Original Investigation

Pregnant Women With Posttraumatic Stress Disorder and Risk of Preterm Birth

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IMPORTANCE Posttraumatic stress disorder (PTSD) occurs in about 8% of pregnant women. Stressful conditions, including PTSD, are inconsistently linked to preterm birth. Psychotropic treatment has been frequently associated with preterm birth. Identifying whether the psychiatric illness or its treatment is independently associated with preterm birth may help clinicians and patients when making management decisions.

OBJECTIVE To determine whether a likely diagnosis of PTSD or antidepressant and benzodiazepine treatment during pregnancy is associated with risk of preterm birth. We hypothesized that pregnant women who likely had PTSD and women receiving antidepressant or anxiolytic treatment would be more likely to experience preterm birth.

DESIGN, SETTING, AND PARTICIPANTS Longitudinal, prospective cohort study of 2654 women who were recruited before 17 completed weeks of pregnancy from 137 obstetrical practices in Connecticut and Western Massachusetts.

EXPOSURES Posttraumatic stress disorder, major depressive episode, and use of antidepressant and benzodiazepine medications.

MAIN OUTCOMES AND MEASURES Preterm birth, operationalized as delivery prior to 37 completed weeks of pregnancy. Likely psychiatric diagnoses were generated through administration of the Composite International Diagnostic Interview and the Modified PTSD Symptom Scale. Data on medication use were gathered at each participant interview.

RESULTS Recursive partitioning analysis showed elevated rates of preterm birth among women with PTSD. A further split of the PTSD node showed high rates for women who met criteria for a major depressive episode, which suggests an interaction between these 2 exposures. Logistic regression analysis confirmed risk for women who likely had both conditions (odds ratio [OR], 4.08 [95% CI, 1.27-13.15]). For each point increase on the Modified PTSD Symptom Scale (range, 0-110), the risk of preterm birth increased by 1% to 2%. The odds of preterm birth are high for women who used a serotonin reuptake inhibitor (OR, 1.55 [95% CI, 1.02-2.36]) and women who used a benzodiazepine medication (OR, 1.99 [95% CI, 0.98-4.03]).

CONCLUSIONS AND RELEVANCE Women with likely diagnoses of both PTSD and a major depressive episode are at a 4-fold increased risk of preterm birth; this risk is greater than, and independent of, antidepressant and benzodiazepine use and is not simply a function of mood or anxiety symptoms.

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Preterm birth (<37 weeks' gestation) is thought to be responsible for two-thirds of all infant deaths.[1] Psychosocial stress is a behavioral factor implicated in risk of preterm birth,[2-10] although negative associations are also found in the literature.[11-18] Activation of the hypothalamic-pituitary axis, which occurs with stress and promotes preterm delivery, may underlie an association.[19] If the link between stress and preterm birth is causal, one would expect that severe stress-related conditions such as posttraumatic stress disorder (PTSD) would be linked to preterm birth. However, studies[20-25] have been inconsistent, with most having had limited power and typically a single assessment point with or without controlling for critical confounding variables. Antidepressant or anxiolytic treatment and major depressive episodes (MDEs) are important confounders to consider because they have also been associated with preterm birth and commonly occur with PTSD.[8,26-41]

Clinicians and patients are concerned about the possible risks associated with psychiatric illness during pregnancy and the medications used for treatment. If the use of psychotropic medication increases the risk of preterm birth, then women who are able to at least temporarily discontinue treatment may elect to do so. If the underlying illness is associated with preterm birth, then a woman may wish to receive treatment during pregnancy or forestall pregnancy until her condition is stable. Given that management decisions may rely on perceived risks and benefits, we explore the possible associations between preterm birth, PTSD, and the agents used to treat PTSD. We used data from a longitudinal, prospective, multisource assessment study to examine whether a probable diagnosis of PTSD during pregnancy, with or without other current psychiatric disorders (MDE, generalized anxiety disorder, or panic disorder) and psychopharmacological treatment, is associated with an increased risk of preterm birth. We posited that pregnant women with a current diagnosis of PTSD would be more likely to experience preterm birth, although this would be moderated by other psychiatric conditions. Based on prior work,[35] we also hypothesized that treatment with antidepressants and benzodiazepine would be independent risk factors for preterm birth.

