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The Effects of Posttraumatic Stress Disorder on Pregnancy Outcomes

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Abstract

THE EFFECTS OF POSTTRAUMATIC STRESS DISORDER ON PREGNANCY OUTCOMES.
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The purpose of this study was to determine the effect of posttraumatic stress disorder (PTSD), diagnosed prospectively during pregnancy, on the occurrence of low birthweight (<2500 grams) and preterm delivery (<37 weeks gestational age). A cohort of 1362 women was recruited from prenatal care visits and screened for depression, panic disorder, posttraumatic stress disorder, and substance use. Current episodes of PTSD were assessed using the MINI International Neuropsychiatric Interview. Pregnancy outcomes were abstracted from hospital records after delivery, and the data were analyzed using logistic regression. Two hundred sixty two women (33%) were lost to follow-up due to unavailable medical records, leaving 1100 women in the final analyses. Among these 1100 women, 31 (3%) were found to have PTSD during pregnancy. Substance use in pregnancy, panic disorder, major and minor depressive disorders, and prior preterm delivery were significantly associated with PTSD in the sample, while age, language spoken, and race were not. Low birthweight (LBW) was present in 6.5% of sampled women and was not significantly associated with a diagnosis of PTSD in pregnancy when adjusting for potential confounders. However, LBW was significantly associated with minor depressive disorder OR= 1.82 (CI=1.01, 3.29). Preterm delivery occurred in 7.0% of those without and 16.1% of those with PTSD (p=0.055). Because prior preterm delivery data were not available for 33% of women with PTSD, this variable was included only in secondary analyses. However, the association between PTSD and preterm delivery depended on this variable, with OR= 2.82 (0.95, 8.38) before controlling for prior preterm delivery and OR=3.35 (1.04, 10.85) after controlling for prior preterm delivery. These data suggest that a possible association of PTSD and preterm delivery was limited by the low rates of PTSD in this cohort and the inability to control for all confounders. Taken together, these findings provide limited support for the hypothesized association between PTSD and preterm delivery and no support for an association of PTSD with LBW.

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Background & Rationale

One of the greatest public health challenges facing the United States is the persistently high infant mortality rate (IMR), which remains a marker of continued health disparities in this country. The infant mortality rate in 2000 was 14.1 per 1000 live births among African-Americans compared to 5.7 per 1000 live births among Caucasian Americans (1). Estimates suggest that up to 60% of IMR may be attributable to low birth weight (LBW) (2), implying that identifying the determinants of low birth weight is essential to improving the IMR. LBW occurs among infants born preterm and infants who are small for gestational age.

There is a growing body of evidence that psychosocial variables may influence pregnancy outcomes. It has long been established that smoking (3) and starvation (4) are risk factors for low birth weight. Despite the copious literature exploring the relationship between stress during pregnancy and adverse pregnancy outcomes, there is relatively little literature exploring associations between posttraumatic stress disorder (PTSD) and birth outcomes. PTSD is an illness that develops when an individual is exposed to an extremely stressful life event. The diagnosis requires confronting actual or perceived threat of death or serious injury resulting in a sense of horror and helplessness. Individuals with PTSD develop at least 1 symptom of re-experiencing the trauma, 2 symptoms of persistent avoidance, and 3 symptoms of persistent arousal (Fig. 1—DSM IV criteria (5)). Given the recent occurrence of multiple disasters such as the bombing of the World Trade Centers, the Tsunami in Southeast Asia, and Hurricane Katrina in the US, there is an increasing interest in the sequelae of PTSD. The six-month period prevalence of PTSD in an urban population of women was recently estimated as 4.6%

(6). Recent evidence indicates that among an urban pregnant population, approximately 3-7.7% of women may experience PTSD (7) (8). The effects of PTSD on pregnancy outcomes are largely unknown, despite the fact that the pathophysiology of PTSD suggests that it is likely to have a role in poor perinatal outcomes.

Figure 1: 309.81 DSM-IV Criteria for Posttraumatic Stress Disorder (5)

A. The person has been exposed to a traumatic event in which both of the following have been present:
1. The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
2. The person's response involved intense fear, helplessness, or horror. **Note:** In children, this may be expressed instead by disorganized or agitated behavior.

B. The traumatic event is persistently reexperienced in one (or more) of the following ways:
1. Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. **Note:** In young children, repetitive play may occur in which themes or aspects of the trauma are expressed.
2. Recurrent distressing dreams of the event. **Note:** In children, there may be frightening dreams without recognizable content.
3. Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur upon awakening or when intoxicated). **Note:** In young children, trauma-specific reenactment may occur.
4. Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.
5. Physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:
1. Efforts to avoid thoughts, feelings, or conversations associated with the trauma
2. Efforts to avoid activities, places, or people that arouse recollections of the trauma
3. Inability to recall an important aspect of the trauma
4. Markedly diminished interest or participation in significant activities
5. Feeling of detachment or estrangement from others
6. Restricted range of affect (e.g., unable to have loving feelings)
7. Sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span)

D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:
1. Difficulty falling or staying asleep
2. Irritability or outbursts of anger
3. Difficulty concentrating
4. Hypervigilance
5. Exaggerated startle response

E. Duration of the disturbance (symptoms in Criteria B, C, and D) is more than one month.

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
Specify if:
Acute: if duration of symptoms is less than 3 months
Chronic: if duration of symptoms is 3 months or more
Specify if:
With Delayed Onset: if onset of symptoms is at least 6 months after the stressor

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The primary aim of this study was to determine the association between exposure to PTSD in pregnancy and resultant adverse pregnancy outcomes. The hypothesis of this study was that the presence of PTSD, compared to the absence of PTSD, during pregnancy, would increase the odds of preterm delivery and low birthweight. The secondary aims included determining the prevalence rates of PTSD during pregnancy in a large, urban population and assessing the degree of comorbid depression, panic disorder, and substance use among women with PTSD in pregnancy.

The Effect of Stress on Pregnancy Outcomes—Literature Review

A number of studies have examined the impact of stress during pregnancy on gestational outcomes. The definition of stress has varied broadly in these studies, and exposure has included Life Events Checklists, symptoms of depression or anxiety, traumatic events, and infrequently, a diagnosis of PTSD. A detailed enumeration of measures, outcomes, populations, and results for the individual studies can be found in Appendix A.

Abuse

Few studies have examined the impact of physical, emotional, or sexual abuse on birth weight. Of these studies, two found significantly lower birth weights for the offspring of abused women. The single study that did not show a significant effect of abuse on birth weight examined ever-abused women without excluding post-partum abuse, and, included only one woman who had been abused specifically in pregnancy (9).

One study found the psychosocial stress due to abuse, but not the occurrence of abuse alone, was associated with an OR of 2.1 (1.2, 3.6) and an associated significant average decrease in birth weight of 236 grams (10). Another found an average decrease in birth weight from 3310 grams to 3144 grams, and the group with the greatest statistically significant decrement were women physically abused during their pregnancy (11). However, studying physical abuse is complicated by the fact that the mechanism may be direct trauma causing spontaneous abortion and placental abruption. Conversely, it may be that stress from abuse is a necessary mediator in cases where direct physical trauma is not the cause of poor outcome, and this was measured in only one of the studies. In summary, it appears that the stress from abuse may be associated with decrease in birthweight.

Life Events

Several studies have examined the exposures of life events and associated stress without use of psychiatric disorder measures. These studies have differed in that some measured only number of events and others added a measure of subjective distress. The use of different scales and differential weighting of life events may account for differences in the outcomes of the following studies.

The first study to specifically address this question found that the number of life events alone was significantly related to the odds of preterm birth (12). However, this study was limited by retrospective design. Other studies have suggested that the distress associated with the events may be more important than the events themselves. One study found the frequency of life events was not significantly related to gestational age at

delivery, while the presence of certain events (the death of a sister or mother) was associated with delivery an average of 4.6 weeks earlier (13). That these perhaps more stressful events were associated with decreased gestational age at delivery may indicate that the degree of emotional distress associated with a particular event plays a critical role in determining the impact of the event, but this study did not include measures of distress. To correct for this, it has been suggested that investigations include a specific measure of associated distress with events to predict the impact on pregnancy outcomes (10). Accordingly, one study found that each 14.7 units of a combined measure of life-event stress, which involved both the frequency and subjective severity of each event, corresponded to a 55g decrease in birth weight (14). Similarly another study found that prenatal stress, but not number of life events, was associated with a decrease in birth weight (15).

Accordingly, several studies have found that it may not be sufficient to measure number of events alone. In 2002, one group investigated a threshold hypothesis of number of events and resultant preterm birth and found an inconsistent relationship between these measures, which depended on the year of birth (16). This indicates the potential for a threshold effect, which implies that it is more than the number of events alone that determines gestational age at delivery. Similarly, another study found that the number of stressful event in the year prior to delivery was not significantly associated with gestational age at birth (17).

Thus, the evidence from the life events measures alone indicates that there may be a role for life events in determining pregnancy outcomes, but that the stress associated with the life events, and not the events themselves, may contribute to adverse pregnancy

outcomes, indicating the importance of weighting and measuring the stress associated with the events in these studies.

Symptoms of Depression and Anxiety

Symptoms of depression and anxiety have been broadly studied. The majority of the studies assessed both stress, typically in the form of a life events inventory, and a measure of anxiety or depression, as operationalized in many different ways across the studies. The results of these studies have been equivocal. However, they generally suggest two distinct associations. Anxious symptoms seem to be associated with preterm delivery and depressive symptoms with LBW.

There have been a number of negative studies, several of which suggest mediating factors between mental health and birth outcomes. Several studies have looked at specifically at preterm delivery and found no significant impact of symptoms of depression or anxiety (18), or that the impact of depressive symptoms was only significant in underweight women (19). In a series of studies from one cohort, one found "psychological stress" (as defined by a combining a subjective measure of anxiety and depression with depression and anxiety as measured with the General Health Questionnaire, or GHQ) was unrelated to preterm delivery (20), while another found no association between the GHQ, poor social support, perceived income problems, or adverse life events and low birthweight once controlling for smoking (21). Similarly, another study found the GHQ, life events scale, and social support were associated with smoking but not directly with LBW (22). In fact, several studies found no association between psychological stress via the GHQ and LBW (23) (21) (22). Two large,

prospective studies found no association of depression and anxiety symptoms with LBW or preterm delivery (24) (25), however the second used a 29-variable combined outcome. The final negative study used a combined exposure measure and found that controlling for optimism eliminated the effects of their stress measure (26). Thus, it appears from the negative studies that weight and smoking may mediate the impact of mental health on LBW and that optimism may be another mediator of mental health measures. These studies also indicate the need for independent measures of mental health variables, rather than combined exposure measures, in order to tease apart effects.

In contrast to the studies with negative findings, there were many more studies with positive results. Several of the studies with positive results had significant methodological limitations. Cliver *et al.* (27) used a combined measure of stress that gave participants 1 point for "high risk" scores on each of the following: trait anxiety, self-esteem, mastery, depression, social support, and stress. This study found that weight modified the relationship between stress and LBW, where the thinner women demonstrated a stronger positive relationship between the variables than non-thin women. Two of the studies that found positive results for depressive and anxious symptoms and preterm delivery used postpartum mental health assessments (28) (29), which preclude determination of the direction of causality. One French cohort study, looking at preterm labor but not preterm delivery, found depressive symptoms were associated with preterm labor only among underweight women and that trait and state anxiety were only associated with preterm labor among women with a history of preterm labor and women with vaginal bleeding, respectively (19). However, as was noted in the article, preterm labor is not perfectly correlated with preterm delivery. Thus, there have been some

studies suggestive of effects of mental health measures on preterm delivery and LBW that have had methodological limitations to application in the context of this study.

