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Association of Antenatal Depression Symptoms and Antidepressant Treatment With Preterm Birth

Kartik K. Venkatesh, MD, PhD,

Laura Riley, MD,

Victor M. Castro, MS,

Roy H. Perlis, MD, MSc,

Anjali J. Kaimal, MD, MAS

Department of Obstetrics and Gynecology, Massachusetts General Hospital and Brigham and Women's Hospital, the Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, and the Center for Experimental Drugs and Diagnostics, Department of Psychiatry, Massachusetts General Hospital, and the Center for Human Genetic Research, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Abstract

OBJECTIVE: To evaluate the association of antenatal depression symptoms with preterm birth and small for gestational age (SGA).

METHODS: This was an observational cohort study conducted among women who completed Edinburgh Postnatal Depression Scale screening and delivered at 20 weeks of gestation or greater. The primary outcomes were preterm birth and an SGA neonate at birth (less than 10th percentile for gestational age); the primary predictor was an Edinburgh Postnatal Depression Scale antepartum score of 10 or greater, indicating symptoms of depression. Logistic regression models were used with and without consideration of antidepressant exposure during pregnancy.

RESULTS: Among 7,267 women, 831 (11%) screened positive for depression. In multivariable analyses adjusting for maternal age, race, income, body mass index, tobacco use, lifetime diagnosis of major depression and anxiety, diabetes, hypertension, and preeclampsia, women who screened positive for depression experienced an increased risk of preterm birth (less than 37 weeks of gestation) (adjusted odds ratio [OR] 1.27, 95% confidence interval [CI] 1.04–1.55) and very preterm birth (less than 32 weeks of gestation) (adjusted OR 1.82, 95% CI 1.09–3.02) as well as of having an SGA neonate (adjusted OR 1.28, 95% CI 1.04–1.58). In secondary analyses, among women who were treated with an antidepressant during pregnancy (19% of those who screened positive and 5% of those who screened negative), depressive symptoms were not associated with a significantly increased risk of preterm and very preterm birth or an SGA neonate.

CONCLUSIONS: In a large cohort of women screened for depression antepartum, those with depressive symptoms had an increased likelihood of preterm and very preterm delivery as well

Corresponding author: Kartik K. Venkatesh, MD, PhD, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA; kvenkatesh@partners.org.

having an SGA neonate. Such risk was not apparent among women who were treated with an antidepressant medication.

Increasing efforts have been underway to recommend universal screening for depression in pregnancy, because depression may affect up to 15% of pregnant women.[1–3] Although improvement in maternal mental health outcomes is one rationale for universal screening and subsequent treatment, the potential link between maternal depression and poor obstetric outcomes, particularly preterm birth, is another. Early data suggested an association between depression as well as exposure to antidepressants and increased risk of preterm birth, but follow-up studies have had conflicting results, perhaps arising from differences in depression screening instruments, timing and frequency of screening during pregnancy, and, most importantly, relatively small samples sizes and inability to control for potential confounding variables.[4–7] One recent study supporting the association between depressive symptoms and preterm birth included more than 14,000 women but included limited information regarding potential confounding variables and did not address the effect of treating depression.[8]

In light of conflicting data about the association between maternal depression and obstetric outcomes as well as uncertainty regarding the risk–benefit ratio of antidepressant utilization in pregnancy, estimating the value of screening in the context of treatment is of particular importance to clinical providers. Given the prevalence of both depression and antidepressant medication exposure during pregnancy, it is important to understand not only the association between depression and adverse pregnancy outcome, but also the effect of antidepressant treatment on the risk of preterm birth[9] as well as other features associated with depression during pregnancy that could confound the observed associations. The current observational study examined the relationship between antenatal depressive symptoms with preterm delivery and a small-for-gestational-age (SGA) neonate at birth in a large, well-characterized clinical cohort undergoing routine antepartum depression screening to better understand the consequences of such symptoms and the influence of treatment.

