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Maternal History of Childhood Abuse Predicts Preterm Delivery and Low Birth Weight in Offspring

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Maternal History of Childhood Abuse Predicts Preterm Delivery and Low Birth Weight in Offspring

By

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M.D., Northwestern University Feinberg School of Medicine, 2003

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An abstract of
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Abstract

Maternal History of Childhood Abuse Predicts Preterm Delivery
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Background: Maternal depression has been identified as a risk factor for low birth weight and preterm delivery. However, depression can often be associated with a history of childhood maltreatment, which itself has been associated with long-term physiological alterations that could potentially affect the course and outcome of pregnancy. This study examined the influence of maternal history of childhood abuse on pregnancy outcome while accounting for the effects of comorbid psychiatric conditions.

Methods: This was a retrospective cohort analysis using existing data on a subset of subjects (n=268) drawn from a cohort of women followed prospectively while receiving outpatient perinatal psychiatric care at the Emory Women's Mental Health Program (WMHP).

Results: Women with a history of two or more types of severe childhood abuse were more likely than those without such abuse to deliver a low birth weight (LBW) baby (OR 7.88, 95% CI 1.82-34.03). Women with this severe abuse were also more likely to have a preterm delivery (OR 4.20, 95% CI 1.16 - 15.22). The risk of LBW and preterm delivery (PTD) remained significant even after controlling for confounding factors including depression, PTSD, substance abuse, smoking, medication exposures, age, obesity, race, education, and parity.

Discussion: In this clinical sample of patients followed during pregnancy, maternal history of severe childhood abuse was associated with increased risk of PTD and having a LBW baby. This study provides preliminary evidence that women with a history of abuse are at risk for LBW and PTD which in turn puts their developing child at risk for future psychiatric and medical problems. It also raises the possibility that women with a history of childhood abuse may represent an at-risk group that might benefit from close monitoring and early preventative measures. The data also suggest that maternal history of child abuse may in part be responsible for some of the previously reported effect of depression and/or psychopharmacologic treatment on LBW and PTD.

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Introduction

Low Birth Weight (LBW) and Preterm Delivery (PTD) are important determinants of neonatal mortality[1] and have been associated with significant long-term health complications for the offspring. For example, LBW and PTD have been associated with increased risk of adverse adult outcomes including major depression (MDD), anxiety disorders, suicidality, impaired functioning, hypertension, type 2 diabetes, cardiovascular disease, and stroke.[2-7]

The impact of maternal depression on perinatal outcome has generated considerable attention in the literature. The relationship between depression and adverse pregnancy outcomes including PTD, LBW, and Intrauterine Growth Restriction (IUGR) has been replicated in a number of studies (see Field et al for review).[8] While there have been discordant data, some studies have linked lower birth weight and/or shorter duration of gestation with either antidepressant medication[9, 10] or depressive symptoms. However, little attention has been paid to other clinical factors prevalent in this population that could be associated with pregnancy outcome and could potentially explain the association between depression/antidepressant use and pregnancy outcome.

It has been well documented that a history of childhood abuse is associated with increased risk of depression later in life.[11-16] Individuals with a history of child abuse are more likely to have co-morbid psychiatric illness including PTSD. The prevalence of lifetime PTSD can range from 33% to 86% among individuals exposed to childhood sexual abuse (CSA),[17] and approximately 40% of females who were physically abused in childhood develop PTSD.[18] The potential for adverse pregnancy outcome in women with

a history of abuse is of particular interest given the natural neuroendocrine stress of pregnancy and the fact that child abuse may result in long term aberrations in neuroendocrine function. Numerous studies have demonstrated an association between prenatal glucocorticoid exposure and adverse sequelae in the offspring in both the neonatal period and adulthood.[19-30] In addition, trauma history and PTSD have also been associated with unplanned pregnancy, poor prenatal care, substance abuse, high smoking rates, increased medication use, poorer social supports, and exposure to intimate partner violence; these factors may further impact perinatal development in women with a history of child abuse. See Figure1 for a model of the possible mechanisms through which a maternal history of child abuse could affect pregnancy outcome.

Unfortunately, studies of the impact of early life abuse on obstetrical outcome are limited. The studies that have been done have had significant methodological limitations, have lacked sufficient power, have not adequately examined the effects of multiple abuse types, and have not fully controlled for confounding factors such as depression, PTSD, and risk behaviors linked to poor perinatal outcomes.[31-34] Similarly, most studies examining perinatal outcomes and PTSD, depression, and antidepressant treatment have not examined the possible contribution of abuse to these outcomes.[8, 35-39] As a result, it is still unclear whether abuse is a truly a risk factor for poor pregnancy outcomes, and if so, what role psychiatric comorbidity, risk behaviors/associated exposures (such as substance abuse), or abuse-related physiological changes may play in the association between abuse and pregnancy outcome.

The current study was designed to examine the effect of maternal child abuse history on PTD and LBW and to examine the relative contribution of confounding factors such as

depression, PTSD, substance abuse, and other risk behaviors. The sample was composed of women with clinically meaningful psychiatric illness and was limited to women with a history of depression. Using data already collected for a larger prospective, observational study of perinatal mental illness/psychiatric care, a subset of women with a history of depression was selected for this retrospective cohort study of the risk of PTD and LBW in women with and without a history of childhood abuse while controlling for psychiatric illness, treatment effects, substance abuse, and common behavioral risk factors for poor pregnancy outcome.

Methods

Description of WMHP sample

This was a retrospective cohort analysis using existing data on a subset of subjects drawn from a cohort of women receiving outpatient perinatal psychiatric care at the Emory Women's Mental Health Program (WMHP). The WMHP cohort included participants from several large prospective, observational studies of perinatal psychiatric illness and treatment. The majority of clinic patients were referred for care by their obstetricians, primary care physicians, or psychiatrists, and a small number of women came to the clinic in response to flyers posted at Emory hospital and related clinics. All women followed in the clinic were offered participation in the ongoing cohort study.

Inclusion/Exclusion Criteria for the Current Analysis

Data from a subset of eligible subjects in the larger WMHP cohort were used to conduct a retrospective cohort analysis examining the association between maternal history of childhood abuse and subsequent risk for preterm delivery (PTD) and having a low birth weight infant (LBW). Inclusion criteria for the current analysis were: 1) enrollment in the study prior to 24 weeks estimated gestational age (EGA); 2) completion of at least one third trimester psychiatric symptom evaluation; 3) history of depressive disorder; 4) completion of the Childhood Trauma Questionnaire (CTQ); and 4) live singleton delivery. Women with a history of bipolar disorder or primary psychotic disorder were excluded from the analysis. For women who completed more than one pregnancy during participation in the WMHP studies, only first pregnancy meeting criteria for each subject was included in the current analysis. Only subjects with data on EGA at delivery and/or birth weight for the index pregnancy were included in the final dataset. Subjects who did

not complete all questions on the three abuse subsections of the CTQ were also excluded from the analysis. See Figure 2 for the inclusion/exclusion flow chart.

Clinical Care and General Study Procedures for the WMHP Cohort

Since the WMHP cohort studies were observational in nature, treatment was provided by the clinic physicians based on the clinical needs of the patients. The WMHP research protocols did not stipulate any treatment algorithms or guidelines. For the current analysis, subjects had to enter treatment at the clinic no later than 24 weeks EGA although the majority of women joined the study prior to conception or during the first trimester. Visits occurred at regular intervals throughout pregnancy (more often if clinically indicated).

Assessments

Demographic information was ascertained by self-report at the time of study intake. The Structured Clinical Interview for Diagnosis (SCID) was used to establish current and lifetime DSM-IV Axis I diagnoses at baseline. At set intervals throughout pregnancy study participants completed the Hamilton Rating Scale for Depression (HRSD), a clinician-administered rating scale widely used to assess current depressive symptoms. The Childhood Trauma Questionnaire (CTQ) was completed at baseline to provide an operationalized measure of exposure to child abuse. Psychiatric ratings were performed in a blinded manner by members of the study team; these ratings were independent of the treating physician's evaluation and management of the patient. Medication use was monitored with tracking sheets completed by the treating physician; the tracking sheets charted all medications used for every week since the last study visit. Maternal preconception weight and height were obtained by measurement, records, or self report

and were used to calculate the preconception BMI. Information on pregnancy complications and outcomes were obtained through self-report and obstetrical records; this information was then coded in standardized manner.

Abuse History

Determination of abuse status was made based on CTQ responses. The CTQ consists of a series of 25 questions about abuse and neglect experienced before the age of 18. For this analysis, only questions related to abuse were considered. The CTQ has a total of 15 abuse questions (5 each for physical abuse, sexual abuse, and emotional abuse). Subjects were asked to mark their response to each question on a scale from 1 to 5 with 1 representing "Never True" and 5 representing "Always True". Responses were tallied according to the abuse category with each subscale yielding a score on the scale from 5 – 25 for each type of abuse (total abuse scores range from 15 to 75). Established norms were used to transform CTQ raw scores into ordinal categories for each abuse type. For the purpose of these analyses, abuse of any severity was defined as a subscale score of >7 for physical abuse, >5 for sexual abuse, and >8 for emotional abuse. Moderate to severe abuse was defined as a subscale score of $\geq$ 10 for physical abuse, $\geq$ 8 for sexual abuse, and $\geq$ 13 for emotional abuse. Severe abuse was defined as a subscale score of $\geq$ 13 for physical abuse, $\geq$ 13 for sexual abuse, and $\geq$ 16 for emotional abuse. Past research has suggested that biological alterations are often evident only in more severely abused individuals and that exposure to two or more types of abuse yields a marker of abuse that correlates well with risk for psychiatric illness and biological alterations. Exposure to more than one type of abuse is assoc4iated with increased risk of poor psychiatric outcome, and some authors have found a graded effect of number of types of abuse on

medical morbidity in adulthood suggesting that physiological effects may be more evident in subjects exposed to more than one type of abuse.[11, 15, 40-43] Furthermore many studies of the long-term effects of abuse focus on only the most severe forms of abuse.[44-47] Thus, the abuse variables were further collapsed into groups of individuals exposed to: 1) moderate to severe abuse of two or more types or 2) severe abuse of two or more types. Moderate to severe abuse of two or more types is often the most clinically useful variable, but given the evidence that biological sequelae may be difficult to detect in milder cases of abuse, the effects of exposure to severe abuse of two or more types were also assessed.

Low Birth Weight and Preterm Delivery Outcomes

Pregnancy outcome measures were ascertained through maternal self report and medical record review. Weight at delivery was recorded in grams. Infants weighing less than <2500g were considered to be low birth weight while those $\geq$ 2500 g were coded as not low birth weight. EGA at delivery was recorded in fractions of weeks. Individuals delivering prior to week 37 EGA were coded as preterm while those delivering at or after 37 weeks were coded as not preterm.