Two studies, both using combined measures, found stress influenced both preterm delivery and LBW. Copper *et al.* (30), using a combined measure of symptoms of anxiety and depression, found those who scored in the highest 25th percentile had significantly more LBW babies (13.5% versus 9.6%) and preterm deliveries (5.3% versus 3.0%). Dominguez *et al.* (31) found a life events scale predicted gestational age, and all psychosocial variables together (including anxious but not depressive symptoms) predicted 7% of the variance in birth weight, although the only significant predictors in the model, event distress and intrusive thoughts, explained only a small part of the variance. These studies again indicate the need to separate psychosocial exposure variables in order to determine their effects.

Several studies have shown an association of depression with LBW, though a few found this association only in a sub-population. Paarlberg *et al.* (32) found depressive mood in the first trimester was associated with LBW (OR=1.12). While the number of first trimester daily stressors was associated with LBW (OR=1.04), there was no association of anxiety or somatic symptoms with LBW. Reeb *et al.* (33) found depression to be significantly associated with LBW. However, both family functioning and stressful life events were better predictors of LBW than depression. Among studies that demonstrated effect modification, one found an association between depressive symptoms and a decrease in birth weight only among low SES women (34), while the other found an association of depression with LBW, preterm delivery, and SGA among adults but not adolescents (35). The last was the only to find a concomitant increase in

preterm delivery with depression. These studies collectively indicate a likely relationship between depression and LBW that may be stronger for lower weight women (i.e. women who are not eating as a result of depression), for older women, or for more socially vulnerable women with lower SES.

Several studies have found anxious symptoms or stress were associated with preterm delivery but not LBW (36) (37) (38). In 2003, Dole *et al.* (39) found an increased risk of preterm delivery with pregnancy related anxiety (RR=1.8), life events with negative impact (RR=1.8), and perception of racial discrimination (RR=1.4) but no association between depressive symptoms and preterm delivery. In 2004, Dole *et al.* (40) found no association of preterm delivery with depressive symptoms but that preterm delivery was associated with coping mechanism and racial discrimination among African-Americans and with increased life events and not living with the father of the baby among whites. As with the connection between depressive symptoms and LBW, the connection between anxiety and preterm delivery may be dependent on other factors. Specifically, it appears that the later in pregnancy the anxious symptoms occur, the more likely preterm delivery. One study found that high GHQ scores were associated with LBW (RR=1.97) when measured early in pregnancy and with preterm delivery (RR=2.32) when measured late in pregnancy (41). Similarly, Hedegaard *et al.* found a dose-response relationship between preterm delivery and high distress at 30 weeks but no relationship between stress at 16 weeks and preterm delivery (42).

Interestingly, these studies indicate two potential types of associations, that of depression with LBW, and that of stressful events or anxiety with preterm delivery. Using this framework, it may be that the negative studies missed an association because

they looked at anxiety and life events and their association with LBW, rather than preterm delivery. Also, it may be that the timing of the measurement is of the utmost importance in predicting the impact, as was seen in the final two studies, or that the population studied modifies the effects of the mental health parameters, as was seen with the depression studies. Potentially because of effect modification, the literature is not in agreement as to the relationship of anxious and depressive symptoms and pregnancy outcomes.

Other Specific Psychosocial Stressors

Several specific chronic stressors have been studied. One study in urban Russia demonstrated that birth weight significantly decreased as the crowding or perceived stress increased (43) . A follow-up study found that spontaneous preterm birth increased significantly with stress in work and home (OR=2.15) but that crowding did not affect gestational age at delivery (44). Another study (45) found that a decline in social status, as defined as the job ranking on a 3 tiered scale using the partner with the higher status, between previous and index birth was associated with a 5% increase in LBW among those who had previously not had a LBW baby. One study (46) assessed the impact of racism on preterm delivery and found statistically significant roles for unfair treatment at work (OR=1.3) and people acting afraid of them at least once a week (OR=1.4). In 1991, Magann and Nolan demonstrated that women in active military duty, when compared to wives of partners in active duty, have increased rates of cesarean section, pregnancy-induced hypertensive syndromes, and increased intrauterine growth retardation (47). Though PTSD is higher in the military than civilian population, PTSD was not measured

in this study. These studies indicate a role for understudied complex chronic stressors that may impact birth weight and preterm delivery.

Single Traumatic Events

Three studies that were reviewed assessed the impact of a single, community-wide, acute event and its impact on birth outcomes.

In 1991, Chang *et al.* found that the exposure to an earthquake in pregnancy was associated with LBW in those women who also had spousal death, unstable living conditions, or abdominal injury (48). In another earthquake study, the authors evaluated the impact of the timing of the earthquake on appraisals of stress and timing of delivery(49). This study demonstrated that the earthquake was rated as more stressful when it occurred earlier in pregnancy. Additionally, this study measured plasma levels of corticotropin releasing hormone (CRH) as a marker for stress and found that CRH variation at 32 weeks and the timing of earthquake in pregnancy could jointly account for 41% of the variation in gestational age at delivery, indicating the importance of event timing on the subjective stress response and possibly on the physiological stress response.

In a unique study, Lederman *et al.* (50) assessed the relationship between working and living in proximity to the World Trade Centers (WTC) in the four weeks after the September 11th tragedy and found that babies of women who lived within two miles of the WTC had a significant decrease in birth weight (-122 g) and birth height (-0.74 cm), after adjusting for gestational age. Those in their first trimester at exposure also had gestational age at delivery significantly shortened by 3.6 days, independent of location. This study indicates that the timing of stress may be important to its effects on birth

outcomes. Because there was no direct measure of stress in this study, environmental toxic exposures and psychosocial factors cannot be distinguished.

Thus, the traumatic event literature is scant but demonstrates the importance of event timing on impact of events as well as indicating a potential role for PTSD as the mediator between events and outcomes.

PTSD

Despite the estimated prevalence of PTSD in the pregnant population of 3-7.7% (8), only one study has directly assessed PTSD in a large number of women (51). In this study, the authors determined PTSD status using ICD-9 codes on insurance forms, likely an insensitive measure. They found that PTSD was unrelated to preterm delivery, preeclampsia, poor fetal growth, or type of delivery. However, PTSD was associated with higher odds of spontaneous abortion (OR=1.9), preterm contractions (OR=1.4), and other complications of pregnancy. Interestingly, there was a nearly significant relationship between PTSD and excessive fetal growth (OR=1.5, CI=1.0, 2.2). Though they did not find a significant association between PTSD and preterm labor, PTSD was associated with preterm contractions, which can lead to preterm labor and birth. This study likely misclassified many women who actually had PTSD because of the use of insurance claims to define PTSD. Also, this study's estimate of a 0.4% prevalence rate of PTSD is an order of magnitude less than the prevalence in the general population. Substance abuse was equally likely to be missed in this study. Other major limitations of this study were the lack of assessment of LBW and the inability to assess the temporal

relationship between PTSD and pregnancy outcome, as the timing of PTSD was not limited to pregnancy, thus potentially biasing the association toward null findings.

Two recent articles focused on birth outcomes in women exposed to the World Trade Center disaster of 2001. Using a PTSD symptoms checklist (PTSS), they assessed 187 pregnant women who lived or worked near the WTC, only 4 of whom had PTSD symptoms. The first study in this series compared these 187 women to a consecutive prenatal sample outside of the affected area and found no association between PTSD symptoms and IUGR, preterm delivery, or LBW (52). However, the group close to the WTC experienced a two-fold risk of IUGR, adjusting for race, sex, age, parity, and tobacco, which they attributed to environmental exposure, as opposed to PTSD.

In the other study using the same 187 women (53), only 51 were included in the analysis, and again only 4 women had PTSD symptoms. Authors reported a statistically significantly higher gestational age at delivery as PTSS score increased (for each increase in score by 1, the gestational age increased by 0.04 weeks). However, the average gestational ages were 40.6 weeks in the likely PTSD group and 39.6 in the non-PTSD group, which was not clinically or statistically significant. Head circumference was found to significantly decrease with each increase in PTSS score, however in the PTSD group the average size was 34.1 cm, and in the non-PTSD group it was 34.4 cm, which was not significantly different. There was no significant difference in birthweight by PTSD exposure group in this report.

Problems with these studies include the inclusion of women who were recruited and diagnosed with PTSD after delivery, which could bias the results to the null. The use of a symptom scale and not a diagnosis of PTSD also may have altered the results. Most

far been insufficient data to examine the connection between PTSD and pregnancy outcomes.

Conclusions from the Literature Review

In summary, the association between stress and pregnancy outcomes has not been consistent. It appears from life events research that the perceived stress associated with life events may be more important than the number of events alone. It may be that certain chronic, severe stressors, such as living conditions, decline in social status, and experiences of racism are associated with preterm delivery and LBW, although there is little literature on chronic stressors. Studies of specific population-level traumas have found that the timing of the events and the resultant stress of the events may be important to preterm delivery and LBW, although these studies have been limited in number and have had inherent design limitations. The abuse literature is sparse and often has had methodological issues. However, the positive studies have found large effect sizes for change in birth weight. The most studied stress-indicators have been either the presence of depressive or anxious symptoms alone or in combination with life events. These studies demonstrate the potential for an association of stress and preterm delivery, possibly separate from an association of depression and LBW. However, the literature is not yet in perfect agreement. Three populations of women have been studied in PTSD studies. One did not use a prospective measure of PTSD in pregnancy and the other included only 4 women with PTSD. Thus, there is a need for studies prospectively assessing the effects of PTSD in a large group of pregnant women.

Pathophysiology of Stress and Pregnancy Outcome

There have been a number of theories put forth in the literature as to the potential mechanism of stress and adverse pregnancy outcome. Some indicate that the relationship could be entirely accounted for by behavioral mediation. With PTSD, continued exposure to stress after the inciting event via flashbacks and re-experiencing often leads to disruptions of sleep or appetite and increased substance use, which create a non-optimal maternal environment and could lead to low birth weight and preterm delivery. This hypothesis is in accordance with the findings of the two studies that found an association with LBW and stress only through the association of both with smoking (21) (22) . However, it is also possible that stress could directly alter the hormonal and immunological state of the maternal system, thus impacting timing of birth and birth weight.

The overlapping pathophysiological mechanisms of stress and preterm delivery support the hypothesis that stress during pregnancy can cause preterm labor, preeclampsia, and resultant low birth weight. As a defined psychiatric entity and a severe reaction to stress, PTSD may relate specifically to the early onset of labor.

Pathophysiology of PTSD

Multiple circuits are involved in PTSD, as reviewed in one paper that describes the involvement of the hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic nervous system, and other pathophysiological changes associated with PTSD (55). In the hormonal cascade of the HPA axis, corticotropin releasing hormone (CRH) is released

from the hypothalamus, stimulating adrenocorticotropin hormone (ACTH) release from

the anterior pituitary, which stimulates the adrenal release of cortisol, which then

normally negatively feeds back on the hypothalamus to decrease production of ACTH

and CRH and decrease the sympathetic nervous system response. PTSD has been

traditionally thought to increase CRH release, with resultant blunting of ACTH response,

leading to low levels of cortisol, thus decreasing the negative feedback on the

hypothalamus. While many investigators have found unchanged or decreased cortisol

levels peripherally in PTSD, the CSF concentration of CRH has been found to be

elevated in combat veterans with PTSD (56) (57). This increased central CRH stimulates

the amygdala, locus ceruleus, and hippocampus to secrete adrenergic hormones (58) and

an increase in the inflammatory cytokines and sympathetic nervous system activation

(59), which have been implicated in preterm birth. It is thought that is able to occur

without the dampening effect of cortisol on the CRH release because of down-regulation

of the negative feedback that occurs with PTSD (60). Another hypothesis set forth to

explain the high central and low peripheral HPA axis activation is that there are

insufficient glucocorticoids to down-regulate the production of CRH (61). Because, as

reviewed in this paper, glucocorticoids attenuate the activation of norepinephrine,

inflammation, and CRF, they can prevent the effects of inflammatory and noradrenergic

stimulation that are conversely allowed to increase unchecked in those with PTSD.

