OBSTETRICS

Trajectories of antenatal depression and adverse pregnancy outcomes

Emily S. Miller, MD, MPH; George R. Saade, MD; Hyagriv N. Simhan, MD; Catherine Monk, PhD; David M. Haas, MD, MS; Robert M. Silver, MD; Brian M. Mercer, MD; Samuel Parry, MD; Deborah A. Wing, MD, MBA; Uma M. Reddy, MD, MPH; William A. Grobman, MD, MBA

BACKGROUND: Antenatal depression affects approximately 1 of 7 pregnancies, with an increasing prevalence across gestation. Data regarding the associations between antenatal depression and adverse pregnancy outcomes yielded conflicting results. However, previous studies evaluated the cross-sectional prevalence of depression at various time points and not the depressive symptom trajectory across gestation.

OBJECTIVE: This study aimed to identify whether the trajectory of antenatal depressive symptoms is associated with different risks of adverse pregnancy outcomes.

STUDY DESIGN: This was a secondary analysis of a large multisite prospective cohort of nulliparous women across the United States. The Edinburgh Postpartum Depression Scale was administered at 2 study visits: between 6 and 14 weeks' gestation and between 22 and 30 weeks' gestation. The Edinburgh Postpartum Depression Scale score trajectories were categorized as improved, stable, or worsened based on whether the scores changed by at least 1 standard deviation between the 2 visits. The frequencies of adverse pregnancy outcomes (hypertensive disorders of pregnancy, abruption, cesarean delivery, preterm birth [ie, <37 weeks' gestation], small for gestational age neonates, neonatal intensive care unit admission, and maternal readmission) were compared with depression trajectories across gestation in bivariable and multivariable analyses. Secondary analyses evaluated the frequencies of spontaneous and medically indicated preterm births and frequencies of spontaneous and medically indicated preterm births before 35, 32, and 28 weeks' gestation.

RESULTS: Of the 8784 women who completed the 2 antenatal Edinburgh Postpartum Depression Scale screens, 1141 (13.0%) had improved, 6663 (75.9%) had stable, and 980 (11.2%) had worsened depressive symptom trajectories across gestation. Compared with women with improved or stable depressive symptoms, those with worsened symptoms were more likely to experience preterm birth (8.3% vs 7.4% vs 9.9%, respectively; P=.018). After controlling for potential confounders, worsened depressive symptoms remained associated with more frequent preterm birth (adjusted odds ratio, 1.68; 95% confidence interval, 1.10–2.57).

CONCLUSION: Women with depression symptoms that worsen as pregnancy progresses have increased odds of preterm birth. Future research is warranted to optimize and implement effective prevention, screening, and treatment protocols for antenatal depressive symptoms as a strategy to prevent preterm birth.

Key words: adverse pregnancy outcomes, antenatal depression, mood disorder, perinatal depression, preterm birth, prevention of perinatal depression, trajectory

Introduction

Perinatal depression is one of the most common complications of pregnancy, affecting at least 1 of 7 American women,[1–3] with a disproportionate impact on women with adverse social determinants of health.[4–6] Perinatal depression can have debilitating effects on the mother if left untreated.[7] Depression not only does incur serious maternal risks but also has been associated with adverse perinatal outcomes, including preeclampsia,[8] placental abruption,[9] cesarean delivery,[10] preterm birth,[11–13] fetal growth restriction,[11,12,14,15] low Apgar scores,[16] neonatal intensive care (NICU) admission,[16] and maternal postpartum readmission.[17] These complications are responsible for most neonatal morbidities and mortalities across the United States and are an enormous economic burden to the healthcare system. Moreover, untreated perinatal depression is independently associated with long-term adverse neurodevelopmental consequences in offspring with effects particularly pronounced in socioeconomically disadvantaged populations.[18]

Data regarding the relationships between antenatal depression and adverse pregnancy outcomes have yielded conflicting results. The inconsistent findings were likely because of the pervasive use of a cross-sectional design in these studies. Growth curve mixture modeling data demonstrated that antenatal depressive symptoms are often not static across gestation.[19–23] Thus, results of analyses assessing the exposure of depression early in gestation may differ from those assessing this same exposure occurring in the third trimester of pregnancy. Furthermore, depressive sympto2m trajectories, rather than an overt diagnostic categorization of depression, may better reflect the evolution of an underlying physiological dysregulation. As this evolving pathophysiology may contribute to the risk of adverse pregnancy outcomes, the analyses of depressive symptom trajectories may be a more biologically appropriate framework for the analyses of adverse pregnancy outcomes.

This study aimed to identify whether differing antenatal depressive symptom

Cite this article as: Miller ES, Saade GR, Simhan HN, et al. Trajectories of antenatal depression and adverse pregnancy outcomes. Am J Obstet Gynecol 2022;226:108.e1-9.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2021.07.007

AJOG at a Glance

Why was this study conducted?

