A prospective study of antepartum anxiety screening in patients with and without a history of spontaneous preterm birth

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BACKGROUND: Maternal stress has been identified as one of the most common clinical phenotypes associated with preterm birth. The American College of Obstetricians and Gynecologists recommends anxiety screening at least once in the perinatal period. The prevalence of perinatal anxiety is challenged by the absence of formalized screening protocols and underreporting in high-risk populations, such as those with a history of adverse pregnancy outcomes.

OBJECTIVE: This study administered a validated anxiety screening tool in a cohort of patients with and without a previous spontaneous preterm birth and compared differences in score and rate of a positive screen between groups. Moreover, this study evaluated perinatal outcomes associated with a positive screen and described a referral protocol involving evaluation by a perinatal mental health counselor and clinical diagnoses. A hypothesis was made that patients with a previous history of spontaneous preterm birth would have higher self-reported anxiety symptoms than controls and that those with recurrent preterm delivery at <35 weeks of gestation would have the highest anxiety screening scores.

STUDY DESIGN: This was a prospective observational cohort study administering the Generalized Anxiety Disorder 7-item screen to patients enrolled in 2 prenatal care clinics at our institution. The preterm birth cohort consisted of patients with a history of spontaneous preterm labor, premature rupture of membranes, or cervical insufficiency compared with the control cohort without this history. Screening was initiated at entry to prenatal care or referral to our high-risk obstetrical clinic. The inclusion criteria included English- or Spanish-speaking patients and singleton pregnancy, and the exclusion criteria included pregnancies complicated by a major congenital anomaly, enrollment after 34 weeks of gestation, delivery at <20 weeks of gestation, and incomplete delivery data. Referral to a mental health counselor was offered to those with a Generalized Anxiety Disorder 7-item screen score of ≥10. Perinatal outcomes as a comparison between the Generalized Anxiety Disorder 7-item screen −positive group and Generalized Anxiety Disorder 7-item screen−negative group were performed with statistical methods, including the Student *t* test, chi-square test, and Wilcoxon rank-sum test, with a *P* value of <.05 to determine significance.

RESULTS: Between September 2020 and December 2021, 1349 participants were analyzed, with 143 patients (11%) in the previous preterm birth cohort and 1206 (89%) patients in the control cohort. Patients with a history of preterm birth and subsequent delivery at ≤35 weeks of gestation in the study pregnancy had significantly higher Generalized Anxiety Disorder 7-item screen scores than controls with delivery after 35 weeks of gestation (median score: 4 [interquartile range, 1−9] vs 2 [interquartile range, 0−6], respectively; *P*=.006). Overall, 187 participants (14%) screened positive with significantly higher rates in the previous preterm birth group than in the control group (20% vs 13%; *P*=.036). Of note, 117 patients (63%) accepted a referral, and 32 patients (17%) with a positive screen were diagnosed with a perinatal mood disorder.

CONCLUSION: Patients with recurrent preterm birth have higher self-reported anxiety using the Generalized Anxiety Disorder 7-item screen than controls. Of those with a positive screen, 17% were diagnosed with a perinatal mood disorder.

Key words: adverse pregnancy outcomes, antenatal anxiety, cervical insufficiency, depression, generalized anxiety disorder, mental health, mood disorder, perinatal anxiety, preterm labor

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The authors report no conflict of interest.

Patient consent is not required because no personal information or details is included.

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Why was this study conducted?

Anxiety in pregnancy has been associated with preterm birth (PTB) and low birthweight. Those with a history of adverse obstetrical outcomes may be at increased risk of anxiety symptoms in a subsequent pregnancy. We assessed antepartum anxiety symptoms using the Generalized Anxiety Disorder 7-item (GAD-7) screen in patients with and without a history of spontaneous PTB. We reported on the use of a referral protocol for those with a positive screen and associated birth outcomes.

Key findings

Patients with a history of spontaneous PTB and recurrent preterm delivery have higher anxiety screening scores and rates of a positive screen than controls. Of those with a positive GAD-7 screen, 17% were diagnosed with a mood disorder.

What does this add to what is known?

Patients with a history of spontaneous PTB and subsequent recurrence are at increased risk of anxiety symptoms in the antepartum period.

