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The Effects of Prenatal Cocaine-Exposure on Problem Behavior in Children 4-10 Years

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Abstract

Background—Children prenatally exposed to cocaine may be at increased risk for behavioral problems due to disruptions of monaminergically regulated arousal systems and/or environmental conditions.

Objective—To assess behavioral outcomes of cocaine (CE) and non-cocaine exposed (NCE) children, 4 through 10 years old, controlling for other prenatal drug exposures and environmental factors.

Methods—Low socioeconomic status (SES), primarily African-American children (n = 381 (193 (CE), 188 (NCE)) were recruited from birth. Generalized Estimating Equation (GEE) analyses were used to assess the predictive relationship of prenatal cocaine exposure to odds of caregiver reported clinically elevated behavioral problems at 4, 6, 9 and 10 years of age, controlling for confounders.

Results—Prenatal cocaine exposure was associated with increased rates of caregiver reported delinquency (OR=1.93, CI: 1.09-3.42, p<.02). A significant prenatal cocaine exposure by sex interaction was found for delinquency indicating that only females were affected (OR=3.57, CI: 1.67-7.60, p<.001). There was no effect of cocaine on increased odds of other CBCL subscales. Higher prenatal tobacco exposure was associated with increased odds of externalizing symptoms at 4, 9 and 10 years of age. For CE children, those in foster or adoptive care were rated as having more behavior problems than those in biologic mother or relative care. Greater caregiver psychological distress was associated with increased behavioral problems. There were no

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independent effects of elevated blood lead level on increased behavior problems after control for prenatal drug exposure and other environmental conditions.

Conclusion—Prenatal cocaine and tobacco exposure were associated with greater externalizing behavior after control for multiple prenatal drug exposures, other environmental and caregiving factors and lead exposure from 4 through 10 years of age. Greater caregiver psychological distress negatively affected caregiver ratings of all CBCL domains. Since cocaine and tobacco use during pregnancy and maternal psychological distress have the potential to be altered through prenatal educational, drug treatment and and mental health interventions, they warrant attention in efforts to reduce rates of problem behaviors in children.

Keywords

behavior; delinquency; prenatal cocaine-exposure; lead exposure; longitudinal

1. Introduction

Behavioral outcome studies of children prenatally exposed to cocaine have yielded equivocal results regarding the behavioral domains affected and their developmental course, underscoring the need for longitudinal evaluations with an adequate number of subjects and control for multiple prenatal drug exposures and confounding environmental and biologic factors. Among the biologic factors likely to affect a large percentage of low socioeconomic status prenatally cocaine-exposed children, as well as negatively impact behavioral outcomes, are prenatal exposure to other drugs and alcohol [1], postnatal passive exposure to tobacco and drugs [2, 3] and elevated blood lead [4, 5]. Previous studies of prenatal cocaine exposure have rarely evaluated the potential confounding effects of elevated lead levels, yet the effects of prenatal cocaine-exposure on functional behavioral outcomes cannot be fully understood without addressing both biologic insults and accompanying environmental risks.

Disruptions in brain neurotransmitters, particularly the monoamine system [6], known to play a key role in self regulatory behavior, combined with negative environmental conditions related to parental drug use, are thought to contribute to behavioral problems among prenatally cocaine/polydrug exposed children. Additional biologic assaults to the central nervous system can occur through elevated blood lead [5] which can affect both cognitive and behavioral development. Ingestion of lead, which readily crosses the blood brain barrier, targets both calcium dependent proteins and neurotransmitter receptors [7]. Among African American children, the estimated rate of lead exposure ≥ 10 ug/dL is 8.65% [8]. Among high risk cocaine/polydrug exposed children rates have been found as high as 28% to 36% [9]. Since adverse effects of lead have been found at even lower levels of exposure (<10ug/dL) [10, 11], there are likely greater numbers of children with elevated blood lead and at risk for the negative cognitive and behavioral effects.

Aggression [12, 13], anxiety, decreased socialization [14], predisposition to drug seeking [15], alterations in regulatory and coping behavior, and elevated responsivity to acute and chronic stress, are behaviors found in prenatally cocaine-exposed animals [16] [17] [18]. Early research using caregiver report on preschool children prenatally exposed to cocaine also indicates higher rates of behavioral problems [19, 20] compared to non-cocaine-exposed children. Several studies have found that hyperactivity and externalizing behaviors are increased among prenatally cocaine-exposed children. Using child self report at age 6 and controlling for child placement and other drug exposures, an effect of prenatal cocaine exposure was found for symptoms of oppositional defiant disorder [21]. In another study of 206 5 year olds, prenatal cocaine exposure, being male and living in a high risk environment were predictive of more aggressive behavior assessed using multiple methods including experimenter, teacher and parent ratings [22]. In the same cohort at age 10.5 years, cocaine-

exposed boys self reported the highest level of aggressive behavior on the Youth Risk Behavior Survey [23]. Research has also revealed differences in teacher reported behavior among prenatally cocaine-exposed children by gender [24], with prenatally cocaine-exposed boys having more behavioral problems, particularly hyperactivity, than non-exposed boys, whereas girls did not show this difference. In one of the only longitudinal studies of caregiver reported behavioral outcomes in cocaine-exposed children, higher levels of prenatal cocaine exposure (≥ 3 times per week in the first trimester) were associated with higher CBCL behavior problem T scores (internalizing, externalizing and total behavior problems) compared to some or no cocaine exposure with consistent effects through age 7 [25]. These studies did not simultaneously control for the effects of environmental lead exposure or child placement status while investigating the negative behavioral effects of cocaine, limiting the ability to assess effects of cocaine on behavior.