Methods

Study Design

This prospective cohort study of pregnant women was conducted between March 2005 and May 2009.[35] The Yale University School of Medicine in New Haven, Connecticut, and study-affiliated hospitals provided human subjects approval.

Inclusion/Exclusion Criteria

Women at least 18 years of age who had not yet completed 17 weeks of pregnancy and were willing and able to provide informed consent were potentially eligible. Women were not eligible if they (1) had a known multiple pregnancy, (2) were undergoing treatment with insulin for diabetes mellitus, (3) did not speak English or Spanish, (4) did not have access to a telephone, (5) had plans to relocate, or (6) intended to terminate their pregnancy.

Recruitment and Assessment Procedures

We recruited from 137 obstetrical practices in Connecticut and Western Massachusetts. Pregnant patients were given letters inviting them to participate; these letters were returned to the central data collection site. Study staff members contacted women by telephone, obtained written consent, and administered a structured screening questionnaire. We offered participation to women who had used an antidepressant, experienced an MDE in the last 5 years, or experienced a traumatic event and had symptoms of reexperiencing the trauma. We also randomly selected one-third of potentially eligible women without these characteristics to participate as "nonexposed" comparison participants. At the subsequent face-to-face evaluation, we obtained written consent for the interviews and medical record review. The initial home interview was conducted before 17 completed weeks of gestation, whereas follow-up interviews were conducted by telephone at 28 (±2) weeks' gestation and again 8 (±4) weeks after delivery. Participants received $20 for each interview. Women who were having an episode of psychiatric disorder and not receiving care were offered treatment referrals, or, if there was a question of safety, we quickly conducted a psychiatric assessment.

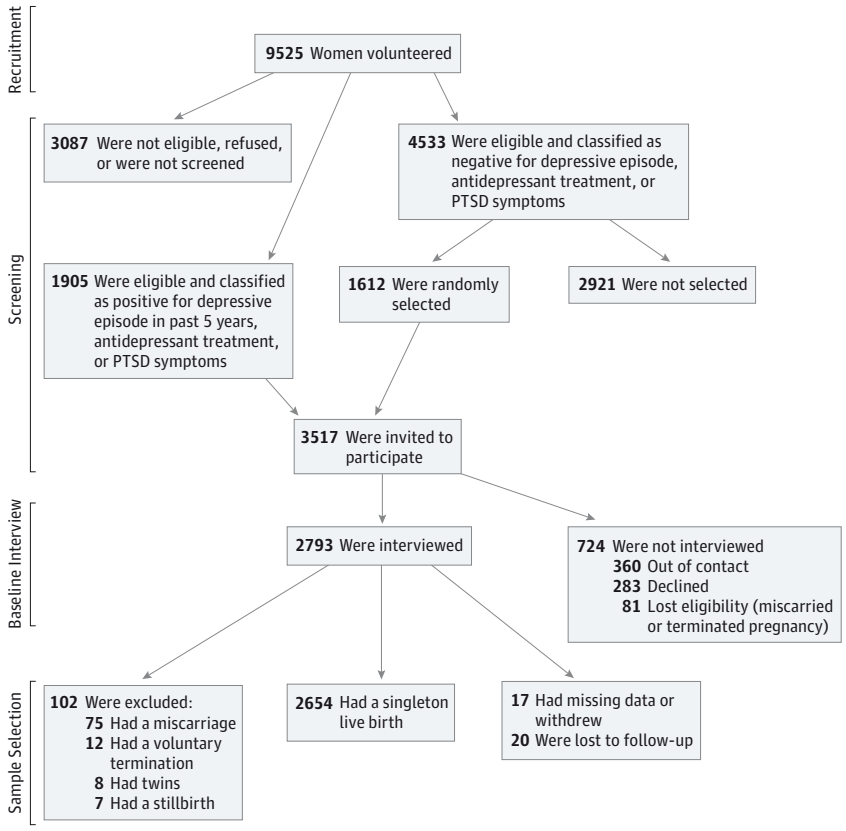
Exposure and Outcome Measures

We used modules from the World Health Organization World Mental Health Composite International Diagnostic Interview (CIDI), version 2.1, to collect information on symptoms consistent with an MDE, generalized anxiety disorder, and panic disorder at each interview. In addition to the standard lifetime modules, we collected monthly data from the beginning of pregnancy (at the home interview) and since the prior interview (for subsequent interviews). The CIDI interview is a fully structured lay interview[42] that has been administered to more than 150 000 people from 28 countries, including nearly 500 pregnant women.[43,44] It has high concordance with the Structured Clinical Interview for *DSM-IV* for prevalence during a 12-month period.[45] The area under the receiver operating characteristic curve between the semistructured clinical interview and the CIDI interview is between 0.8 and 0.9 for a depressive disorder.[45] The interview is similarly reliable when administered by telephone.[45]

