


Original Investigation

Pregnant Women With Posttraumatic Stress Disorder and Risk of Preterm Birth

Kimberly Ann Yonkers, MD; Megan V. Smith, DrPh; Ariadna Forray, MD; C. Neill Epperson, MD; Darce Costello, EdD; Haiqun Lin, PhD, MD; Kathleen Belanger, PhD[†]

 Supplemental content at jamapsychiatry.com

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.

Author Affiliations: Department of Psychiatry, Yale School of Medicine, New Haven, Connecticut (Yonkers, Smith, Forray, Costello); Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale School of Medicine, New Haven, Connecticut (Yonkers); Yale School of Public Health, New Haven, Connecticut (Yonkers, Smith, Lin, Belanger); Child Study Center, Yale School of Medicine, New Haven, Connecticut (Smith); Penn Center for the Study of Sex and Gender in Behavioral Health, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia (Epperson); Department of Obstetrics and Gynecology, Perelman School of Medicine, University of Pennsylvania, Philadelphia (Epperson).

Corresponding Author: Kimberly Ann Yonkers, MD, Department of Psychiatry, Yale School of Medicine, 142 Temple St, Ste 301, New Haven, CT (kimberlyyonkers@yale.edu).

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2014.558
Published online June 11, 2014.

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, studies²⁰⁻²⁵ 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, multi-source 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 tele-

phone, (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.

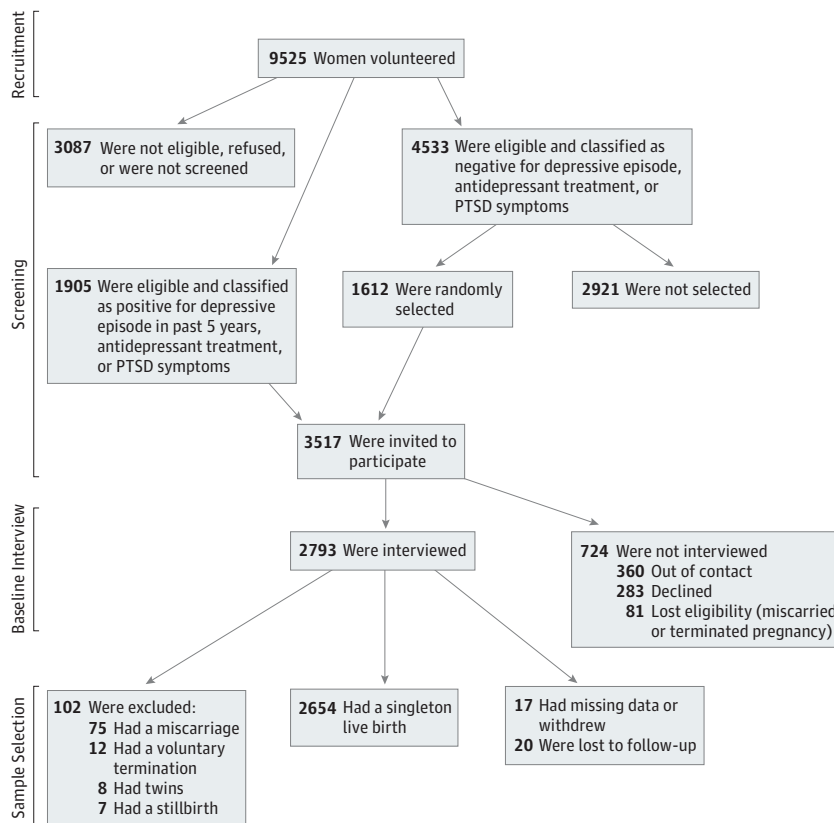
Exposure and Outcome Measures

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 interview⁴² 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 pregnancy⁴⁸ 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 PTSD⁵² 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.