Data examining the association between antenatal depressive symptoms and adverse pregnancy outcomes are often cross-sectional and yielded conflicting results. This study aimed to identify whether the trajectory of antenatal depressive symptoms is associated with adverse pregnancy outcomes independent of depression status.

Key findings

Women whose depressive symptoms worsened during pregnancy had an increased odds of preterm birth (ie, <37 weeks' gestation).

What does this add to what is known?

These findings indicated that depressive symptoms can change as pregnancy progresses and that worsening symptoms may be associated with more frequent adverse pregnancy outcomes. Future research is warranted to optimize and implement effective prevention, screening, and treatment protocols for antenatal depression as a strategy to prevent preterm birth.

trajectories are associated with adverse pregnancy outcomes independent of initial depression status. Based on extant associations of perinatal depression in the literature, we hypothesized that a worsened antenatal depressive symptom trajectory would be associated with an increased risk of adverse pregnancy outcomes, including hypertensive disorders of pregnancy, placental abruption, cesarean delivery, preterm birth, small-for-gestational-age (SGA) births, low Apgar score, NICU admission, and maternal postpartum readmission.

Materials and Methods

The Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-To-Be (nuMoM2b) was a prospective cohort study designed to identify maternal characteristics predictive of adverse pregnancy outcomes.[24] Women were enrolled from geographically diverse hospitals affiliated with 8 clinical centers. Women were eligible for inclusion if they were nulliparous and had a singleton gestation between 6 0/7 and 13 6/7 weeks' gestation. Women were excluded if they were <13 years of age, had ≥3 previous spontaneous abortions, had a suspected fatal fetal malformation or known aneuploidy, conceived using a donor oocyte, had a multifetal reduction, or planned to terminate the pregnancy.

The women underwent a series of surveys and interviews at various time points in pregnancy. Pertinent to this analysis, sociodemographic characteristics and an assessment of medical comorbidities were assessed at visit 1 (between 6 0/7 and 13 6/7 weeks' gestation). Antenatal depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS)[25] administered at study visit 1 and again at study visit 3 (between 22 0/7 and 29 6/7 weeks' gestation). Detailed interviews to assess medication use were performed at study visit 1, study visit 2 (between 16 0/7 and 21 6/7 weeks' gestation; note that the EPDS was not obtained at this study visit), study visit 3, and after delivery. Pregnancy outcomes were collected after delivery via medical record abstraction.

For this analysis, women were classified into 3 groups by their depressive symptom trajectory: "improved," "stable," or "worsened." These groups were defined by a change in the EPDS score between visit 1 and visit 3 by at least 1 standard deviation (4 points, as defined by a previous large epidemiologic cohort study[1]). Adverse pregnancy outcomes examined included gestational diabetes mellitus, preeclampsia, placental abruption, cesarean delivery, preterm birth (ie, <37 weeks' gestation), etiology of preterm birth (ie, spontaneous or medically indicated), SGA birthweight (<10th percentile at delivery defined using Alexander norms[26]), 5-minute Apgar score of <7, NICU admission, and postpartum maternal hospital readmission. Secondary analyses evaluated the frequencies of spontaneous and medically indicated preterm births and frequencies of spontaneous and medically indicated preterm births before 35, 32, and 28 weeks' gestation.

The frequency of each adverse pregnancy outcome was compared across trajectory categories using Mann-Whitney *U* and chi-square analyses for continuous and categorical variables, respectively. Multivariable logistic regression analyses were performed to assess whether various categories of depressive symptom trajectory were independently associated with each adverse pregnancy outcome. For multivariable analyses, women with worsened symptom trajectories were compared with women with either improved or stable symptom trajectories. Variables that significantly ($P<.05$) differed by trajectory in bivariable analyses were included in multivariable regression analyses. Multivariable analyses used a generalized linear model using a binomial distributional assumption and a logit link to generate adjusted relative risks (aRRs). These models controlled for a positive baseline screen status for depression (ie, an EPDS score of ≥13) to allow the assessment of whether depressive symptom trajectory was associated with adverse pregnancy outcomes independent of the overt categorization of baseline depression. Psychiatric medication use was considered a priori to be an important potential confounder. Reported medications were categorized on the basis of whether a psychiatric indication for their use exists. Sensitivity analyses were performed to assess whether the reported indication for use was a psychiatric diagnosis and to include only psychiatric medications taken throughout the pregnancy (ie, initiated at visit 1 and continued through delivery). A Breslow-Day test for homogeneity was used to identify whether there were differences in the magnitude of the association between depressive symptom trajectory and preterm birth

after stratification by depression screen status at baseline.