However, not all studies have found an association between prenatal cocaine exposure and behavioral problems. Accornero and colleagues [26, 27] used the CBCL caregiver report to assess low income 5 and 7-year-old children and found that recent caregiver drug use and psychological symptoms, but not prenatal cocaine exposure, were predictors of behavioral problems. Maternal psychological distress [28] and depression [29], but not prenatal cocaine exposure, were also associated with negative behavior in other studies.

Researchers have also found evidence of inattention in prenatally cocaine-exposed human cohorts [21, 30-33]. At age four, increased rates of commission errors, indicating greater impulsivity, were found using an adapted version of the Connors' Continuous Performance Test [34]. In the same cohort, prenatally cocaine-exposed 6-year-olds self reported more symptoms of inattention than a polydrug/non-cocaine-exposed control group [21]. Attention is particularly vulnerable to the effect of several other drugs of abuse, including alcohol [35, 36], marijuana [36] and tobacco [35, 36], as well as low levels of lead exposure[11]. These findings highlight the importance of controlling for multiple prenatal drug exposures [37, 38] and lead exposure when evaluating the behavioral effects of prenatal cocaine exposure.

An important factor to consider when investigating the behavioral effects of prenatal cocaine exposure on behavioral outcomes is that children born prenatally exposed to cocaine are often placed outside of their birth mother's custody. The type of out-of-home placement (i.e. placement in relative care vs. foster or adoptive care) is also essential to consider when evaluating the effects of cocaine on behavior. Adoptive and non-birth family foster caregivers provide higher quality home environments, through better caregiver educational attainment, vocabulary levels, and psychological status and lower child lead exposure [39, 40]than relative care.

It is also necessary to consider cognitive ability when assessing behavioral problems. While behavior problems and elevated blood lead level [4] have been associated with lower cognitive function, lower full scale IQ has not been found among prenatally cocaine-exposed children. Rather, more specific neurocognitive deficits in perceptual reasoning and attention have been identified [1, 34, 39, 40]. Therefore, the possible mediating role of Perceptual Reasoning IQ on cocaine's association with behavioral problems will be investigated in this study.

The purpose of this study was to evaluate rates of behavior problems in prenatally cocaine-exposed children longitudinally from 4 to 10 years of age, controlling for other prenatal drug exposures and confounding factors. Children prenatally exposed to cocaine were hypothesized to have higher levels of externalizing behavior problems and attention difficulty compared to non-cocaine-exposed children. Behavior problems were expected to rise over time at the same rate for the cocaine-exposed children compared to a control group.

Finally, we hypothesized that elevated blood lead would have independent negative effects on behavior problems, in addition to that of prenatal cocaine exposure.

2. Methods

2.1 Subjects

Participants in the study were 415 children born between 1994 and 1996 in a large urban teaching hospital in the Midwest and their birth mothers or other caregivers. Children were primarily African American of low socioeconomic status receiving public assistance at the time of birth. Children were placed in the cocaine-exposed (CE) or non cocaine-exposed groups (NCE) based on self-report and biologic data collected from birth mothers and from infant meconium screening. Urine toxicology screens were given to mothers at delivery due to their high-risk status. High-risk status was defined as mothers who did not receive prenatal care, exhibited behavior suggesting intoxication, had previous involvement with child protective services or self-admitted drug use to hospital or research staff.

Urine was screened using the Syva Emit method of enzyme immunoassay (Syva Company, Palo Alto, CA), which detects the presence of benzoylecgonine (BZE), meta-hydroxybenzoylecgonine (m-OH-bze), and cocaethylene, the major metabolites for cocaine, as well as metabolites of other drugs of abuse including barbiturates, cannabinoids (THC), opiates, phencyclidine, amphetamines, and benzodiazepines. The specificity of the test for benzoylecgonine is 99% at a 0.3 mg/ml concentration. Detection of drug use was confirmed with follow-up gas chromatography. Infant meconium was collected at birth to investigate for cocaine and drug metabolites [41, 42].

Identification of prenatal cocaine exposure was based on positive results of maternal or infant urine, infant meconium or maternal interviews by hospital and research study staff. Non cocaine-exposed (NCE) children were negative for cocaine on all drug-screening measures. Cocaine group status was further divided into lighter or heavier use determined by either self-report or cocaine metabolites measured in infant meconium above or below the 70^{th} percentile [1]. CE and NCE groups were similar in race and socioeconomic status (Table 1). Children whose mothers had other major confounding conditions including diagnosis of major depression, schizophrenia or bipolar disorder, low intellectual status, age <19, positive HIV status, or children with fetal alcohol syndrome or other serious birth defects were excluded.

Of 415 women who agreed to participate in the study, 218 were cocaine using and 197 were non-cocaine using. Of the active and living participants in the study (n=381; 193 CE, 188 NCE), 298 (147 CE; 151 NCE) had blood drawn and analyzed for lead levels at either the 2 or 4 years.

All women were recruited and screened by a nurse practitioner that obtained signed consent forms, approved by the hospital's Institutional Review Board, shortly before or after childbirth. A Writ of Confidentiality preventing the release of any research data concerning maternal substance abuse or child drug exposure histories (Writ # DA-04-03) was obtained from the National Institute on Drug Abuse.

2.2 Procedure

Initial subject screening and consents were gathered in the hospital just before or after infant birth. Subsequent behavioral assessments were performed at the same child development laboratory at 2, 4, 6, 9, and 10 years after the infant's birth. Caregivers were given a stipend of $50 for the 4 and 6-year old assessments, and $100 ($50 each for caregiver and child) for the 9 and 10-year assessments.

2.3 Measures

2.3.1 Demographics—Maternal and infant demographic and medical characteristics were taken from hospital birth records and included birth weight, height, head circumference, race, age, parity, number of prenatal care visits, family composition, maternal education and work history. A Hollingshead score of IV or V [43] was used as an indicator of low socioeconomic status. At each follow-up interview, information was updated.