Statistical Analysis

Data were analyzed using SAS version 9.2. Separate analyses were conducted for LBW and PTD outcomes. Descriptive/diagnostic analyses were run to determine whether statistical assumptions for analyses were met and whether continuous measures should be transformed to categorical variables based on nonlinear association with outcome. Variables were selected for univariate analysis based on potential relevance based on known or hypothesized associations with abuse or outcome. Variables were also

examined if they were considered confounders based on the population being examined or the study design. Chi square comparisons were conducted for univariate analysis of categorical variables and when appropriate Fisher's exact test was used when cell counts were below acceptable limits. Unadjusted odds ratios (OR) and 95% confidence intervals (CI) were also calculated. Pearson correlations were used to examine the relationship between 2 sets of continuous variables. To examine the significance of continuous variables as predictors of categorical outcome variables, logistic regression models were run with the continuous variable of interest entered as the only independent variable. The effects of medication exposures and substance use were examined by trimester and for pregnancy as a whole since it was not known a priori when a given exposure might have the greatest impact. The same was true for depression. Average HRSD for third trimester and for all of pregnancy was calculated by averaging all available HRSD ratings for that time period. Because different exposures might affect birth weight and duration of gestation through different biological/developmental mechanisms, the peak period of vulnerability for each of the two exposures could be different. Therefore, the univariate analyses examined the association between exposure and outcome individually for each medication and substance exposure during each trimester and then for a summary variable indicating exposure at any time during pregnancy. When selecting which variables to include in the stepwise regression analysis, the variable with the strongest effect was generally chosen unless there was minimal difference between the exposures effect at different time points or unless there was a compelling scientific reason to do otherwise. If a medication or substance appeared to be associated with an outcome, both the 3rd trimester and "any trimester" exposures were generally included for possible

selection in stepwise model. When there was little evidence of a significant effect for an exposure and there was no evidence that exposure during one time period was more important than exposure during the other time periods, the "any trimester" exposure variable was selected for inclusion in the model because this provided the broadest, most general estimate of the exposure's impact on outcome. In the case of alcohol, both third trimester and any trimester exposures were included because it is not uncommon for women to report 1st trimester ETOH consumption that occurred very early in pregnancy before pregnancy was confirmed. As a result, most women are coded positive for the "any trimester" exposure to ETOH even though this exposure is unlikely to have as significant an impact on in utero development as repeated, prolonged, or late pregnancy exposures might have. On the other hand, some of the relevant effects of ETOH may occur before third trimester. Since ETOH use is a known risk factor for LBW and PTD, both third and any trimester ETOH variables were included for consideration in the stepwise procedure.

An unadjusted α threshold was set at 0.05 for significance in the univariate analyses but a threshold of 0.10 was set for selection of variables to be considered eligible for inclusion in the multivariate analyses. Variables with p values $\geq$.10 in the univariate analyses were included in the multivariate analyses if they were considered to be known or suspected confounding factors or if they were considered to be of biological or clinical relevance. Stepwise regression analyses were conducted with 0.10 as threshold for entry and exit from the model at each step of the analysis. Variables that were identified as significant in the stepwise analysis were then manually entered into a follow-up regression with the full dataset to maximize precision of the model since the stepwise procedure eliminates

any subjects with missing data points for any of the variables considered in the model. In addition, if variables of interest or known risk factors for LBW and PTD did not remain significant in the stepwise analysis but were considered important to control for, these variables of interest were forced into another regression model with the previously identified significant variables; this was done to ensure that the effects of important known/hypothesized risk factors were accounted for in the analyses.

Results

Demographics/Sample Characteristics

A total of 268 subjects were included in the current analysis. The mean maternal age was 33.67 (sd 4.75). The sample was predominantly Caucasian (87%) with African Americans representing 8% of the sample and other ethnic groups such as Asian Americans and Native Americans making up less than 5% of the sample. Most subjects were married and had at least some college education. On the whole, the subjects came from upper middle SES backgrounds. The mean Hollingshead score (available for only a subset of subjects) was 54.07 (sd 9.89). Just less than half of the sample was primiparous. All subjects had a history of unipolar depressive disorder, and 13.21% of subjects had a history of Posttraumatic Stress Disorder (PTSD). Approximately half of the subjects in the study had at least one major depressive episode (MDE) during pregnancy (based on SCID mood module diagnosis). See Table 1 for detailed demographic and obstetrical characteristics of the sample, and see Table 2 for psychiatric characteristics of the sample.

Exposures during Pregnancy

Antidepressants were the most common psychiatric medication taken by subjects during pregnancy with more than three quarters of subjects taking at least one antidepressant at some point in pregnancy. Anxiolytics were also commonly prescribed with nearly 1/5th of subjects taking an anxiolytic at some point in pregnancy. A smaller proportion of subjects were prescribed hypnotics, antiepileptic mood stabilizers, or antipsychotic agents. Exposures to caffeine, tobacco, alcohol, and drugs were also assessed. Most women reported some exposure to caffeine at some point in pregnancy 166 (83.42%)

with slightly fewer exposed to caffeine in third trimester 134 (67.34%). 72 (26.87%) of subjects reported ETOH exposure at least one time during pregnancy, and 26 (9.70%) of subjects reported ETOH exposure at least one time during 3rd trimester. Approximately 1 in 10 subjects (12.56%) acknowledged smoking during pregnancy. More than a quarter of subjects had alcohol at least some point in pregnancy, and nearly 10% indicated some ETOH use during 3rd trimester. Self report of illicit drugs was less common; 2% of subjects admitted to marijuana and less than 1% of subjects acknowledged cocaine use during pregnancy. Table 2 highlights the key exposures for the sample.

Periodic urine drug screens completed on a subset of subjects suggested similar rates of substance exposure as those based on self-report with 1.64% of this subset of subjects testing positive for marijuana and 1.09% testing positive for cocaine. Urine cotinine was positive in a small percentage (less than 5%) of subjects who denied smoking during pregnancy.

Maternal History of Child Abuse

More than half of the subjects (61.19%) reported exposure to at least one type of childhood abuse on the CTQ, 20.9% reported exposure to at least one type of severe abuse during childhood, and 4.1% of all subjects reported exposure to at least two or more types of severe abuse. Table 3 lists the frequency of exposure to various types of abuse. Not surprisingly, a number of risk factors for LBW and PTD were more common among severely abused women. Women exposed to 2 or more severe types of abuse had lower levels of education, were more likely to be of a minority race, were more likely to be single, divorced, or separated, were more likely to be primiparous, and were more likely to report an unplanned pregnancy. Severely abused subjects had more significant

psychiatric comorbidity. They were far more likely to have PTSD than those who were not exposed to two or more types of severe abuse (45.45% versus 11.81%), were more likely to have a history of substance abuse, and had a higher incidence of depression during pregnancy (especially in the third trimester). Interestingly, subjects in the severely abused cohort were not more likely to smoke during pregnancy (in fact, none of the subjects in this severely abused cohort were smokers) and were not more likely to use alcohol during pregnancy. Surprisingly, severely abused subjects were slightly less likely to be on antidepressant treatment although they were more likely to be on a mood stabilizer, antipsychotic, or hypnotic agent than those who were not severely abused.

Outcomes

Within the entire sample, 6.11% of subjects had LBW infants. Of the LBW infants, 9 (60%) were born premature. In all, 13.04% of subjects had PTD. Table 4 lists the mean birth weight and delivery EGA based on the number of types of severe abuse the mother was exposed to in childhood. Figures 3 and 4 illustrate the gradual decrease in birth weight and delivery EGA associated with increases in the number of types of severe abuse experienced in childhood.

Descriptive Analyses/Diagnostic Analyses

There did not appear to be a linear association between birth weight and maternal age or between EGA at delivery and maternal age. Furthermore, there was not a linear association between the log odds of LBW or PTD and maternal age. Since past literature has noted high rates of LBW and PTD in teenage mothers as well as mothers of more advanced age, it was decided that subjects would be broken into categories according to

age. The sample did not include any subjects < age 18 so there was no need for a teenage mother category. Mothers were then classified into one of two categories: younger mothers (age > 18 but < 35) and older mothers (age ≥ 35).

The association between BMI and birth weight also appeared to be non-linear. Based on prior evidence of either non-linear or U shaped association between maternal weight and birth weight, subjects were broken into 3 categories based on BMI: underweight (BMI<18.5), obese (BMI ≥ 30), or normal to overweight (BMI≥ 18.5 but <30). The prevalence of LBW was higher in both obese and underweight subjects than women with a BMI in the normal to overweight range. Since the LBW rate was nearly identical in obese and underweight subjects and power was limited by small group size in the underweight group, the obese and underweight subjects were collapsed together into a joint category of underweight or obese individuals for LBW analyses. The effect of maternal BMI on LBW did not differ according to whether a two or three group categorical variable was used. The association between PTD and maternal BMI did not follow the same pattern, however. Underweight women had the lowest risk of PTD, obese women had the highest, and normal to overweight women had a risk between the two. Therefore, a three-group categorization of maternal BMI was used for PTD analyses.

There was some evidence of a linear association between depression severity and both birth weight and EGA at delivery. Further, the log odds of LBW or PTD did appear to be related to depression severity in a linear manner. To maximize power, depression was entered as a continuous variable in the regression analyses. Since repeated assessments of depression were completed over time for each subject, the strength of association

between depression scores at various times in pregnancy and risk for LBW and PTD was considered. The following summary scores of HRSD ratings were examined to determine which summary measure exhibited the strongest association with LBW and PTD: 1) Maximum HRSD score during third trimester, 2) Maximum HRSD during pregnancy regardless of trimester, 3) Average HRSD during third trimester, 4) Average HRSD during pregnancy as a whole, and 5) Average of the Maximum HRSD from each trimester during pregnancy (the mean of the maximum HRSD from trimester 1, maximum HRSD from trimester 2, and maximum HRSD from the third trimester). None of the HRSD summary measures exhibited a particularly strong association with LBW. The strongest association between HRSD summary score and PTD was seen using the average of the maximum HRSD score from all three trimesters. As a result, this summary measure was used whenever depression was considered in the remainder of the analyses in the study.

Low Birth Weight Univariate Analyses

Univariate comparisons were completed to examine the possible association between LBW and each of the variables/exposures of interest. Chi square comparisons revealed associations between LBW and several risk factors including maternal history of abuse. See Table 4 for select univariate comparisons. Women with a history of two or more types of moderate to severe abuse were not significantly more likely to have LBW babies than to those without abuse (9.1% versus 5.5%; χ^2=0.82, p=0.320; OR 1.72, 95% CI 0.53-5.59). Among the most severely abused group (women exposed to two or more types of severe abuse), 30.0% of subjects delivered LBW babies whereas only 5.2% of women not exposed to this severe abuse had LBW infants. The odds of delivering a LBW

infant were nearly 8 times greater for the most severely abused individuals than those without such abuse (OR 7.88, 95% CI 1.82-34.03). See Figure 5 for a graphical representation of the association between LBW and severe abuse exposure. A history of PTSD was not associated with increased risk of LBW. In fact, individuals with PTSD had a non-significantly lower risk of LBW. Anxiety disorders other than PTSD were not significantly associated with LBW. Subjects with SCID-determined major depressive episode (MDE) during pregnancy had modestly higher rates of LBW but the association did not achieve statistical significance. Treatment with an anxiolytic during pregnancy was associated with a more than 3 fold increased odds of LBW (OR 3.47, 95% CI 1.23-9.82), but no other psychotropic medications were associated with a significant increase in LBW. Not surprisingly LBW was more common in women who smoked during pregnancy, and this effect was most prominent in women who smoked during third trimester (OR 13.54, 95% CI 3.68-49.78). Other factors associated with LBW included cannabis use, minority race, lower levels of education, and maternal report that pregnancy was not desired or was experienced with ambivalence. Use of alcohol, cocaine, or other drugs was not associated with LBW although few subjects reported such exposures. LBW was more common in obese or underweight women than women with BMI's in the normal to overweight range but this association did not achieve statistical significance. There was no significant difference between prevalence of LBW infants among primiparous versus multiparous women. Univariate regressions examining the association between depression scores and LBW did not reveal a significant main effect of depression on LBW in this sample (Wald χ^2=0.784, p=0.377). Categorical analyses

did not perform any better in the models suggesting that the lack of clear effect was not simply due to a nonlinear effect of depression on LWB.