MATERIALS AND METHODS

This was an observational cohort study using a longitudinal cohort drawn from Massachusetts General Hospital (Boston, Massachusetts), a large tertiary care academic medical center. Among all women who delivered at the obstetrics unit at Massachusetts General Hospital between July 2010 and October 2013, we identified those who delivered at 20 weeks of gestation or greater for inclusion in the current study. We included a priori all available women with Edinburgh Postnatal Depression Scale scores and obstetric outcome data available based on the timing of implementation of universal Edinburgh Postnatal Depression Scale screening at our medical center to maximize our sample size. During the study period, 98% of eligible women cared for at the sites participating in the universal screening program had complete antepartum depression screening data. A universal depression screening program was initiated in July 2010 with the intention of screening all women for depression antepartum and then again postpartum. All women were screened at a routine prenatal visit generally between 24 and 28 weeks of gestation with the Edinburgh Postnatal Depression Scale. Women with a positive Edinburgh Postnatal Depression Scale screen were then referred for initial outpatient evaluation by social work

followed by referral for further diagnostic evaluation and treatment by a social worker, psychologist, or psychiatrist as needed. All completed depression screens were reviewed and scored in real time and total scores were entered into the patient's electronic health record.

The present analysis utilized data from the Partners Healthcare electronic health record using i2b2 server software, which is a scalable computational framework for managing human health data. Further details about the i2b2 platform can be found in earlier analyses by this group.[10,11] This study was approved by the Partners Healthcare institutional review board with a waiver of the informed consent requirement because it utilized deidentified data only.

The following sociodemographic and clinical characteristics were assessed from the electronic health record: age, race, household zip code, parity, reported prepregnancy body mass index (BMI, calculated as weight (kg)/[height (m)]^2), maternal comorbid conditions (including diabetes, hypertension, and preeclampsia during current pregnancy), tobacco use during pregnancy, and enrollment in a government insurance program. Median household income was imputed using 2013 U.S. Census Bureau data for the patient's residential zip code. The following psychiatric characteristics were assessed: past and current antidepressant use based on e-prescribing data, past and current diagnosis of major depressive disorder as well as other diagnoses in the International Statistical Classification of Diseases and Related Health Problems-9, psychiatry chapter, and Edinburgh Postnatal Depression Scale results. Data on use of antidepressant medication were derived from the electronic health record and the inpatient pharmacy record. Electronic prescribing became standard practice across the hospital by 2010; medication reconciliation to incorporate all medications, regardless of prescriber, was mandatory at hospital discharge and primary care visits and encouraged at all clinical visits, which included all obstetric visits as well as other clinical care patient encounters.

The Edinburgh Postnatal Depression Scale, a 10-item questionnaire, focuses on psychic symptoms of depression and is designed to reduce the focus on somatic symptoms (ie, poor sleep, weight gain or loss) that are common among women with depression.[12] The Edinburgh Postnatal Depression Scale has established psychometric properties and is one of the most widely used self-reported instruments to assess depressive symptoms in pregnant and postpartum women, including minorities and teenagers.[23] The cutoff point used to identify women as high risk for postpartum depression varies with most studies using a cutoff score of 10 or greater or 12 or greater.[13,14] A cutoff score 10 or greater detects a depressive episode with sensitivities of greater than 90% and specificities greater than 80%.[12,13,15]

Primary obstetric study outcomes included preterm birth, very preterm birth, neonatal birth weight (grams), and neonatal diagnosis of SGA defined as less than tenth percentile for gestational age at birth. Preterm birth was defined in accordance with World Health Organization criteria, namely: 1) preterm delivery at less than 37 weeks of gestation, 2) very preterm delivery at less than 32 weeks of gestation, and 3) extremely preterm delivery at less than 28 weeks of gestation.[16] Small for gestational age at birth was calculated by matching neonatal weights to standardized birth weights for gestational age using a U.S. national reference[17] without specific adjustment for race–ethnicity. Other secondary

obstetric outcomes assessed included: mode of delivery (vaginal delivery compared with cesarean delivery); induction or augmentation of labor; among term deliveries (ie, greater than 37 weeks of gestation), early-term delivery between 37 and 39 weeks of gestation; and neonatal Apgar score of less than 7 at 5 minutes of life.

To evaluate the primary outcome of preterm delivery, women were categorized as "higher risk" or "lower risk" based on their Edinburgh Postnatal Depression Scale screening results; the primary predictor was an Edinburgh Postnatal Depression Scale antepartum score of 10 or greater, which was utilized to designate women with significant symptoms of depression.