2.3.2 Child Behavioral Outcome—The Child Behavior Checklist (CBCL) 4-18 years [44] was completed by the child's primary caregiver at each assessment point. The CBCL has 118 items that yield three broadband scores (total problem, externalizing and internalizing) and 8 narrow band scores (withdrawn, somatic complaints, anxious or depressed, social problems, thought problems, attention problems, delinquent behavior, and aggressive behavior). All items are written at the fifth grade level and take about 15 minutes to complete. Resultant T scores were standardized for gender and age. They dichotomized according to the following procedural guidelines due to non normal distribution of T-scores: Subscales T-score ≥ 67 indicated ratings at or above the borderline/clinical cut-off; broadband scores T-score ≥ 60 indicated ratings at or above the borderline/clinical cut-off. Scores below these levels were considered nonclinical in nature. Due to the low incidence of children above the borderline/clinical cut-off for anxiety and withdrawn subscales, these two outcomes were not statistically modeled.

The following number of subjects received the CBCL at each time point: 4 years n=358 (182 CE; 176 NCE); 6 years n=371 (188 CE; 183 NCE); 9 years n=367 (188 CE; 179 NCE); 10 years n=340 (169 CE; 171 NCE). Among the subgroup of subjects with hematologic measures, the following number of subjects received the CBCL at each time point: 4 years n=287 (147 CE; 140 NCE); 6 years n=290 (147 CE; 143 NCE); 9 years n=291 (148 CE; 143 NCE); 10 years n=268 (134 CE; 134 NCE).

2.3.3 Hematologic Measures—A subset of children was assessed for lead exposure [9]. Venous blood samples could not be obtained from some children due to lack of parental consent, excessive stress related to the blood draw, child sickness or logistical difficulties. Valid hematologic measures were available for 143 two-year and 274 four-year old children. Measures were averaged for the 122 children seen at both assessment points resulting in 298 valid assessments. Blood collection and analyses of lead were performed by the affiliate University Hospital Laboratory Services Foundation accredited by The College of American Pathologists and in compliance with Clinical Laboratory Improvement Amendment (CLIA) regulations. The laboratory was in the Center for Disease Control (CDC)/World Health Organization (WHO) proficiency testing program blood for lead and was Occupational Safety and Health Organization (OSHA) approved for blood lead analysis. A trained phlebotomist drew approximately 5ml of venous blood into a lead free container containing an anticoagulant. Blood lead concentration was determined by atomic absorption spectrophotometry using a graphite furnace and matrix modification to eliminate chemical interferences (Varian). Continuous blood lead values were used in the statistical analyses.

2.3.4 Environmental and Caregiver Characteristics—Psychological distress in caregivers was assessed using the Global Severity Index of the Brief Symptom Inventory (BSI) [45], a 53-item self-report questionnaire. The Home Observation for Measurement of the Environment (HOME)[46, 47] was administered in an interview format to assess the quality of the caregiving environment at child ages 4, 6 and 9.

The Peabody Picture Vocabulary Test – Third Edition (PPVT-III) [48] was used to assess caregiver receptive vocabulary. The Block Design and Picture Completion subtests of the

Wechsler Adult Intelligence Test-Revised (WAIS-R) [49] were used to assess non-verbal intelligence.

Detailed substance use histories were obtained using an adaptation of the Maternal Post-Partum Interview [37, 50] and were completed for all biologic mothers immediately post-partum for the assessment of substance use during pregnancy. A modified version of the interview was re-administered to the primary caregiver at each follow up assessment to assess current ongoing substance use in the home. Amount and frequency of use were quantified for cocaine, tobacco, alcohol and marijuana for the month prior to pregnancy and each trimester of pregnancy. For the follow-up data collection, this information was collected for the prior 30-day period. For tobacco, the number of cigarettes smoked per day was collected. For marijuana, the number of marijuana joints smoked per day and for alcohol, the number of drinks of beer, wine, or hard liquor per day was acquired. Each drink was equivalent to .5ml of absolute alcohol. Frequency of drug use was based on average number of days of drug use each week and multiplied by amount of use per day to yield an average amount of use per week. This was computed for each trimester in pregnancy and for each follow up period. The average scores for each trimester were then averaged over the pregnancy for each drug used during pregnancy.

2.4 Statistical Analysis

Positively skewed self-report drug use, BSI and lead data were transformed using $\log_e (X+1)$ to reduce the influence of outlying values prior to analyses. For ease of interpretation, means and standard deviations were reported for the non-transformed variables. Demographic characteristics, prenatal substance use, and birth outcome measures were examined by cocaine status.

A Generalized Estimating Equation (GEE) [51] for logistic regression was used to compare dichotomous CBCL subscale scores over 4 time points, controlling for covariates. Cocaine exposure was considered to be a significant predictor if it remained $p<.05$, 2-tailed after control for confounding variables. Potential covariates had to meet two statistical criteria in order to be considered for analysis in the longitudinal regression model. First, the covariate had to differ by cocaine group status at $p\leq.20$. Second, regression slopes, which were derived by fitting a logistic regression model for each individual subject, with the outcome being a specific dichotomous CBCL subscale and the independent variable being child's age, were correlated ($p\leq0.20$ criteria) with potential covariates. This procedure was use to identify variables that had an interaction with age. The association of elevated blood lead, which was different by cocaine status, and has been shown to be associated with disruptive behavior and inattention in other research, was explored in the sub-sample who had hematological assessments.