Preterm Delivery Univariate Analyses

Univariate analyses were completed to examine the association between PTD and key risk factors before controlling for confounding factors. See table 6 for select univariate analyses on the association between maternal factors and PTD. Women with a maternal history of two or more types of moderate to severe abuse were not significantly more likely to have PTD (17.1%) than those without such a history (12.3%; χ^2=0.70, p=0.403, OR 1.47, 95% CI 0.59-3.66). However, a maternal history of two or more types of severe abuse was associated with PTD (χ^2=5.51, p=0.0410, OR 4.20, 95%CI 1.16 - 15.22) such that PTD was more common among women with this abuse history (36.4%) than without this abuse history (12.0%). See Figure 6 for an illustration of this relationship. Women with a history of PTSD had a slightly higher prevalence of PTD but this did not attain statistical significance. Women with MDE during pregnancy (based on SCID) had a greater risk of PTD (OR 3.29, 95% CI 1.10 - 9.86) but the effect of third trimester MDE was not significant. There was a trend towards increased risk of PTD in women treated with anxiolytic medication during pregnancy but treatment with an anxiolytic in third trimester itself was not associated with PTD. Treatment with a hypnotic agent anytime during pregnancy and treatment with a hypnotic during third trimester were both associated with an increased risk of PTD. Treatment with antidepressant medications, mood stabilizers, or antipsychotics did not predict an increased risk of PTD. Smoking anytime during pregnancy or in third trimester was associated with approximately a three fold increased odds of PTD, but these associations only approached significance at the

level of a trend. No other substance exposures significantly predicted PTD. Univariate regressions demonstrated a significant effect of depression on risk for PTD (Wald χ^2=7.33, p=0.0068). A one point increase on the HRSD was associated with a 1.12 times increased odds of PTD (CI 1.032 - 1.218).

Low Birth Weight Multivariate Analyses

Potential predictor variables were entered for consideration in the stepwise regression modeling probability of having a low birth weight (<2500g) baby. A total of 157 subjects were included in the stepwise regression (111 observations were removed because of missing data for any of the variables considered for entry into stepwise regression). Predictor variables included for consideration in the regression included: Severe abuse of at least two or more types, maximum HRSD rating for each trimester averaged across all three trimesters (continuous), history of PTSD, history of anxiety disorder other than PTSD, anxiolytic treatment during any trimester, treatment with antidepressant in any trimester, treatment with hypnotic during third trimester, treatment with hypnotic in any trimester, treatment with mood stabilizers during any trimester, treatment with antipsychotic agent in any trimester, treatment with any habit forming drug during any trimester, smoking in any trimester, 3rd trimester smoking (yes versus no), caffeine intake anytime during pregnancy, any marijuana use, any alcohol use during pregnancy, alcohol exposure during 3rd trimester, maternal race (race other than Caucasian versus Caucasian), maternal age (<35 or >=35), BMI category (group 1: normal weight to overweight with BMI $\geq$ 18.5 but <30 and group 2: underweight or obese with BMI<18.5 or BMI$\geq$30), parity (primiparous versus multiparous), timing of first WMHP clinic visit (preconception or first trimester versus second trimester or later),

marital status (married or partnered versus single, divorced, or separated), education (some college or more versus high school or less), gender of baby, maternal report that pregnancy was desired versus not desired or viewed with ambivalence, having an unplanned versus planned pregnancy. Threshold p value for selection during stepwise procedure was 0.10. From among these factors, only severe abuse of two or more types (CE=1.3050, SE=0.4892, Wald χ^2=7.12, p=0.0076 OR 13.60, CI 2.00-92.55) and 3rd trimester tobacco exposure (CE=1.4489, SE=0.3950, Wald χ^2=13.46, p=0.0002 OR 18.13, CI 3.86-85.29) remained in the model. Based on the results of the stepwise selection procedure, third trimester smoking exposure and severe abuse of two or more types were then reentered manually into a forced model with no other risk factors so that the model could be run on the larger sample (since a significant number of subjects were excluded from the dataset in the stepwise procedure). See Table 7 for results of this two-predictor regression.

Given that a number of factors shown to impact LBW risk in prior studies did not end up in the model identified by the stepwise procedure, a follow-up forced model included not only abuse and smoking exposure but also the following variables to ensure that the effects of known or hypothesized risk factors were accounted for in the model: race, depression severity (based on HRSD scores), history of PTSD, treatment with anxiolytic during any trimester, treatment with an antidepressant during any trimester, parity, maternal age, marital status, maternal preconception BMI (two category variable), and unplanned pregnancy. None of these additional factors attained significance in the final model. Even after accounting for these factors, abuse remained a significant predictor of LBW. See Table 8 for the results of the final model.

Preterm Delivery Multivariate Regression Analysis

The variables entered for consideration in the LBW stepwise regression were also entered for consideration in the PTD stepwise regression with the exception of the two-level categorical preconception BMI variable which was replaced by the three-level categorical variable for preconception BMI for the reasons outlined above. Threshold p value for selection during stepwise procedure was 0.10. There were 150 subjects included in the stepwise regression (118 observations were removed because of missing data for any of the variables considered for entry into stepwise regression). Three factors were selected for inclusion in the model: two or more types of severe abuse (CE=1.5551, SE=0.4288, Wald χ^2=13.16, p=0.0003, OR=22.43, 95% CI 4.18-120.41), 3rd trimester smoking (CE=1.1027, SE=0.3858, Wald χ^2=8.17, p=0.0043, OR=9.07, 95% CI 2.00 - 41.18), and 3rd trimester treatment with a hypnotic agent (CE=1.1614, SE=0.3563, Wald χ^2=10.62, p=0.0011, OR=10.21, 95% CI 2.52 - 41.25). As planned, these three variables were then entered manually into a forced model on their own in an attempt to improve the precision of the model estimates with a larger sample size. The revised model did provide estimates with tighter confidence intervals as follows: two or more types of severe abuse (OR=15.59, CI 3.17 -76.77), 3rd trimester smoking (OR=4.42, CI 1.18 - 16.56), and treatment with a hypnotic agent (OR=6.38, CI 2.01- 20.22). See Table 9 for details.

To ensure that potential confounders of known relevance were adequately controlled for in the multivariate regression, the three variables identified in the stepwise analysis – two or more types of severe abuse, 3rd trimester smoking, and 3rd trimester hypnotic treatment, were included in a model along with the following other risk factors of interest: race, depression severity, PTSD, maternal age, unplanned pregnancy, parity,

preconception BMI (three-level categorical variable), anxiolytic treatment during any trimester, antidepressant treatment during any trimester, and marital status. In this revised model, significant predictors of PTD included: two or more types of severe abuse (OR=11.42, 95% CI 1.64 - 79.69), unplanned pregnancy (OR=4.33, 95% CI 1.35 - 13.86), 3rd trimester hypnotic (OR=5.00, 95% CI 1.10 - 22.78), and marital status (OR=0.05, 95% CI <0.01 - 0.63) with women who were divorced, separate, or single surprisingly having a lower risk of PTD than women who were married or partnered. There was also a trend towards a significant effect of maternal age as well (Wald χ^2=3.69, p=0.0548; OR=3.13, 95% CI 0.98 - 10.01). The effect of third trimester smoking was no longer a statistically significant predictor of PTD in the final model though the point estimate of the OR was similar to that in the previous model (OR= 3.72, 95% CI 0.55 - 24.94). Depression and PTSD did not achieve statistical significance as predictors in the model. Thus, even when accounting for a number of known risk factors for PTD and potential confounders, abuse remained a strong predictor of risk for PTD. Table 10 outlines the results of the full model.

Secondary Analyses

We conducted a series of secondary analyses to address the following questions: 1) Does PTD mediate effect of abuse on LBW, 2) does the study population vary in a meaningful way by year of enrollment since there were some modifications in the focus of WMHP protocols over the years, and 3) do specific types of abuse seem to be primariy responsible for the observed effects of two or more types of abuse? To examine whether PTD mediates the effect of abuse on LBW, we conducted a regression analysis with both PTD and abuse as predictors of LBW. In this case, PTD was a significant predictor, and

there was a trend towards a significant residual effect of abuse on LBW. Thus, it appears that the association between LBW and abuse may be partially mediated by PTD but there is some evidence of an independent effect as well. We then conducted a series of regression analyses to examine whether the study sample varied in meaningful ways by year of study enrollment. Year of study enrollment was significantly associated with PTD but not LBW. However, year of study enrollment was no longer significantly associated with either outcome when entered into a regression along with abuse, and year of enrollment did not significantly diminish the effect of abuse on either outcome. Last, we conducted some additional analyses to examine whether particular types of abuse appeared to be responsible for the association between abuse and LBW and PTD. See tables 11 and 12 for results of these analyses. Severe physical abuse seems to be the type of abuse most strongly associated with PTD. However, it does not appear to have as disproportionately strong effect on LBW. No one type of abuse seems to account for the majority of the LBW x abuse association.

Discussion

This was a retrospective cohort study of the association between maternal childhood abuse history and low birth weight (LBW) and preterm delivery (PTD) in women with a history of depression based on an analysis of a subset of women participating in a larger prospective observational study of perinatal mental illness. A maternal history of severe abuse of two or more types was associated with increased risk of PTD and of having a LBW baby. There appeared to be an inverse linear association between abuse and duration of gestation but the relationship between birth weight and abuse did not appear to be a 1:1 dose dependent effect. A statistically significant and clinically meaningful increase in risk for LBW and PTD was primarily seen in women with the most severe abuse histories (those with a history of two or more types of severe abuse). PTD occurred in 36.4% of women with the most severe abuse histories compared to 12.0% of women without similar abuse histories, and 30.0% of the women in the most severely abused cohort gave birth to LBW babies as compared to 5.2% of the women without a history of severe abuse. Not surprisingly, abuse history was associated with increased psychiatric comorbidity including depression and PTSD, risk behaviors, and exposures to medications as well as illicit drugs. However, the effects of abuse remained significant even after accounting for common LBW and PTD risk factors and controlling for other potential confounds. Thus, women with a history of such abuse had more than 11 fold increased odds of PTD and a nearly 30 fold increase in the odds of delivering a LBW infant even after controlling for potential confounds such as smoking, obesity, race, parity, unplanned pregnancy, depression, PTSD, and exposure to psychotropic medications during pregnancy.