We determined a likely diagnosis of PTSD by administration of the Modified PTSD Symptom Scale (MPSS).[46] The scale has 17 items and generates a *DSM-III-R* diagnosis; items are scored from 0 to 3 for frequency and from 0 to 4 for severity and can be summed to estimate illness severity. We added a question about responding to the trauma with fear, helplessness, or horror (the A-2 criterion) and revised the algorithm to determine *DSM-IV* PTSD. The MPSS demonstrates good overall concurrent validity with *DSM-III-R* PTSD and internal consistency ($\alpha = 0.96$ for treatment and $\alpha = 0.97$ for community samples).[46] A dimensional score of 28 correctly classifies 74% of individuals with sensitivity of 0.89 and specificity of 0.65.[47]

To determine preterm births (births of <37 completed weeks), we obtained self-reports of the last menstrual pe-

Figure 1. Patient Flowchart



PTSD indicates posttraumatic stress disorder.

riod, and we collected data from medical records on fetal ultrasonographic results and on the number of weeks of pregnancy. We used an algorithm to determine preterm birth that prioritized the validity of the data source. Thus, ultrasonographic data prior to 18 weeks were the primary outcome measures, and self-reports of last menstrual period were used if data on early ultrasonography were not available. If neither of those outcome measures were available, the clinician assessment at birth was used.

Potential Confounding Variables

Information about prior pregnancies, including prior preterm delivery, was obtained at study intake. At each visit, we collected information about the amount and dates of medication use, cigarette smoking, alcohol use, illicit drug use, and pregnancy complications. For this analysis, we focused on benzodiazepines and serotonin reuptake inhibitors (SRIs) because they are associated with preterm birth and are commonly used during pregnancy[48] and for treatment of our target disorders. Although we had obtained written consent from our participants for access to their medical records from outpatient providers (to access data on medication prescriptions), many clinicians declined to provide the data, rendering the data inadequate for analysis.

Interviewers and Quality Control

Interviewers received extensive training that included a minimum of 4 days of instruction and completion of at least 6 practice and 4 supervised interviews. We obtained permission to audiotape interviews and randomly selected 10% of the audiotapes, including telephone interviews, for quality-control assessments.

Study Enrollment

Study enrollment is illustrated in **Figure 1**. Of the 3517 women invited to participate, 2793 (79%) were interviewed. In the analysis, we include only singleton live births (n = 2654). Of these 2654 women, 2487 (94%) completed at least 1 of the 2 remaining interviews, and 2208 (83%) completed both interviews. Data on birth outcomes were available for 99% of these women.

Statistical Methods

Preterm birth was the outcome variable of interest. We used recursive partitioning, simple, and multivariable logistic regression analysis to examine the relationship between preterm birth and a likely diagnosis of PTSD.

Recursive partitioning analysis is a nonparametric method that can be used as an exploratory method to detect complex interactions among individuals who share characteristics as-

sociated with an outcome of interest.[49-51] Given the complexity of estimating associations with participants who received more than 1 psychiatric diagnosis and have potential clusters of health behaviors, this method allowed us to identify potential interactions that could be used in confirmatory logistic regression models. The nodes in recursive partitioning analyses occur in hierarchies (splits) that identify risk factors that most robustly partition the sample according to the likelihood of experiencing the main outcome (ie, preterm birth). We separated the sample into training (n = 1995; 75% of total sample) and testing (n = 659; 25% of total sample) subsamples to validate the recursive partitioning results. Stopping rules were set at a maximum depth of 6 levels with a minimum node size of 25, or approximately 1% of the total sample.