All CBCL trajectories were determined to be linear with the exception of the externalizing scale, which was found to be cubic. Covariates were retained in the model if they changed the regression estimate for cocaine by 15%. For the cubic trajectory (externalizing), potential covariates that were different by cocaine status were evaluated in the model one at a time to determine if they were related to the slope. The same criteria for inclusion in the model applied upon evaluation (if the variable changed the regression estimate for cocaine by 15%). First, HOME score, maternal and current caregiver demographics were entered separately in the model. Second, prenatal exposures and current caregiver cigarette, alcohol, and marijuana use were entered separately. Third, current caregiver type (biologic/relative or foster/adoptive care) was entered. Lead exposure was entered last due to the reduced sample size. Potential moderators included child's gender and race. Potential mediators, because of their significant relationship to both prenatal cocaine exposure and behavioral outcomes,

included the child's gestational age, birth length, birth head circumference, birth weight [37] and Perceptual Reasoning IQ[39].

3. Results

3.1 Sample Characteristics

Table 1 presents maternal demographic data by cocaine status. Women in both groups were primarily African American and low socioeconomic status. Mothers who used cocaine during pregnancy were older, had fewer prenatal care visits and had more children than women who did not use cocaine during pregnancy. Cocaine-using women had more psychological distress, lower vocabulary scores, and were less likely to be employed or married. Table 2 indicates that women who used cocaine during their pregnancy were more likely to have used greater amounts of alcohol, marijuana and tobacco on average during all three trimesters of their pregnancy than women who used other substances but not cocaine. Table 3 shows that CE children in the sample had lower gestational age, lower birth weight, and length and head circumference (adjusted for gestational age) than the NCE group. NCE children had higher lead levels than the CE children. There were no gender, race, Apgar, or Hobel risk score differences between CE and NCE children. A test for group differences in anemia was not possible due to the low number of observations in the NCE group (n=2) versus the CE group (n=9). Caregiver demographics shown in Table 4 were compared for CE adoptive/foster care, CE biologic/relative care or NCE. CE children in foster/adoptive care had lower lead levels than CE children in biologic/relative care and NCE children. Results indicate significant group differences in current caregiver tobacco use and lead exposure. There was a trend for HOME scores of CE children in biologic/relative care to be lower than CE children in foster/adoptive care and NCE children. Tobacco use was the highest among caregivers of CE children living in biologic parent or relative care. Other demographic variables including vocabulary scores, WAIS-R Performance subscale scores, psychological distress and education level were not different by caregiver group.

Demographic characteristics of children who received hematologic assessments were compared to those who did not receive the assessments. The CE group with hematologic assessments had more prenatal care (84.77% vs. 66.87%, $p<.01$), lower levels of average prenatal cigarette exposure (10.4 vs. 15.4 cigarettes per day, $p=0.03$), lower levels of 2^{nd} trimester alcohol exposure (6.96 vs. 11.73 average units per week, $p=0.02$), and lower levels of 2^{nd} trimester cocaine- exposure (21.7 vs. 44.05 average units per week, $p<.03$) than children who did not have a hematologic assessment. CE children with hematologic assessments also had larger head circumference (32.4 vs. 31.8 cm, $p=0.02$) than CE children without blood data. Among the NCE group, those with blood data were more likely to be African American (84.4% vs. 63.4%), had higher levels of alcohol exposure during the 2nd and 3rd trimesters (.69 vs. .04 drinks per week 2nd trimester and 1.35 vs. .05 drinks per week 3rd trimester), and had lower average prenatal cigarette exposure (3.4 vs. 6.9 cigarettes per day) than those who did not have blood data assessed ($p's<.05$). NCE children with hematologic assessments had larger head circumference (33.6 vs. 33.0 cm, $p=0.04$) than children who did not have assessments.

3.2 Unadjusted Effects of Cocaine on Rates of Behavioral Problems

The unadjusted percentage of borderline clinical CBCL scores by cocaine status at each time point are presented in Table 5. Cocaine-exposed children had a higher percentage of attention problems at 4 years than NCE children. At nine years, CE children had a higher percentage of delinquency and externalizing problems than NCE children. There were higher percentages of thought problems and externalizing problems among cocaine-exposed children.

3.3 Adjusted Effects of Cocaine, Other Prenatal Drug Exposures on Behavioral Problems

Very low rates of clinically elevated anxiety and withdrawn symptoms in this population prohibited adjustment for confounders on these subscales. Table 6 shows that after adjusting for confounders, there was an association between prenatal cocaine-exposure and clinically elevated delinquent behavior (OR=2.08, CI: 1.10-3.94, p<.02). Evaluation of moderating factors yielded a significant prenatal cocaine-exposure by sex interaction for delinquency indicating that only girls were adversely affected (OR=3.57, CI: 1.67-7.60, p<.001). There were no effects of cocaine on increased odds of other CBCL subscales. Greater prenatal tobacco exposure had a varied effect over time on externalizing symptoms with increased odds at 4 (p<.003), 9 (p<.01) and 10 (p<.04) years but not at 6 years. There were non-significant trends for greater prenatal exposure to alcohol to be related to decreased odds of clinically elevated somatization (OR=0.82, CI: 0.66-1.03, p<.09) and increased odds thought problems (OR=1.22, CI: 0.97-1.53, p<.08) and aggression (OR=1.27, CI: 0.97-1.66, p<.08). Greater marijuana exposure during the first trimester was associated with increased odds of internalizing behavior (OR=2.69, CI: 1.33-5.45, p< 0.01).