All tests were 2 tailed, and a *P* value of <.05 was used to define statistical significance. Analyses were conducted using Stata (version 15.0; StataCorp LLC, College Station, TX). Each site's local institutional review board approved the parent study, and all participants gave written informed consent for the use of their data.

Results

Of the 10,038 women in the nuMoM2b cohort, 9685 completed the EPDS screen at visit 1, and 8784 (88% of the cohort) completed the EPDS screen at 2 visits, representing the analyzable sample. Of women who completed EPDS screens at 2 time points, 1141 (13.0%) had improved, 6663 (75.9%) had stable, and 980 (11.2%) had worsened depressive symptoms. Of the 980 women with worsened depressive symptoms, only 277 (28%) had an EPDS score of ≥13.

The sociodemographic and medical characteristics of women, stratified by depressive symptom trajectory, are shown in Table 1. There were differences in maternal age, race and ethnicity, education obtained, insurance, relationship status, household income, endorsement of the pregnancy as planned, body mass index at visit 1, and substance use histories between depressive symptom trajectory groups. Notably, there was no difference in the frequencies of psychiatric medication use, psychiatric medication use for a reported psychiatric indication, or use of a psychiatric medication throughout pregnancy among the depressive symptom trajectory groups (Table 2). Women who had improved symptom trajectories had a higher median EPDS score and were more likely to have a positive EPDS screen at visit 1 than women who had stable or worsened symptom trajectories.

There was no difference in the incidence of preeclampsia, abruption, cesarean delivery, 5-minute Apgar score of <7, NICU admission, or maternal postpartum readmission among the depressive symptom trajectory groups (Table 3). However, women with worsened depressive symptom trajectories had more frequent preterm birth and delivery of SGA neonates compared with women with stable or improved depressive symptom trajectories. When analyzing the subtype of preterm birth, there was no difference in the incidence of spontaneous preterm birth among the depressive symptom trajectory groups. However, women with worsened depressive symptom trajectories had more frequent medically indicated preterm births. Additional subgroups of preterm birth demonstrated similar trends, although predominantly not statistically significant because of small sample sizes (Table 4).

After controlling for potential confounders, women with worsened depressive symptom trajectories had increased odds of preterm birth compared with women with stable or improved depressive symptom trajectories (aRR, 1.61; 95% confidence interval [CI], 1.10−2.34) (Table 5). The association between depressive symptom trajectory and medically indicated preterm birth did not retain significance after controlling for potential confounders (aRR, 1.63; 95% CI, 0.89−2.96). Similarly, the association between depressive symptom trajectory and delivery of an SGA infant was nonsignificant after controlling for potential confounders (aRR, 1.30; 95% CI, 0.92−1.84).

Sensitivity analyses, including only medications whose reported indication for use was a psychiatric diagnosis and only psychiatric medications taken throughout the pregnancy, did not appreciably change the findings. The magnitude of the increased risk of preterm birth did not significantly differed between women with and without a positive baseline screen for depression (*P*=.94).

Comment

Principal findings

In this analysis of prospectively collected data from a diverse cohort of nulliparous women, a worsened depressive symptom trajectory across gestation was associated with more than 60% increased risk of preterm birth. This observed association was independent of baseline depression status and was not associated with depression pharmacotherapy. As most women with worsened depressive symptoms never had a positive depression screen, these findings seemed to be driven by the association of the trajectory of symptoms rather than overt depression itself. The association between worsened depressive symptoms and preterm birth seemed to be attributable to medically indicated preterm births rather than spontaneous preterm births.

Results

Our findings of differences in patient characteristics across antenatal depressive symptom trajectories supported those of Wikman et al,[27] who demonstrated clear distinctions in sociodemographic and clinical characteristics associated with divergent trajectories of perinatal depression. However, even after controlling for differences in these underlying patient characteristics, women with worsened depressive symptom trajectories were more likely to deliver before term. Although pregnancy complications may confound the observed relationship between depressive symptom trajectory and preterm birth, these data raised the possibility that the deterioration of depressive symptoms itself might contribute to this somatic outcome.

Clinical implications

These findings hold considerable public health impact. Despite evidence-based guidelines for both prevention[28] and treatment,[29] an estimated 400,000 women are affected by depressive symptoms during their pregnancy each year in the United States. Unfortunately, interventions to prevent perinatal depression are rarely implemented, and among women who experience perinatal depression, only 15% receive adequate treatment.[30] Collectively, these data suggested that a worsened depressive symptom trajectory is not uncommon. Our results supported these epidemiologic findings; in this cohort, 11% of women experienced worsened depressive symptoms throughout pregnancy.