Women who screened positive for depression were first compared with women who screened negative for relevant sociodemographic, clinical, psychiatric, and obstetric characteristics in univariate analyses. We then utilized multivariable logistic regression to evaluate the association between obstetric outcomes, including preterm delivery and SGA at birth, and the risk of screening positive for depression during pregnancy. Confounding variables were selected a priori by reviewing the literature on depression in pregnancy and preterm birth. The following covariates were controlled for in multivariable models: maternal age, race, parity, imputed household income, prepregnancy BMI, tobacco use during pregnancy, past diagnosis of major depressive disorder, past diagnosis of an anxiety disorder, and maternal comorbidities (diabetes, hypertension, and preeclampsia during current pregnancy).

We also assessed whether treatment of depression with antidepressant medications differentially affected (ie, exhibited effect measure modification of) the association between a positive depression screen and preterm birth and SGA by fitting multivariable regression models adjusting for the previously mentioned confounding variables among women exposed to an antidepressant medication during pregnancy and then among women who were unexposed to an antidepressant medication during pregnancy.

In sensitivity analyses, we also assessed whether the association between preterm birth and SGA with depression persisted after 1) excluding women with multiple gestations; 2) only adjusting for those variables that were significant at baseline, namely age, parity, race, insurance status, imputed income, BMI, tobacco use, and prior psychiatric history; 3) including the Edinburgh Postnatal Depression Scale as a continuous rather than dichotomous measure; and 4) using a higher Edinburgh Postnatal Depression Scale cutoff score 12 or greater (rather than 10 or greater). All analyses used STATA 10.0.

RESULTS

Among 7,267 women, 831 (11%) screened positive for depression antepartum with an Edinburgh Postnatal Depression Scale score 10 or greater. The median age was 33 years (interquartile range, 30–36), 51% were nulliparous, and 53% self-identified as white (Table 1). Women who screened positive were significantly more likely to be younger, already have children, be of a minority race, smoke during pregnancy, and be overweight or obese ($P<.05$). Women who screened positive were also more likely to live in zip code areas with lower incomes and to be enrolled in a government insurance program.

When psychiatric history was compared, nearly one third of women (247 [30%]) who screened positive had been diagnosed with depression in the past compared with 12% of those with a negative depression screen (odds ratio [OR] 3.24, 95% confidence interval [CI] 2.74–3.83).

Overall, 15% of women delivered preterm at less than 37 weeks of gestation, 2% very preterm at less than 32 weeks of gestation, and 0.2% extremely preterm at less than 28 weeks of gestation (Table 2). More than 1 in 10 neonates (13%) were classified as SGA at birth, and 8% of neonates were less than 2,500 g at birth. One third of women (32%) had a cesarean delivery. In unadjusted analyses, women who screened positive for depression during pregnancy were significantly more likely to deliver preterm at less than 37 weeks of gestation, very preterm at less than 32 weeks of gestation, and extremely preterm at less than 28 weeks of gestation as well as to have a neonate with a birth weight less than 2,500 g and classified as SGA at birth (Table 2).

In adjusted analyses, after controlling for maternal age, race, parity, imputed household income, prepregnancy BMI, tobacco use during pregnancy, past diagnosis of major depressive disorder, past diagnosis of an anxiety disorder, and maternal diabetes, hypertension, and preeclampsia, women who screened positive for depression antepartum were still significantly more likely to deliver preterm at less than 37 weeks of gestation (adjusted OR 1.27, 95% CI 1.04–1.55), very preterm at less than 32 weeks of gestation (adjusted OR 1.82, 95% CI 1.09–3.02) as well as to have a neonate with a birth weight less than 2,500 g (adjusted OR 1.41, 95% CI 1.10–1.81) and classified as SGA at birth (adjusted OR 1.28, 95% CI 1.04–1.58) (Table 2). There was no significant association between screening positive for depression and mode of delivery, early-term delivery between 37 and 39 weeks of gestation, and neonatal Apgar scores at birth.

We repeated the primary analyses among women who were, or were not, treated with an antidepressant during pregnancy. In all, 518 (7%) women were exposed to an antidepressant medication during pregnancy: 19% of those who screened positive for depression and 5% of women who screened negative (OR 4.04, 95% CI 3.30–4.95). Those women who were treated for depression with an antidepressant medication did not have a significantly increased likelihood of preterm birth, very preterm birth, or having an SGA neonate (Table 3). As in the cohort as a whole, depressive symptoms significantly increased the risk of preterm birth, very preterm birth, and SGA at birth among women who were not treated for depression with an antidepressant medication ($P<.05$; Table 3).