Interpretation of Key Findings

This study provides further data to help clarify the effects of child abuse on pregnancy outcome. Prior studies on the topic have been mixed but have been insufficiently powered and have not accounted for the effects of other types of abuse or the effects of psychiatric comorbidity. One prospective study initially found an increased risk of LBW, small for gestational age (SGA), and PTD in adolescents with a history of physical or sexual abuse, but LBW was the only outcome that remained significant after controlling for confounds.[32] Another prospective study found no significant effect of CSA on PTD or LBW, even when examining individuals with more severe sexual abuse.[48] A case control study found that women with LBW babies did not have higher rates of past exposure to CSA although the raw data indicate that mothers of LBW infants were twice as likely to have been exposed to more severe forms of CSA, and among women without LBW babies, those who reported a history of CSA had significantly higher rates of PTD and premature rupture of the membranes than the non-abused women.[33] In one study sexual abuse was associated with increased birth weights and longer gestational periods, but this study was based on retrospective reports of pregnancy outcomes in 28 women with and without a history of CSA.[34]

The effect of abuse on PTD seemed to be stronger than the effect on LBW. This likely stems in part from the heterogeneity encompassed within the concept of LBW. Lumping two etiologically/biologically heterogeneous groups into one LBW category by including both SGA/IUGR and appropriate-for-age preterm infants may have obscured some of the important features of the relationship between abuse and pregnancy outcome. It is likely that some if not all of the association between abuse and LBW occurs because of the

association between shortened gestational duration and low birth weight. It is possible that abuse is not as clearly associated with IUGR or it is possible that the affect of abuse on IUGR is in the opposite direction. It is also possible that depression and PTSD influence IUGR in opposing directions. Since there is a high degree of comorbidity of either depression, PTSD, or both in abused individuals, it is possible that the effect of abuse on IUGR in an individual depends in part on whether that individual has MDD, PTSD, or both. Also, if there were an interaction between abuse and either MDD or PTSD with respect to IUGR, it might be difficult to detect because of treating LBW at one entity instead of 2 separate "groups". Determining whether abuse is in fact associated with IUGR rather than just LBW due to PTD might help shed further light on the possible pathophysiology of the process. In addition, in order to understand the effect of PTSD on LBW, it will likely be necessary to distinguish between IUGR babies and those who are appropriate weight for EGA.

PTSD itself was not significantly associated with LBW or PTD in this study. However, we did not examine the effect of current PTSD symptoms on pregnancy outcome in this analysis; we only examined the effect of lifetime history of PTSD diagnosis on outcome. Active PTSD may have different or more substantial effects on pregnancy outcome than a past history of PTSD.

A review of Medicaid claims data for 1093 pregnant women with and without PTSD found an increased risk of various complications including preterm contractions and excessive fetal growth.[39] In a large prospective study of 1100 pregnant, PTD occurred more frequently in women with PTSD, but neither PTD nor LBW were significantly associated with PTSD after controlling for confounding factors .[38] A small pilot

community study of pregnant women found that there was a strong negative correlation between PTSD symptom score and the mean perinatal outcome optimality index (specific outcomes not reported), and salivary cortisol was lower in the pregnant women meeting criteria for PTSD.[49] In preliminary results from a study of 101 women seeking prenatal care at an obstetrical clinic in Hawaii, PTSD was not significantly associated with any of the birth outcomes though the authors acknowledged that the study was underpowered for moderate effect sizes). Women with PTSD did have higher rates of depression and anxiety, alcohol and drug use as well as smoking in pregnancy, poor prenatal care, and abnormal perinatal weight gain. Although some data were collected on maternal history of child abuse, no analysis of the relationship between childhood abuse and pregnancy outcome was reported.[36] Another study found that the association between intimate partner violence (IPV) and LBW was stronger among women who were also experiencing PTSD and/or depression.[50]

Researchers in New York have been following a cohort of women who were pregnant at the time of exposure to the world trade center attack on 9/11 along with a control cohort of NY women who delivered around the same time period as the exposed women but had not been in lower Manhattan on 9/11. In one study they examined pregnancy outcomes in a subset of the exposed women who had completed a psychiatric evaluation prior to delivery. In these women, maternal PTSD symptoms predicted smaller neonatal head circumference and both PTSD symptoms and moderate depressive symptoms predicted longer gestational durations.[51] These results suggest that outcomes may be affected differently when PTSD and depression occur following exposure to an intense trauma during pregnancy. A Dutch study of more than 3000 women found that women who

were pregnant at the time of 9/11 had higher rates of LBW babies than control women who were pregnant 1 year from the date of 9/11.[50] The fact that the increased LBW could not be accounted for by shorter gestational duration suggests that the LBW may be more likely IUGR. The authors argue that pregnant women watching the intense media coverage of 9/11 felt some fear for their own safety and developed somewhat of a trauma response which led to IUGR. Other work seems to support the notion that intense traumatic experiences can lead to LBW. A study of Earthquakes in Taiwan found that in pregnant earthquake survivors, the death of a woman's spouse predicted increased risk of delivering a LBW baby.[52]

Some findings in the literature suggest that PTSD may be associated to some degree (whether due to an association with abuse, its association with depression, or its own specific effects) with PTD but also with macrosomia. If this were the case, the association with PTD might be responsible for some association between PTSD and LBW while on the other hand, the macrosomic effect would counter the decrease in birth weight associated with PTD. Although there was no significant effect of PTSD on LBW, it did appear that the direction of effect suggested that PTSD provided some protection against LBW. Without distinguishing between IUGR and LBW babies who are LBW because they are preterm, it would be difficult to make any meaningful interpretations about the association or lack thereof. That being said, an association between PTSD and macrosomia could make sense given what is known about the biological changes seen with PTSD. Macrosomia would be in keeping with the expected effect of low cortisol. In contrast, depression and exposure to an intense acute trauma would be more likely to be lead to increased cortisol. These effects also seem consistent with the animal and

human literature on steroids. Ewes treated with steroids had increased IUGR. It is also possible that other systems such as immune system or the sympathetic nervous system plays a role and influences LBW in a direction that is different from what affects the HPA axis would have alone. Although some studies have suggested an association between PTSD and pregnancy outcome, these studies have not adequately taken into account the role of maternal history of abuse and other confounding factors in their analyses. Therefore, it is not clear whether the lack of PTSD effects in the current study were likely related to controlling for abuse, were related to studying lifetime rather than current PTSD symptoms, or because of lack of distinction between IUGR and LBW.

Gestational duration was not controlled for in the primary analyses of LBW because PTD was expected to be a key step in the causal pathway leading from abuse to LBW. Secondary analyses did indicate that PTD partially mediated the association between abuse and LBW but that there was still a significant association between LBW and abuse even after taking into account PTD. In the future, it would be useful to study the effects of PTSD, abuse, and depression on IUGR instead of simply LBW to better clarify how abuse and related exposure variables relate to IUGR specifically.

As mentioned above, the elevated risk of PTD and LBW was primarily limited to women with extremely severe childhood abuse. As a result of the small number of LBW and PTD outcomes that occurred in this sample, the power to detect effects of more modest effect sizes may have been diminished. Thus, it is possible that a significantly elevated risk of LBW and PTD might be detectable in a much larger sample or a case control study specifically seeking to examine a large number of cases.

As expected, some common risk factors for LBW and PTD such as smoking were significant in the analyses from this study. Depression was not significant after controlling for other factors but this likely relates to the study design (selecting only subjects with a history of depression), active treatment (intended to ensure that if a woman becomes depressed in pregnancy, her symptoms are promptly addressed and controlled as quickly as possible which limits the duration and intensity of exposure to depression.

Recent attention has been paid to the potential association between some psychiatric medications and adverse pregnancy outcome. Antidepressants have been associated with LBW and PTD in several studies but most of these studies have not adequately controlled for the effect of depression, other psychiatric illnesses, or some important medications often prescribed along with antidepressants.[35, 37] These recent studies have not adequately addressed the possibility that depression or even trauma history could be confounding the association and might actually be responsible for LBW rather than the medication itself. In this study, after controlling for the effects of depression, psychiatric comorbidity, and childhood abuse an association between antidepressants and outcome was not evident. However, there was no clear association even prior to controlling for these factors in analysis. This is likely because these factors were in a sense controlled for by design since all women in the study had a history of depression. It is also possible that detecting an effect if one does exist was hindered by the fact that only a small number of subjects were not on antidepressants at least some point in pregnancy, limiting the power to examine this issue. In general, the effects of psychotropic medication or the

lack of effects in this case need to be replicated with larger samples and analyses specifically designed and powered to look at this.

In the current study, there was a significant association between PTD and use of hypnotic agents. This association remained significant after controlling for depression, PTSD, and abuse exposure. It is possible that the association is causal in nature. However, since medication administration was not randomly assigned it likely indicates the presence of active symptoms such as insomnia and anxiety. Anxiety scores were not specifically examined in this analysis and little data were available on sleep habits and insomnia. As a result, it is difficult to say whether they hypnotic agents are truly linked to PTD or whether they are simply proxy indicators of more severe medical or psychiatric illness or poor sleep habits which might affect pregnancy outcome. Indeed, it is possible that poor sleep is associated with medical complications in pregnancy which in turn could influence risk of PTD. This finding needs to be replicated in a larger sample and to be studied in the context of controlling for confounding medical, sleep, and psychological factors before drawing decisive conclusions or influencing treatment decisions.

It was surprising that depression did not have a significant effect on LBW and PTD after controlling for other factors. One possibility is that the effects generally seen with depression are partially mediated by the effects of abuse. This seems unlikely given the strength of the literature on the effects of depression on pregnancy outcome. Instead, it seems more likely that an effect wasn't evident because all of the women in this sample had a history of depression and most of them had some degree of depressive symptoms even when relatively less depressed than others in this study. Thus, it is possible that there is a relatively low threshold for the effects of depression on pregnancy outcome and

that almost all of the subjects were above that threshold. The subjects who were coded as "not depressed" may actually have had enough depression to affect outcome. In addition, it is possible that some of the effects of depression on pregnancy outcome are actually trait effects rather than state effects. In this case, since all of the women in this study had a history of depression, the effect might wash out since all subjects had it. Also, a large majority of the subjects were on medications; it is possible that the impact of depression was significantly mitigated by limiting severity, duration, and biological impact of depression. In fact, while most of the subjects in this study were not "depressed" by stricter definitions, very few subjects were entirely free of depressive symptoms. As such, the impact of depression may be underestimated by this study because of lack of truly non-depressed comparison group (although the rate of PTD and LBW was not extraordinarily high in the WMHP group relative to the general population as might be expected for a group with psychiatric illness, the baseline rates of PTD and LBW for a demographically comparable comparison group would likely be even lower because of the high SES, high levels of education, and good access to care).

With respect to all of the secondary risk factors/covariates examined. It is worth remembering that this study was not powered to examine the significance of all of the covariates examined. Caution should be employed when interpreting the significance or lack thereof of many of the exposure variables beyond the primary exposures of interest.