TABLE 1
Maternal characteristics stratified by depressive symptom trajectory category

Characteristic	Depressive symptoms improved (n=1141)	Depressive symptoms remained stable (n=6663)	Depressive symptoms worsened (n=980)	*P* value
Sociodemographic characteristics				
Maternal age (y)	25 (21–30)	28 (23–31)	26 (21–31)	.012
Race and ethnicity				.075
Non-Hispanic White	594 (52.1)	4347 (65.2)	534 (54.5)	
Non-Hispanic Black	203 (17.8)	742 (11.1)	174 (17.8)	
Hispanic	226 (19.8)	985 (14.8)	175 (17.9)	
Asian	50 (4.4)	268 (4.0)	41 (4.2)	
Other	68 (6.0)	321 (4.8)	56 (5.7)	
Education				<.001
Degree work beyond college	179 (15.1)	1689 (25.4)	196 (20.0)	
Completed college	245 (21.5)	2028 (30.4)	232 (23.7)	
Associates or technical degree	135 (11.8)	669 (10.0)	97 (9.9)	
Some college	262 (23.0)	1193 (17.9)	196 (20.0)	
High school or GED	176 (15.4)	683 (10.3)	135 (13.8)	
Less than high school grad	144 (12.6)	400 (6.0)	124 (12.7)	
Public insurance	430 (38.1)	1581 (23.9)	342 (35.2)	.024
Current partner or significant other	113 (9.9)	285 (4.3)	66 (6.7)	<.001
Household income				.002
<100% FPL	215 (24.3)	746 (13.3)	148 (19.2)	
100%–200% FPL	154 (17.4)	732 (13.1)	135 (17.5)	
>200% FPL	515 (58.3)	4115 (73.6)	488 (63.3)	
Clinical characteristics				
Gravidity category				.934
1	846 (74.2)	5029 (75.5)	727 (74.2)	
2	214 (18.8)	1246 (18.7)	181 (18.5)	
≥3	81 (7.1)	388 (5.8)	72 (7.4)	
Pregnancy planned	596 (52.3)	2428 (36.5)	473 (48.3)	.008
BMI at visit 1 (kg/m^2)	24.9 (21.8–29.3)	24.5 (21.9–28.8)	25.2 (22.3–30.1)	.021
Obesity	252 (22.4)	1383 (21.1)	245 (25.3)	.150
Tobacco use (3 mo before pregnancy)	296 (25.9)	1057 (15.9)	202 (20.6)	<.001
Alcohol use (3 mo before pregnancy)	708 (72.2)	4382 (76.9)	624 (72.9)	.585
Drug use				
Any previous use of illegal drugs	450 (39.4)	2236 (33.6)	357 (36.4)	.089
Problem use (n=3400)	52 (11.7)	148 (6.7)	29 (8.2)	.031
Medical comorbidities				
Chronic hypertension	32 (2.9)	163 (2.5)	22 (2.3)	.392
Diabetes mellitus	22 (2.0)	88 (1.4)	17 (1.8)	.621

Data are presented as median (interquartile range) or number (percentage), unless otherwise indicated.

BMI, body mass index; *FPL*, federal poverty level; *GED*, general educational development.

Miller et al. Trajectories of antenatal depression. Am J Obstet Gynecol 2022.

TABLE 2
Psychiatric characteristics stratified by depressive symptom trajectory category

Characteristic	Depressive symptoms improved (n=1141)	Depressive symptoms remained stable (n=6663)	Depressive symptoms worsened (n=980)	*P* value
Psychiatric medications taken	149 (13.1)	596 (9.0)	111 (11.3)	.102
For psychiatric indication	138 (12.1)	503 (7.6)	105 (10.7)	.132
Used throughout pregnancy	68 (6.0)	249 (3.7)	53 (5.4)	.374
EPDS score at visit 1	10 (8–14)	4 (2–7)	4 (2–7)	<.001
EPDS screen positive at visit 1	361 (31.6)	234 (3.5)	31 (3.2)	<.001
EPDS score at visit 3	4 (2–7)	4 (2–7)	10 (7–13)	<.001
EPDS screen positive at visit 3	40 (3.5)	239 (3.6)	277 (28.3)	<.001

Data are presented as number (percentage) or median (interquartile range), unless otherwise indicated.

EPDS, Edinburgh Postnatal Depression Scale.

Miller et al. Trajectories of antenatal depression. Am J Obstet Gynecol 2022.

We observed a 2.4% absolute increase in the chance of preterm birth associated with a worsened depressive symptom trajectory.