We conducted several analyses to examine the robustness of our results. First, after excluding 443 women (6.1%) with nonsingleton pregnancies, women who screened positive for depression continued to be more likely to deliver preterm at less than 37 weeks of gestation (adjusted OR 1.34, 95% CI 1.08–1.68) and to have a neonate born SGA (adjusted OR 1.41, 95% CI 1.06–1.89) adjusting for the previously mentioned confounders. Next, after adjusting only for those variables that were significant at baseline, the results were similar to the primary analysis (preterm delivery at less than 37 weeks of gestation adjusted OR 1.24, 95% CI 1.01–1.51 and SGA adjusted OR 1.39, 95% CI 1.08–1.78). When the Edinburgh Postnatal Depression Scale was considered as a continuous measure

in multivariable analyses, we noted a significant association with SGA at birth (adjusted OR 1.02, 95% CI 1.00–1.03), very preterm delivery at less than 32 weeks of gestation (adjusted OR 1.03, 95% CI 1.00–1.07), and extremely preterm delivery at less than 28 weeks of gestation (adjusted OR 1.10, 95% CI 1.00–1.21), but no significant association with preterm delivery at less than 37 weeks of gestation (adjusted OR 1.01, 95% CI 0.99–1.02). These associations with preterm delivery (adjusted OR 1.25, 95% CI 0.97–1.61) and SGA (adjusted OR 1.16, 95% CI 0.88–1.53) were attenuated and CIs no longer excluded 1 when we applied a greater Edinburgh Postnatal Depression Scale cutoff score of 12 or greater to screen positive for depression.

DISCUSSION

We identified a statistically significant association between prenatal depressive symptoms and preterm birth and as well as having an SGA neonate at birth in this large cohort of women after extensive adjustment for sociodemographic, clinical, and psychiatric confounding variables. Our results extend prior reports that identified risk in smaller cohorts or without detailed consideration of confounding.[8,18,19] In secondary analyses, we found that in women receiving antidepressant medications during pregnancy, the association between depressive symptoms and adverse obstetric outcomes was not seen; however, given that only 160 of 831 women who screened positive were exposed to an antidepressant, our power to compare outcomes in this smaller group was limited. This finding merits additional study, particularly because it is in contrast to previous studies, which found that women treated with an antidepressant during pregnancy may be at risk of worse obstetric outcomes.[20,21] Although some earlier studies have noted a relationship between depression risk in pregnancy and preterm birth, few studies have clearly demonstrated an association with very preterm birth at less than 32 weeks of gestation, have utilized the Edinburgh Postnatal Depression Scale to assess for depressive symptoms, or included an assessment of the effect of multiple confounding factors and antidepressant treatment.[4,6]

In general, these findings support current national efforts underway to expand universal antepartum depression screening in pregnancy as part of routine prenatal care to further the goal of optimizing both maternal and neonatal outcome.[3,22] If additional studies support the finding of decreased risk among women being treated with antidepressants, this would suggest that early identification and treatment of women with depression in pregnancy may not only improve maternal well-being, but potentially affect obstetric outcome.

Strengths of the current study include assessment of a large, diverse cohort of pregnant women using uniform methodology and ascertainment of depression and obstetric outcomes using an electronic health record, avoiding the risk of recall bias seen in some earlier studies that relied on ascertainment of depression postpartum. Through detailed characterization of these pregnant women, we were able to control for important confounding variables associated with preterm birth as well as multiple indices of psychiatric disease severity.

The current study has limitations as well. We were unable to adjust for a history of prior preterm birth, although we were able to take into account many other demographic and clinical risk factors associated with preterm birth. A recent study that was able to adjust

for prior preterm birth, but that did not adjust for the range of confounders as the current analysis, noted an adjusted OR that was similar to the current study.[8] Although all women were screened for depression as part of routine obstetric care, the timing of initiation of antidepressants in relationship to screening was not known, and some women who screened negative were receiving an antidepressant, presumably for prevention of relapse or recurrence. In addition, there are many characteristics of women receiving antidepressants that may affect outcomes and differ from those who are not receiving treatment (ie, health literacy, resiliency) that we were unable to account for in the current analysis. Finally, although we sought to maximize our sample size, our power to explore effects in particular subgroups was limited; notably, when a screening cutoff of 12 or greater was used rather than 10 or greater, the ORs for preterm birth and SGA were similar but not statistically significant, likely as a result of the number of women who screened positive decreasing from 831 to 477, diminishing our ability to assess for a significant difference in outcome.