Limitations of Study

The subjects in the WMHP may not be representative of women with a history of child abuse in the community. The frequency of abuse exposure was relatively high in this sample more than 60% of the women reporting exposure to at least one type of abuse of

mild intensity or greater although exposure to two or more types of severe abuse was less common, with only about 4% of the sample giving such a history. Since a history of child abuse is associated with poorer psychiatric outcomes and since women are often referred to the WMHP clinic because the severity of illness warrants care by a specialist, the WMHP sample is more likely to include abused women who were more profoundly affected by the negative influence of their abuse. Women who suffered abuse but who were particularly resilient would be unlikely to end up in the WMHP clinic sample. As such, it is possible that the results of this study may not be generalizeable to a non-clinical sample of abused women in the general population. On the other hand, one might expect that the effects of abuse on PTD and LBW might be underestimated in a sample with multiple other risk factors for PTD and LBW such as smoking, unplanned pregnancy, depression, and substance abuse because of a smaller relative contribution of abuse to these outcomes in the face of other significant risk factors. Even though it will be important to study the effects of abuse in a non-clinical population, there is particular value in studying the role of abuse in PTD and LBW in a clinical population with a high risk for poor outcomes as this group may need and may particularly benefit from early intervention and monitoring to help mitigate risk. Furthermore, because of the complex interplay between the neurobiological changes associated with childhood abuse and the biological and physiological changes associated with depression, teasing out the relative effects of abuse and depressive symptoms by studying abused and non-abused women with depression can potentially help shed further light on the pathophysiology of PTD and LBW in these women. Furthermore, in depth information on psychiatric symptoms, abuse history, risk behaviors, and substance exposures is rarely available in studies of the

general population. As a result, few studies have been able to examine the interaction between all of these factors together. Knowing that a history of child abuse is associated with PTD and LBW is less useful if the mechanism behind the association is not understood and little is known about how much of the association is related to potentially modifiable factors such as smoking, untreated depression, etc and how much is due to complex longstanding biological changes that may be less amenable to intervention. Since all of these things are so closely interrelated it is important to take these factors into account at the same time. For example, the small number of studies examining the association between pregnancy outcome and abuse in the past did not carefully examine depression, PTSD, drug use, and other risk behaviors. As such it was not possible to determine to what degree the association between abuse and pregnancy outcome was simply related to these mediating factors or whether abuse had its own effects independent of these. Although there are still a number of behavioral, psychiatric, and social factors that need to be explored in more depth, this study provides preliminary evidence that the effects of abuse on PTD and LBW are not entirely accounted for by common confounding exposures and risk factors.

This study only examined the effect of lifetime PTSD on pregnancy outcome. Unfortunately, repeated measures of current PTSD symptom severity were not available for most women because this was only recently added to study protocols. It is possible that individuals with current PTSD will have different outcomes than those with lifetime PTSD but no current symptoms. Having a continuous measure of PTSD symptom severity during 3rd trimester and around the time of delivery might show a much stronger effect than that seen with a dichotomous measure of lifetime symptoms.

Similarly, a dichotomous indicator of medication and substance exposure may not be the most appropriate way to examine the association between medications/substances and pregnancy outcome. A quantitative measure of caffeine, alcohol, and medications might provide different results than the dichotomous outcomes used. To control broadly for medication confounds, summary variables of exposure to classes of medications by trimester were employed. However, it is possible that other details of treatment are important such as the dose used, the specific medication prescribed, subject compliance with medication, the effects of polypharmacy, etc. It would be worth examining this topic in much greater detail with the larger sample while better controlling for severity of active psychiatric symptoms. Furthermore, it is hard to interpret treatment effects when treatments were not randomly assigned. Because treatment is so closely linked to clinical status, it may be hard to determine whether an effect is related to the medication or whether it is related to the illness unless treatment is randomly assigned.

Another problem with the study is that SES may not have entirely been controlled for because SES data were not available for the majority of subjects. Race and education were considered in the analyses. In this sample, race and education are relatively good proxy measures of SES. However, confounding related to SES cannot be ruled out, and in the future more focused attempts to examine these questions will be needed.

Little data on medical comorbidity were available for this analysis. While we did take into account the effect of maternal BMI on outcome, we did not look at other important health variables. It is possible that the long-term cardiovascular and metabolic changes that have been associated with childhood abuse in other studies could play a role in the

mechanism behind adverse pregnancy outcomes and maternal child abuse history. This should be studied more specifically in future studies.

There are some possible confounding psychosocial/behavioral factors that were not examined in this study that should be explored further in future studies. The role of repeated/adult trauma exposure, current exposure to domestic violence, increased total life stress, nutritional intake, eating disorders, or noncompliance with recommended medical care were not examined.

Significance of Findings and Suggestions for Future Studies

Some researchers have proposed theories suggesting that prenatal stress alters in utero neuroendocrine programming which can lead to substantial neuroendocrine derangements and can persist into adulthood and predict risk for later life psychiatric and medical illnesses.[5, 9, 53, 54] In this context, LBW and PTD may be markers of disrupted in utero development and signal an elevated risk for particular illnesses later in life.

Based on the neurobiology of child abuse, there is reason to expect that maternal exposure to childhood maltreatment might from a theoretical perspective be associated with a predisposition to LBW and PTD with HPA axis being a likely candidate for mediating the association between trauma/abuse related disorders and pregnancy outcome. HPA function has been shown to be dysregulated in abused, depressed, and traumatized individuals, and it is thought to play a major role in several different aspects of fetal development and in regulating the timing of delivery. Furthermore, trauma history and PTSD may influence pregnancy outcome in a number of ways. Women with high anxiety scores can have higher uterine artery resistance and changes in blood flow

pattern.[55] Cytokines are another possible biological mediator of the relationship between trauma related illnesses and pregnancy outcomes. Trauma history and PTSD have also been associated with unplanned pregnancy, poor prenatal care, substance abuse, high smoking rates, increased medication use, poorer social supports, and be exposed to intimate partner violence. Thus, there are a number of ways in which PTSD and trauma history might theoretically influence pregnancy outcome. The response to pregnancy is likely multifactorial including the effects of numerous environmental, psychosocial, behavioral, genetic, and physiological factors that may contribute to risk. A small pilot study of detected elevated cardiac response to orthostatic challenge in pregnant domestic violence victims compared to pregnant women who were not abused and to abused nonpregnant women.[56]

It has also been proposed that prenatal neuroendocrine programming could help explain the intergenerational transmission of trauma. This study adds preliminary evidence that such as mechanism is feasible since women with a history of abuse are at risk for LBW and PTD which in turn puts their developing child at risk for future psychiatric and medical problems. If research can eventually clarify the neurobiology behind preterm delivery and low birth weight in abused women, perhaps identifying at-risk women will have significant clinical utility. While it is likely that the etiology is multifactorial, significant benefit can be derived by determining the relative contribution of the different contributing factors so that appropriate targets for behavioral and medical interventions can be identified as possible candidates for prevention of PTD and LBW.

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Figure 1. Model of potential mechanisms through which maternal history of childhood abuse could influence pregnancy outcome and therefore adult risk of mental illness