Though low peripheral cortisol has been found by many to be the prevailing

pathophysiology in those with PTSD, in a review of the pathophysiology of PTSD,

Rasmusson and colleagues explain that no single pathophysiology characterizing

PTSD(62). According to this review, twenty-four-hour urinary cortisol has been

generally shown to be low in combat veterans but high in premenopausal women and children when compared to controls. A pattern of increased cortisol response to ACTH and CRF has also been seen more consistently among women and children, while vets are generally thought to have a decreased response. The differences may be due to a number of factors, perhaps the most intriguing of these is nicotine use, which is more common among veterans and is known to attenuate the HPA axis. Also interesting is that patterns of activity may alter the HPA axis. For example, owing to PTSD-related avoidance, many are less likely to experience the novel situations that can increase ACTH. Thus those with avoidant symptoms of PTSD, and those with PTSD who are severely ill and thus more sedentary, are more likely to have reduced trophic effects of ACTH and thus decreased cortisol response to stress. One interesting component of this review is the inclusion of dehydroepiandrosterone (DHEA) and its metabolite dehydroepiandrosterone sulfate (DHEAS) in the hormonal cascade of PTSD. Premenopausal women with PTSD have been found to have increases in this hormone which is made by the adrenal and the inactivation of which is inhibited by estrogen. The importance of estrogen may explain why male veterans have low baseline DHEA and thus different HPA axis responsiveness than premenopausal and perhaps pregnant women. DHEA has an antiglucocorticoid effect, which results in sensitization to CRF administration such that there is an increased response of ACTH and cortisol via inhibition of the negative feedback effects of cortisol. DHEA may be the upregulator of the HPA axis in PTSD. DHEA may also contribute noradrenergic stimulation. Thus, the pathophysiology does not appear consistent in all populations, which may be the result of hormonal cascades that differ based on estrogen. What unites these two pathophysiological faces of PTSD is the fact that the DHEA

causes this antiglucocorticoid effect, which could block cortisol's containing effects on the noradrenergic or immune systems. Thus, peripherally there may be "low cortisol" effects even in the face of "not low" cortisol levels.

In addition to stimulation by CRH, which is uniformly thought to be centrally high in PTSD, the sympathetic nervous system is stimulated directly in PTSD, with tonically elevated levels of norepinephrine and epinephrine (59), which serve to activate the "fight-or-flight" response of the body, increasing vasoconstriction, respiration, and heart rate. The indirect increase in noradrenergic systems with the dampening of cortisol was previously discussed. These changes may interact with the normal regulation of parturition time and result in preterm birth.

Interaction of the Mechanisms of Preterm Delivery and PTSD

Parturition is determined by a number of signals that indicate preparation of the uterus including upregulation of prostaglandins, increase in oxytocin receptors in the uterus, and increase in the connections of myometrial cells in the mother. The final trigger to parturition is thought to be activation of the fetal HPA axis, also called the "placental clock". As pregnancy progresses, CRH levels rise by increases in maternal, fetal, and placental production. A binding protein is also produced, which attenuates the bioactivity of the CRH until parturition, when the CRH is increased and the binding protein is decreased. This is thought to potentially stimulate parturition through a complicated feed forward loop that results in increased fetal cortisol production. (63) Preterm delivery is associated with increased placental CRH earlier in pregnancy. Maternal CRH is correlated with fetal cortisol more closely than with maternal cortisol

and in turn with gestational age(64). Because stress and PTSD result in increased central CRH (56) (57), this could theoretically contribute to the process of preterm delivery, both through the increase in inflammatory cytokines and increasing the fetal levels of cortisol, directly through stress response and through placental passage of maternal cortisol.

Equally, there are clues as to how the sympathetic dysregulation in stress and PTSD may contribute to adverse pregnancy outcomes. One study investigating 100 pregnant women, found that those who screened positive for anxiety, as determined by the Spielberg Questionnaire had increased uterine artery resistance (65), which has been found to result in fetal growth restriction and preeclampsia (66). Teixeira *et al.* hypothesize that the relationship between stress and uterine artery resistance was mediated by the sympathetic nervous system, which drives vasoconstriction (67). The increase in catacholamines seen with PTSD (68) may thus drive vasoconstriction associated with SGA via fetal growth restriction and preeclampsia. Thus, there is a plausible mechanism for an association of preterm delivery and psychosocial stress in pregnancy.

Similarly, there are immune-mediated mechanisms that relate to parturition and may be altered by stress. Culhane *et al.* have shown that the rate of bacterial vaginosis (BV) increases with stress in pregnancy (69). This indicates a role of stress in early parturition through BV directly as well as through decrease in adaptive immune function as indicated by the BV. Conversely, the increase in inflammatory cytokines IL-1 and IL-6 with PTSD (70) can result from decreased cortisol. Normally, the response of the inflammatory cytokines is to increase cortisol, which then decreases the ability of the body to dampen the adrenergic increase associated with stress. However, because of

insufficient cortisol, due either to low cortisol levels or functionally low cortisol levels, in women with PTSD this dampening cannot occur and NE is allowed to increase along with the inflammatory response. The inflammatory response itself, and IL-6 in particular, have been shown to be associated with increased infection and preterm delivery (71). Inflammatory mediators have been shown to up-regulate prostaglandin and be associated with elastase and metalloproteinase production via granulocyte stimulation, both of which have been associated with early parturition (72, 73) (74). One review proposes a resolution to the apparent contradiction of increased innate immunity with decreased adaptive immunity found in PTSD with the hypothesis that insufficient glucocorticoid function results in increased inflammatory cytokines which decrease the function of the adaptive immune system(61), thus potentially allowing the development of BV.

Thus the combination of altered noradrenergic, HPA, and immune systems associated with PTSD can be postulated to influence timing of parturition such that PTSD would be associated with increased preterm delivery.

Summary

Because of the great public health importance of maternal and fetal health as well as the relatively high prevalence of PTSD in the pregnant population, it is important to determine the effects of PTSD on preterm delivery and LBW. This need is augmented by the fact that there is insufficient literature examining outcomes from a pregnancy cohort with a prospective diagnosis of PTSD.

Methods

This project was a part of a larger prospective cohort study of women in pregnancy enrolled as a part of the Healthy Start Depression Initiative in Connecticut. Women were prospectively assessed for PTSD in their pregnancy. Delivery information was subsequently abstracted from the maternal and infant records by blinded researchers. The effects of PTSD on pregnancy outcomes were assessed using SAS database.

Participation:

Urban and underserved women living in the New Haven area were targeted for enrollment and recruited in two waves. The study used a convenience sample including pregnant women from the Women's Center affiliated with Yale, the Bridgeport Hospital Clinic, Hill Health Center, and the Hospital of St. Raphael. Women provided written and verbal informed consent and were administered screening forms. Inclusion criteria included pregnancy, ability to speak either English or Spanish, and enrollment in prenatal care at either one of three hospital-based prenatal care clinics or a community health centers in the New Haven area. Yale University and each participating site granted institutional review board approval. Women were approached at their prenatal visits over a two-year period between 2001 and 2003 on days chosen by expected high patient volume. The study was explained as a study of moods during pregnancy and the participants who agreed signed a written consent form. Screening occurred in private, either in a private section of the waiting room or in an office or patient room. Compensation included a package of diapers given following the interview. The women

were screened once during pregnancy. In order to protect the safety of participants, women who screened positive for suicide ideation were reported to their physicians.

Women were given a battery of tests, in English or Spanish depending on subject preference. Screening was done by trained research assistants from the Yale PMS and Perinatal Research Program, occurred once at any point in pregnancy, and included measures of depression, panic disorder, and PTSD in order to measure the current mental health disorders active in pregnancy. In the first cohort, 91.4% of the women approached agreed to participate, and in the second 87.1% agreed. In cohort 1, 387 women were screened, and 86 (22%) were lost to follow-up, while in cohort 2, 975 women were screened, and 365 (37.5%) were lost to follow-up. Loss to follow-up was the result of problems with obtaining records from all of the hospitals where women may have delivered. There was a group of women who moved out of the Yale New Haven Hospital catchment area and also a group of women for whom records could not be obtained because of privacy issues (such as women who were hospital employees).

Procedures, Measures, and Evaluations

Women were given structured interview-based questionnaires while waiting for their prenatal care provider visits. Trained personnel gave questionnaires that assessed previous diagnoses and treatments of mental health disorders and other medical problems. The primary exposure of PTSD was measured using the MINI International Neuropsychiatric Interview. This instrument is based on the DSM-IV criteria for PTSD (Table 1) and has been validated in both English (75) and Spanish (75). A diagnosis of PTSD required that women experience or witness a traumatic event, respond with

"intense fear, helplessness or horror", respond "yes" to re-experiencing the event over the last month and respond "yes" to at least 3 of the following: avoidance, amnesia, decreased interest in activities, detachment, numbing, foreshortened future, and at least 2 of the following: trouble sleeping, irritability, difficulty concentrating, nervousness, and feeling easily startled—for "several days" or more as well as distress from these problems.

Screenings for probable diagnoses of panic disorder and major and minor depressive disorders were made using the Primary Care Evaluation of Mental Disorders (PRIME-MD) Brief Patient Health Questionnaire (BPHQ). The BPHQ is based on the DSM-IV diagnostic criteria for the mental health disorders and has been validated against judgment of mental health professionals (76) (77), and has been used in an obstetric and gynecologic setting (78). It has also been compared to the SCID and found to have a reliability for major depressive disorder of 92 percent, for minor depression of 89 percent, and for panic disorder of 96 percent (77). The instrument has also been validated in Spanish (78).

Using the BPHQ, a diagnosis of panic disorder was given to women who responded "yes" to all of the following: they experienced a panic attack, the attack "came out of the blue," the attack resulted in a change of behavior, and the attack was associated with somatic symptoms. The diagnosis of major depressive disorder was made when women endorsed either depressed mood or anhedonia and met at least four other DSM-IV criteria for more than half of the days over a two-week period. A diagnosis of minor depressive disorder required endorsement of either anhedonia or depressed mood with

one to three other symptoms of depression for more than half the days over a two-week period.

Other information taken at the time of screening included demographic data, substance use, including alcohol use, active tobacco exposure, background medical and pregnancy history, and any complications of the current pregnancy. These items were assessed using questionnaires read from a script by the bilingual research assistants to the participants. For this analysis a subset of the information obtained at screening was used. Age was ascertained by asking women their age during the interview, and race was ascertained by asking participants to define their race as either black or African-American, non-Hispanic white, Hispanic, or other and recoded as non-Hispanic white and non-white. Primary language was used as a proxy for assimilation and was defined in the interview by the participant. Smoking during pregnancy was ascertained by asking the pregnant woman if she had smoked during her pregnancy at the time of screening. Alcohol use during pregnancy was ascertained by asking the pregnant woman if she had any alcohol during her pregnancy at the time of screening. Drug use during pregnancy was similarly ascertained by asking the pregnant woman if she had used illicit drugs during her pregnancy at the time of screening. Smoking, alcohol use, and other substance use during pregnancy were collapsed into a substance use during pregnancy variable. Previous preterm delivery was determined by chart abstraction and was recoded from number of prior preterm deliveries into a yes/no variable.