Introduction

Preterm birth (PTB) accounts for 10% of all births in the United States and is the largest contributor to infant morbidity and mortality.[1] Several etiologies of PTB have been identified with a recurrence risk approximating 30% for those patients with a previous history of PTB.[2] Maternal stress has been identified as the most common clinical phenotype identified in more than half of patients experiencing preterm delivery.[2] The complex neuroendocrine pathway involving corticotropin-releasing hormone and cortisol as mediators of a "placental clock" has been suggested as a potential mechanism of timing of premature delivery in response to stress.[3−6]

The importance of identifying anxiety symptoms in pregnancy is underscored by the American College of Obstetricians and Gynecologists (ACOG) in their previous recommendation for universal anxiety screening at least once during the perinatal period with newer guidelines suggesting screening at the initiation of prenatal care, during pregnancy, and after delivery.[7,8] Estimates of up to 35% of pregnant patients and 20% of postpartum patients will experience clinical anxiety, and an even greater proportion will be affected by anxious emotions and pregnancy-specific stress, both impactful on maternal mental health.[9−11] Generalized anxiety disorder as a clinical diagnosis may affect up to 8% of the perinatal population.[12] The true incidence and prevalence of perinatal stress and anxiety are challenged by the absence of routine screening. Furthermore, it may be underreported in specific high-risk populations, such as those with a history of poor pregnancy outcomes.[13] Aside from PTB, patients with anxiety affecting pregnancy may be at risk of future adverse perinatal outcomes, including low birthweight or small for gestational age (SGA), postpartum depression, poor maternal-infant bonding, and impaired infant neurocognitive development.[14−17]

The presence of anxiety symptoms in a cohort of patients with a history of spontaneous PTB has been largely unaddressed. This is important for at least 2 reasons. First, patients who have experienced the potential trauma of a PTB or unexpected early delivery may be psychologically affected by that history in subsequent pregnancies. Second, if the relationship between stress and PTB exists, perhaps it is a contributor to its recurrence. For these reasons, our objective was to evaluate anxiety symptoms using the Generalized Anxiety Disorder 7-item (GAD-7) questionnaire in a cohort of patients with and without a history of spontaneous PTB. We hypothesized a higher degree of anxiety symptoms associated with a history of PTB and further anticipated the highest GAD-7 scores in patients with recurrent PTB in the study pregnancy than in those without a PTB history. We explored the association of a positive screen with perinatal outcomes. Lastly, for those with a positive anxiety screen, we reported on the findings of a referral protocol in terms of success of contact with a perinatal mental health professional and subsequent clinical diagnoses.

Materials and Methods

Study design

This was a prospective observational cohort study of the administration of the GAD-7 screen (Figure 1) to patients enrolled in 2 separate prenatal care clinics at our institution between September 2020 and December 2021. Serving a medically underserved obstetrical population, our prenatal care system is composed of a centralized high-risk obstetrical clinic staffed by maternal-fetal medicine faculty and fellows and receives referrals from 9 medically integrated Women's Health Centers (WHC). The PTB cohort consisted of patients with a history of PTB by spontaneous preterm labor, premature rupture of membranes, or cervical insufficiency (defined as delivery in the second trimester of pregnancy because of cervical dilation in the absence of signs or symptoms of labor) identified on referral to the high-risk obstetrical clinic for further evaluation and management. Patients receiving prenatal care at a single predetermined WHC site were approached for participation as a comparison cohort of patients without a history of spontaneous preterm delivery or cervical insufficiency. Participants were approached at the first obstetrical visit in the WHC or at the first visit after referral to the high-risk obstetrical clinic. The inclusion criteria for enrollment included literacy in a primary language of English or Spanish. Patients with a multifetal pregnancy, major congenital anomaly, established gestational age at enrollment after 34 weeks of gestation, delivery at <20 weeks of gestation, second delivery in the study timeframe, delivery outside of our institution, or incomplete GAD-7

FIGURE 1
Generalized Anxiety Disorder 7-item screening questionnaire

Over the last 2 weeks, how often have you been bothered by the following problems *(Use "✓" to indicate your answer)*	Not at all	Several days	More than half the day	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