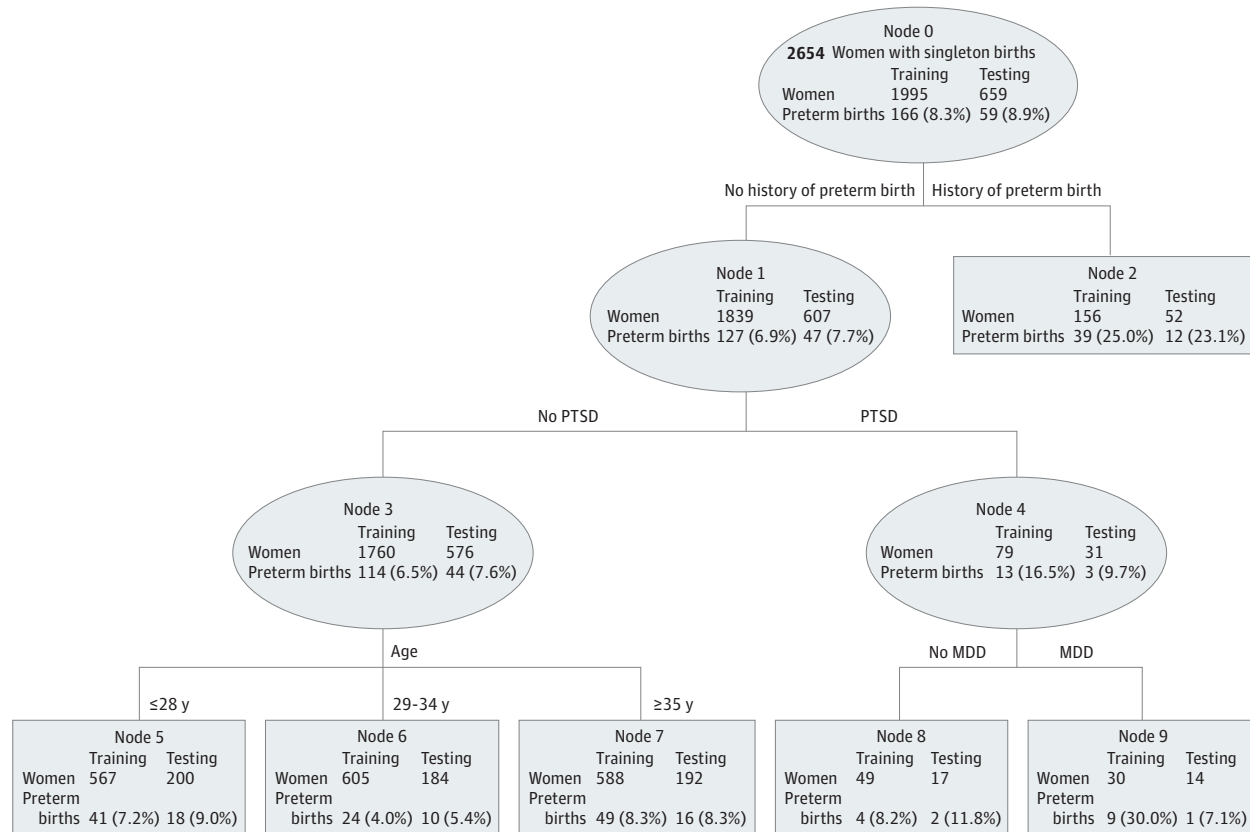
Logistic Regression Analyses Using the Syndromal PTSD Diagnosis

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 study²⁰ 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 | | | | | |
| 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

†Deceased.

Submitted for Publication: September 26, 2013; final revision received January 7, 2014; accepted February 18, 2014.

Published Online: June 11, 2014.
doi:10.1001/jamapsychiatry.2014.558.

Author Contributions: Drs Yonkers and Costello had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Yonkers, Smith, Belanger.
Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Yonkers, Forray, Costello.
Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Yonkers, Costello, Lin.

Obtained funding: Yonkers, Belanger.

Administrative, technical, or material support: Yonkers, Smith, Belanger.

Study supervision: Yonkers, Smith, Belanger.

Conflict of Interest Disclosures: In the past year, Dr Yonkers received royalties from UpToDate. Dr Epperson discloses receipt of Investigator-Initiated Research support from Pfizer, Johnson and Johnson, Abbott, AbbVie, and Merck. No other disclosures are reported.

Funding/Support: This study was supported by National Institute of Child Health and Human Development grant 5 R01HD045735 to Drs Belanger and Yonkers entitled "Effects of Perinatal Depression on PTB and LBW." Dr Smith was supported by grant T32MH014235 from the National Institute of Mental Health. Dr Epperson is supported by grant P50 MH099910 from the National Institute of Mental Health.

Role of the Sponsor: The funding agencies had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We would like to acknowledge Brian Merry, MA, for assistance with model programming; Nathan Gotman, MA, for assistance with data cleaning; and Anita Sung, PhD, for data cleaning. All of these individuals are from the Yale School of Medicine. Nathan Gotman was supported by the parent grant from the National Institute of Child Health and Human Development.

REFERENCES

1. Centers for Disease Control and Prevention (CDC). Publications and Information Products. National Vital Statistics Report. Infant mortality

statistics from the 2009 period linked birth/infant dataset. CDC website. <http://www.cdc.gov/nchs/products/nvsr.htm>. Accessed May 9, 2014.