After delivery, record abstractions were performed by the thesis writer and several research assistants, all who were blinded to psychiatric diagnoses not included in the chart. The abstracted pregnancy outcomes included birth weight, gestational age at

delivery, complications of pregnancy or delivery, prior preterm delivery, and newborn medical problems resulting in admission to the Newborn Special Care Unit. Other data that was collected included medical history, documented use of substances, and medications taken during pregnancy and used during delivery. For the purposes of this study, LBW was defined as less than 2500 grams and very low birth weight as less than 1500 grams. Preterm delivery was defined as delivery at less than 37 completed weeks of pregnancy. Gestational age was calculated from first trimester ultrasound, or when this was unavailable, from the date of the last menstrual period. Preterm delivery was also recoded into the following smaller units 28 weeks, 28- less than 32 weeks, 32- less than 34 weeks, 34-less than 37 weeks, and greater than 37 weeks for further analysis.

Analysis

The first author, using data entered and cleaned by the lab statistician, performed recoding and analysis. The exposed group (women with PTSD) was compared to the non-exposed group to determine the relative risk of the dependent variables of LBW and PTD while controlling for confounding factors. All analyses were performed using SAS 9.1. The Pearson Chi Square test and Student's T-test were used to compare associations between PTSD and the potential confounders of race, language, tobacco, alcohol, and illicit drug use in pregnancy, maternal age, diagnosis of major and minor depression, the presence of panic disorder, and prior preterm delivery. Age was left as a continuous variable, while the remaining variables were dichotomized. Race was categorized into Hispanic, Non-Hispanic Caucasian, African-American, and other and collapsed into Non-Hispanic white and other. Prior preterm delivery was dichotomized into yes/no. A figure

was made to demonstrate the gestational age at delivery by PTSD status in order to break preterm delivery into smaller units and demonstrate where the differences occurred. For this table a variable was created from gestational age variable that categorized gestational age as less than 28 weeks, 28- less than 32 weeks, 32- less than 34 weeks, 34-less than 37 weeks, and greater than 37 weeks. A graph was then made using Excel. The mean birth weight and gestational age were computed using proc means and the percent of those who were low birth weight and preterm were calculated using Pearson Chi Square test. These values were calculated for the entire sample and then for each exposure group. Logistic regression were used to estimate whether PTSD as the primary exposure, as well as the potential confounders, contributed to models predicting preterm delivery or delivery of a low birth weight baby. Models were run separately for outcomes of LBW and preterm delivery. A backwards elimination model was then used to determine the most parsimonious model, keeping variables whose elimination changed the point estimate by 10% or more. A secondary analysis was performed, with the only difference being the inclusion of a variable for previous preterm delivery. The inclusion of this variable was done in secondary analysis because of the high number of missing data points for this variable in the exposed group. After the logistic regression of PTSD on both preterm delivery and LBW, backwards elimination using the same 10% criteria for confounders was completed. Following this an analysis was performed using chi-square and t-tests to find if those with PTSD who were missing prior preterm delivery data differed from those who had data available. Finally, an assessment of the sample size needed to show statistical significance in a future study was completed. Additionally, a retrospective power calculation was performed for the preterm delivery outcome.

Results

Table 1 shows the associations between potential confounders and the exposure of PTSD. PTSD was significantly related to increases in substance use in pregnancy, panic disorder, and major and minor depression, and prior preterm delivery. PTSD was not related to age, race, or primary language spoken in this sample. One third of the women in the PTSD group were missing previous preterm delivery data, justifying its exemption from the primary analysis.

Table 1. Description of Sample, by PTSD Status*

Characteristic	No PTSD (N=1079)	PTSD (N= 31)	p**
Age	24.5 ± 5.8	24.3 ± 5.6	0.869
Language			0.868
English	667 (61.8)	18 (58.1)	
Spanish	409 (37.9)	13 (41.9)	
Race/ethnicity			0.991
Non-Hispanic white	140 (13.0)	4 (12.9)	
Non-white	939 (87.0)	27 (87.1)	
Substance Use in Pregnancy			0.008
No	799 (74.0)	16 (51.6)	
Yes	211 (19.6)	13 (41.9)	
Panic Disorder			<0.001
No	1057 (98.0)	22 (71.0)	
Yes	22 (2.0)	9 (29.0)	
Major Depressive Disorder			<0.001
No	1042 (96.6)	24 (77.4)	
Yes	37 (3.4)	7 (22.6)	
Minor Depressive Disorder			<0.001
No	931 (86.3)	20 (64.5)	
Yes	148 (13.7)	11 (35.5)	
Previous Preterm Delivery			<0.001
No	947 (87.8)	19 (61.3)	
Yes	35 (3.2)	2 (6.5)	

 *Table values are mean ± sd for continuous variables and n (column%) for categorical variables
Numbers may not sum to 100% due to missing data and rounding

**P-value is for t test (continuous variables) or chi square (categorical variables)

Among the group of 1100 women, the mean birth weight was 3288.6 grams
(sd=538.24) and the gestational age at delivery was 39.04 weeks (sd=1.99). Overall,
6.5% of the women in the study delivered low birthweight babies, and 7.4% delivered

preterm, as defined as less than 37 weeks gestational age. Table 2 demonstrates the bivariate analysis done using t-tests to measure the average birthweight and gestational age at delivery among those with and without PTSD. The average child of a mother with PTSD weighed 9.7 grams less and was born an average of 0.5 weeks earlier, but these differences were not statistically significant. The percent of those born low birthweight was nearly identical between the PTSD and non-PTSD groups. However, the difference in percentage of those born preterm approached statistical significance, with 7.0% of those without PTSD and 16.1% of those with PTSD delivering preterm, as defined as less than 37 weeks gestational age.

Table 2. Bivariate Analysis: Pregnancy outcome, by PTSD status

Outcome	No PTSD	PTSD	p value
Birth Weight	3288.8 ± 539.0	3279.1 ± 519.5	0.921
LBW (<2500g)			0.994
No	1009 (93.5)	29 (93.6)	
Yes	70 (6.5)	2 (6.5)	
GA at Delivery	39.1 ± 2.0	38.6 ± 1.8	0.266
PTD (<37 weeks)			0.055
No	1003 (93.0)	26 (83.9)	
Yes	76 (7.0)	5 (16.1)	

*Table values are mean ± sd for continuous variables and n (column%) for categorical variables
Numbers may not sum to 100% due to missing data and rounding

**P-value is for t test (continuous variables) or chi square (categorical variables)

Figure 2 demonstrates the differences in gestational age by weeks according to PTSD status. The groups were clustered into less than 28 weeks, 28-32 weeks, 32-34 weeks, 34-27 weeks, and greater than 37 weeks and the percentage of members of the PTSD or non-PTSD groups labeled on the chart. It appears that the largest discrepancy

between the PTSD and non-PTSD groups was in the 34-37 week interval. 5.4%

(58/1100) of those without PTSD delivered between 34-37 weeks compared to 16.1%

(5/31) of those with PTSD, while in the other intervals the differences in percentages

delivering were similar between groups.

Figure 2. Plot of gestational age by PTSD status
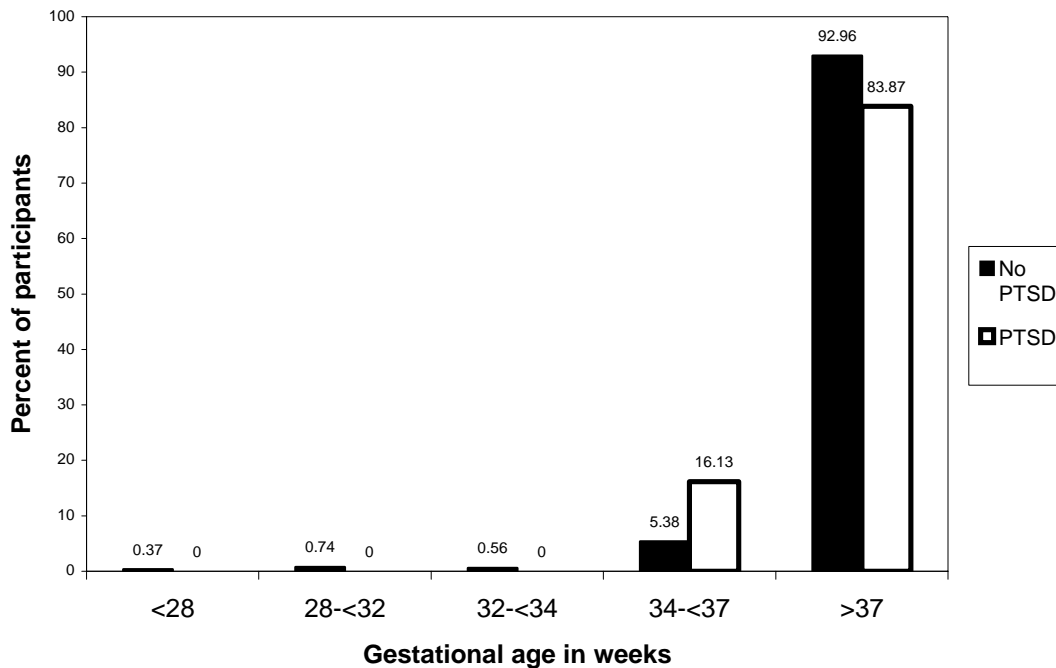
Tables 3 through 6 illustrate the model when all potential confounders *other than*

previous preterm delivery were included in the analysis. Exclusion of prior preterm

delivery from the main models was justified by the fact that data was missing from 30%

of those with PTSD. Tables 3 and 4 show the results of the logistic regression of PTSD

on LBW. In the full model, minor depressive disorder was significantly associated with

LBW, with a 25% increase in LBW with a 91% increase in the odds of LBW. PTSD was

actually negatively, though not significantly, associated with LBW in this model, as were language and age, once controlling for all of the other variables in the model. The final model included PTSD and variables that were considered confounders (because they changed the point estimate of the PTSD OR by more than 10%), including major and minor depressive disorders. It is important to note that in the elimination major and minor depressive disorder were removed together and not individually. With the removal of those factors that were not confounders by our criteria, minor depressive disorder became slightly less strongly associated with LBW.

Table 3. Full model of logistic regression of PTSD on LBW without prior preterm delivery

Variable	Odds Ratio	95% confidence interval
PTSD	0.87	0.18 to 4.17
Older Age	0.96	0.91 to 1.1
Non-White Race	1.30	0.56 to 3.01
Spanish Language	0.75	0.42 to 1.34
Substance use in pregnancy	1.14	0.62 to 2.11
Major depression	1.25	0.36 to 4.30
Minor depression	1.91	1.02 to 3.56*
Panic disorder	1.09	0.22 to 5.26

*statistically significant at the p≤0.05 level

Table 4. Final model of logistic regression of PTSD on LBW without prior preterm delivery

Variable	Odds Ratio	95% confidence interval
PTSD	0.83	0.19 to 3.66
Major depression	1.21	0.36 to 4.09
Minor depression	1.82	1.01 to 3.29*

*statistically significant at the p≤0.05 level

Tables 5 and 6 show the results of the regression of PTSD on preterm delivery, again excluding prior preterm delivery. Table 5 shows the full model and demonstrates that PTSD to be strongly positively associated with preterm delivery, with an OR of 2.72 (0.91, 8.14). The p-value at a level of 0.074 for this association was not statistically significant, however it was suggestive of a relationship between the exposure and outcome. Other variables that were positively associated with preterm delivery included major and minor depressive disorders and language, while the others, most notably panic disorder, were negatively associated with outcome. The reduced model, after backwards elimination, included major and minor depression, substance use, and panic disorder. None of the variables were significantly associated with preterm delivery, but major and minor depressive disorders were again positively associated with the outcome. PTSD was again not significantly, but suggestively, positively associated with preterm delivery with an OR of 2.82 (0.95, 8.38).