3.4 Time Varying Effects of Other Covariates on Behavior

There were no interactions of cocaine exposure status and age. Odds of elevated internalizing behavior (OR=1.22, CI: 1.11-1.33, p<.0001) increased with age while thought problems (OR=0.49, CI 0.25-0.94, p < .03) decreased with age. There was a significant time varying effect for current caregiver education indicating increased odds of thought problems for both older children and higher caregiver education (OR=1.06, CI 1.00-1.12, p < .05). There was also a significant time varying effects for current caregiver tobacco use indicating decreased odds of aggression with increased age and tobacco use (OR=0.92, CI 0.86-1.00, p < .04). A non-significant trend for odds of delinquency to increase with child age and prenatal tobacco exposure (OR=1.06, CI 1.00-1.14, p < .06) was also found. The effect of first trimester marijuana exposure on internalizing symptoms varied over time with lower odds of internalizing symptoms as age and prenatal marijuana exposure increased (OR=0.88, CI 0.81-0.97, p < .01).

3.5 Evaluation of Lead Exposure on Behavioral Outcomes

Lead exposure was not associated with behavioral domains including delinquency, anxiety, withdrawn, somatization, social, thought and attention problems, aggression, internalizing, externalizing, or total behavioral problems after control for drug exposures and other environmental conditions.

3.6 Environmental Effects on Behavior

Table 6 shows that greater current caregiver psychological distress had a consistent association with behavioral problem ratings indicating a 2-3 times greater odds of reporting clinically elevated somatization, social problems, thought problems, attention problems, delinquency, aggression and internalizing, externalizing and total problems (all p values <. 001).

3.7 Effects of Perceptual Reasoning IQ on Behavioral Ratings

The mediating effects of Perceptual Reasoning IQ on odds of delinquency were investigated. Results indicate that higher Perceptual Reasoning IQ did not mediate cocaine's effect on delinquent behavior. When Perceptual Reasoning IQ was evaluated as a covariate it was found to be associated with increased rates of attention problems, aggression, externalizing behavior and total problems (p′s <.05). However, controlling for perceptual reasoning IQ did not change any of the relationships previously found between predictors and outcomes.

3.8 Effects of Adoptive or Foster Care Status Among Cocaine-Exposed Children

The effects of foster or adoptive care versus birth mother or relative care within the CE children are presented in Table 7. Foster/adoptive caregivers rated their CE children as having more clinically elevated social, thought and attention problems, as well as delinquency and aggression (all p′s <.01). In all three broadband scores, internalizing, externalizing and total problems, CE children in foster or adoptive care were 4.9 to 9.7 times more likely to be rated as having clinically elevated scores compared to CE children living in birth mother or relative care.

4. Discussion

This longitudinal study is among the first to evaluate the effects of prenatal cocaine-exposure on caregiver ratings of behavior in children 4 -10 years, controlling for other prenatal drug exposures, postnatal blood lead levels and caregiver factors including child placement status. The hypothesized association between prenatal cocaine-exposure and externalizing symptoms and inattention was partially realized in this study. Prenatal cocaine exposure was associated with increased odds of the delinquency after control for confounders. Examination of a cocaine by sex interaction indicated that the effect was found only for prenatally cocaine-exposed girls. This finding is consistent with studies indicating increased behavioral problems in prenatally cocaine-exposed animals [12, 13] and delinquency or oppositional behavior in humans [22, 23]. The association of prenatal cocaine exposure on increased odds of delinquency among girls has not been reported previously although increased aggressive and hyperactive behavior have been reported among prenatally cocaine- exposed boys (ref 22,23, 24).

No other behavioral problems were associated with prenatal cocaine exposure after controlling for covariates. Caregiver report of behavior did not indicate attention problems as described in other studies of cocaine-exposed children employing child self- report or neuropsychological test results [21, 30, 32-34]. Further, there was no cocaine status by age interactions indicating that both groups had similar rates in changes in behavioral problems over time. Lead exposure was not associated with externalizing behaviors, either aggression or delinquency, in this sample as was hypothesized. This finding does not support the association between lead exposure and delinquency [52, 53] found in other studies.

Other prenatal drug exposures were found to be associated with increased behavior problems. Average prenatal tobacco exposure was associated with increased odds of externalizing symptoms at 4, 9 and 10 years, a finding that is consistent with other studies [54]. Higher 1st trimester marijuana exposure was associated with increased odds of internalizing behavior but not depressive symptoms as has been found in other studies [55, 56]. There was a trend for prenatal alcohol exposure was associated with decreased odds of somatization, thought problems and aggression.

The significance of caregiver type among prenatally cocaine-exposed children was highlighted by results indicating that among prenatally cocaine-exposed children, those living in foster or adoptive care were rated as having more behavioral symptoms than cocaine-exposed children living in birth mother or relative care. These results are consistent with our previous report indicating that foster or adoptive caregivers rate their prenatally cocaine-exposed children as having more behavioral problems at age 6 [21] than did biologic or relative caregivers of cocaine-exposed children. Adoptive or foster parents may be particularly sensitive to behavioral symptoms and therefore report them more often and/or may not be objective in their ratings. Interpretation of this data is limited because a comparative group of non-cocaine-exposed children living in foster/adoptive care was not available for evaluation in this study. There was also an association between increased

psychological distress and increased odds of reporting elevated behavioral problems on most behavioral domains. This pattern has also been consistently identified in other studies [21, 57]

Findings from this study raise some important methodological issues and potential limitations. Previous studies have indicated that prenatal cocaine exposure was related to increased negative behaviors in children ages 1-6 years [19, 20, 22, 25]. This study design extends previous findings by examining specific behavioral domains of cocaine exposed children longitudinally through age 10 while also exploring the association of elevated blood lead on behavioral outcomes and controlling for prenatal drug exposures and environmental conditions. An unexpected finding was that the effect of prenatal cocaine exposure was observed only among girls. This finding could suggest that self- regulatory function of females is more sensitive to the negative effects of prenatal cocaine exposure. Alternatively, these findings may reflect a trend toward greater ease of reporting delinquent behaviors among females, especially those known to be at some biologic risk such as prenatal cocaine-polydrug exposure.