These data called into question the current approach to depression screening in pregnancy. Current clinical practice[29,31] includes screening for depression at least once antenatally and again after delivery. These data suggested that repeated screening—coupled with evidence-based interventions to prevent worsening of symptoms—may be an important opportunity to identify women at risk of and potentially reduce the chance of preterm birth. In addition, these data supported the US Prevention Health Services Task Force recommendation for interventions to prevent perinatal depression.[28]

Biologic plausibility for the observed association between worsened symptoms and preterm birth exists. Marcus et al[19] identified that infants born to women with worsened depressive symptom trajectories, even in the absence of an overt major depressive disorder, had elevated cord blood adrenocorticotrophic hormone. These data pointed to an underlying dysregulation in the hypothalamic-pituitary-adrenal axis in the setting of antenatal depression that may contribute to preterm birth. Specifically, stressful stimuli, such as depressive symptoms, may increase the synthesis and release of corticotropin-releasing hormone (CRH) from the hypothalamus. Precocious elevation of CRH, in turn, has been associated with an increased risk of spontaneous preterm birth.[32] Another potential biologic pathway is

TABLE 3
Bivariable analyses of the associations between depressive symptom trajectory category and adverse perinatal outcomes

Variable	Depressive symptoms improved (n=1141)	Depressive symptoms remained stable (n=6663)	Depressive symptoms worsened (n=980)	*P* value
Hypertensive disorder of pregnancy	265 (23.8)	1510 (23.1)	230 (23.9)	.813
Placental abruption	5 (0.5)	57 (0.9)	10 (1.0)	.271
Cesarean delivery	296 (26.5)	1767 (27.1)	292 (30.3)	.083
Preterm birth (<37 wk)	95 (8.3)	492 (7.4)	97 (9.9)	.018
Spontaneous preterm birth (<37 wk)	52 (4.6)	262 (3.9)	46 (4.7)	.375
Medically indicated preterm birth (<37 wk)	43 (3.8)	230 (3.5)	51 (5.2)	.025
Small for gestational age (<10th percentile)	114 (10.2)	659 (10.1)	131 (13.6)	.005
5-min Apgar score of <7	19 (1.7)	119 (1.8)	21 (2.2)	.697
Neonatal intensive care unit admission	190 (17.1)	1098 (16.9)	166 (17.3)	.950
Maternal postpartum readmission	26 (2.3)	108 (1.7)	14 (1.5)	.223

Data are presented as number (percentage), unless otherwise indicated.

Miller et al. Trajectories of antenatal depression. Am J Obstet Gynecol 2022.

TABLE 4
Bivariable analyses of the associations between depressive symptom trajectory category and adverse perinatal outcomes for subgroups of preterm births

Variable	Depressive symptoms improved (n=1141)	Depressive symptoms remained stable (n=6663)	Depressive symptoms worsened (n=980)	*P* value
Preterm birth at <35 wk	29 (2.5)	195 (2.9)	41 (4.2)	.06
Spontaneous preterm birth at <35 wk	12 (1.1)	100 (1.5)	14 (1.4)	.54
Medically indicated preterm birth at <35 wk	17 (1.5)	95 (1.4)	27 (2.8)	.01
Preterm birth at <32 wk	11 (1.0)	57 (0.9)	12 (1.2)	.51
Spontaneous preterm birth at <32 wk	5 (0.4)	29 (0.4)	4 (0.4)	1.00
Medically indicated preterm birth at <32 wk	6 (0.5)	28 (0.4)	8 (0.8)	.24
Preterm birth at <28 wk	1 (0.1)	8 (0.1)	2 (0.2)	.68
Spontaneous preterm birth at <28 wk	0 (0.0)	6 (0.1)	1 (0.1)	.67
Medically indicated preterm birth at <28 wk	1 (0.1)	2 (0.03)	1 (0.1)	.25

Data are presented as number (percentage), unless otherwise indicated.
Miller et al. Trajectories of antenatal depression. Am J Obstet Gynecol 2022.

dysregulation of the immune system. Inflammation has been causally related to the development of subtypes of depression,[33–35] and individuals with depression have exhibited elevated plasma levels of C-reactive protein, tumor necrosis factor, and interleukin (IL)-1β and IL-6 compared with euthymic controls.[34–36] As these same inflammatory cytokines have been associated with spontaneous preterm birth,[37] an activated immune system may serve as the biologic underpinning of both the evolution of depressive symptoms and its connection to preterm birth.

In addition to the pathophysiological processes described above, there were behavioral and social factors that also have plausibility as mediators of the relationship between worsened antenatal depressive symptoms and preterm birth. These included underutilization of healthcare; use of alcohol, tobacco, or other drugs; and loss of interpersonal support.[18,38,39]

Research implications

The findings from this study underscored the adverse impact of the progression of antenatal depressive symptoms on the maternal-fetal dyad. Multiple evidence-based strategies for the prevention, screening, and treatment of antenatal depression exist but are often underutilized by obstetrical clinicians.[30] Research focused on the implementation of strategies to optimize the utilization of these evidence-based practices within obstetrics practices is essential. In addition, research focused on the mechanistic underpinnings of this association between worsened depressive symptom and preterm birth may uncover adjuvant preterm birth prevention agents for women identified to have worsened depressive symptoms during pregnancy. In the general psychiatry literature, multiple trials of anti-inflammatory agents as either monotherapy or adjuvant therapy for the treatment of a major depressive disorder have demonstrated some promise for the treatment of refractory depression.[40] Whether these agents would have benefit for preterm birth prevention among women with worsening antenatal depressive symptoms has not been examined in prospective trials.