Table 5. Full model of logistic regression of PTSD on preterm delivery without prior preterm delivery

Variable	Odds Ratio	95% confidence interval
PTSD	2.72	0.91 to 8.14
Older Age	0.99	0.95 to 1.03
Non-White Race	0.89	0.41 to 1.92
Spanish Language	1.25	0.74 to 2.11
Substance use in pregnancy	0.93	0.50 to 1.74
Major depression	1.72	0.62 to 4.77
Minor depression	1.46	0.78 to 2.74
Panic disorder	0.57	0.12 to 2.76

Table 6. Final model of logistic regression of PTSD on preterm delivery without prior preterm delivery

Variable	Odds Ratio	95% confidence interval
PTSD	2.82	0.95 to 8.38
Substance use in pregnancy	0.86	0.48 to 1.57
Major depression	1.63	0.59 to 4.49
Minor depression	1.43	0.76 to 2.66
Panic disorder	0.56	0.12 to 2.69

In order to assess the legitimacy of using the variable previous preterm delivery, table 7 was made to show the differences in the 31 women in the PTSD group based on the availability of the data for this variable. The table shows that there were small numbers in each cell, precluding the interpretation of any statistical testing. Birth weight was slightly higher among those with missing data, as was gestational age at delivery, while there were higher percentages of those with missing data than available data who were white, English speaking, and non-substance users. However, those with missing data had more panic disorder and Major Depressive Disorder than those with available, but less Major Depressive Disorder.

Table 7. Differences in PTSD sample by availability of prior preterm delivery data*

Variables	Available Data	Missing Data
Age	24.0±6.1	25.0±4.6
Race		
White	2 (9.5)	2 (20.0)
Non-white	19 (90.5)	8 (80.0)
Language		
English	11 (52.4)	7 (70.0)
Spanish	10 (47.6)	3 (30.0)
Substance use in pregnancy		
No	10 (47.6)	6 (60.0)
Yes	10 (47.6)	3 (30.0)
Major depression		
No	18 (85.7)	6 (60.0)
Yes	3 (14.3)	4 (40.0)
Minor depression		
No	12 (57.1)	8 (80.0)
Yes	9 (42.9)	2 (20.0)
Panic disorder		
No	16 (76.2)	6 (60.0)
Yes	5 (23.8)	4 (40.0)
Birth weight	3208.6±547.3	3427.0±444.8
Gestational age at delivery	38.5±2.0	38.9±1.4

*Table values are mean ± sd for continuous variables and n (column%) for categorical variables.
  Numbers may not sum to 100% due to missing data and rounding.

Tables 8-11 show the results of the secondary analyses, which included prior preterm delivery despite that 33% of the women with PTSD were missing this data. Table 8 shows the complete model of PTSD regressed on low birthweight, and Table 9 demonstrates the results of the backwards elimination. Variables were again considered confounders when their removal changed the point estimate by more than 10%. These

variables included previous preterm delivery, major and minor depression, and language. These models did not have any statistically significant associations, as opposed to the association of LBW and minor depressive disorder in the primary analysis. However, in this model, the association of LBW and PTSD was a positive association with an OR of 1.41 (0.29, 6.88) in the full model and OR of 1.45 (0.32, 6.56) in the reduced model.

Table 8. Full model of the logistic regression of PTSD on LBW

Variable	Odds Ratio	95% confidence interval
PTSD	1.41	0.29 to 6.88
Older Age	0.96	0.91 to 1.01
Non-White Race	1.17	0.50 to 2.75
Spanish Language	0.59	0.32 to 1.11
Substance use in pregnancy	0.98	0.50 to 1.92
Major depression	1.34	0.39 to 4.66
Minor depression	1.84	0.94 to 3.58
Panic disorder	1.24	0.26 to 6.05
Prior preterm delivery	0.93	0.21 to 4.09

Table 9. Final model of the logistic regression of PTSD on LBW

Variable	Odds Ratio	95% confidence interval
PTSD	1.45	0.32 to 6.56
Spanish Language	0.64	0.36 to 1.13
Major depression	1.37	0.40 to 4.66
Minor depression	1.75	0.91 to 3.37
Prior preterm delivery	0.82	0.19 to 3.51

Table 10 shows the results complete model of the regression of PTSD on preterm delivery, and Table 11 shows the results of the backwards elimination model. This model demonstrates that PTSD was statistically significantly associated with preterm delivery when adjusting for all of the variables in the model, with an OR=3.48 (1.04, 11.72). The potential confounders in the model that altered the point estimate by more than 10% and were left in the final model included major and minor depression, substance use in pregnancy, and previous preterm delivery. PTSD remained significantly associated with preterm delivery in the final model, with an OR=3.35 (1.04, 10.85).

Table 10. Full model of the logistic regression of PTSD on preterm delivery

Variable	Odds Ratio	95% confidence interval
PTSD	3.48	1.04 to 11.72*
Older Age	0.99	0.95 to 1.04
Non-White Race	0.90	0.40 to 2.06
Spanish Language	1.06	0.60 to 1.87
Substance use in pregnancy	0.84	0.42 to 1.68
Major depression	1.61	0.53 to 4.88
Minor depression	1.26	0.62 to 2.54
Panic disorder	0.78	0.16 to 3.87
Prior preterm delivery	1.80	0.60 to 5.41

*statistically significant at the p≤0.05 level

Table 11. Final model of the logistic regression of PTSD on preterm delivery

Variable	Odds Ratio	95% confidence interval
PTSD	3.35	1.04 to 10.85*
Substance use in pregnancy	0.80	0.41 to 1.56
Major depression	1.52	0.51 to 4.52
Minor depression	1.22	0.61 to 2.45
Prior preterm delivery	1.73	0.58 to 5.13

*statistically significant at the p≤0.05 level

Table 12 summarized the odds ratios for the logistic regressions of PTSD on LBW and preterm delivery in all models. This table demonstrates that prior preterm delivery was a crossover confounder in the regression on LBW, while it was a negative confounder in the regression on preterm delivery.

Table 12. Summary table of odds ratios

Regression Model	Odds Ratio
LBW	
Unadjusted model	0.99 (0.23, 4.25)
Adjusted for all but prior preterm delivery	0.87 (0.18, 4.17)
Reduced model	0.83 (0.19, 3.66)
Adjusted for all including prior preterm	1.41 (0.29, 6.88)
Reduced model	1.45 (0.32, 6.56)
Preterm Delivery	
Unadjusted model	2.54 (0.95, 6.80)
Adjusted for all but prior preterm delivery	2.72 (0.91, 8.14)
Reduced model	2.82 (0.95, 8.38)
Adjusted for all including prior preterm	3.48 (1.04, 11.72)*
Reduced model	3.35 (1.04, 10.85)*

*statistically significant at the $p \leq 0.05$ level

The sample size calculation performed to determine the number of women needed in a hypothetical future study in order to demonstrate statistical significance using the

rates of preterm delivery in the PTSD and non-PTSD groups found that at least 193 women would be needed in each exposure category. Acknowledging the limitations of retrospective power calculations, for the preterm delivery outcome, there was only 49% power to detect differences.

Discussion

Study Interpretation

The results of this study provide limited support of the hypothesis that PTSD is associated with preterm delivery and do not support a relationship between PTSD and LBW. In this population, PTSD was not associated with age, language, or race, but was associated with the depressive disorders, panic disorder, and substance use, as was expected Nearly 42% of those who had PTSD were using tobacco, alcohol, or illicit drugs in pregnancy, pointing to a connection to another important public health problem. Though substance use is known to be comorbid with PTSD, it was interesting to see the association hold in pregnancy. The association of PTSD with prior preterm delivery was interesting, but difficult to interpret, as 30% of the women in the exposed group had missing data for this variable. Because of the missing data, it was decided that the primary analysis would exclude prior preterm delivery, which was then added into a secondary analysis.

It was notable that the difference in preterm delivery clustered around the 34-37 week period. This was as expected, as it would be rare, based only on probability, to see any births prior to 34 weeks in the small PTSD group. Additionally, this may be in accordance with the notion that extremely early deliveries are due to infectious and

inflammatory processes, while stress may impact more on late pregnancy complications, potentially because of the magnitude of CRH needed for stress to impact preterm delivery (79). This would be in accordance with the findings of Hedegaard *et al.* found a dose response relationship between preterm delivery and high distress at 30 weeks but no relationship between stress at 16 weeks and preterm delivery (42).

Prior preterm delivery is an important risk factor for preterm delivery. However, the data were missing in one third of exposed women, likely because of unreliable or insufficiently detailed information in the charts. More missing data occurred with women who had PTSD, but this was thought to be a chance occurrence. Table 7 was made in order to assess differences in the women who had missing versus available data. This table shows that there may have been important differences between the groups, although the numbers were too small to assess statistically significance. Women with missing data were actually a higher risk group for poor birth outcomes in general, having more English-speaking women, panic disorder, and major depressive disorder. However, they did have less minor depressive disorder. The women with missing data were women with possibly more risk factors for poor birth outcomes paradoxically had higher birthweights and higher gestational age at delivery. Including this factor in the analysis thus could have increased, rather than decreased confounding. The other problem with using prior preterm delivery is the fact that the variable does not adjust for parity. Thus, women may have had no history of preterm delivery simply because they had not given birth in the past. The reason parity was not included was because the measures of parity were not consistent in the dataset, and a large number of women were missing the prior preterm delivery field or the parity field. It was attempted to calculate the parity by

subtracting abortions and ectopic pregnancies from the gravida value. The result was a value that largely differed from parity either in the chart or reported by the woman for those women who did have parity recorded. Thus, it was deemed best not to include parity, as the measure was, unfortunately, inaccurate. Thus, we cannot say for certain whether the changes in the data that followed from adding this important variable into the analysis were accurate, though the results were interesting.