2. Berkowitz GS, Kasl SV. The role of psychosocial factors in spontaneous preterm delivery. *J Psychosom Res*. 1983;27(4):283-290.

3. Copper RL, Goldenberg RL, Das A, et al; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. The preterm prediction study: maternal stress is associated with spontaneous preterm birth at less than thirty-five weeks' gestation. *Am J Obstet Gynecol*. 1996;175(5):1286-1292.

4. Dole N, Savitz DA, Hertz-Picciotto I, Siega-Riz AM, McMahon MJ, Buekens P. Maternal stress and preterm birth. *Am J Epidemiol*. 2003;157(1):14-24.

5. Hedegaard M, Henriksen TB, Secher NJ, Hatch MC, Sabroe S. Do stressful life events affect duration of gestation and risk of preterm delivery? *Epidemiology*. 1996;7(4):339-345.

6. Kuvacic I, Skrablin S, Hodzic D, Milkovic G. Possible influence of expatriation on perinatal outcome. *Acta Obstet Gynecol Scand*. 1996;75(4):367-371.

7. Rini CK, Dunkel-Schetter C, Wadhwa PD, Sandman CA. Psychological adaptation and birth outcomes: the role of personal resources, stress, and sociocultural context in pregnancy. *Health Psychol*. 1999;18(4):333-345.

8. Rondó PHC, Ferreira RF, Nogueira F, Ribeiro MCN, Lobert H, Artes R. Maternal psychological stress and distress as predictors of low birth weight, prematurity and intrauterine growth retardation. *Eur J Clin Nutr*. 2003;57(2):266-272.

9. Ruiz RJ, Fullerton J, Brown CE, Schoolfield J. Relationships of cortisol, perceived stress, genitourinary infections, and fetal fibronectin to gestational age at birth. *Biol Res Nurs*. 2001;3(1):39-48.

10. Wadhwa PD, Sandman CA, Porto M, Dunkel-Schetter C, Garite TJ. The association between prenatal stress and infant birth weight and gestational age at birth: a prospective investigation. *Am J Obstet Gynecol*. 1993;169(4):858-865.

11. Chalmers B. Psychosocial factors and obstetric complications. *Psychol Med*. 1983;13(2):333-339.

12. Honnor MJ, Zubrick SR, Stanley FJ. The role of life events in different categories of preterm birth in a group of women with previous poor pregnancy outcome. *Eur J Epidemiol*. 1994;10(2):181-188.

13. Stein A, Campbell EA, Day A, McPherson K, Cooper PJ. Social adversity, low birth weight, and preterm delivery. *Br Med J (Clin Res Ed)*. 1987;295(6593):291-293.

14. Klebanoff MA, Shiono PH, Rhoads GG. Outcomes of pregnancy in a national sample of resident physicians. *N Engl J Med*. 1990;323(15):1040-1045.

15. Omer H, Elizur Y, Barnea T, Friedlander D, Palti Z. Psychological variables and premature labour: a possible solution for some methodological problems. *J Psychosom Res*. 1986;30(5):559-565.

16. Lu MC, Chen B. Racial and ethnic disparities in preterm birth: the role of stressful life events. *Am J Obstet Gynecol*. 2004;191(3):691-699.

17. Krabbendam L, Smits L, de Bie R, Bastiaanssen J, Stelma F, van Os J. The impact of maternal stress on pregnancy outcome in a well-educated Caucasian population. *Paediatr Perinat Epidemiol*. 2005;19(6):421-425.

18. St-Laurent J, De Wals P, Moutquin JM, Niyonsenga T, Noiseux M, Czernis L. Biopsychosocial determinants of pregnancy length and fetal growth. *Paediatr Perinat Epidemiol*. 2008;22(3):240-248.

19. Wadhwa PD, Culhane JF, Rauh V, et al. Stress, infection and preterm birth: a biobehavioural perspective. *Paediatr Perinat Epidemiol*. 2001;15(2)(suppl 2):17-29.

20. Loveland Cook CA, Flick LH, Homan SM, Campbell C, McSweeney M, Gallagher ME. Posttraumatic stress disorder in pregnancy: prevalence, risk factors, and treatment. *Obstet Gynecol*. 2004;103(4):710-717.

21. Lipkind HS, Curry AE, Huynh M, Thorpe LE, Matte T. Birth outcomes among offspring of women exposed to the September 11, 2001, terrorist attacks. *Obstet Gynecol*. 2010;116(4):917-925.