Results indicate that elevated blood lead was not an independent predictor of externalizing behavior problems; a finding that is in contrast to some previous studies from the lead literature indicating a relationship. There are some measurement issues that may have obscured an association of lead with behavioral outcomes. For example, the hematologic assessments were completed when the children were two and four years of age and the behavioral data was collected between 4 and 10 years of age. Previous studies indicate that concurrently measured lead level and outcome data are more highly related than data collected at different ages [58]. Another measurement issue is that the CBCL subscales were dichotomized into borderline clinically relevant and above vs. below clinical cutoff due to data that is not normally distributed. However the dichotomized CBCL data may be less sensitive than continuous data and therefore obscuring a relationship with elevated lead level. It is also possible that the restricted range of elevated blood lead in our sample (1.5-25.2 μg/dL, with 75% of the sample having blood lead levels less than 9.5 μg/dL) contributed to the lack of an association with behavioral outcomes.

Another potential limitation to this study is that blood lead levels were available for only 78% of children and therefore the sample size was reduced when examining the effects of lead. Children with hematologic assessments were different on several variables indicating that they may have had less drug exposure overall and were healthier at birth. Therefore, the sample of children with blood lead levels was biased toward healthier children and the analyses examining the association of lead on behavioral outcomes may have underestimated the effects of prenatal drug exposures.

Behavioral ratings in this study are reported by the current caregiver and are strongly influenced by the caregiver's relationship with the child and their own current psychological status and current drug use habits. While the study design allowed for the statistical control of many of these caregiver variables known to affect child behavior ratings such as psychological distress and current alcohol, marijuana and tobacco use, control for current cocaine use was not possible because women very rarely reported continued use in follow-up assessments. However, since the overall HOME environment was well controlled for in the analyses the conclusion that delinquency is associated with prenatal cocaine exposure rather than postnatal caregiver use of cocaine is reasonable. The findings would also be strengthened by additional behavioral evaluations from multiple informants including the child and teacher.

Among the many strengths of this study is the prospective, longitudinal design. A large number of subjects were studied prospectively over four time points, reducing the chance of Type II error. A large number of confounders were examined which increases confidence in the current findings. Evaluation of caregiver status among cocaine-exposed children allowed for insight into the role of caregiver perspective and child placement on behavioral outcomes in prenatally cocaine-exposed children. The method used for prenatal drug use screening completed at birth combined biologic and self-report measures for an average measure of prenatal cocaine exposure, thus increasing the likelihood that subjects were accurately grouped.

The results of this study indicate that prenatal cocaine and tobacco exposure and caregiver psychological distress have independent contributory roles in the expression of delinquent behaviors among high risk prenatally cocaine/polydrug exposed children. Intervention specialists should consider prenatal cocaine exposure as a marker for the potential development of problem behaviors particularly among females and should focus on caregiver education and behavioral intervention for prevention of externalizing behavior problems. Building positive cognitive behavioral skills that can aid prenatally children in forming important social relationships and reinforcement for the practice of social behavioral rules may be helpful in the prevention of delinquent behavior among prenatally cocaine-exposed children. In addition, the level of psychological distress and continued drug use among caregivers should be addressed in a therapeutic drug treatment setting. This will not only relieve caregiver distress but potentially enhance behavioral outcomes in this high risk group. Ongoing, regular assessments by pediatricians for evidence of behavioral difficulties, as well as referral for behavioral intervention and caregiver support should continue through later childhood.

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Table 1

Maternal demographic characteristics by cocaine status

Maternal Demographics	Cocaine Use (n=193)		Non-Cocaine Use (n=188)		T	p-value
	Mean	SD	Mean	SD		
Mother's age at birth (years)	29.72	4.98	25.60	4.79	-8.24	<0.0001
Number of prenatal visits	5.20	4.61	8.72	4.89	7.22	<0.0001
Parity	3.51	1.88	2.70	1.84	-4.29	<0.0001
Maternal Education (years)	11.58	1.69	11.96	1.43	2.42	0.02
PPVT Standard Score	73.87	15.43	77.83	14.91	2.49	0.01
WAIS-R Block Design Scale	6.89	2.10	7.17	2.12	1.28	0.20
WAIS-R Picture Completion Scale	6.72	2.13	7.04	2.38	1.36	0.18
Global Severity Index	0.83	0.74	0.49	0.53	-5.34	<0.0001
	n	%	n	%	χ^2	p-value
African-American	160	80.32	151	80.32	0.42	0.52
Married	16	8.29	33	17.55	7.29	0.007
Employed	11	5.73	38	20.32	17.92	<0.0001
Low Socioeconomic Status *	188	97.92	184	97.87	0.001	0.98

* Defined by Hollingshead score (IV or V)