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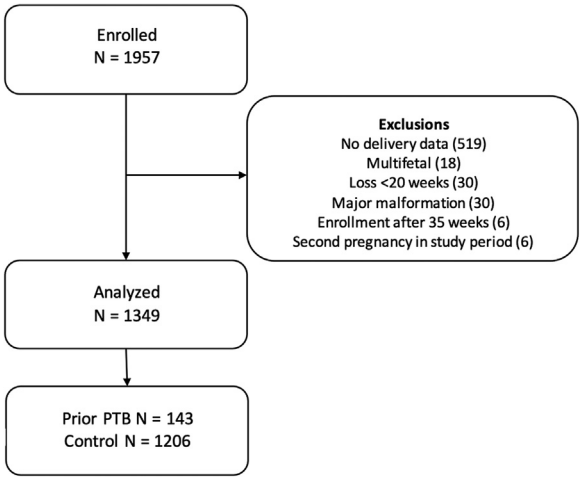
screen were excluded from analysis (Figure 2).

For our primary outcome, we calculated that an analysis of 1260 delivered participants would be necessary to detect a difference of 2 points in GAD-7 scores between patients with recurrent PTB (ie, history of previous preterm delivery and recurrence of preterm delivery at <35 weeks of gestation in the study pregnancy) and those without a history of PTB and delivery at >35 weeks of gestation in the study pregnancy, with 80% power and a *P* value of <.05 defined as significant. We anticipated an 8% primary PTB rate in our general obstetrical population and a 25% recurrent PTB rate based on previous historical estimates. In addition, based on previous prenatal clinic attendance rates, we anticipated a ratio of enrollment per clinic location of 1:11 of the PTB clinic to the WHC clinic site.

The study was approved by the institutional review board with hospital site approval.

FIGURE 2
Study flow diagram



PTB, preterm birth.

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Generalized Anxiety Disorder 7-item screen

Patients who agreed to participate completed the GAD-7 screen, a self-administered measure used for the detection of probable anxiety disorder and classification of severity (Figure 1).[18] The items describe anxiety symptoms (ie, "trouble relaxing") to which 1 of 4 responses is given, classifying the duration of the experienced symptom in a 2-week period—"not at all," "several days," "more than half the days," or "nearly every day." Each item is assigned a score of 0 to 3, with a maximum score of 21. A cutoff of 10 classifies moderate symptoms with a sensitivity of 89% and a specificity of 82% by the original validating study.[18] In a perinatal sample, including Spanish-speaking patients, Zhong et al[19] described a prevalence of 17% of a score of ≥10, with a sensitivity of 43% and specificity of 83%. It is further validated in an adolescent population and is a recommended tool by ACOG for anxiety screening in a perinatal sample.[8,20]

Participants with a score of ≥10 were offered a referral for further assessment by a mental health counselor (MHC). At our institution, MHCs practice under the supervision of a licensed psychologist and complete a formal assessment of the patient, including assigning clinical diagnoses, as appropriate, based on the Diagnostic Statistical Manual 5

TABLE 1
Demographics by history of PTB cohort vs controls

Variable	Previous PTB (n=143)	Control (n=1206)	*P* value
Age	29.8±5.7	27.9±6.3	<.001
Race			<.001
Black	31 (22.0)	92 (8.0)	
White	9 (6.0)	24 (2.0)	
Hispanic	103 (72.0)	1078 (89.0)	
Other	0 (0)	12 (1.0)	
BMI (kg/m^2)	34.0+7.8	32.6+6.0	.035

Data are presented as number (percentage) or mean±standard deviation, unless otherwise indicated.

BMI, body mass index; *PTB*, preterm birth.

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(DSM-5). For those deemed to require a higher level of care or need of medication therapy, further assessment was performed by a licensed psychiatrist within our hospital system with experience in the care of patients with perinatal mood disorders. Formalized treatment plans may be initiated, as indicated, although not dictated by our study protocol. Because of the SARS-CoV-2 pandemic coinciding with the study timeframe, assessments were performed via telemedicine.

Data analysis

The GAD-7 screen responses were scored by the obstetrical provider after completion by the participant and recorded by research nurses within the Department of Obstetrics. Perinatal outcomes were referenced using a formal computerized database of all delivered patients and their neonates within our hospital system. This database is maintained by our departmental statistician and research staff. Information is collected and verified by trained research nurses at the time of delivery through a datasheet and abstraction of information from hospital discharge records. The electronic medical record was queried for MHC referral information, including success of contact with the mental health counselor, clinical diagnoses, and treatment plans, as relevant.

