studies.[145-147] Wisner et al[68] recently found that infants who were continuously exposed to either SSRIs or major depression throughout the 3 trimesters of pregnancy were more likely to be born preterm than were infants with partial or no exposure. Differentiating between the effects of depression or depressive symptoms and the effects of antidepressants on birth outcomes is challenging because (1) researchers typically investigate the effects of one without controlling adequately for the other; (2) use of antidepressants during pregnancy occurs at different times, dosages, and durations; (3) recognition and treatment of depression by the physician is often associated with depression severity and persistence; and (4) depression is also associated with the use of additional prescription and nonprescription medications[148] and other potential confounders, such as smoking or substance use disorders.

Finally, prior evidence has shown that key variables in addition to depression, such as substance use or abuse, race/ethnicity or SES, and previous PTB, are strongly and consistently predictive of negative birth outcomes. Most of the studies in our meta-analysis (80%) controlled for at least 2 of these key predictors, but few controlled for all of them. In addition, most of the studies did not control for stressful life events and other psychiatric comorbidities of depression, such as antenatal anxiety, which has been linked with adverse birth outcomes in some studies.[6] A recent meta-analysis of anxiety symptoms and birth outcomes, however, did not show evidence of this association.[149]

Only 5 of 29 studies in our meta-analysis assessed major depression during pregnancy by using diagnostic criteria adhering to or compatible with the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).[150] Most studies used relatively short screening tools to evaluate levels of depressive symptoms and to set cutoff scores for describing clinically significant depressive symptoms. Although categorizing depressive symptom levels may be related to the diagnosis of clinically significant depression, it is not a substitute nor may it be as accurate as a structured interview. Finally, although we found possible publication bias, the findings of an elevated risk of PTB and LBW associated with categorically defined depression remained robust to trim-and-fill analyses that corrected for this bias.

Limitations of the studies reviewed suggest the need for a large prospective epidemiological study to simultaneously evaluate the RRs during pregnancy of depression, SSRI use, smoking, substance use disorders, key sociodemographic variables, obstetric/medical variables, and important behavioral health practices, including engagement in adequate prenatal and medical care and nutrition. Multiple assessments of major and minor antenatal depression should be performed, using criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) as well as measures assessing depression severity. The RRs of anxiety disorders and anxiety severity should also be assessed because these psychopathologic conditions typically accompany depression and were found to be related in some, but not all, studies to adverse birth outcomes. Ideally, this future study would prospectively gather data during the prepregnancy, pregnancy, and postpartum periods, considering that a broader perspective on a woman's health status may be necessary to better understand the risk factors associated with harmful birth outcomes.[58,151,152]

Our overall pattern of findings in this meta-analysis highlights the salient public health risk of PTB and LBW posed by antenatal depression, particularly for socioeconomically disadvantaged women in developing countries and in the United States. Furthermore, mounting evidence from this meta-analysis and other sources[68] suggests that untreated major depression during pregnancy is as likely to lead to poor birth outcomes as is treatment with SSRIs. An important implication of these findings is that pregnant women should be universally screened for depression and provided guideline-level treatment before childbirth. Given that untreated antenatal depression is the most robust predictor of postpartum depression and has additional serious adverse consequences for infant and child development beyond harmful birth outcomes, women and their obstetrics professionals will need to weigh the costs and benefits of treating antenatal depression pharmacologically, especially when treatment with evidence-based psychotherapy is not available or desired.

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