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Table 2

Maternal drug use during pregnancy

Maternal Drug Use	Cocaine Use (n=193)		Non-Cocaine Use (n=188)		T	p-value
	Mean	SD	Mean	SD		
Number of cigarettes per day						
Month Prior	13.32	12.40	5.72	10.30	−9.40	<0.0001
1st Trimester	12.45	12.43	4.33	8.71	−10.47	<0.0001
2nd Trimester	10.55	11.69	3.34	7.21	−10.10	<0.0001
3rd Trimester	9.39	11.18	3.17	6.29	−8.99	<0.0001
Average during pregnancy	11.49	11.18	4.14	7.66	−10.42	<0.0001
Alcohol dose per week						
Month Prior	12.76	22.45	2.51	7.70	−8.67	<0.0001
1st Trimester	11.97	23.60	1.30	3.85	−9.61	<0.0001
2nd Trimester	7.97	19.58	0.56	2.98	−8.61	<0.0001
3rd Trimester	6.23	16.98	1.08	7.74	−7.63	<0.0001
Average during pregnancy	9.73	17.45	1.36	4.53	−10.81	<0.0001
Marijuana dose per week						
Month Prior	1.60	3.79	1.53	9.93	−3.57	0.0002
1st Trimester	1.48	4.04	0.59	3.73	−3.85	0.0001
2nd Trimester	1.29	4.24	0.19	1.68	−4.33	<0.0001
3rd Trimester	0.97	3.81	0.10	0.75	−3.79	0.0001
Average during pregnancy	1.33	3.44	0.60	3.46	−4.28	<0.0001
Cocaine units per week						
Month Prior	32.88	71.47	0	0	n/a	n/a
1st Trimester	33.96	70.73	0	0	n/a	n/a
2nd Trimester	26.57	69.23	0	0	n/a	n/a
3rd Trimester	12.24	27.06	0	0	n/a	n/a
Average during pregnancy	24.29	45.73	0	0	n/a	n/a

Table 3

Child demographic and medical characteristics

Child Demographics	Cocaine Exposed (n=193)		Non-Cocaine Exposed (n=188)		t	p-value
	Mean	SD	Mean	SD		
1 Minute Apgar	7.98	1.43	7.93	1.67	-0.33	0.74
5 Minute Apgar	8.79	0.64	8.78	0.70	-0.11	0.91
Gestational Age (weeks)	37.77	2.83	38.48	2.83	2.44	0.02
Hobel Neonatal Risk Score	7.45	16.46	5.70	15.61	-1.06	0.29
Birth Length (cm) *	47.31	3.95	49.11	3.69	4.10	<0.0001
Head Circumference (cm) *	32.26	2.12	33.46	2.35	6.08	<0.0001
Birth Weight (grams) *	2706.88	644.68	3101.61	692.57	5.01	<0.0001
Lead Exposure (μg/dL) **	6.98	4.10	8.02	4.58	2.10	0.04
	n	%	n	%	χ^2	p-value
Male	88	45.60	90	47.87	0.20	0.66
African-American	159	82.38	150	79.79	0.42	0.52
Microcephalic	28	14.74	9	4.84	10.38	0.001
Small for Gestational Age	24	12.63	4	2.14	15.09	0.0001
Anemia **	9	5.96	2	n/a	n/a	n/a

* Adjusted for gestational age

** Lead/Anemia sub-sample (CE = 151, NCE = 147)

Table 4

Caregiver and Child Characteristics at 10 years by Caregiver Placement Status

Current Caregiver Demographics (T8)	CE Biological Parent or Relative (n=130)		CE Adopted or Foster care (n=39)		Non-Cocaine Exposed n=(171)		F	p-value
	Mean	SD	Mean	SD	Mean	SD		
Education (years) *1, 2, 3*	11.91	1.82	13.31	2.89	12.53	1.70	8.08	0.0004
PPVT Standard Score *1*	74.83	14.85	88.00	14.44	78.42	15.71	3.97	0.02
WAIS-R Block Design Scale	6.89	1.97	7.15	2.76	7.23	2.15	0.87	0.42
WAIS-R Picture Completion Scale	6.85	2.19	7.08	3.06	7.13	2.41	0.46	0.63
Global Severity Index *1*	0.36	0.43	0.20	0.22	0.34	0.46	2.10	0.12
Tobacco (cigarettes per day) *1, 2*	6.70	8.16	2.03	5.50	3.17	5.67	17.90	<0.0001
Alcohol (dose per week) *1*	1.94	5.50	0.75	2.79	1.12	2.45	2.33	0.10
Marijuana (dose per week)	0.44	2.99	0	0	0.07	0.41	1.24	0.29
Cocaine (units per week)	0.73	6.71	0	0	0	0	n/a	n/a
Home Score **1, 2*	41.76	7.60	44.73	4.97	43.78	6.23	5.12	0.006
Child Lead Exposure (µg/dL) ***1,3*	7.44	4.13	4.86	3.23	8.02	4.58	8.98	0.0002
	n	%	n	%	n	%	χ^2	p-value
Child Anemia ****	8	6.45	1	3.70	2	1.36	n/a	n/a

*Home Score measure taken at time 7 (age 9 years)

**Lead/Anemia sub-sample (CE-Bio/Relative = 124, CE-Adopted/Foster = 27, NCE = 147)

*1*CE-Bio/Relative significantly different from CE-Adopted/Foster at p≤0.05.

*2*CE-Bio/Relative significantly different from NCE at p≤0.05.

*3*CE-Adopted/Foster significantly different from NCE at p≤0.05.

Table 5

Unadjusted number and percentage of children above borderline/clinical cut-off, by age