22. Engel SM, Berkowitz GS, Wolff MS, Yehuda R. Psychological trauma associated with the World Trade Center attacks and its effect on pregnancy outcome. *Paediatr Perinat Epidemiol*. 2005;19(5):334-341.

23. Rogal SS, Poschman K, Belanger K, et al. Effects of posttraumatic stress disorder on pregnancy outcomes. *J Affect Disord*. 2007;102(1-3):137-143.

24. Seng JS, Oakley DJ, Sampselle CM, Killion C, Graham-Bermann S, Liberzon I. Posttraumatic stress disorder and pregnancy complications. *Obstet Gynecol*. 2001;97(1):17-22.

25. Seng JS, Low LK, Sperlich M, Ronis DL, Liberzon I. Post-traumatic stress disorder, child abuse history, birthweight and gestational age: a prospective cohort study. *BJOG*. 2011;118(11):1329-1339.

26. Xiong X, Harville EW, Mattison DR, Elkind-Hirsch K, Pridjian G, Buekens P. Exposure to

- Hurricane Katrina, post-traumatic stress disorder and birth outcomes. *Am J Med Sci*. 2008;336(2):111-115.
27. Calderon-Margalit R, Qiu C, Ornoy A, Siscovick DS, Williams MA. Risk of preterm delivery and other adverse perinatal outcomes in relation to maternal use of psychotropic medications during pregnancy. *Am J Obstet Gynecol*. 2009;201(6):579.e1-579.e8.
28. Nordeng H, van Gelder MM, Spigset O, Koren G, Einarson A, Eberhard-Gran M. Pregnancy outcome after exposure to antidepressants and the role of maternal depression: results from the Norwegian Mother and Child Cohort Study. *J Clin Psychopharmacol*. 2012;32(2):186-194.
29. Colvin L, Slack-Smith L, Stanley FJ, Bower C. Dispensing patterns and pregnancy outcomes for women dispensed selective serotonin reuptake inhibitors in pregnancy. *Birth Defects Res A Clin Mol Teratol*. 2011;91(3):142-152.
30. 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(8):898-906.
31. Wen SW, Yang Q, Garner P, et al. Selective serotonin reuptake inhibitors and adverse pregnancy outcomes. *Am J Obstet Gynecol*. 2006;194(4):961-966.
32. Maschi S, Clavenna A, Campi R, Schiavetti B, Bernat M, Bonati M. Neonatal outcome following pregnancy exposure to antidepressants: a prospective controlled cohort study. *BJOG*. 2008;115(2):283-289.
33. Lund N, Pedersen LH, Henriksen TB. Selective serotonin reuptake inhibitor exposure in utero and pregnancy outcomes. *Arch Pediatr Adolesc Med*. 2009;163(10):949-954.
34. Reis M, Källén B. Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. *Psychol Med*. 2010;40(10):1723-1733.
35. Ross LE, Grigoriadis S, Mamisashvili L, et al. Selected pregnancy and delivery outcomes after exposure to antidepressant medication: a systematic review and meta-analysis. *JAMA Psychiatry*. 2013;70(4):436-443.
36. Yonkers KA, Norwitz ER, Smith MV, et al. Depression and serotonin reuptake inhibitor treatment as risk factors for preterm birth. *Epidemiology*. 2012;23(5):677-685.
37. 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(10):1012-1024.
38. Dayan J, Creveuil C, Marks MN, et al. Prenatal depression, prenatal anxiety, and spontaneous preterm birth: a prospective cohort study among women with early and regular care. *Psychosom Med*. 2006;68(6):938-946.
39. Hedegaard M, Henriksen TB, Sabroe S, Secher NJ. Psychological distress in pregnancy and preterm delivery. *BMJ*. 1993;307(6898):234-239.
40. Jesse DE, Seaver W, Wallace DC. Maternal psychosocial risks predict preterm birth in a group of women from Appalachia. *Midwifery*. 2003;19(3):191-202.
41. Neggers Y, Goldenberg R, Cliver S, Hauth J. Effects of domestic violence on preterm birth and low birth weight. *Acta Obstet Gynecol Scand*. 2004;83(5):455-460.
42. 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(9):797-802.
43. Wittchen HU. Reliability and validity studies of the WHO—Composite International Diagnostic Interview (CIDI): a critical review. *J Psychiatr Res*. 1994;28(1):57-84.
44. Kessler RC, Nelson CB, McGonagle KA, Liu J, Swartz M, Blazer DG. Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US National Comorbidity Survey. *Br J Psychiatry Suppl*. 1996;168(30):17-30.