The interpretation of the data including prior preterm delivery is complex. Prior preterm delivery is known to be associated with preterm delivery. Not controlling for this variable could thus have resulted in a positive association on the basis of confounding given that prior preterm delivery was also associated with PTSD status in this population. Thus, having a prior, complicated preterm delivery with poor outcome could cause PTSD and also cause preterm delivery in the future. Alternatively, it is possible that the prior preterm delivery could be the result of having had PTSD. The limitations of this variable indicate a need for caution with interpretation. When the prior preterm delivery variable was included in the secondary analysis the results changed. In terms of the outcome of preterm delivery, controlling for prior preterm delivery resulted in a statistically significant relationship between PTSD and preterm delivery. A significantly higher percent of those with PTSD and available data had prior preterm delivery than those without PTSD, as can be seen in table 1. LBW seemed to be more strongly associated with the depressive disorders than with PTSD. In this cohort, there was no difference in the percent of women who delivered LBW based on PTSD status. Depression and PTSD were highly comorbid in this population, with 22.6% and 35.5% of the women in the PTSD group meeting criteria for major and minor depressive disorders

respectively. The association of depressive disorders and LBW was in accordance with
the relationship between LBW and depressive symptoms suggested in the literature
review. The fact that some of the other confounders in the model changed with the
inclusion of prior preterm delivery in the model, indicate the more robust nature of the
depression measures, which were confounders in all permutations of the model of LBW
and PTSD. It was interesting to see that the inclusion of the prior preterm delivery
variable changed the association of PTSD and LBW from a negative association to a
positive one. However, the associations were weak between PTSD and LBW in all
models. Language was a confounder in the model with prior preterm delivery, which
makes sense given the somewhat controversial "Hispanic Paradox", which states that
women from Spanish-speaking countries have lower rates of preterm delivery prior to
acculturation than after acculturation (80-82). This is consistent with our model, in
which women who spoke Spanish had a decreased risk of LBW versus English-speakers.
The LBW analyses indicate that LBW is more strongly associated with depressive
disorders than with PTSD. However, it is possible that with a larger sample size and
more adequate control of prior preterm delivery, nutritional factors, and other potential
confounders of LBW, PTSD may emerge as an important risk factor for LBW.

The association of PTSD more strongly with preterm delivery than LBW is
equally in accordance with the relationship between high anxiety symptoms and LBW in
the literature. In both analyses there was a strong positive association of PTSD and
preterm delivery, which was made statistically significant with the addition of the prior
preterm delivery variable. The changes in confounders in the final models were of note.
In the primary analysis, panic disorder was an important negative confounder, while in

the model with prior preterm delivery, panic was replaced by prior preterm delivery. Substance abuse and depressive disorders were important in both models. Substance abuse is a known risk factor for preterm delivery, and is known to be associated with PTSD. Depression was associated with PTSD and in this model was associated with preterm delivery, although, in the case of minor depression, not as strongly as with LBW. The appearance of a negative association of preterm delivery with panic disorder, once controlling for the other variables, does not mesh with the hypotheses idea that anxiety and related disorders would increase negative outcomes. However, it does highlight the importance of studying distinct clinical entities rather than "stress" when measuring its effects on preterm delivery and other pregnancy outcomes.

Study Critique

The strengths of this study include its prospective design and the use of a large, ethnically diverse cohort recruited from a population-based sample. Because it is a cohort, temporality can be inferred and there is unlikely to be selection bias. Additionally, this study made the diagnosis of PTSD using DSM-IV criteria, rather than relying on symptoms of psychiatric disorders alone, using among the best possible instruments to measure the primary exposures and potentially confounding other psychiatric diagnoses. These measures also were available in Spanish and the BPHQ had been used in pregnant populations in previous studies. Major confounders including maternal age, race, and language spoken as a proxy for assimilation were measured adequately. Additionally, there was blinding of record abstractors preventing bias in that

regard. Most importantly, the study question was unique and important to public health and the provision of medical care to pregnant women.

Though this was the largest cohort of pregnant women with PTSD assembled, one weakness was the relatively low prevalence of both adverse outcomes and PTSD in the population, which resulted in limited power to detect differences between exposed and non-exposed groups. One disadvantage of using a population-based cohort was that the women were not recruited from high-risk clinics, which may have decreased the numbers of adverse outcomes and lowered the power to detect associations. Similarly, the women with PTSD in a population that was not at high risk may have had unmeasured social buffers to protect from adverse outcomes. Though this study included only women with a diagnosis of full PTSD, using women with sub-clinical PTSD, who by definition have 2 avoidance symptoms or 1 arousal symptom, would have increased the power to detect differences between the groups. It may make sense to include these women in future studies, as there has been evidence in the past that women with sub-clinical PTSD have similar functional and physiologic impairment to those with full criteria for PTSD (83, 84). Accordingly, one weakness of the study was an inability to examine the impact of varying levels of PTSD severity on outcomes. Also, the timing of mental health disorder in pregnancy may modify the effect on pregnancy outcomes. Because the timing was not uniform and the measures were not taken at multiple times in pregnancy, there was not adequate control for the length of mental illness and the timing of the illness in the pregnancy.

It was not feasible to measure all potential confounders, resulting in likely residual confounding. The most important unavailable variable was weight gain during

pregnancy, which may be a critical mediator of the relationship between psychosocial variables and pregnancy outcomes. This variable was not reliably in the charts that were reviewed, and, because women were assessed only in the middle of pregnancy, research staff could not clinically assess it. Variables related to nutrition and maternal baseline health could not be included despite their likely importance to birth outcomes. Residual confounding of imperfectly measured variables was also likely a problem. This is particularly true for substance use variables, which were self-reported, leading to likely desirability bias and were collapsed into one category to preserve degrees of freedom. Collapsing the categories is also problematic because the different substances may confound in different directions. Another limitation was the missing data from the prior preterm delivery measurement. The data was missing more frequently in the PTSD group, and this may have biased the results. Because of the critical nature of this variable as a potential confounder, as it is known to be related to future preterm delivery and was associated with PTSD status in the sample, it was included in secondary analysis despite the missing data. A final limitation of the study was the large number of women who were screened for whom records could not be obtained. This was the result of both women leaving the catchment area of the hospitals as well as women for whom records could not be obtained for privacy reasons (such as hospital employees). However, this could have potentially biased the results if the women had differences in PTSD status as well as perinatal outcomes.

Overall, this study was a valuable addition to the literature given its specific measurement of both exposure and outcome in the largest prospective cohort study of

women with PTSD ever assessed. However, there were significant limitations in this study.

Implications

Currently, there exists a tremendous racial disparity in infant mortality rates (IMRs), with an African Americans rate of 14.1 per 1000 live births compared to a Caucasian American IMR of 5.7 per 1000 live births as of 2000 (1). The US is known to have one of the highest infant mortality rates in the developed world, and as such, there is a high priority on finding the mediators of infant mortality, so that they can be modified in order to decrease health disparities. One of the known mediators of infant mortality is low birth weight, which is related to preterm delivery, small for gestational age infants, and preeclampsia. An infant of very LBW (VLBW), or less than 1500 grams, has a greater than 200 fold risk of dying in the neonatal period compared to an infant whose birthweight is ≥2500 g, and the infant mortality rate is more than 90 times as great among VLBW infants compared to those not LBW (85). Thus, much of the racial disparity in IMRs in the US is thought to be due to a disparity in the number of low birth weight babies. As of 2002 the rate LBW babies was 13.4% of babies born to African American women compared to 6.9% of infants born to Caucasian Americans are low birth weight (86).

This study addresses two public health problems identified by the Healthy People 2010 goals: racial disparities and high infant mortality rates. By assessing a population of predominantly underserved members of minority racial and ethnic groups in New Haven County, we intended to address problems of racial disparities as well as contribute to the knowledge of mediators of the high US IMR.   It is hoped that this study will

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contribute to mounting evidence of the importance of treatment and prevention of mental health problems such as PTSD in order to prevent their sequelae, which may indirectly include increased infant mortality. However, the public health impact of poor pregnancy outcome extends beyond infant mortality rate. The impact of having an infant in intensive care or having an infant die naturally impacts the health of the mother and her family. Poor pregnancy outcomes can actually cause PTSD and the associated morbidity and cost (87). Cost is associated not only with loss of productivity of those affected but also in terms of treatment for LBW infants. One author estimated that the consequences of low birthweight account for 10% of childhood healthcare spending and that about six billion dollars could have been saved if all children 0-15 who were born LBW had not been LBW (88).

The effects of poor birth outcome do not stop in the neonatal nursery. For those who are preterm and survive, there is an increased risk of morbidity later in development, including an increased risk of attention deficit hyperactivity disorder (89). Those who are born preterm have been found to have an increased risk of cognitive and motor impairment at age 7 as measured by the Weschler-III IQ test and Movement Assessment Battery for Children (90). One sample of German children at age 5 to 6 found those pre-term with LBW, when compared to controls, had impairments in attention, language comprehension, and intellectual development, and required more interventions to compensate for these impairments than control children (91). Another study found, after controlling for gestational age at birth, that children of women with preeclampsia had significantly lower IQs at age 3 than those born to women who did not suffer from preeclampsia (92). There is thus suggestive evidence that children born preterm, with

low birth weight and/or preeclampsia, have cognitive and developmental impairments that often require treatment. The public health impact of pregnancy outcomes thus extends beyond the immediate effect of healthcare for infants and continues to impact children and their families through childhood.

This project has potential implications not only for reducing IMR and the sequelae of poor pregnancy outcomes but also relates to the social and behavioral determinants of health by its examination of mental health in these underserved women. African-American and Hispanic women are known to have decreased rates of detection of mental health disorders (93), and increasing awareness of the prevalence of mental health issues in these populations may increase screening, detection, and prevention of the deleterious effects of depression, anxiety, and PTSD. Screening for mental health disorders is not a routine component of prenatal care. Though there has been much attention to the negative consequences of postpartum depression, there is evidence that over half of those who will have post-partum depression are depressed during pregnancy (94). The early screening, identification and treatment of these disorders could help women to better care for their new infants.

Women, infants, and children are all affected by poor pregnancy outcomes, with members of underserved minority groups being disproportionately affected in the United States. The broad public health implications of this include raising awareness about screening for mental health disorders in pregnancy, avoiding cognitive and attention impairments in children, and decreasing future psychiatric morbidity associated with having adverse pregnancy outcomes.

That this study suggests a positive association between PTSD and preterm delivery means that it provides limited support for the hypothesized connection based on the literature connecting anxiety with preterm delivery and with the mechanism potentially connecting PTSD and preterm labor. This finding is relevant to understanding ways to lower the rate of preterm deliveries and thus decrease infant mortality. The need for screening in pregnancy for traumatic experience and PTSD is highlighted by the moderately high prevalence of PTSD in this urban population. Future research may include repeating this study with a sample specifically designed for and powered to answer this question, with the ability to control for more of the potential confounders, and to decrease the residual confounding within the categories of substance use and prior preterm delivery. Important potential confounders may include weight gain in pregnancy, PTSD severity, and history of PTSD in pregnancy. The measure of PTSD in the future should be at uniform times throughout the pregnancy in order to test the effects of PTSD timing and severity on the pregnancy outcomes. Additionally, future research into the effects of PTSD treatment in pregnancy in order to prevent the increase in preterm delivery or to determine the impacts of various traumas would contribute greatly to the literature on this topic.

Conclusion

These findings provide limited support for the hypothesized association of PTSD with preterm delivery and no support for an association of PTSD with LBW. Because of limitations of the current study, particularly the limited power associated with low rates of PTSD, the current study cannot be considered a definitive test of these relationships.

However, the relationship between PTSD and preterm delivery reached significance and nearly missed reaching significance depending on the inclusion of prior preterm delivery. The PTSD group was more likely than others to have missing data pertaining to prior premature delivery, thus precluding the inclusion of this variable in the primary analysis. The 3% prevalence of PTSD among this pregnant population implies a need for screening in prenatal clinics for PTSD as well as potentially for treatment in pregnancy. A larger study with more women with PTSD and more refined control of potential confounders, particularly prior preterm delivery, is needed to demonstrate the impact of PTSD on pregnancy outcomes. Future research should focus on the role of trauma with and without PTSD as well as the role of mental health treatment in preventing adverse outcomes.