Statistical analysis using SAS (version 9.1; SAS Institute Inc, Cary, NC) included chi-square analysis, Student *t* test, Wilcoxon rank-sum test, and log-binomial regression, as appropriate. The results are presented as frequencies with percentages, means with standard deviations, or medians with first and third quartiles, with levels <.05 considered significant.

Results

A total of 1957 patients were enrolled in the study timeframe with an analysis performed on 1349 patients after exclusions were applied (Figure 2). Our cohort of patients with a history of spontaneous PTB or cervical insufficiency consisted of 143 patients compared with our control cohort of 1206 patients. Demographic differences between cohorts were pertinent for average maternal age at delivery, self-identified race with a higher proportion of Black patients in the history of PTB cohort and Hispanic women in the control cohort, and higher average body mass index (BMI) in the PTB cohort (Table 1). Gestational age at delivery of <35 weeks in the study pregnancy was more common in those with a history of spontaneous PTB than in controls (27% vs 4%; *P*<.001, respectively).

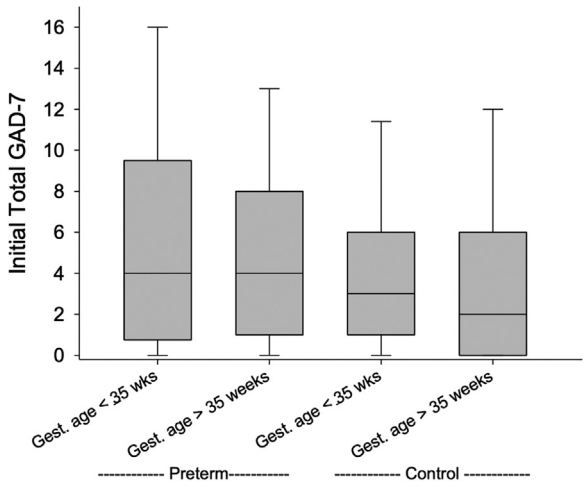
Figure 3 demonstrates a comparison of GAD-7 scores as a function of both previous history (PTB group vs control cohorts) and gestational age at delivery in the study pregnancy (delivery at <35 weeks vs delivery after 35 weeks). There was a 2-unit difference in the median GAD-7 scores between those with a previous history of PTB and delivery in the study pregnancy at ≤35 weeks (median score: 4 [interquartile range (IQR), 1−9]) compared with controls without a previous history of spontaneous PTB and delivery after 35 weeks (median score: 2 [IQR, 0−6]) (*P*=.006).

Figure 4 demonstrates the frequency distribution of GAD-7 scores with an overall positive screen rate of 14% (187) across groups. There was a significantly higher rate of positive screens in the history of PTB cohort (20%) than in the control cohort (13%) (*P*=.036). This finding remained true after controlling for demographic differences between our PTB and control cohorts, including race, BMI, and maternal age (*P*=.041).

For those with a positive screen, there were significant demographic differences noted in younger mean age and non-Hispanic Black self-identified race (Table 2). There was no notable difference between those with and without a positive screen in terms of selected perinatal outcomes, including cesarean delivery, PTB, or SGA (Table 2).

Of the 187 patients with a positive screen, a referral to a mental health counselor was accepted by 117 patients (63%). For those who accepted a referral, 91 patients (78%) had successful contact with a mental health counselor and/or perinatal psychiatrist. Figure 5 demonstrates the proportion of clinical diagnoses assigned to include 21 patients with anxiety disorder alone or comorbid anxiety or depressive disorder (11% of those screened). Moreover, 10 patients (5%) were diagnosed with depressive disorder alone, 1 patient (0.5%) was diagnosed with bipolar disorder, 29 patients (16%) were diagnosed with anxiety symptoms not meeting specific criteria for a clinical diagnosis or presence of significant psychosocial stressors, and 6 patients (3%) were diagnosed with an adjustment disorder. Overall, 17% of those with a positive screen were diagnosed with a perinatal mood disorder. All participants that

FIGURE 3
GAD-7 score distribution by history of PTB and current study pregnancy



GAD-7, Generalized Anxiety Disorder 7-item; *PTB*, preterm birth.