Recursive partitioning analysis is biased against risk factors that are few in number, unless they have very large effects. Logistic regression can handle this limitation, can include covariates that in theory may have affected our results, and can provide measures of association. We thus used multivariable models, which included the identified interactions from recursive partitioning analysis and controlled for other psychiatric diagnoses indicated by the CIDI (MDE, generalized anxiety disorder, or panic disorder) during pregnancy; age; self-reported race/ethnicity; education (a proxy for socioeconomic status); use of cigarettes, illegal drugs, alcohol, or psychotropic medications (SRIs and benzodiazepines) during pregnancy; and previous pregnancy outcomes. We present unadjusted and adjusted odds ratio (OR) estimates and 95% CIs between the exposure, the confounding variables, and preterm birth.

We used the following conventions: If a woman met criteria for a psychiatric diagnosis at any point during pregnancy, she was classified as positive for that disorder. If a woman had partial data (eg, missed 1 or 2 interviews) and was classified as negative for a particular disorder, we considered her as negative during pregnancy. Heavy alcohol use was defined as 4 or more drinks per week or 3 or more drinks in 1 sitting any time during pregnancy. Previous pregnancy outcomes were coded as a dichotomous variable (previous preterm birth vs term births or no previous live births). Age (<25, 25-34, or ≥35 years), race/ethnicity (Hispanic, black, white, or other), and education (<12, 12, 13-15, or ≥16 years) were categorical variables.

We performed sensitivity analyses to examine the robustness of our psychiatric disorder classifications and to probe the effects of depressive and anxiety symptoms. First, we expanded the PTSD category to include women with subsyndromal PTSD[52] operationalized as endorsement of at least 1 symptom from any of the *DSM-IV* PTSD symptom clusters (B, C, or D). Second, we used the MPSS as a dimensional measure. Third, we explored the effect of mood severity on preterm birth by the use of a dimensional measure, the Edinburgh Postnatal Depression Scale (EPDS), which was given at each interview. Fourth, because PTSD is an anxiety disorder, we used the anxiety subscale of the EPDS and information on panic attacks rather than the *DSM* category for anxiety disorders to explore the association between anxiety and preterm birth. For all models, we included covariates for SRI and benzodiazepine use, as well as the confounding variables already noted. We used SPSS Answer Tree version 3.1 (SPSS Inc) to conduct the recursive partitioning analysis and SAS version 9.2 (SAS Institute Inc) for all other analyses.

Results

Symptoms consistent with a *DSM-IV* diagnosis of PTSD during pregnancy were endorsed by 129 (4.9%) women, including 78 in the first, 43 in the second, and 33 in the third trimester. The eTable in the Supplement provides demographic and diagnostic information about women with and without a likely diagnosis of PTSD.

Recursive Partitioning Analyses

Within each node, the numbers and percentages of women for the training sample and for the testing sample are displayed in **Figure 2**. The estimates for training and testing generally agree, with the exception of nodes 4 and 9, which had very small numbers in the testing sample that likely affected the stability of the estimate. The primary split was based on prior preterm birth, which suggests that it is the most informative factor. The node for women with no history of preterm birth (node 1) was further split based on whether or not the woman met the diagnostic criteria for PTSD anytime during pregnancy. The node for women without PTSD (node 3) was split again based on age. The node for women with a probable PTSD diagnosis (node 4) was split again based on whether or not the woman met the diagnostic criteria for MDE anytime during pregnancy. This split suggested that the association between preterm birth and PTSD during pregnancy was moderated by MDE during pregnancy, a potential interaction that we further tested in the logistic regression analyses.