Strengths and limitations

This study was strengthened by the utilization of the nuMoM2b cohort, a large nationally representative sample of nulliparous women that maximized external generalizability. In addition, utilization of this cohort afforded a relatively large sample size of women with serial depressive symptom assessments during pregnancy, which allowed the detection of small but clinically meaningful differences in adverse pregnancy outcomes. Nevertheless, there were limitations. For example, although the overall sample size was large, most women in this cohort, as has been reported in other cohorts,[41] had a stable symptom profile across the antenatal period. Thus, the number of women who experienced a worsened depressive symptom trajectory was relatively small, precluding the identification of smaller, but clinically significant, differences in other adverse perinatal outcomes. In addition, nuMoM2b only assessed depressive symptoms at 2 data points during pregnancy, precluding the utilization of more complex trajectory modeling. The utilization of the simple categorical metrics of change may mask other associations, such as the timing of the depressive symptom inflection or other heterogeneities in the symptom trajectories. However, the simplicity of the categorization of exposure in our analysis did not negate the observed significant association between worsened

TABLE 5
Multivariable analyses for the outcomes of preterm birth and small for gestational age birthweight

	Preterm birth		Medically indicated preterm birth		SGA	
Variable	aRR	95% CI	aRR	95% CI	aRR	95% CI
Worsened depressive symptom trajectory[a]	1.62	1.11–2.36	1.53	0.83–2.81	1.32	0.93–1.88
Maternal age	1.05	1.02–1.08	1.08	1.03–1.13	1.01	0.98–1.05
Education						
Less than high school graduate	1.00	Ref	1.00	Ref	1.00	Ref
High school graduate or GED	1.26	0.63–2.53	0.92	0.28–3.07	0.58	0.33–1.00
Some college	0.90	0.44–1.85	1.12	0.35–3.55	0.67	0.40–1.12
Associate or technical degree	1.19	0.54–2.60	0.71	0.18–2.83	0.67	0.35–1.30
Completed college	0.54	0.24–1.22	0.67	0.18–2.50	0.51	0.26–0.98
Degree work beyond college	0.68	0.30–1.56	0.66	0.17–2.56	0.53	0.27–1.05
Public insurance	1.10	0.68–1.79	1.21	0.56–2.61	0.94	0.60–1.45
Current partner or significant other	0.99	0.53–1.83	0.36	0.09–1.50	0.90	0.52–1.54
Household income						
<100% FPL	1.00	Ref	1.00	Ref	1.00	Ref
100%–200% FPL	1.10	0.58–1.75	1.53	0.67–3.48	1.14	0.71–1.84
<100% FPL	1.54	0.87–2.73	2.20	0.89–5.48	1.34	0.81–2.23
Pregnancy planned	0.98	0.68–1.41	1.13	0.64–2.02	0.99	0.72–1.36
BMI at visit 1 (kg/m^2)	1.01	0.99–1.04	1.05	1.02–1.09	0.96	0.94–0.99
Tobacco use (3 mo before pregnancy)	1.03	0.73–1.45	0.94	0.55–1.64	0.82	0.61–1.09
Problem drug use	0.84	0.50–1.42	0.93	0.39–2.21	1.31	0.78–2.20
EPDS screen positive at visit 1	1.07	0.64–1.80	0.46	0.14–1.47	1.21	0.80–1.84
Psychiatric medication taken	1.11	0.74–1.67	1.28	0.69–2.36	1.08	0.76–1.55

aRR, adjusted risk ratio; *BMI*, body mass index; *CI*, confidence interval; *FPL*, federal poverty level; *GED*, general educational development; *SGA*, small for gestational age.

[a] Referent group includes women with either stable or improved depressive symptom trajectories.

Miller et al. Trajectories of antenatal depression. Am J Obstet Gynecol 2022.

depressive symptom trajectory and preterm birth. Finally, temporality could not be affirmed, and it was possible that some of the observed adverse perinatal outcomes (eg, hypertensive disorders of pregnancy) could have been diagnosed before the collection of the second EPDS screen (ie, between 22 0/7 and 29 6/7 weeks' gestation). However, given the epidemiologic rarity of the diagnosis of a hypertensive disorder of pregnancy before 30 weeks' gestation,[42] this was an unlikely source of bias.