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were in contact with a mental health counselor received information on available mental health resources and, if a follow-up plan was not specifically indicated by the patient's clinical condition, were given contact information for the perinatal mental health counselors.

Comment

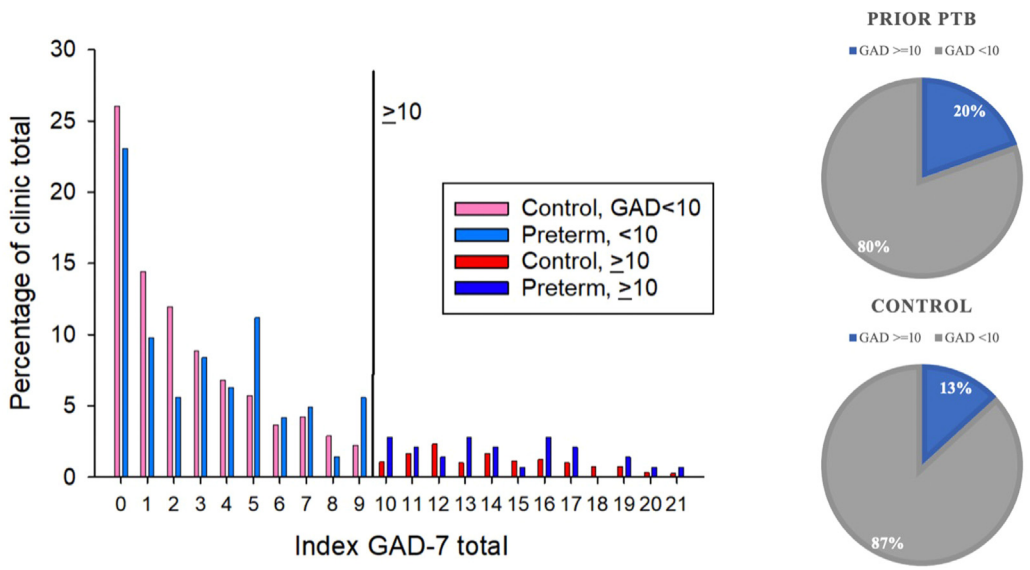
Principal findings

There were 4 primary findings in this analysis. First, we identified higher GAD-7 screening scores in patients with a previous spontaneous PTB and recurrence in the study pregnancy than in patients without a PTB history. Second, we found a higher proportion of GAD-7 positive screens among patients with PTB history than controls. Demographic factors associated with a positive screen included younger mean age and non-Hispanic Black race. There was no significant difference in selected perinatal outcomes of those with a positive screen compared with those with a negative screen. Third, in those with a positive screen and accepting referral, 78% of those had successful contact with a mental health provider. Fourth, 17% of those with a positive GAD-7 screen were ultimately diagnosed with a perinatal mood disorder.

Results

We identified that patients with a history of spontaneous PTB or cervical insufficiency had higher GAD-7 scores and rates of positive screens than our control cohort. Furthermore, the highest scores were identified in those with recurrent PTB during the study pregnancy. As most patients will have a negative screen, differences in median scores may be less clinically significant, but the difference in the rates of a

FIGURE 4
Frequency diagram and rates of GAD-7 positive screen by 2 study cohorts



GAD-7, Generalized Anxiety Disorder 7-item; *PTB*, preterm birth.

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TABLE 2
Demographics and selected perinatal outcomes as comparison of GAD-7—positive screen compared with those with a negative screen

Variable	GAD-7 score of ≥10 (n=187)	GAD-7 score of <10 (n=1162)	*P* value
Age	26.9+6.2	28.3+6.3	.006
Race			<.001
Black	28 (15.0)	95 (8.0)	
White	14 (7.0)	19 (2.0)	
Hispanic	142 (76.0)	1039 (89.0)	
Other	3 (2.0)	9 (1.0)	
BMI (kg/m^2)	33.5+7.2	32.6+6.0	.109
Gestational age at delivery (wk)			
<35	10 (5.0)	48 (4.0)	.447
<37	19 (10.0)	102 (9.0)	.539
Cesarean delivery	61 (33.0)	340 (29.0)	.351
Stillbirth	0 (0)	5 (0)	.369
NICU admission	11 (6.0)	46 (4.0)	.225
SGA of <10th percentile	25 (13.0)	114 (10.0)	.144
5-min Apgar score of <3	2 (1.0)	7 (1.0)	.466
NND	0 (0)	2 (0)	.570

Data are presented as number (percentage) or mean±standard deviation, unless otherwise indicated.