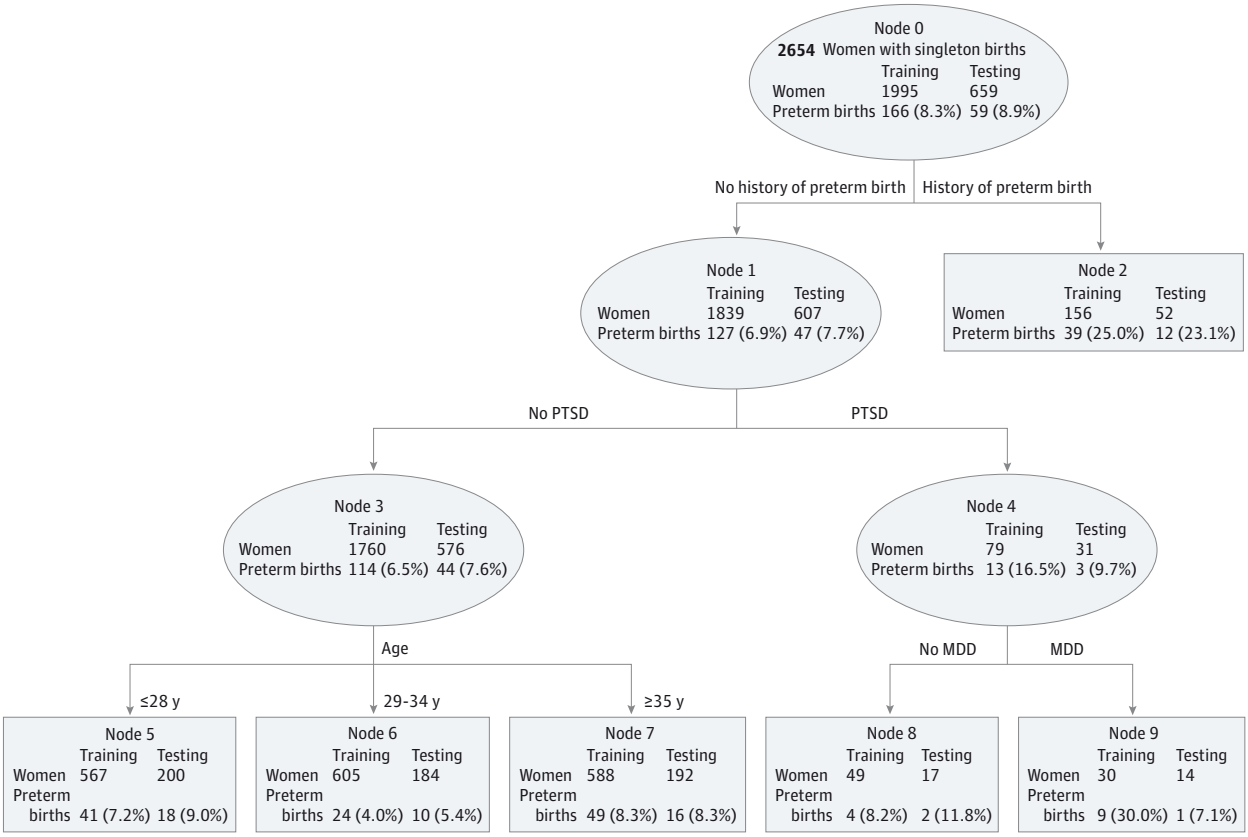
Logistic Regression Analyses Using the Syndromal PTSD Diagnosis

The **Table** shows results for the unadjusted and adjusted logistic regression analyses. Preterm birth was positively associated with SRI use (OR, 1.55 [95% CI, 1.02-2.36]) and preterm birth history (OR, 4.37 [95% CI, 3.02-6.33]) and was negatively associated with mother's age (25-34 years compared with ≥35 years; OR, 0.62 [95% CI, 0.45-0.85]). There was a significant interaction between likely diagnosis of PTSD and likely diagnosis of MDE, with an estimated OR of preterm birth that was 4-fold higher than that for women without threshold symptoms of both PTSD and MDE (OR, 4.08 [95% CI, 1.27-13.15]). In contrast, the estimated odds of preterm birth when adjusting for all factors listed in the Table were not significantly different between women with a likely diagnosis of PTSD and women with a likely diagnosis of MDE.

Sensitivity Analyses

Inclusion of women with subsyndromal PTSD symptoms attenuated the interaction with MDE slightly (OR, 3.82 [95% CI, 1.29-11.28]), but the other significant associations were nearly unchanged. The severity of symptoms according to the MPSS scores (range, 0-110) was nonlinear because many women had

Figure 2. Classification Tree for Risk of Preterm Birth



Ovals indicate decision nodes, and rectangles indicate terminal nodes. The number of women and the preterm birth rate (in parentheses) are displayed within each node for the women in the training sample and for the women in the testing sample. MDD indicates major depressive disorder; PTB, preterm birth; and PTSD, posttraumatic stress disorder.

no trauma/intense fear or horror, and thus scored a "0." A model with nonzero MPSS scores (as well as variables for PTSD, MDE, and the PTSD-MDE interaction) found the MPSS score to be a trend (OR, 1.01 [95% CI, 1.00-1.02]) suggesting possible weak relationships between PTSD symptoms and risk of preterm birth or between the historical exposure to trauma and risk of preterm birth. The EPDS score (range, 0-30), considered in 6-point increments, or 1 SD, was not associated with preterm birth in the adjusted analysis (OR, 1.10 [95% CI, 0.94-1.28]). Neither the anxiety subscale scores of the EPDS nor panic attacks were significantly associated with preterm birth in adjusted analyses.