Not all women who screened positive in the current study would meet diagnostic criteria for major depressive disorder; however, the current study suggests that women with milder depressive symptoms are still at risk of deleterious obstetric outcomes and provides information about the possible effect of treating depression on these outcomes. Although a randomized trial would be required to establish causation,[24] these results suggest at a minimum that identification and treatment of depression represent an opportunity to meaningfully affect obstetric and neonatal outcomes.[1,2] Although this finding might seem self-evident in light of the other compelling reasons for depression treatment, the persistence in the mass media of experts claiming otherwise suggests the need to demonstrate such benefit.[25] A recent clinical trial found that women treated for depression during pregnancy had improved depressive and functional outcomes,[26] but a large-scale analysis of Medicaid data from more than 200,000 recipients found that upward of 75% of women with antidepressant prescriptions before pregnancy discontinued treatment before or during the first trimester of pregnancy given persistent concern about the safety of antidepressants during pregnancy.[27] Our results provide additional support for greater public health and clinical efforts aimed at universal screening for maternal depression during pregnancy as a means of identifying individuals at greater risk for adverse obstetric outcomes. They further suggest the possibility that intervention for depression may provide an opportunity to moderate such risk.

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Table 1.

Sociodemographic, Clinical, and Psychiatric Characteristics of Pregnant Women Overall and by Screening Positive Antepartum for Depression (N=7,267)

Characteristic	Positive Screen for Depression (n=831)	Negative Screen for Depression (n=6,436)	OR (95% CI) Comparing Women Who Screen Positive With Women Who Screen Negative
Sociodemographic and clinical characteristics			
Maternal age at delivery (y)			
Younger than 27	222 (26.7)	892 (13.8)	Referent
Less than or equal to 27–32	216 (25.9)	1,961 (30.5)	0.44 (0.36–0.54)*
32–36	217 (26.1)	2,043 (31.7)	0.42 (0.34–0.52)*
Older than 36	176 (21.1)	1,540 (23.9)	0.45 (0.37–0.56)*
Parity			
0	376 (45.3)	3,340 (51.9)	Referent
1	291 (35.0)	2,196 (34.1)	1.17 (1.00–1.38)*
2 or more	164 (19.7)	900 (13.9)	1.61 (1.32–1.97)*
Self-identified race–ethnicity			
White	346 (41.6)	3,506 (54.5)	Referent
Black	65 (7.8)	491 (7.6)	1.34 (1.01–1.77)*
Latina	65 (7.8)	313 (4.9)	2.10 (1.57–2.80)*
Asian	75 (9.0)	223 (3.5)	3.40 (2.56–4.52)*
Other or unknown	280 (33.7)	1,903 (29.5)	1.49 (1.26–1.76)*
Mother enrolled in government insurance	245 (29.5)	934 (14.5)	2.46 (2.09–2.90)*
Median imputed household income ($)†			
1st quartile (less than 51,863)	313 (37.9)	1,399 (21.9)	Referent
2nd to 3rd quartile (51,864–92,399)	359 (43.5)	3,157 (49.4)	0.50 (0.43–0.59)*
4th quartile (greater than 92,400)	154 (18.6)	1,838 (28.8)	0.37 (0.30–0.45)*
BMI (kg/m^2)†			
Less than 25	401 (49.1)	3,650 (58.1)	Referent
25–30	241 (29.5)	1,672 (26.6)	1.31 (1.10–1.55)*
Greater than 30	175 (21.4)	963 (15.3)	1.65 (1.36–2.00)*

Characteristic	Positive Screen for Depression (n=831)	Negative Screen for Depression (n=6,436)	OR (95% CI) Comparing Women Who Screen Positive With Women Who Screen Negative
Tobacco use during pregnancy	43 (5.2)	108 (1.7)	3.19 (2.22–4.58)*
Medical history			
Diabetes	7 (0.8)	49 (0.8)	1.10 (0.49–2.45)
Hypertension	44 (5.3)	339 (5.3)	1.00 (0.72–1.38)
Preeclampsia in current pregnancy	30 (3.6)	278 (4.3)	0.82 (0.56–1.21)
Psychiatric characteristics			
Diagnosis of major depressive disorder ever	247 (29.7)	743 (11.5)	3.24 (2.74–3.83)*
Diagnosis of an anxiety disorder ever	124 (14.9)	290 (4.5)	3.71 (2.97–4.65)*
Antidepressant exposure during Pregnancy	160 (19.3)	358 (5.6)	4.04 (3.30–4.95)*
Antidepressant exposure all three trimesters of pregnancy	58 (7.0)	146 (2.3)	3.23 (2.36–4.42)*

OR, odds ratio; CI, confidence interval; BMI, body mass index.