45. Kessler RC, Üstün TB. The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *Int J Methods Psychiatr Res*. 2004;13(2):93-121.
46. Kessler RC, Avenevoli S, Costello EJ, et al. National comorbidity survey replication adolescent supplement (NCS-A), II: overview and design. *J Am Acad Child Adolesc Psychiatry*. 2009;48(4):380-385.
47. Yonkers KA, Smith MV, Gotman N, Belanger K. Typical somatic symptoms of pregnancy and their impact on a diagnosis of major depressive disorder. *Gen Hosp Psychiatry*. 2009;31(4):327-333.
48. Falsetti S, Resnick H, Resick P, Kilpatrick D. The modified PTSD symptom scale: a brief self-report measure of posttraumatic stress disorder. *Behav Therapist*. 1993;16:161-162.
49. Coffey SF, Dansky BS, Falsetti SA, Saladin ME, Brady KT. Screening for PTSD in a substance abuse sample: psychometric properties of a modified version of the PTSD Symptom Scale Self-Report. *Posttraumatic stress disorder*. *J Trauma Stress*. 1998;11(2):393-399.
50. Mitchell AA, Gilboa SM, Werler MM, Kelley KE, Louik C, Hernandez-Diaz S; National Birth Defects Prevention Study. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. *Am J Obstet Gynecol*. 2011;205(1):51.e1-51.e8.
51. Zhang HP, Singer B. *Recursive Partitioning in the Health Sciences*. New York, NY: Springer Verlag; 1999.
52. Strobl C, Malley J, Tutz G. An introduction to recursive partitioning: rationale, application, and characteristics of classification and regression trees, bagging, and random forests. *Psychol Methods*. 2009;14(4):323-348.
53. Lemon SC, Roy J, Clark MA, Friedmann PD, Rakowski W. Classification and regression tree analysis in public health: methodological review and comparison with logistic regression. *Ann Behav Med*. 2003;26(3):172-181.
54. Stein MB, Walker JR, Hazen AL, Forde DR. Full and partial posttraumatic stress disorder: findings from a community survey. *Am J Psychiatry*. 1997;154(8):1114-1119.
55. Morland L, Goebert D, Onoye J, et al. Posttraumatic stress disorder and pregnancy health: preliminary update and implications. *Psychosomatics*. 2007;48(4):304-308.
56. Seng JS, Low LK, Sperlich M, Ronis DL, Liberzon I. Prevalence, trauma history, and risk for posttraumatic stress disorder among nulliparous women in maternity care. *Obstet Gynecol*. 2009;114(4):839-847.
57. Fischer PE, Zarzaur BL, Fabian TC, Magnotti LJ, Croce MA. Minor trauma is an unrecognized contributor to poor fetal outcomes: a population-based study of 78,552 pregnancies. *J Trauma*. 2011;71(1):90-93.
58. Harville E, Xiong X, Buekens P. Disasters and perinatal health: a systematic review. *Obstet Gynecol Surv*. 2010;65(11):713-728.
59. Wadhwa PD, Culhane JF, Rauh V, Barve SS. Stress and preterm birth: neuroendocrine, immune/inflammatory, and vascular mechanisms. *Matern Child Health J*. 2001;5(2):119-125.
60. Bremner JD, Licinio J, Darnell A, et al. Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. *Am J Psychiatry*. 1997;154(5):624-629.
61. Baker DG, West SA, Nicholson WE, et al. Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. *Am J Psychiatry*. 1999;156(4):585-588.
62. Vrekoussis T, Kalantaridou SN, Mastorakos G, et al. The role of stress in female reproduction and pregnancy: an update. *Ann N Y Acad Sci*. 2010;1205(1):69-75.
63. Wadhwa PD, Entringer S, Buss C, Lu MC. The contribution of maternal stress to preterm birth: issues and considerations. *Clin Perinatol*. 2011;38(3):351-384.
64. McLean M, Bisits A, Davies J, Woods R, Lowry P, Smith R. A placental clock controlling the length of human pregnancy. *Nat Med*. 1995;1(5):460-463.
65. Culhane JF, Rauh V, McCollum KF, Hogan VK, Agnew K, Wadhwa PD. Maternal stress is associated with bacterial vaginosis in human pregnancy. *Matern Child Health J*. 2001;5(2):127-134.
66. Cammack AL, Buss C, Entringer S, Hogue CJ, Hobel CJ, Wadhwa PD. The association between early life adversity and bacterial vaginosis during pregnancy. *Am J Obstet Gynecol*. 2011;204(5):431.e1-431.e8.