BMI, body mass index; *GAD-7*, Generalized Anxiety Disorder 7-item; *NICU*, neonatal intensive care unit; *NND*, neonatal demise; *SGA*, small for gestational age.

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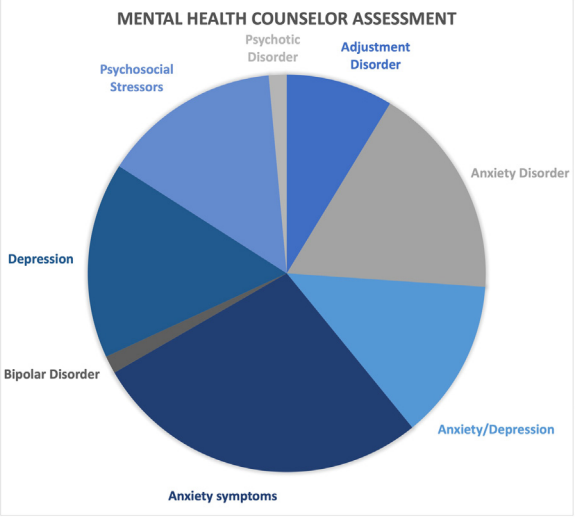
FIGURE 5
Clinical diagnosis assigned after referral for a positive GAD-7 screen



GAD-7, Generalized Anxiety Disorder 7-item.

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positive screen reflects that those with PTB history are disproportionately affected by anxiety symptoms. This is consistent with previous studies that demonstrate an association between adverse pregnancy outcomes and higher rates of anxiety in subsequent pregnancies. In a prospective cohort of patients diagnosed with an early pregnancy loss, 24% of patients reported moderate to severe anxiety the month after their loss.[13] Researchers identified 2 additional points of interest: (1) even in the control cohort of those with a subsequent viable pregnancy identified, 13% of patients reported significant anxiety symptoms, and (2) those with a subsequent nonviable study pregnancy had a higher likelihood of a positive screen. This suggests that anxiety symptoms exist even in otherwise appropriately progressing pregnancies and that those with recurrence of their adverse outcome may be at the highest risk. In another prospective study on the association of previous adverse pregnancy outcomes with mental health in subsequent pregnancies, researchers identified that previous miscarriage, ectopic pregnancy, or stillbirth was associated with anxiety symptoms that persisted over a decade later.[21] Lastly, researchers in Brazil evaluated anxiety symptoms in a heterogeneous cohort of patients with either recurrent pregnancy loss, fetal death, PTB, or neonatal demise and found significantly higher rates of anxiety in this group.[22] Their statement, "evaluating the extent to which trauma of adverse pregnancy outcomes is an event that might trigger psychological disorders in women during subsequent pregnancy is the first step," is most in line with our sentiment and the purpose of this study.

Other associated demographic factors associated with a positive GAD-7 screen include non-Hispanic Black race. It is well accepted that "racism, not race," is the primary contributor to health outcome disparities. Racism and other forms of discrimination have been identified as an important mediator of stress and a crucial contributor to inequities in adverse obstetrical outcomes, including PTB.[23]