Discussion

The present study estimated associations between PTSD, other psychiatric conditions, and their treatments with regard to risk of preterm birth. Risk of preterm birth was elevated in women with a likely diagnosis of PTSD, but this was accounted for by individuals who also reported symptoms consistent with concurrent MDE. The magnitude of the effect of PTSD with MDE was large because the risk of preterm birth for women with this psychiatric comorbidity pattern was nearly as high as the risk conferred by having had a previous preterm birth. The estimated risk of this pattern of psychiatric comorbidity was much larger than that for either SRI or benzodiazepine treatment, although wide and overlapping 95% CIs temper this inference.

Previous work investigating a possible association between preterm birth and a diagnosis of PTSD has not consistently been supported,[23,25,53] although some studies[25,53] included very few participants with PTSD. Other studies[20,22,54] suggest that PTSD is a risk factor for preterm birth. A registry study[20] reported that women with PTSD as a result of the September 11, 2001, terrorist attacks had a greater than 2-fold increased risk of preterm birth. Pregnant women with PTSD (98 with a current diagnosis and 157 with a past diagnosis) were also shown to deliver smaller babies than those without the diagnosis; there was a trend for participants with current PTSD to deliver preterm as well.[24] A history of childhood sexual abuse in this group increased the risk of adverse birth outcomes, although MDE was not addressed. Certainly, childhood sexual abuse places women at risk for both PTSD and MDE.

In addition to the syndromal categories for mood and anxiety disorders, we examined whether trauma and PTSD symptoms contribute to risk of preterm birth. We found that exposure to traumatic events and lifetime symptoms may confer

Table. Main Exposure, Demographic Characteristics, and Potential Confounding Factors by Preterm Birth

Characteristic	Women, No. (%)			Odds Ratio (95% CI)	
	All (n = 2654)	Term (n = 2429)	Preterm (n = 225)	Unadjusted	Adjusted
Age, y					
<25	440 (17)	397 (16)	43 (19)	0.87 (0.59-1.29)	0.93 (0.58-1.50)
25-34	1509 (57)	1405 (58)	104 (46)	0.60 (0.44-0.81)	0.62 (0.45-0.85)
≥35	705 (27)	627 (26)	78 (35)	1 [Reference]	1 [Reference]
Race/Ethnicity					
White	1957 (74)	1799 (74)	158 (70)	1 [Reference]	1 [Reference]
Black	195 (7)	172 (7)	23 (10)	1.52 (0.96-2.42)	1.18 (0.70-1.98)
Hispanic	383 (14)	348 (14)	35 (16)	1.14 (0.78-1.68)	1.15 (0.75-1.79)
Other	119 (4)	110 (5)	9 (4)	0.93 (0.46-1.87)	1.03 (0.50-2.11)
Education, y					
<12	172 (6)	158 (6)	14 (6)	1.09 (0.61-1.94)	0.68 (0.33-1.39)
12	382 (14)	345 (14)	37 (16)	1.32 (0.89-1.94)	1.02 (0.64-1.63)
13-15	599 (23)	538 (22)	61 (27)	1.39 (1.00-1.93)	1.22 (0.85-1.76)
≥16	1501 (57)	1388 (57)	113 (50)	1 [Reference]	1 [Reference]
Any cigarette use during pregnancy	389 (15)	355 (15)	34 (15)	1.04 (0.71-1.52)	0.69 (0.44-1.08)
Illegal drug use[a]	209 (8)	185 (8)	24 (11)	1.45 (0.92-2.27)	1.31 (0.79-2.16)
Heavy alcohol use[b]	24 (1)	20 (1)	4 (2)	2.18 (0.74-6.43)	2.26 (0.74-6.94)
Psychiatric disorders[c,d]					
PTSD	129 (5)	106 (4)	23 (10)	2.50 (1.55-4.01)	1.22 (0.57-2.61)
MDD	222 (8)	196 (8)	26 (12)	1.49 (0.96-2.30)	0.70 (0.37-1.33)
GAD	252 (9)	225 (9)	27 (12)	1.34 (0.87-2.04)	0.92 (0.55-1.52)
Panic disorder	98 (4)	82 (3)	16 (7)	2.19 (1.26-3.81)	1.57 (0.83-2.94)
PTSD and MDD	51 (2)	37 (2)	14 (6)	4.31 (2.29-8.11)	4.08 (1.27-13.15)
Psychotropic drug use[c]					
SRIs	293 (11)	257 (11)	36 (16)	1.61 (1.10-2.35)	1.55 (1.02-2.36)
Benzodiazepines	67 (3)	55 (2)	12 (5)	2.43 (1.28-4.61)	1.99 (0.98-4.03)
Pregnancy history					
No previous live births	1140 (43)	1036 (43)	104 (46)	1 [Reference]	1 [Reference]
Term births only	1306 (49)	1236 (51)	70 (31)		
At least 1 preterm birth	208 (8)	157 (6)	51 (23)	4.24 (2.98-6.03)	4.37 (3.02-6.33)