Conclusions

This secondary analysis of data collected prospectively from a large, multisite cohort identified a statistically and clinically significant association between antenatal depressive symptom trajectory and preterm birth. These findings underscored the need to focus public health interventions and clinical research efforts within the field of maternal mental health to optimize the health of the maternal-infant dyad. ■

References

1. Wisner KL, Sit DK, McShea MC, et al. Onset timing, thoughts of self-harm, and diagnoses in postpartum women with screen-positive depression findings. JAMA Psychiatry 2013;70:490–8.

2. Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. Obstet Gynecol 2005;106:1071–83.

3. Ko JY, Rockhill KM, Tong VT, Morrow B, Farr SL. Trends in postpartum depressive symptoms - 27 states, 2004, 2008, and 2012. MMWR Morb Mortal Wkly Rep 2017;66:153–8.

4. Banti S, Mauri M, Oppo A, et al. From the third month of pregnancy to 1 year postpartum. Prevalence, incidence, recurrence, and new onset of depression. Results from the perinatal depression-research & screening unit study. Compr Psychiatry 2011;52:343–51.

5. Norhayati MN, Hazlina NH, Asrenee AR, Emilin WM. Magnitude and risk factors for postpartum symptoms: a literature review. J Affect Disord 2015;175:34–52.

6. O'Hara MW, McCabe JE. Postpartum depression: current status and future directions. Annu Rev Clin Psychol 2013;9:379–407.

7. Nicholson WK, Setse R, Hill-Briggs F, Cooper LA, Strobino D, Powe NR. Depressive

symptoms and health-related quality of life in early pregnancy. Obstet Gynecol 2006;107:798–806.
8. Hu R, Li Y, Zhang Z, Yan W. Antenatal depressive symptoms and the risk of preeclampsia or operative deliveries: a meta-analysis. PLoS One 2015;10:e0119018.
9. de Paz NC, Sanchez SE, Huaman LE, et al. Risk of placental abruption in relation to maternal depressive, anxiety and stress symptoms. J Affect Disord 2011;130:280–4.
10. Chung TK, Lau TK, Yip AS, Chiu HF, Lee DT. Antepartum depressive symptomatology is associated with adverse obstetric and neonatal outcomes. Psychosom Med 2001;63:830–4.
11. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch Gen Psychiatry 2010;67:1012–24.
12. Oberlander TF, Warburton W, Misri S, Aghajanian J, Hertzman C. Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. Arch Gen Psychiatry 2006;63:898–906.
13. Orr ST, James SA, Blackmore Prince C. Maternal prenatal depressive symptoms and spontaneous preterm births among African-American women in Baltimore, Maryland. Am J Epidemiol 2002;156:797–802.
14. El Marroun H, Jaddoe VW, Hudziak JJ, et al. Maternal use of selective serotonin reuptake inhibitors, fetal growth, and risk of adverse birth outcomes. Arch Gen Psychiatry 2012;69:706–14.
15. Wisner KL, Bogen DL, Sit D, et al. Does fetal exposure to SSRIs or maternal depression impact infant growth? Am J Psychiatry 2013;170:485–93.
16. Dowse E, Chan S, Ebert L, et al. Impact of perinatal depression and anxiety on birth outcomes: a retrospective data analysis. Matern Child Health J 2020;24:718–26.
17. Clapp MA, Little SE, Zheng J, Robinson JN. A multi-state analysis of postpartum readmissions in the United States. Am J Obstet Gynecol 2016;215:113.e1–10.
18. Stein A, Pearson RM, Goodman SH, et al. Effects of perinatal mental disorders on the fetus and child. Lancet 2014;384:1800–19.
19. Marcus S, Lopez JF, McDonough S, et al. Depressive symptoms during pregnancy: impact on neuroendocrine and neonatal outcomes. Infant Behav Dev 2011;34:26–34.
20. Christensen AL, Stuart EA, Perry DF, Le HN. Unintended pregnancy and perinatal depression trajectories in low-income, high-risk Hispanic immigrants. Prev Sci 2011;12:289–99.
21. Kuo SY, Chen SR, Tzeng YL. Depression and anxiety trajectories among women who undergo an elective cesarean section. PLoS One 2014;9:e86653.
22. Kuo SY, Yang YL, Kuo PC, Tseng CM, Tzeng YL. Trajectories of depressive symptoms and fatigue among postpartum women. J Obstet Gynecol Neonatal Nurs 2012;41:216–26.
23. Mora PA, Bennett IM, Elo IT, Mathew L, Coyne JC, Culhane JF. Distinct trajectories of perinatal depressive symptomatology: evidence from growth mixture modeling. Am J Epidemiol 2009;169:24–32.
24. Haas DM, Parker CB, Wing DA, et al. A description of the methods of the Nulliparous Pregnancy Outcomes Study: monitoring mothers-to-be (nuMoM2b). Am J Obstet Gynecol 2015;212:539.e1–24.
25. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry 1987;150:782–6.
26. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. Obstet Gynecol 1996;87:163–8.
27. Wikman A, Axfors C, Iliadis SI, Cox J, Fransson E, Skalkidou A. Characteristics of women with different perinatal depression trajectories. J Neurosci Res 2020;98:1268–82.
28. US Preventive Services Task Force, Curry SJ, Krist AH, et al. Interventions to prevent perinatal depression: US Preventive Services Task Force recommendation statement. JAMA 2019;321:580–7.
29. Siu AL, US Preventive Services Task Force (USPSTF), Bibbins-Domingo K, et al. Screening for depression in adults: US Preventive Services Task Force recommendation statement. JAMA 2016;315:380–7.
30. Cox EQ, Sowa NA, Meltzer-Brody SE, Gaynes BN. The perinatal depression treatment cascade: baby steps toward improving outcomes. J Clin Psychiatry 2016;77:1189–200.
31. The American College of Obstetricians and Gynecologists Committee Opinion no. 630. Screening for perinatal depression. Obstet Gynecol 2015;125:1268–71.
32. Sandman CA, Wadhwa PD, Chicz-DeMet A, Dunkel-Schetter C, Porto M. Maternal stress, HPA activity, and fetal/infant outcome. Ann N Y Acad Sci 1997;814:266–75.
33. Hiles SA, Baker AL, de Malmanche T, Attia J. A meta-analysis of differences in IL-6 and IL-10 between people with and without depression: exploring the causes of heterogeneity. Brain Behav Immun 2012;26:1180–8.
34. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med 2009;71:171–86.
35. Raedler TJ. Inflammatory mechanisms in major depressive disorder. Curr Opin Psychiatry 2011;24:519–25.
36. Köhler CA, Freitas TH, Maes M, et al. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. Acta Psychiatr Scand 2017;135:373–87.
37. Gomes J, Au F, Basak A, Cakmak S, Vincent R, Kumarathasan P. Maternal blood biomarkers and adverse pregnancy outcomes: a systematic review and meta-analysis. Crit Rev Toxicol 2019;49:461–78.
38. Howard LM, Molyneaux E, Dennis CL, Rochat T, Stein A, Milgrom J. Non-psychotic mental disorders in the perinatal period. Lancet 2014;384:1775–88.
39. Metz TD, Rovner P, Hoffman MC, Allshouse AA, Beckwith KM, Binswanger IA. Maternal deaths From suicide and overdose in Colorado, 2004-2012. Obstet Gynecol 2016;128:1233–40.
40. Kohler O, Krogh J, Mors O, Benros ME. Inflammation in depression and the potential for anti-inflammatory treatment. Curr Neuropharmacol 2016;14:732–42.
41. Baron E, Bass J, Murray SM, Schneider M, Lund C. A systematic review of growth curve mixture modelling literature investigating trajectories of perinatal depressive symptoms and associated risk factors. J Affect Disord 2017;223:194–208.
42. Lisonkova S, Sabr Y, Mayer C, Young C, Skoll A, Joseph KS. Maternal morbidity associated with early-onset and late-onset preeclampsia. Obstet Gynecol 2014;124:771–81.