We did not find an association between a positive screen with perinatal outcomes, including PTB in the study pregnancy or birthweight parameters, as is suggested in the literature. In a systematic review and meta-analysis performed by Grigoriadis et al,[24] antenatal anxiety was associated with both PTB overall and spontaneous PTB, lower mean birthweight, and SGA, whereas others additionally identified an association with neonatal intensive care unit admission, Apgar score, and length of hospitalization.[25] We believe several factors may have contributed to the lack of association in our findings. First, anxiety parameters were defined as either a clinical diagnosis of anxiety or a screen correlating with high anxiety. Our study was not specifically powered to detect outcome differences, and we used a cutoff for moderate anxiety symptoms without subgroup analysis of those with a clinical diagnosis. Furthermore, it has been suggested that anxiety disorders in the untreated state have the highest risk of poor obstetrical outcomes. In our pragmatic study, those with a positive screen were offered a referral to a mental health provider and initiated treatment, as appropriate. Lastly, several studies included in the Grigoriadis meta-analysis reflected second- and third-trimester anxiety assessment, whereas we reported anxiety symptoms at the initiation of prenatal care. It is suggested that gestational age at which anxiety is manifested has implications for PTB outcomes.[26] In summary, we do not propose that perinatal outcomes are not affected by anxiety but instead acknowledge that our study design and analysis may have masked or left unrevealed the association.

Clinical implications

We propose to provide relevant information for those considering the feasibility of anxiety screening in the antepartum period. In a recent continuing medical education review, the authors state that "it is time for routine screening for perinatal mood and anxiety disorders in obstetrics and gynecology settings."[27] They cite a responsibility to screen for perinatal mood disorders, provide mental health education, and have familiarity with referral and treatment as a means to reduce adverse perinatal outcomes and improve postpartum mental health. This is similarly addressed in a Consensus Bundle on Maternal Mental Health from the Council on Patient Safety in Women's Health Care, providing recommendations for the "readiness" of providers to use mental health screening tools, "recognition and prevention" to conduct screening in both antepartum and postpartum settings, "response" to a positive screen, and "reporting and systems learning" as a means to create a "culture of safety." As a large county hospital serving a medically underserved patient population, we seek to use our internal data represented in this prospective study to further reflect on how our institution can align with these goals and encourage others to do the same.

Research implications

Further research is needed to determine the optimal timing and frequency of perinatal anxiety screening. Although consensus guidance is needed on the ideal screening modality for perinatal anxiety, we acknowledge that the consistent use of any validated tool may be preferred to the alternative of an unscreened population. Identification of other at-risk patient populations is warranted. However, without universal screening, we may never truly reflect on the burden of perinatal mental health disorders or reliably identify affected patients. Lastly, the identification of those with perinatal mood disorders allows us to consider intervention strategies for ameliorating adverse effects of either the disorder itself or having an unaddressed, untreated medical condition.

Strengths and limitations

We note several strengths of our study, including the implementation of a widely used, validated anxiety screening tool in both a high-risk and "low-risk," largely unselected cohort, which may inform practitioners of its use in a general obstetrical population. We report on both a screening strategy and a referral protocol that include formal assessment by mental health professionals dedicated to the care of a perinatal patient population. Our institution serves a largely medically underserved patient population. As many women may only receive medical care for the duration of their pregnancy, the early administration of the GAD-7 allows for a longer period in which a patient interfaces with the prenatal care system, giving more opportunity for those with a positive screen to be evaluated by a mental health provider and improve diagnostic yield. Moreover, this allows patients to access and integrate resources during a time when they are regularly accessing medical care.

We acknowledge several limitations of our study. Selection bias limits our ability to comment on how those who declined participation differ from our participants. This may be especially important for those with perinatal mood disorders, who may be less likely to actively engage with the medical system. We further acknowledge our inability to make commentary on obstetrical outcomes for those delivered at an outside facility, as this subgroup was specifically not included in our analysis. Lastly, this was an observational study of patients receiving otherwise routine and indicated prenatal care, including treatment for history of spontaneous PTB or cervical insufficiency, as appropriate, through either progesterone therapy or cervical cerclage. As such, this may have additionally mediated perinatal outcomes evaluated in our study.

Conclusions

We reported on the higher level of anxiety symptoms identified in patients with a history of spontaneous preterm labor, which may be useful in identifying an at-risk patient population for targeted screening. We urge providers to further assess the feasibility of universal anxiety screening, as even those without identifiable antecedents may have an unrecognized mood disorder or risk of developing one during the perinatal period. For our purposes, we sought a pragmatic approach—administer a validated screening measure and

implement a referral protocol for further assessment and management in patients otherwise receiving standard of care as appropriate for their underlying history or medical conditions. We seek to provide information that is useful to practitioners in a real-world context and to motivate further commitment to the mental health of some of our most vulnerable patient populations. ■

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