Data are n (%) unless otherwise specified.

*Reflects statistically significant association $P<.05$.

†Missing data on 47 women (0.6%) for income and 165 (2.3%) for BMI.

Table 2.

Unadjusted and Adjusted Analyses of Obstetric Outcomes Associated With a Positive Antepartum Depression Screen, Edinburgh Postnatal Depression Scale Score 10 or Greater (N=7,267)

Outcome	Positive Screen for Depression (n=831)	Negative Screen for Depression (n=6,436)	OR (95% CI) Comparing Women Who Screen Positive With Women Who Screen Negative	Adjusted OR (95% CI)*
Preterm delivery (less than 37 wk of gestation) (wk)				
37 or greater	680 (81.8)	5,508 (85.7)		
Less than 37	151 (18.2)	922 (14.3)	1.32 (1.09–1.60)†	1.27 (1.04–1.55)†
Very preterm delivery (less than 32 wk of gestation) (wk)				
32 or greater	810 (97.5)	6,341 (98.6)		
Less than 32	21 (2.5)	89 (1.4)	1.84 (1.14–2.98)†	1.82 (1.09–3.02)†
Extremely preterm delivery (less than 28 wk of gestation) (wk)				
28 or greater	826 (99.4)	6,420 (99.8)		
Less than 28	5 (0.6)	10 (0.16)	3.88 (1.35–11.39)†	2.49 (0.77–8.02)
Neonatal birth weight (g)				
2,500 or greater	739 (89.0)	5,931 (92.2)		
Less than 2,500	91 (11.0)	502 (7.8)	1.45 (1.14–1.84)†	1.41 (1.10–1.81)†
SGA at delivery				
No	698 (84.0)	5,633 (87.5)		
Yes	133 (16.0)	803 (12.5)	1.33 (1.09–1.63)†	1.28 (1.04–1.58)†
Mode of delivery				
Vaginal	580 (69.8)	4,363 (67.8)		
Cesarean	251 (30.2)	2,073 (32.2)	0.91 (0.77–1.06)	0.95 (0.80–1.12)
Among women delivering at term, gestational age at delivery (wk)				
39 or greater	360 (52.9)	3,156 (57.3)		
37–39	320 (47.1)	2,352 (42.7)	1.19 (0.91–1.38)	1.14 (0.97–1.35)
5-min Apgar score				
7 or greater	723 (87.0)	5,735 (89.1)		
Less than 7	108 (13.0)	701 (10.9)	1.22 (0.98–1.51)	1.09 (0.66–1.79)

OR, odds ratio; CI, confidence interval; SGA, small for gestational age.

Data are n (%) unless otherwise specified.

*Models adjusted for maternal age, race, parity, baseline body mass index, imputed household income, tobacco use during pregnancy, past diagnosis of major depressive disorder, past diagnosis of an anxiety disorder, and maternal comorbidities (diabetes, hypertension, and preeclampsia during current pregnancy).

†Reflects statistically significant association $P<.05$.

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Table 3.

Association Between Preterm Delivery and Screening Positive for Depression by Antidepressant Exposure Status During Pregnancy

Outcome	Exposed to Antidepressants	Unexposed to Antidepressants
Preterm delivery (less than 37 wk of gestation)	1.44 (0.86–2.43)	1.28 (1.00–1.56) *
Very preterm delivery (less than 32 wk of gestation)	1.08 (0.18–6.35)	2.01 (1.18–3.42) *
SGA at delivery	1.67 (0.95–2.94)	1.25 (1.00–1.57) *

SGA, small for gestational age.

Data are adjusted odds ratio (95% confidence interval).

Models adjusted for maternal age, race, parity, baseline body mass index, imputed household income, tobacco use during pregnancy, past diagnosis of major depressive disorder, past diagnosis of an anxiety disorder, and maternal comorbidities (diabetes, hypertension, and preeclampsia during current pregnancy).

* Reflects statistically significant association $P<.05$.