Abbreviations: GAD, generalized anxiety disorder; MDD, major depressive disorder; PTSD, posttraumatic stress disorder; SRIs, serotonin reuptake inhibitors.

[a] Illegal drugs included marijuana, cocaine, heroin, lysergic acid diethylamide, phencyclidine, methamphetamines, and any other illegal drug used during pregnancy.

[b] Defined as having 4 or more drinks per week or 3 or more drinks in 1 sitting during pregnancy.

[c] During pregnancy.

[d] Psychiatric disorder diagnoses are not mutually exclusive.

elevated risk of preterm birth. Although others have also found that exposure to traumatic events increases the risk of preterm birth,[55] the results are not uniform, which suggests that additional factors might play a role.[56]

The notion that stress and stress-related disorders increase the risk of preterm birth is biologically plausible.[57] Stress stimulates the hypothalamic-pituitary axis, which, for individuals with PTSD, is reflected by elevated central levels of corticotrophin-releasing hormone (CRH).[58,59] During pregnancy, the placenta is an important peripheral source of CRH, which is stimulated by fetal and maternal glucocorticoids and cytokines.[60,61] The level of CRH gradually increases as the pregnancy progresses, thus serving as a "placental clock" that determines the timing of parturition.[62] Severe stress during pregnancy may prematurely increase CRH production, pushing the timing of parturition forward and promoting preterm birth.[10,60] Stress also activates the immune system. Bacterial vaginosis has a well-documented association with preterm birth, and risk of this infection during pregnancy is linked to early life adversity, lifetime trauma, and maternal stress.[63-66]

We note several limitations with our study. First, although we used a well-validated interview to generate possible psychiatric diagnoses, assessments were administered by lay interviewers and not clinicians. Second, we assumed women who were classified as negative for an illness at baseline and missed subsequent interviews remained negative. If instead they had onset of PTSD or MDE, the resulting misclassification could bias findings toward the null and underestimate our associations. Third, given the elevated OR in the unadjusted analysis for panic disorder, it is possible that this condition influences birth outcomes. Our cohort included only 98 participants who met symptom criteria for panic disorder, which limits our ability to test any but the strongest associations with preterm birth. Our analyses suggest that benzodiazepine use during pregnancy may increase the risk of preterm birth, although we had relatively few women who used benzodiazepines during pregnancy (n = 68). Finally,

we did not have a biomarker, such as CRH, that we could use to test associations between symptoms of PTSD and MDE and birth outcomes. If women with PTSD and MDE constitute a group with elevated CRH levels and preterm birth, then that would provide biological evidence of the stress and preterm birth theory.[61] Finally, women with a likely diagnosis of PTSD varied markedly from those with threshold level symptoms in a variety of ways, including socioeconomic status and use of substances. Although, we included these potential confounders in our analysis, residual confounding may contribute to our findings.

Conclusions

In summary, our results suggest that women with likely diagnoses of both PTSD and MDE are at a 4-fold increased risk of preterm birth. This risk appears independent of antidepressant or benzodiazepine use and is not simply a function of mood or anxiety symptoms. Further exploration of the biological and genetic factors will help risk-stratify patients and illuminate the pathways leading to this risk.

ARTICLE INFORMATION

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Study concept and design: Yonkers, Smith, Belanger.
Acquisition, analysis, or interpretation of data: All authors.
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