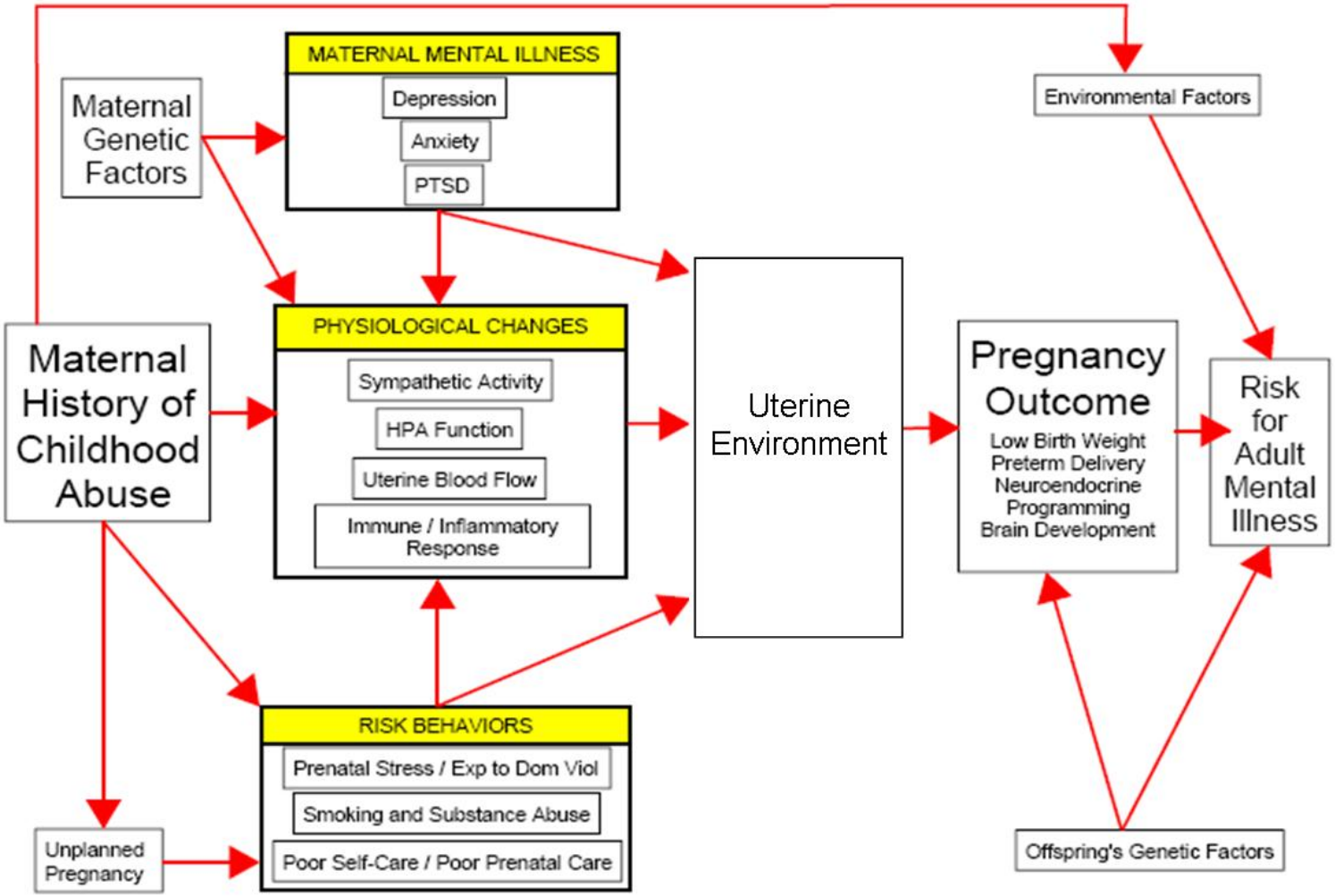

Figure 2. Sample Flow Chart

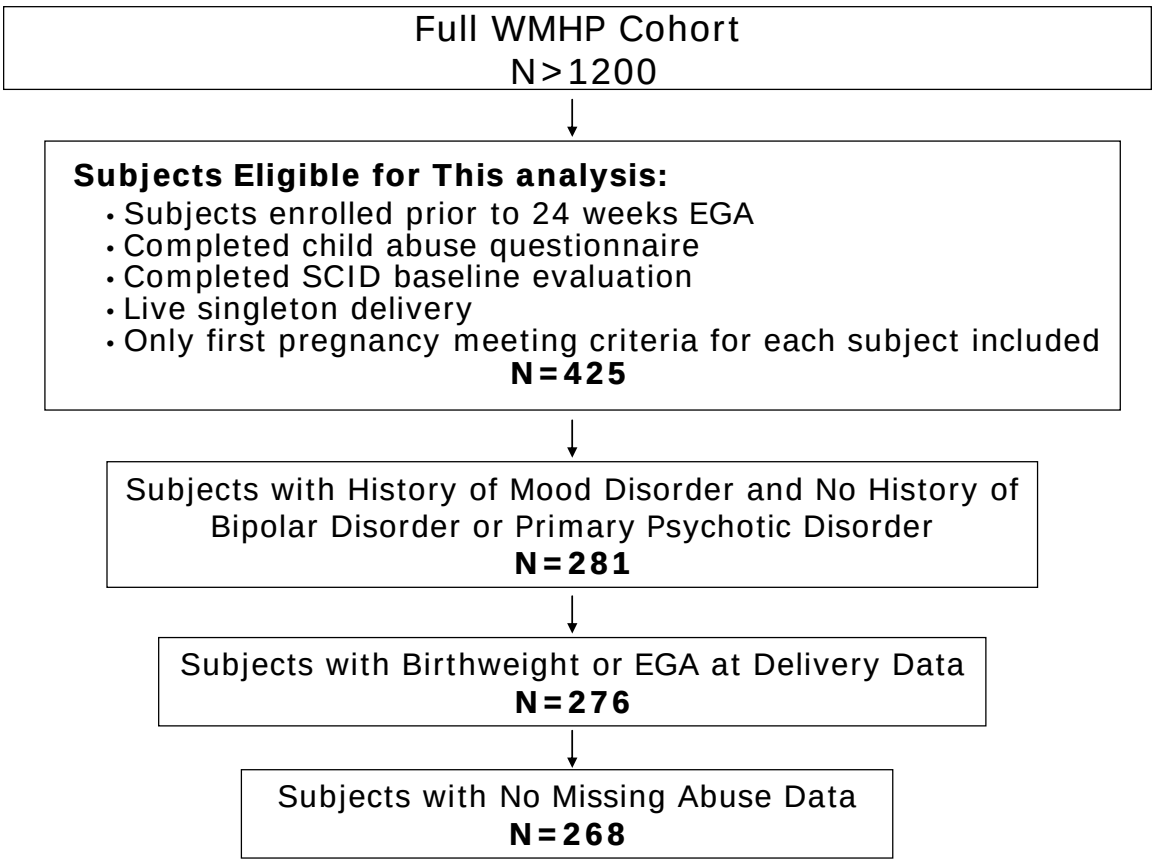

Table 1. Demographics and Obstetrical Characteristics

Characteristic	Severely Abused (2+ types)	Not Severely Abused	Entire Cohort
Sample Size, N (%)	11 (4.10%)	257 (95.90%)	268 (100%)
Mean Age (std)	33.13 (5.16)	33.79 (4.72)	33.67 (4.75)
Education, N (%)			
High School or Less	2 (18.18%)	13 (5.08%)	15 (5.62%)
Some College or College Grad	7 (63.64%)	141 (55.08%)	148 (55.43)
At Least Some Graduate School	2 (18.18%)	102 (39.84%)	104 (38.95%)
Race, N (%)			
Caucasian	9 (81.82%)	234 (91.05%)	243 (90.67%)
African American	1 (9.09%)	12 (4.67%)	13 (4.85%)
Asian	0 (0%)	5 (1.95%)	5 (1.87 %)
Native American	1 (9.09%)	6 (2.33%)	7 (2.61%)
Ethnicity, N (%)			
Hispanic	1 (9.09%)	7 (2.72%)	8 (2.99%)
Non-Hispanic	10 (90.91%)	250 (97.28%)	260 (97.01%)
Marital Status, N (%)			
Married or Cohabitating	10 (90.81%)	257 (100%)	263 (98.13%)
Single, divorced, or separated	1 (9.09%)	0 (0%)	5 (1.87%)
Maternal Preconception BMI (std)	25.02 (4.37)	24.33 (4.65)	24.36 (4.63)
Primiparous subjects, N (%)	6 (54.55%)	112 (45.34%)	118 (45.74%)
Unplanned Pregnancy, N (%)	6 (60%)	62 (27.19%)	68 (28.57%)

Continuous variables: mean is reported followed by standard deviation in parentheses
Categorical variables: number of subjects is reported followed by percent of subjects in parentheses

Table 2. Psychiatric Characteristics and Exposures Table

Characteristic	Severely Abused (2+ types)	Not Severely Abused	Entire Cohort
Sample Size, N (%)	11 (4.10%)	257 (95.90%)	268 (100%)
History of PTSD, N (%)	5 (45.45%)	30 (11.81%)	35 (13.21%)
History of substance abuse, N (%)	7 (63.64%)	101 (39.61%)	108 (40.60%)
Smokers, N (%)	0 (0%)	28 (12.96%)	28 (12.56%)
ETOH use in any trimester, N (%)	1 (9.09%)	71 (27.63%)	72 (26.87%)
Depressed in pregnancy, N (%)	4 (57.14%)	72 (44.72%)	92 (54.76 %)
Depressed in 3rd trimester, N (%)	3 (42.86%)	20 (9.39%)	23 (10.45%)
Antidepressant any trimester, N (%)	8 (72.73%)	216 (84.05%)	224 (83.58%)
Antipsychotic any trimester, N (%)	2 (18.18%)	16 (6.23%)	18 (6.72%)
Anxiolytic any trimester, N (%)	2 (18.18%)	51 (19.84%)	53 (19.78%)
Antiepileptic any trimester, N (%)	3 (27.27%)	25 (9.73%)	28 (10.45%)
Hypnotic any trimester, N (%)	2 (18.18%)	28 (10.89%)	30 (11.19%)

Continuous variables: mean is reported followed by standard deviation in parentheses
Categorical variables: Number of subjects is reported followed by percent of subjects in parentheses

Table 3. Frequency of Childhood Abuse Exposure by Type

Type of Abuse	Abuse Severity	N	% of Sample
Physical Abuse	None	199	74.25
	Mild	27	10.07
	Moderate	23	8.58
	Severe	19	7.09
Sexual Abuse	None	194	72.39
	Mild	20	7.46
	Moderate	27	10.07
	Severe	27	10.07
Emotional Abuse	None	138	51.49
	Mild	59	22.01
	Moderate	45	16.79
	Severe	26	9.70
Any History of Abuse (Any Severity)		164	61.19
No Severe Abuse of Any Type		212	79.10
One Type of Severe Abuse		45	16.79
Two Types of Severe Abuse		6	2.24
Three Types of Severe Abuse		5	1.87

Table 4. Raw Outcomes by Number of Types of Severe Abuse

Characteristic	No Severe Abuse	One Type of Severe Abuse	Two Types of Severe Abuse	Three Types of Severe Abuse
Mean EGA at Delivery in weeks (std)	38.65 (1.45)	38.53 (1.46)	37.60 (2.36)	35.54 (3.85)
Mean birth weight in grams (std)	3322.5 (486.7)	3252.8 (571)	3073.3 (766.1)	2555.0 (761.6)
# Low birth weight deliveries (% within subset)	10 (4.78%)	3 (6.98%)	2 (33.33%)	1 (25%)
# Preterm Deliveries (%)	22 (10.95%)	7 (17.07%)	1 (16.67%)	3 (60%)

Figure 3. Distribution of Baby Weight by Number of Severe Types of Abuse Experienced

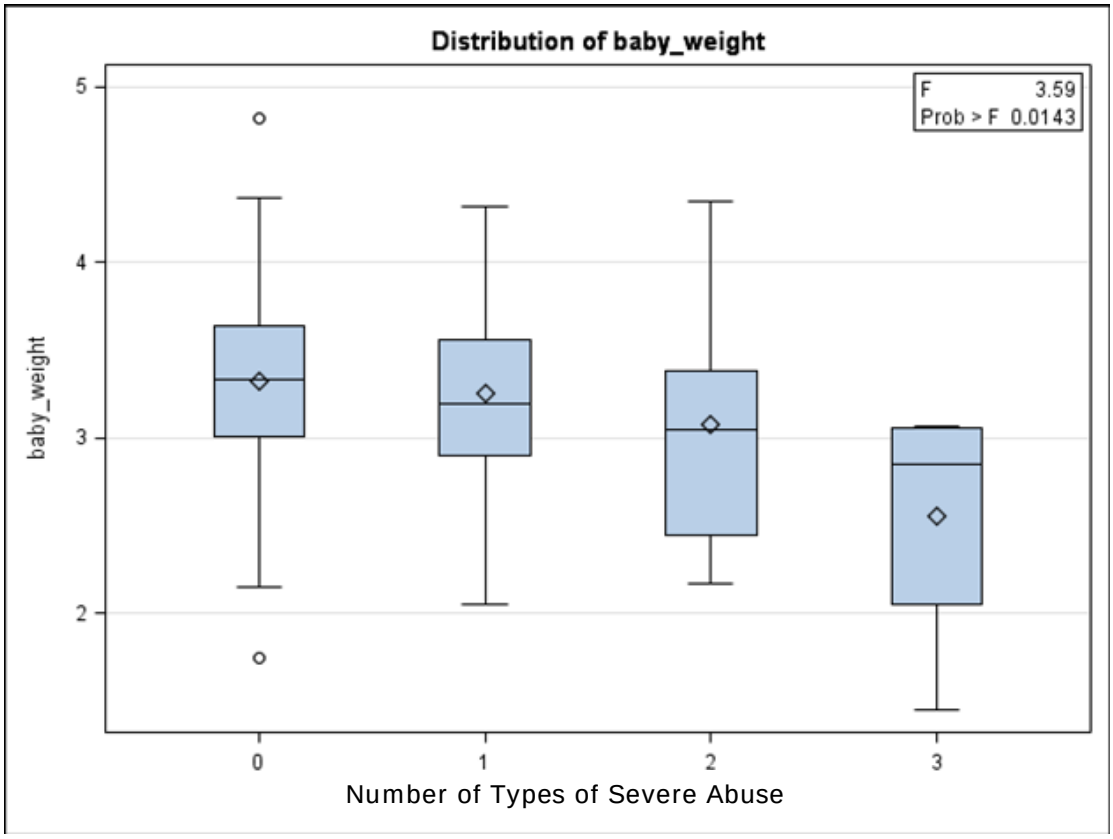

Figure 4. Distribution of Gestational Age by Number of Severe Types of Abuse Experienced