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Appendix

Author date	Population/N	Exposure measures	Outcomes	Results
Anderson 2004 (95)	1465 general Swedish cohort	PRIME-MD measure (uses DSM-IV)—modified to find MDD, dysthymia, somatiform, anxiety (OCD social phobia included), and eating d/o At 16-18 wks GA	PTD SGA	Prevalence any psych d/o=11.6% MDD in 3.1% minor in 3.1% Anxiety in 5.9% (NOS most common) OR for any diagnosis and LBW 1.41 (.58, 3.49) SGA .83 (.16 2.97) PTD 1.04 (.32 2.14) no association for anxiety d/o or MDD alone (borderline increased weight with depression)
Atarac 2002 (10)	808 low SES (94% AA)	Abuse in current pregnancy=8 item violence subscale of conflict tactics scale for members in and also members out of the household made into a dichotomous variable of Phys. Abuse Stress Scale, a Prenatal Psychosocial Profile subscale reporting on hassle in pregnancy b/c of sexual emotional or physical abuse	LBW mean BW	17% delivered LBW, mean score on CES-D=19 (>16 used as cut off normally). 14% reported either physical abuse or stress b/c abuse, only 5% reported both (66% reporting abuse reported no stress b/c abuse) No association bet physical abuse and LBW or mean BW, stress because of abuse associated with adjusted OR 2.1 (1.24 3.55) mean BW 236g lower (significant)
Barbosa 2000 (13)	472 low SES AA women in Baltimore urban clinics	Mid-pregnancy or post-pregnancy measures of Number of life events based on the Life Events Survey (plus 6 items for crime, abuse, and relationships piloted on 20 women) social support questionnaire (ssq6)	GA at delivery	Frequency of LE not related to GA, women who experienced death of sister or mother delivered 4.6 wks earlier than others
Basso 1997 (45)	Historical cohort of 11,069 Danish women with prior LBW babies versus controls with prior non-LBW baby and subsequent birth	Changes in male partner, area of residence, type of job, and social status between 2 births Social status=3 level scale based on partner with higher job ranking based on the International Standard Classification of Industries	LBW	Previous LBW had 18% subsequent LBW, non-LBW had 2.8% risk of LBW Decline in social status between births→5% increased risk of LBW in those without previous LBW, partner change didn't matter
Brooke	1513	Measured at 17, 26, and 32	LBW	TOB most important factor,

1989 (21)	white women in London	weeks Psychosocial stress=adverse life events (modified Paykel's Interview), poor social support, perceived income difficulties Eysenck Personality Questionnaire Anxiety and depression (assessed 3 times in pregnancy by the GHQ)	(corrected for GA)	none of 40 psychosocial variables important after TOB controlled for
Chalmers 1983 (25)	782 white women in Johannesburg	LES (at 22 weeks) MAPI (26 weeks) Rotter internal-external control scale (33 weeks) STAI-state scale (22, 26, 33, postpartum) Illness scale (previous illness)—postpartum	Pregnancy complications scored into 1 variable that combined PTD, LBW and 29 other variables	Menstral history and age at first pregnancy mattered, hi MAPI (good attitude toward pregnancy) associated with more complications No significant effect of STAI (except that those who did not complete it had increased complications)
Chang 2002 (48)	171 Taiwanese women exposed to a major earthquake during their pregnancy	Earthquake Exposure Checklist—30 questions on impact on mood daily life and physical conditions, life events (loss of house or spouse), and personal injury Chinese Health Questionnaire (CHQ-12) PTSD checklist (PTSRC) prior to delivery		29.2% had minor psychiatric morbidity. 7.8% LBW LBW associated with abdominal injury, spousal death, and instability in living conditions
Cliver 1992 (27)	1545 indigent and high risk Para 1 and 2 women in Alabama	Psychosocial stress 24-26 weeks: Trait anxiety Self esteem Mastery Depression 30-32 weeks: Social support Stress Divided all scales into high medium and low scores and gave 1 point for each high score→0-6 scale	BW<15th percentile (FGR)	FGR rate 13.2% Increased RR if 4-6 on psychosocial scale 2.25 (1.24, 4.07) if 5-6 only held for thin women (defined as less than the median weight) stronger relation to psychosocial factors in non-smokers (RR=2.04) than smokers (non-significant)
Copper 1996 (30)	2593 low SES AA women	At 25-28 weeks Abbreviated Scale for the Psychosocial Status in Pregnancy—28 questions on a Likert scale (with adjusted versions of STAI, self-esteem (per a study on adolescents), mastery, depression (CES-D), and stress(per a stress and	PTL (<35 weeks) IUGR (BW<10 % for GA) LBW	Those with score <25th percentile had LBW=13.5% and PTD=5.3% versus LBW=9.6% and PTD=3.0% in those above the 25th percentile on psychosocial scores (significant differences) stress was the only variable

				that remained sig after controlling for confounders OR fir each point on the stress scale =1.16 for PTD and 1.08 for LBW. Nothing associated with IUGR significantly
Dayan 2002 (19)	634 French women	STAI (75th percentile as a cutoff for anxiety, EPDS (standard cutpoint) measured once at 22-28 weeks	PTL (<37 weeks GA)	11.2% had EDS score >15 PTL in 11.4% of women High EDS OR=2.1 (1.1, 4.1) (CI lower limit was .99 once backward elimination was completed In women in low prepregnancy BMI the adjusted) OR=6.9 State and trait anxiety each approached significance trait sig in women with previous PTD
Dole 2003 (39)	1,962 North Carolina	Once between 24-30 weeks GA) Life Experiences Survey (modified language, used 39 events) plus weight the impact of experiences, Social support CES-D (used cutoff of 25 for highest category to account for pregnancy related symptoms of depression), prenatal pregnancy related anxiety (6 questions by Orr), perception of racial or gender discrimination (Kriegler scale), perception of neighborhood safety. Measures divided into tertiles or quartiles based on lit review	PTD (<37 weeks)	RR of PTD with high counts of pregnancy related anxiety=2.1 (1.5, 3.0) life events with negative weight RR=1.8 (1.2, 2.7), perception of racial discrimination RR=1.4 (1.0, 2.0), no association with depression or social support, association remained if controlled for medical comorbidities
Dole 2004 (40)	1,898 women in a University Health Clinic	Life Experiences Survey with impact scale CES-D MOS Social Support Survey Ways of Coping Questionnaire, Living with father and Religiosity (as proxies for social support) Reaction to unfair treatment (Krieger), perceived neighborhood safety, Negative impact of pregnancy-related anxiety (subset of Orr's Prenatal Social Inventory Scale)	PTD (<37 weeks)	AA increased risk of PTD if used distancing as a coping mechanism (RR=1.8, CI=1.0, 3.2) or higher levels of racial discrimination (RR=1.8 CI=1.1, 2.9) Whites at higher risk if not living with partner (RR=1.8, CI=1.2, 2.7) or higher number of life events Pregnancy related anxiety in whites had RR=2.0 (CI=1.3, 3.2) and in AA RR= 1.6 (CI-1.1, 2.3). This was non-significant once

				controlled for medical factors
				No association with PTD of depression, general social support, church attendance
Domingue z 2005 (31)	178 AA	Stressful life events (24 items) summary score of SLEs 1 year before and during pregnancy measured at 18-20 1weeks and 24-26 weeks Event distress (1 to 4 for each item made into a summary score) Intrusive subscale of Impact of Events Scale (5/7 questions about 2 most distressing events) PSS (18-20, 24-26, and 32-36 wks) STAI (3 time periods as above) 1 Pregnancy specific anxiety question at 3 time points 4 pregnancy undesirability questions	BW GA (continuo us)	SLEs predicted 3% of variance in GA Parity, wt gain, and substance use predicted BW All psychosocial stress variables together accounted for 7% of the BW variation, with the significant indicators being intrusive thoughts and event distress
Glynn 2001 (49)	40 women who experience d an earthquak e in pregnancy	Timing of earthquake with rating of how upsetting the earthquake was Life event inventory at 32 weeks and 6 weeks postpartum CRH at 32 weeks GA	Gestationa l age at birth	Earthquake rated most stressful if it occurred early in pregnancy (p<.05 for association of timing and rating), CRH accounted for 24% of variation in timing at birth, with timing these 41% was accounted for
Goldenber g 1996 (24)	1,431 multiparo us women	24-26 weeks: STAI, CES-D, self-esteem (per Rosenberg adolescent study), mastery (per Pearlin), 30-32 weeks: stress (per Schar cardiovascular study), maternal social support index, Life Experiences Survey	BW, GA, IUGR, PTD, LBW	Race, height, weight, BP, DM and TOB accounted for outcomes only, no effect of other psychosocial risk factors
Grimstad 1997 (9)	86 women who delivered LBW vs 92 controls Norway	Physical or sexual abuse by partner ever with partner from index pregnancy (Conflict Tactics Scale) Interview either postpartum in maternity ward or 1 year after delivery	LBW	17% had been abused by partner, but only 1 had been abused during the index pregnancy and only 7% before the index pregnancy, nonsignificant OR for abuse history and LBW
Grjibovski 2004	1,399 Russian	"antenatal" survey Living conditions, crowding	Birth weight	Living in shared apartments (-89g CI=-153, –25),

(43)		(# people greater than 1.5 times the number of rooms), perceived chronic stress (2 questions about work and home if either were positive then stress measure positive)		crowded living (-82 g CI=-136, -28), perceived stress (-61g CI=-136, -28) were associated with decreased BW, TOB decreased BW, maternal ETOH increased and paternal ETOH decreased BW. Living with parents associated with increased BW
Grjibovski 2005 (44)	1,103 Russian	Antenatal questionnaire about Maternal education, self-reported stress (2 questions about work and home), living situation, crowding	Spontaneous PTB (<37 weeks)	5.6% preterm increased risk with decreased education, stress (adjusted OR=2.15 CI=1.20, 3.83), placental complications, smoking, and history of preterm birth
Hansen 1996 (96)	70 stressed and 50 non-stressed women Danish (in Danish)	Case control of women with moderate-severe stressful life events per DSMIIIR in combination with inadequate social network	BW, head circumference	Stress and smoking significantly affected BW. Stress still significant determinant of head circumference when controlled for BW
Hedegaard 1996 (23)	5,839 Danish	GHQ in pregnancy at week 16 and week 30 (30 questions about psychological distress, SLE, social support, occupational exposure, health behavior)	BW, SGA	No association of psychological distress at either time with BW or SGA status
Hedegaard 1993(42)	5,459 Danish	At 16 weeks and 30 weeks 30 item GHQ measuring psychological distress divided into 3 levels (validated and reliable for Danish population)	PTD (<259 days)	3.6% PTD dose response relationship between stress at 30 weeks and PTD, but no relationship to stress at 16 weeks RR for PTD significant only for high distress at 30 weeks RR=1.75 (1.20, 2.54)
Hoffman 2000 (34)	666 (private practice and mostly white)	CES-D (cutoff 16, modified for pregnancy) PERI-LE (life events) Fischer's social network interview External locus of control scale Phone interview at 13 weeks updated at 28 and 36 weeks)	BW, GA at delivery	No association with CES-D and outcomes except among low SES women (-9.1g CI=-16.0, -2.3) for each unit increase on CES-D Other potential interactions non-significant=smokers, adverse outcomes of previous pregnancy, "social vulnerabilities"
Kurki 2000 (97)	623 Finish	Depression with short form of BDI and anxiety with 1 question at 10-17 weeks	Preeclampsia	Preeclampsia in 4.5%, positive association with depression (OR=2.5 CI=1.1, 5.4), anxiety (OR=3.2 CI=1.1, 5.4), and BV plus