Author and article information

From the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine, Chicago, IL (Drs Miller and Grobman); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, The University of Texas Medical Branch, Galveston, TX (Dr Saade); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Pittsburgh, Pittsburgh, PA (Dr Simhan); Departments of Obstetrics and Gynecology and Psychiatry, Columbia University Medical Center, New York, NY (Dr Monk); Department of Obstetrics and Gynecology, Indiana University School of Medicine, Indianapolis, IN (Dr Haas); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Utah Health Sciences Center, Salt Lake City, UT (Dr Silver); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH (Dr Mercer); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia, PA (Dr Parry); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, School of Medicine, University of California, Irvine, MemorialCare Miller Children's & Women's Hospital Long Beach, Irvine, CA (Dr Wing); and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD (Dr Reddy).

Received Sept. 2, 2020; revised July 13, 2021; accepted July 13, 2021.

The authors report no conflict of interest.

This study was supported by grant funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD): RTI International (U10 HD063036), Case Western Reserve University (U10 HD063072), Columbia

University (U10 HD063047), Indiana University (U10 HD063037), University of Pittsburgh (U10 HD063041), Northwestern University (U10 HD063020), University of California, Irvine (U10 HD063046), University of Pennsylvania (U10 HD063048), and University of Utah (U10 HD063053). In addition, support was provided by the respective clinical and translational science institutes of Indiana University (UL1TR001108) and University of California, Irvine (UL1TR000153).

This study was registered on ClinicalTrials.gov (NCT01322529).

The findings of this study were presented as an oral presentation at the 39th annual scientific meeting of the Society for Maternal-Fetal Medicine, Las Vegas, NV, February 11—16, 2019.

Corresponding author: Emily S. Miller, MD, MPH. emily-miller-1@northwestern.edu