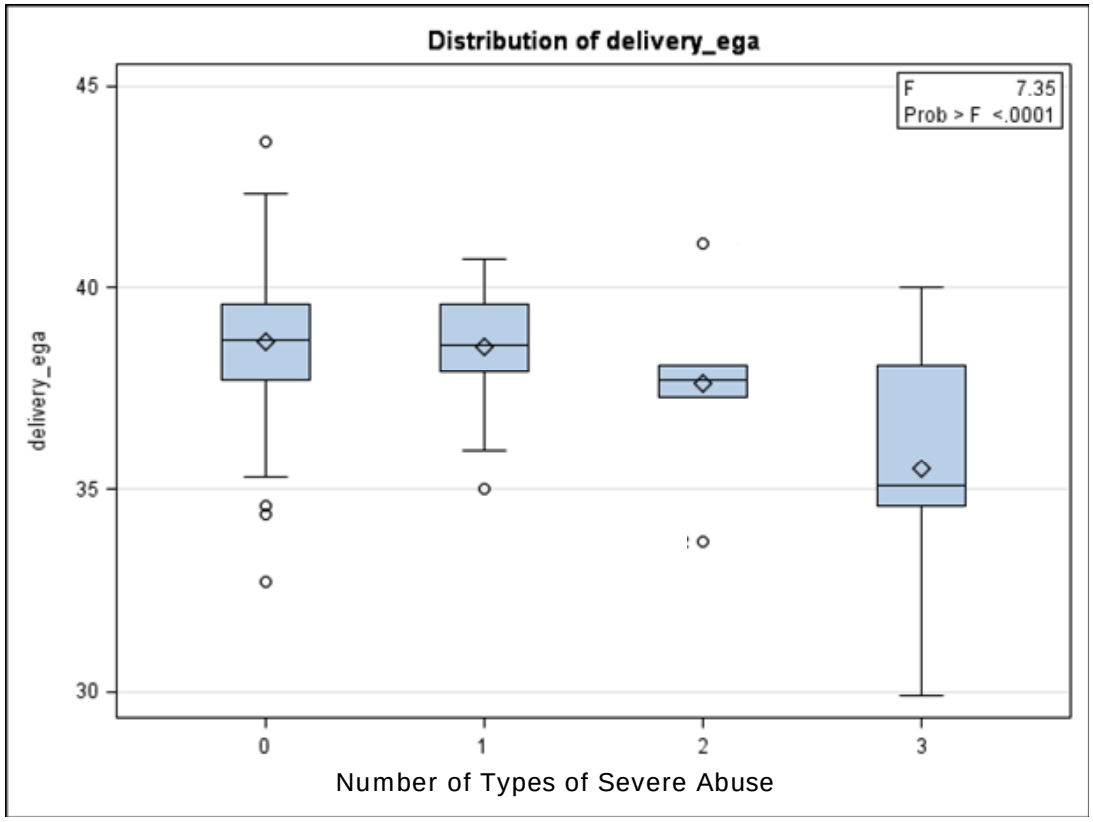

Table 5. Association between Exposure Variables and Low Birth Weight

Exposure Variable	Low Birth Weight						
	% LBW		χ^2	p value	OR LBW	95% CI	
	Reference Group	Risk Group				LL	UL
≥ 2 Types of Moderate to Severe Abuse	5.5%	9.1%	0.82	0.3199*	1.72	0.53	5.59
≥ 2 Types of Severe Abuse	5.2 %	30.0%	10.35	0.0173*	7.88	1.82	34.03
PTSD	6.7%	2.9%	0.71	0.7028*	0.42	0.05	3.32
MDE in 3rd Trimester by SCID	3.6%	4.6%	0.05	0.5829*	1.27	0.15	10.85
MDE in Pregnancy by SCID	3.3%	8.1%	1.88	0.1893*	2.62	0.63	10.85
Antidepressant in 3rd Trimester	4.6%	6.6%	0.38	0.7677*	1.49	0.41	5.41
Antidepressant in any Trimester	4.8%	6.4%	0.16	1.0000*	1.36	0.30	6.21
Anxiolytic in any Trimester	4.3%	13.5%	6.12	0.0218*	3.47	1.23	9.82
Hypnotic in any Trimester	5.6%	10.0%	0.90	0.4065*	1.87	0.50	6.99
AEDMS in any Trimester	5.5%	11.1%	1.31	0.2199*	2.13	0.57	8.02
Antipsychotic in any Trimester	6.5%	0%	1.18	0.6089*	0.40**	0.02	6.91
Smoking in 3rd Trimester	3.9%	35.7%	23.48	0.0005*	13.54	3.68	49.78
Caffeine in any Trimester	0%	7.4%	2.51	0.2217*	5.36**	0.31	92.90
ETOH in 3rd Trimester	6.3%	4.0%	0.21	1.0000*	0.62	0.08	4.88
ETOH in any Trimester	6.3%	5.6%	0.04	1.0000*	0.89	0.28	2.86
MJ in any Trimester	5.5%	33.3%	7.94	0.0455*	8.64	1.46	51.29
Cocaine in any Trimester	6.2%	0%	0.13	1.0000*	2.96**	0.14	64.29
Unplanned Pregnancy	5.4%	10.6%	2.05	0.1596	2.10	0.75	5.88

LBW = Low Birth Weight

All OR calculated comparing odds of LBW for subjects with the risk/exposure versus the reference group without that risk/exposure

* Fischer's Exact Test

** Unable to compute Mantel-Haenszel OR because of cells with zero count; OR estimated using logit estimation based on a correction of 0.5 in every cell of those tables that contain a zero.

Figure 5.

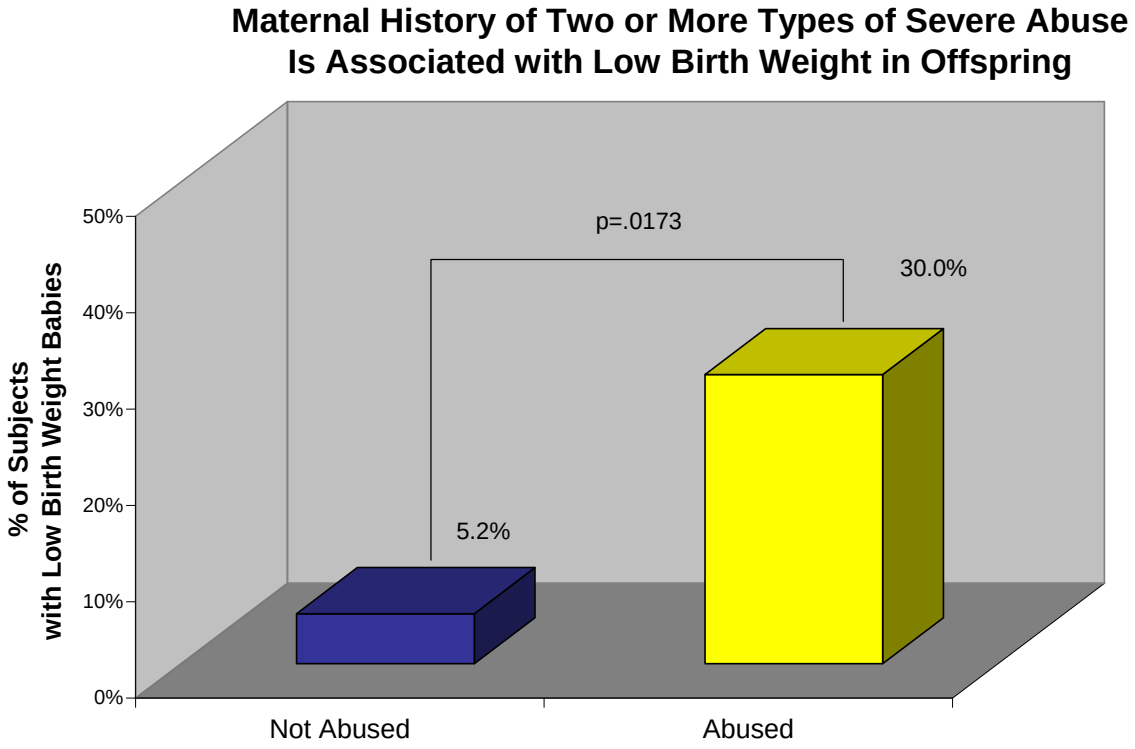
Maternal History of Two or More Types of Severe Abuse
Is Associated with Low Birth Weight in Offspring
% of Subjects
with Low Birth Weight Babies
50%
40%
30%
20%
10%
0%
p=.0173
30.0%
5.2%
Not Abused
Abused

Table 6: Association between Exposure Variables and Preterm Delivery

Exposure Variable	Preterm Delivery (PTD)						
	% PTD		χ^2	p value	OR PTD	95% CI	
	Reference Group	Risk Group				LL	UL
≥ 2 Types of Moderate to Severe Abuse	12.3%	17.1%	0.70	0.4026	1.47	0.59	3.66
≥ 2 Types of Severe Abuse	12.0%	36.4%	5.51	0.0410*	4.20	1.16	15.22
PTSD	12.3%	18.2%	0.86	0.4038*	1.58	0.60	4.18
MDE Anytime in 3rd Trimester	9.8%	13.0%	0.24	0.7112*	1.38	0.37	5.11
MDE Anytime in Pregnancy	5.8%	16.9%	4.95	0.0261	3.29	1.10	9.86
Antidepressant in 3rd Trimester	12.3%	13.3%	0.04	0.8460	1.09	0.45	2.67
Antidepressant in any Trimester	10.0%	13.6%	0.39	0.5333	1.42	0.47	4.28
Anxiolytic in any Trimester	11.2%	21.3%	3.45	0.0633	2.15	0.95	4.89
Hypnotic in 3rd Trimester	11.2%	35.0%	9.23	0.0076*	4.29	1.57	11.71
Hypnotic in any Trimester	10.7%	31.0%	9.35	0.0057*	3.75	1.53	9.16
AEDMS in any Trimester	12.3%	20.0%	1.18	0.3422*	1.79	0.62	5.14
Antipsychotic in any Trimester	12.3%	22.2%	1.44	0.2674*	2.03	0.63	6.59
Smoking in 3rd Trimester	11.7%	30.8%	3.93	0.0698*	3.34	0.95	11.73
Caffeine in any Trimester	7.1%	15.2%	1.28	0.3784*	2.33	0.52	10.46
ETOH in 3rd Trimester	13.2%	11.5%	0.06	1.0000*	0.86	0.24	3.03
ETOH in any Trimester	14.0%	10.5%	0.54	0.4619	0.72	0.30	1.74
MJ in any Trimester	12.6%	33.3%	2.23	0.1770*	3.48	0.61	19.82
Cocaine in any Trimester	13.2%	0%	0.30	1.0000*	1.30**	0.06	27.77
Unplanned Pregnancy	9.4%	25.4%	9.69	0.0018	3.29	1.51	7.16

All OR calculated comparing odds of PTD for subjects with the risk/exposure versus the reference group without that risk/exposure
* Fischer's Exact Test
** Unable to compute Mantel-Haenszel OR because of cells with zero count; OR estimated using logit estimation based on a correction of 0.5 in every cell of those tables that contain a zero.

Figure 6.