				depression (OR=5.3 CI=1.8, 15.0)
Lederman 2004 (50)	300 non-smokers exposed to the World Trade Center disaster	Classification of place and time of exposure by geocoding work and home locations 4 weeks after 9/11	BW	Women living (but not those only working) within 2 miles of WTC versus those farther away had significant decrease in BW (-122g) and birth height (-0.74cm) after adjusting for GA(149 and 0.84 prior to adjustment) Those in 1st trimester had 3.6 day shorter gestation and 0.48 cm smaller head circumference than those later on in pregnancy, regardless of location.
Lobel 2000 (26)	129 private obstetric practice for high risk pregnancy (mostly white and married)	Prenatal maternal stress (perceived stress scale, state form of STAI, Prenatal Distress Questionnaire, prenatal Life Events and distress from those events) Optimism (Life Orientation Test) Assessed 3 times in pregnancy (10-20 weeks, 21-30 weeks, and after 30 weeks)	BW GA	Least optimistic had lower BW than most optimistic Once control for optimism there is no effect of prenatal maternal stress Optimism associated with exercise (a potential confounder)
Lu 2004 (17)	33,542 women from 19 states retrospective cohort	13 stressful events experienced in the year prior to delivery put into 4 constructs (emotional, financial, partner related, traumatic)	PTB	9.9% of the weighted sample delivered preterm (highest in AA) None of the stress constructs significantly associated with PTB, and none added to the predictive value of race-ethnicity on PTB Black women (versus white) were more likely to report all stressors
Mackey 2000 (28)	35 women hospitalized for PTL versus 35 controls matched on age, race, parity, GA, insurance (mostly low SES)	Daily Hassles Scale and Profile of Mood States given postpartum and asked about the previous month	PTL	Women in the PTL group had significantly higher scored on the POMS scale for anxiety and depression AA women in the PTL and white women in the control group had increased fatigue and higher future security on the DHS versus their counterparts
McCormick 1990 (22)	458 low SES women in Harlem	Life events using the modified PERI scale, social support questionnaire (Cohen)_GHQ	LBW	Social support, stress, and mental health were associated with smoking status (never, quit, current) but not LBW directly

Misra 2001 (29)	739 low SES African-American women	Postpartum interview with top versus lower quartiles on the Prenatal Psychosocial Profile Hassles Score (stress), Pregnancy Beliefs Score locus of control), mastery (Pearlin measure), CES-D, social support (per own scale)	PTD	Stress and PTD when controlling for biomedical factors OR=1.86 (p<0.005), locus of control OR=1.86 (p<0.007)
Nelson 2003 (98)	392 cases of SAB versus 807 non-SAB	Physical violence in pregnancy (modified index of spousal abuse, violence by non-intimate partner, neighborhood violence) Social support (number of phone contacts per day)	SAB (loss prior to 22 weeks GA)	No association between SAB and previous violence in pregnancy Very high rates of violence in this population intimate partner violence=47% in controls, 57% in cases)
Newton 1979 (99)	132	Interviewed post-partum using Modified and validated Life Events Inventory (LEI)	PTD	Pregnancies resulting in PTD are more likely to have had more stressful life events p<.05 for mean number of life events in PTD versus non-PTD
Newton 1984 (12)	224	STAI Newton Life Events Scale (objective life events (major life event confirmed by 3rd party), major life events (>60 on 1-100 scale), self rated major life events) at 30 weeks, 37-40 weeks, and post-partum	LBW, PTD	LBW and PTD significantly associated with number of objective major life events but not STAI Self-rated life events significantly associated with PTD but not LBW
Nordentoft 1996 (38)	2.432 Danish	GHQ, Stress Scale (Brown and Harris), social support at week 20,	SGA (<10th percentile), PTD	8.7% PTD rate, 6.3% SGA No relationship between GHQ and SGA or PTD Smokers scored higher on GHQ Stress per the Stress Scale was associated with PTD OR=1.14 for each 1 point increase on the 5 point scale. IUGR associated with social network, TOB, daily drinking, and education
Orr 1996 (100)	1,860 (mostly African American)	At first prenatal visit assessed Prenatal Social Environmental Inventory (PSEI) divided into tertiles	LBW	10.1% LBW Relationship to stressors only significant in AA (not in full sample) OR=1.4 (p=0.05)
Paarlberg 1999 (32)	396 nulliparous Dutch women	At each trimester Everyday Problems Checklist (EPCL=self-report of chronic stressors-114 items) Social Support (Van Sorden; measures social interaction and satisfaction) Dutch version of Hopkins	LBW (using customized centiles), GA	Number of daily stressors in 1st trimester associated with LBW (OR=1.04 CI=1.01, 1.08) as was depressive mood in 1st trimester (OR=1.12 CI=1.01, 1.24) Low subjective severity rating of daily stressors in

		Symptoms Checklist (psychological and somatic well being in pregnancy, workload		1st trimester associated with decreased LBW (OR=0.41 CI=0.17, 0.97) No association between scores later in pregnancy and outcomes, no association with depressed mood or anxiety or somatic complaints
Pagal 1990 (36)	100 (low SES, mostly white)	Rand Corporation Life Events Scale (checklist, separated into 1 year prior to pregnancy and during pregnancy), Family APGAR measure for social support, STAI state	BW, GA, Apgar and 1 and 5 minutes	High anxiety predicted lower GA Life event stress accounted for significant variation in BW, social support and anxiety associated with APGAR
Peacock 1995 (20)	1,513 white British	Psychological stress measured at 4 points (booking, 17, 28, and 36 weeks) "have you suffered any trouble with nerves or depression?", satisfaction with housing/neighborhood, feelings about pregnancy GHQ at 2 points	GA	Trouble with nerves, depression, little association with neighbors, and help from professional agencies were significantly associated with increased risk of PTB, smoking is only associated with delivery at <32 weeks
Perkin 1993 (18)	1860 white British	GHQ measured anxiety and depression at booking, 17, 28, and 36 weeks	PTD, non-spontaneous onset of labor or vaginal delivery, major analgesia use in labor	Depression unrelated to outcome Anxiety accounted for 0.1% of the variation in use of analgesia unrelated to other outcomes
Reeb 1987 (33)	140 urban AA women	At 7 months Stressful life events during pregnancy, (PERI), maternal worry about adjusting to new baby, Emotional and instrumental support (Stack), Depression per Brief Symptom Inventory (BSI), Family Functioning (per Family APGAR, Olsen's FACES, Hudson's Index of Family Relations)	LBW, intrapartum complications	LBW rate=14% Maternal depression associated with LBW. Family functioning the single best predictor of LBW, followed by stressful life events
Renker 1999 (11)	139 pregnant adolescents	Interviewed between 15 and 40 weeks Abuse Assessment Screen (Parker and McFarlane 1991) Modified Social Support Interview Denyes Self-Care Agency and Practice Instruments	BW	22% reported physical abuse during pregnancy. Birth weight of abused was significantly lower than non abused (3,144g versus 3,310g p=.025) abused also had significantly more previous miscarriages, substance

				abuse, and ED visits
Rini 1999 (37)	120 Hispanic and 110 white women	Personal resources (Pearlin's Mastery Scale, 8 Item Life Orientation Test for Optimism, Rosenberg's 8 item self esteem scale) STAI-10 item state-trait Pregnancy related anxiety (Wadhwa)	BW, GA	More mastery/self-esteem/optimism associated with increased BW More stress associated with lower GA at delivery No evidence that resources buffered stress
Rondo 2003 (41)	865 Brazil	16 weeks, 20-26 weeks, and 30-36 weeks stress by PSS, and distress by GHQ and STAI (state and trait)	LBW, PTD, SGA	6.5% LBW rate, 4.2% PTD rate, and 10.8% IUGR rate Maternal distress (GHQ>3) at the second interview associated with LBW (RR=1.97 p<.02) and at the third interview GHQ>3 was associated with PTD PTD (RR=2.32 p<.02) Interaction of smoking and stress at the 2nd interview only IUGR not associated with stress/distress
Rosenberg 2002 (46)	422 AA women with PTD versus 4544 AA women with no PTD	Racism assessed by yes/no on the following: Unfair treatment (at job, in housing, or by police), behaviors toward the participant (poorer service, people act as if I am not intelligent or honest, people are afraid of me, people act like they are better than me) Frequency of thinking about race (scale of 4)	PTD	Adjusted OR=1.3 (1.1, 1.6) for reporting unfair treatment on the job and 1.4 (1.0, 1.9) for reporting that people act afraid of them at least once weekly
Seng 2001 (51)	455 women with ICD-9 coded of PTSD versus 638 women without mental health disorders	PTSD by ICD-9 code on Michigan Medicaid Claims data	PTD, miscarriage, preeclampsia, poor fetal growth and other pregnancy complications	Higher odds of ectopic pregnancy (OR=1.7 CI=1.1, 2.8), spontaneous abortion (OR=1.9 CI=1.3, 2.9) hyperemesis (OR=3.9 CI=2.0, 7.4), preterm contractions (OR=1.4 CI=1.1, 1.9), and excessive fetal growth (OR=1.5 CI=1.0, 2.2), but not PTD, preeclampsia, poor fetal growth, type of delivery
Steer 1992 (35)	323 inner-city adolescents and 389 adults (mostly	BDI in 3rd trimester (total score and cutoff of 21=clinical depression)	LBW, PTD, SGA	No relationship between BDI and outcome in adolescents Adults had a significant increase in risk of all poor outcome 5.7% per point on

				BDI.
				With cutoff of 21 on the BDI risk of LBW=3.97 (3.80, 4.15), PTD=3.39 (3.24, 3.56), and SGA=3.02 (2.88, 3.17)
Wadhwa 1993 (14)	90	3rd trimester chronic stress—14 item PSS episodic stress—117 item Daily Hassles Questionnaire strain—45 item Hopkins checklist pregnancy-related anxiety—5 item (modified from Lederman) Life event stress=sum of the product of frequency and subjective severity of each event since the beginning of the pregnancy. Hassles, chronic stress, and strain were combined in this measure	BW, GA, intrapartum complications	Each unit of life event stress (14.7 total units) was associated with a 55.03g decrease in BW and OR=1.32 Each unit of increased pregnancy-related anxiety (5 total units) was associated with a 3-day decrease in GA at birth
Whitehead 2002 (16)	Compared the PTD and non-PTD cases in 11 states	Modified Life Events Inventory (18 items) self-reported 2-6 months post-partum as a part of PRAMS	PTD	Inconsistent results dependent on year for how number of events affects risk of PTD. The author writes that this suggests a threshold model for number of events and PTD
Zambrana 1999 (15)	1,071 primiparous low SES African-American and Mexican – origin women	Stressful Life Event Inventory-16 item, with the distress associated (5 point scale) Prenatal stress—8 item PSS Social support—6 items about baby's father	BW	AA women had lower birth weight (RR=2.66) and more preterm babies (RR=2.39) than Mexican-American women Predictors of LW were use of TOB/ETOH, prenatal stress, positive attitude toward pregnancy, which accounted for the total ethnic difference in BW

Abbreviations used in above table:

AA=African-American	PTD=preterm delivery
BW=birth weight	RR=relative risk
D/o=disorder	SES=socioeconomic status
ETOH=alcohol	SGA=small for gestational age
GA=gestational age	TOB=tobacco
LBW=low birth weight	
MDD=major depressive disorder	
OCD=obsessive compulsive disorder	
OR=odds ratio	