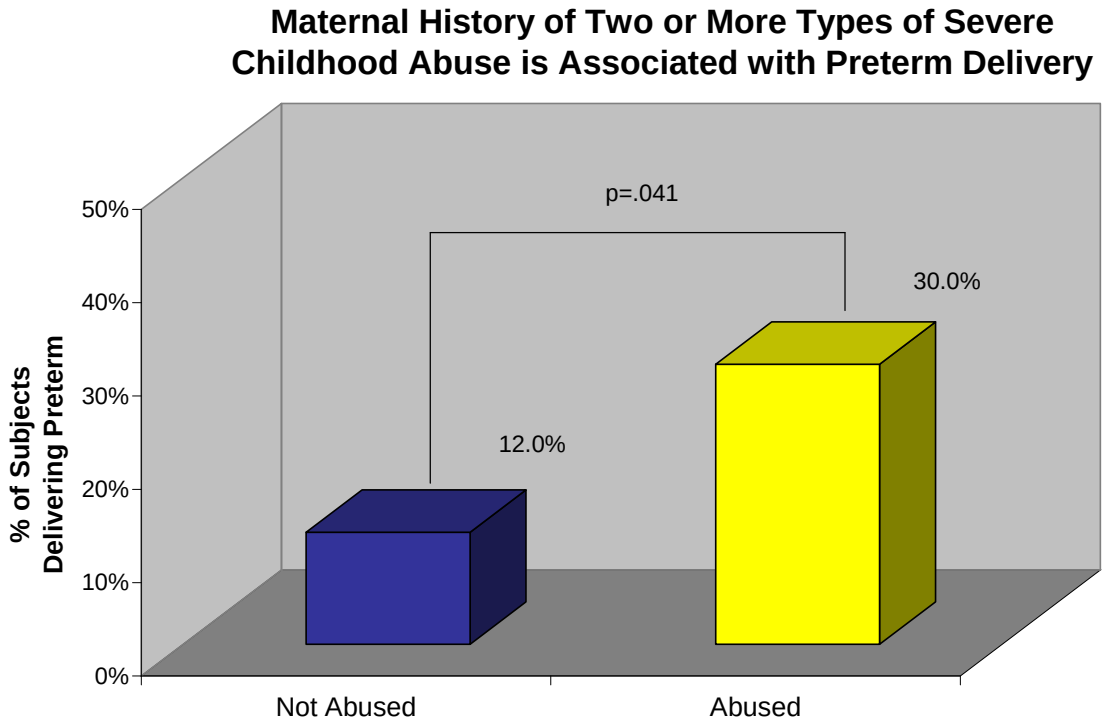
Maternal History of Two or More Types of Severe Childhood Abuse is Associated with Preterm Delivery
% of Subjects Delivering Preterm
50%
40%
30%
20%
10%
0%
p=.041
30.0%
12.0%
Not Abused
Abused

Table 7. Logistic Regression Model of Low Birth Weight Using Full Sample to Examine Variables Identified as Significant in the Stepwise Regression

Parameter	Coefficient Estimate	Standard Error	Wald χ^2	p value	Odds Ratio	95% CI*	
						Lower Limit	Upper Limit
$\geq$ 2 Types of Severe Abuse	1.3837	0.4801	8.31	0.003	15.92	2.42	104.51
3rd Trimester Smoking	1.4364	0.3475	17.09	<0.0001	17.69	4.53	69.05

Coefficient Estimate for Intercept β_0= -0.6405, Standard Error=0.5151
-2 Log Likelihood = 79.600, Likelihood Ratio χ^2= 18.79, p<0.0001

Legend:
N=217 (51 observations removed because of missing data)
$\geq$ 2 Types of Severe Abuse (present versus absent)
3rd Trimester Smoking = Maternal smoking during third trimester (yes versus no)

Forced regression models probability of having low birth weight baby (<2500g) with the two predictors above included in the model (no selection procedure).

Estimates reported are Maximum Likelihood Estimates
*95% Wald Confidence Intervals

Table 8. Forced Logistic Regression Models Abuse and Other Risk Factors for LBW

Parameter	Coefficient Estimate	Standard Error	Wald χ^2	p value	Odds Ratio	95% CI*	
						Upper Limit	Lower Limit
$\geq$ 2 Types of Severe Abuse	1.6729	0.6012	7.74	0.0054	28.39	2.69	299.68
3rd Trimester Smoking	1.6829	0.5230	10.35	0.0013	28.96	3.73	224.93
Race	0.7936	0.5182	2.35	0.1257	4.89	0.64	37.27
Avg Max HRSD	0.0393	0.0832	0.22	0.6365	1.04	0.88	1.22
PTSD	-0.4736	0.7014	0.46	0.4996	0.39	0.03	6.06
Anxiolytic Treatment	0.0461	0.4330	0.01	0.9153	1.10	0.20	5.99
Antidepressant Treatment	-0.0199	0.5506	0.001	0.9712	0.96	0.11	8.32
Parity	0.0379	0.3961	0.01	0.9237	1.08	0.23	5.10
Maternal Age	0.2209	0.3704	0.36	0.5509	1.56	0.36	6.64
Marital Status	-0.2768	0.6269	0.19	0.6589	0.58	0.05	6.71
Maternal Preconception BMI	0.1977	0.4044	0.24	0.6250	1.49	0.30	7.25
Unplanned Pregnancy	-0.3705	0.4932	0.56	0.4525	0.48	0.07	3.29

Coefficient Estimate for Intercept β_0= -0.7578, Standard Error=1.6388
-2 Log Likelihood= 61.801, Likelihood Ratio χ^2 =21.50, p=0.0435

Legend:
LBW=Low Birth Weight
N= 184 (84 observations removed because of missing data for any of the variables)
$\geq$ 2 Types of Severe Abuse (present versus absent)
Race (Race other than Caucasian versus Caucasian)
3rd Trimester Smoking = Maternal smoking during third trimester (yes versus no)
Antidepressant Treatment during any trimester
Anxiolytic Treatment during any trimester
History of PTSD
Avg Max HRSD = maximum Hamilton Depression Scale rating for each trimester averaged across all three trimesters (entered as continuous variable)
Parity (primipara versus multipara)
Maternal age (group 1 age$\geq$ 18 but <35 and group 2 age$\geq$35)
Maternal preconception BMI (group 1: normal weight to overweight with BMI $\geq$ 18.5 but <30 and group 2: underweight or obese with BMI<18.5 or BMI$\geq$30)
Marital status (married or partnered versus single, divorced, or separated)
Unplanned pregnancy

Regression models probability of having low birth weight baby (<2500g)
All variables listed were entered into the model (no selection procedure employed).
Estimates reported are Maximum Likelihood Estimates
*95% Wald Confidence Intervals

Table 9. Logistic Regression Model of Preterm Delivery Using Full Sample to Examine Risk Factors Identified as Significant in the Stepwise Regression

Parameter	Coefficient Estimate	Standard Error	Wald χ^2	p value	Odds Ratio	95% CI *	
						Lower Limit	Upper Limit
$\geq$ 2 Types of Severe Abuse	1.3734	0.4066	11.41	0.0007	15.59	3.17	76.77
3rd Trimester Hypnotic	0.9263	0.2944	9.90	0.0017	6.38	2.01	20.22
3rd Trimester Smoking	0.7434	0.3368	4.87	0.0273	4.42	1.18	16.56

Coefficient Estimate for Intercept β_0=0.5840, Standard Error=0.5617

-2 Log Likelihood= 140.317, Likelihood Ratio χ^2=20.5455, p=0.0001

Legend:

N=209 (59 observations removed because of missing data for any of the variables)

$\geq$ 2 Types of Severe Abuse (present versus absent)

3rd Trimester Hypnotic= Treatment with hypnotic agent at any point in 3rd trimester

3rd Trimester Smoking = Maternal smoking during third trimester (yes versus no)

Regression models probability of Preterm Delivery (delivery before 37 weeks EGA). The variables listed above were all entered into the model (no selection procedure).

Estimates reported are Maximum Likelihood Estimates

*95% Wald Confidence Intervals

Table 10. Forced Logistic Regression Models Abuse and Other Risk Factors for PTD

Parameter	Coefficient Estimate	Standard Error	Wald χ^2	p value	Odds Ratio	95% CI*	
						Lower Limit	Upper Limit
≥ 2 Types Severe Abuse	1.2178	0.4955	6.04	0.0140	11.42	1.64	79.69
Unplanned Pregnancy	0.7325	0.2969	6.09	0.0136	4.33	1.35	13.86
Marital Status	-1.4983	0.6462	5.38	0.0204	0.05	<0.01	0.63
3rd Trimester Hypnotic	0.8047	0.3868	4.33	0.0375	5.00	1.10	22.78
Maternal Age	0.5699	0.2968	3.69	0.0548	3.13	0.98	10.01
Average Max HRSD	0.0852	0.0579	2.16	0.1413	1.09	0.97	1.22
3rd Trimester Smoking	0.6566	0.4856	1.83	0.1763	3.72	0.55	24.94
Preconception BMI dv1	-0.2808	0.5220	0.29	0.5906	1.41	0.10	20.41
Preconception BMI dv2	0.9041	0.5845	2.39	0.1219	4.61	0.28	77.17
Race	0.3714	0.4197	0.78	0.3762	2.10	0.41	10.89
Anxiolytic Use	0.1905	0.3099	0.38	0.5388	1.46	0.43	4.93
Antidepressant Use	0.2784	0.4752	0.34	0.5581	1.75	0.27	11.24
PTSD	0.0399	0.3916	0.01	0.9189	1.08	0.23	5.03
Primiparity	-0.0126	0.2932	<0.01	0.9657	0.98	0.31	3.08

Coefficient Estimate for Intercept β_0=-1.7811, Standard Error=1.3733

-2 Log Likelihood= 102.982, Likelihood Ratio χ^2=41.17, p=0.0002

Legend:
PTD=Preterm Delivery
N= 177 (91 observations removed because of missing data for any of the variables)
≥ 2 Types of Severe Abuse (present versus absent)
Race (Race other than Caucasian versus Caucasian)
3rd Trimester Smoking = Maternal smoking during third trimester (yes versus no)
Avg Max HRSD = maximum Hamilton Depression Scale rating for each trimester averaged across all three trimesters (entered as continuous variable)
Primiparity (primiparous versus multiparous)
Maternal age (group 1 age≥ 18 but <35 and group 2 age≥35)
Preconception BMI [variable has 3 groups: underweight (BMI<18.5), normal to overweight (BMI≥18.5 but <30), and obese (BMI≥30); underweight is reference group]
Model utilizes two BMI design variables:
1) BMI dv1 = 1 if BMI normal to overweight, 0 if obese, -1 if underweight
2) BMI dv2 = 1 if BMI obese, 0 if normal to overweight, and -1 if underweight.
BMI dv1 odds ratio (OR) compares normal/overweight vs underweight;
BMI dv2 OR compares obese vs underweight
Marital status (married or partnered versus single, divorced, or separated)
Antidepressant Use: Antidepressant treatment at anytime during pregnancy
Anxiolytic Use: Anxiolytic treatment at anytime during pregnancy
Regression models probability of Preterm Delivery (delivery before 37 weeks EGA). The variables listed above were all entered into the model (no selection procedure).
Estimates reported are Maximum Likelihood Estimates
*95% Wald Confidence Intervals

Table 11.

Exposure Variable	Low Birth Weight (LBW)			
	% LBW		χ^2	p value
	Reference Group	Exposed Group		
Emotional Abuse (severe)	5.1%	16.0%	4.72	0.0535*
Sexual Abuse (severe)	5.5%	12.0%	1.67	0.1867*
Physical Abuse (severe)	5.3%	17.7%	4.22	0.0750*

Table 12.

Exposure Variable	Preterm Delivery (PTD)			
	% PTD		χ^2	p value
	Reference Group	Exposed Group		
Emotional Abuse (severe)	12.7	16.7	0.31	0.5796
Sexual Abuse (severe)	11.4	28.0	5.47	0.0193
Physical Abuse (severe)	11.1	36.8	10.26	0.0014