CBL Outcome	Age [n (%)]							
	4 Years		6 Years		9 Years		10 Years	
	CE (n=182)	NCE (n=176)	CE (n = 184)	NCE (n = 179)	CE (n = 185)	NCE (n = 178)	CE (n = 161)	NCE (n = 155)
Anxiety	5 (2.75)	2 (1.14)	3 (1.63)	3 (1.68)	7 (3.78)	9 (5.06)	6 (3.73)	6 (3.87)
Withdrawn	12 (6.59)	7 (3.98)	8 (4.35)	9 (5.03)	9 (4.86)	12 (6.74)	8 (4.97)	7 (4.52)
Somatization	6 (3.30)	7 (3.98)	17 (9.24)	9 (5.03)	15 (8.11)	9 (5.06)	14 (8.70)	6 (3.87)
Social Problems	7 (3.85)	7 (3.98)	9 (4.89)	9 (5.03)	17 (9.19)	16 (8.99)	16 (9.94)	9 (5.81)
Thought Problems [c]	14 (7.69)	16 (9.09)	15 (8.15)	16 (8.94)	18 (9.73)	9 (5.06)	16 (9.94)	5 (3.23)
Attention Problems [a]	20 (10.99)	8 (4.55)	13 (7.07)	13 (7.26)	23 (12.43)	17 (9.55)	20 (12.42)	10 (6.45)
Delinquency [b, c]	13 (7.14)	10 (5.68)	18 (9.78)	9 (5.03)	30 (16.22)	15 (8.43)	29 (18.01)	13 (8.39)
Aggression	19 (10.44)	11 (6.25)	18 (9.78)	11 (6.15)	22 (11.89)	14 (7.87)	22 (13.66)	14 (9.03)
Internalizing	21 (11.54)	12 (6.82)	20 (10.87)	22 (12.29)	34 (18.38)	28 (15.73)	27 (16.77)	21 (13.55)
Externalizing [b, c]	35 (19.32)	24 (13.64)	35 (19.02)	25 (13.97)	60 (32.43)	40 (22.47)	48 (29.81)	30 (19.35)
Total Problem	36 (19.78)	25 (14.29)	37 (20.33)	31 (17.42)	45 (24.32)	39 (21.91)	37 (22.98)	26 (16.77)

[a] CE and NCE significantly different at 4-years old ($p \leq 0.05$)

[b] CE and NCE significantly different at 9-years old ($p \leq 0.05$)

[c] CE and NCE significantly different at 10-years old ($p \leq 0.05$)

Table 6

Adjusted effects of prenatal drug exposure and postnatal environmental drug exposure, lead and HOME score on CBCL outcomes (n=298)

CBCL Outcomes	Prenatal [OR (95% CI); p-value]				Postnatal [OR (95% CI); p-value]		
	Cocaine (yes/no)	Alcohol (dose/wk)	Marijuana (dose/wk)	Tobacco (number/day)	Lead	Tobacco (dose/wk)	Current Caregiver GSI
Anxiety *	0.90 (0.41-1.98) p < 0.80				1.00 (0.47-2.13) p < 0.99		
Withdrawn *	1.06 (0.52-2.13) p < 0.88				1.07 (0.58-1.99) p < 0.83		
Somatization	1.26 (0.43-3.73) p<0.67	Month Prior: 0.68 (0.52-0.89) p < 0.01		Average: 1.17 (0.77-1.79) p < 0.46	1.08 (0.51-2.28) p < 0.85	1.13 (0.78-1.64) p < 0.52	2.88 (1.69-4.88) <0.0001
Social Problems	0.91 (0.42-1.94) p<0.80	2nd Trimester: 1.22 (0.78-1.89) p<0.39		Average: 0.68 (0.42-1.11) p < 0.12	1.13 (0.68-1.88) p < 0.64	1.18 (0.79-1.76) p < 0.43	2.46 (1.53-3.94) p < 0.0002
Thought Problems	1.10 (0.50-2.43) p < 0.82	2nd Trimester: 0.98 (0.71-1.35) p < 0.89		Average: 1.07 (0.81-1.43) p < 0.62	1.69 (0.99-2.90) p < 0.06		3.06 (1.78-5.24) p < 0.0001
Attention Problems	1.40 (0.65-3.03) p < 0.39	Average: 0.86 (0.59-1.23) p < 0.41		Average: 0.90 (0.68-1.19) p < 0.46	1.26 (0.73-2.18) p < 0.41		2.19 (1.43-3.36) p < 0.0003
Delinquency	2.08 (1.10-3.94) p < 0.02			1.10 (0.82-1.47) p<0.53	1.39 (0.82-2.36) p < 0.22	0.77 (0.58-1.02) p < 0.07	2.04 (1.45-2.87) p < 0.0001
Aggression [1]	1.87 (0.80-4.38) p < 0.15	1.07 (0.77-1.50) p < 0.68		Average: 1.05 (0.72-1.52) p < 0.81	1.13 (0.65-1.95) p < 0.66	Main: 1.57 (0.78-3.18) p < 0.21 Age * Tobacco Interaction: 0.91 (0.84-0.99) p < 0.03	2.70 (1.85-3.92) p < 0.0001
Internalizing [2]	1.20 (0.64-2.22) p < 0.57	Average: 0.64 (0.48-0.85) p < 0.002	1st Trimester (Main): 2.39 (0.99-5.78) p < 0.05 Age * Marijuana Interaction: 0.89 (0.79-1.00) p < 0.06	Average: 1.18 (0.92-1.50) p < 0.19	1.15 (0.68-1.96) p < 0.60		3.04 (2.22-4.16) p < 0.0001
Externalizing	1.11 (0.63-1.94) p < 0.72	2nd Trimester: 1.10 (0.87-1.39) p < 0.44	1st Trimester: 0.86 (0.58-1.28) p < 0.46	†	1.08 (0.68-1.71) p < 0.74	0.82 (0.60-1.11) p < 0.19	1.97 (1.50-2.58) p < 0.0001

CBCL Outcomes	Prenatal [OR (95% CI); p-value]				Postnatal [OR (95% CI); p-value]		
	Cocaine (yes/no)	Alcohol (dose/wk)	Marijuana (dose/wk)	Tobacco (number/day)	Lead	Tobacco (dose/wk)	Current Caregiver GSI
Total Problem	0.92 (0.51-1.68) p < 0.80	Average: 1.00 (0.79-1.27) p < 0.98	2nd Trimester: 1.21 (0.85-1.71) p < 0.28	Average: 1.22 (0.90-1.65) p < 0.20	1.19 (0.72-1.99) p < 0.50	0.80 (0.61-1.05) p < 0.11	2.85 (2.13-3.82) p < 0.0001

*Adjustments were not evaluated in model due to low incidence of children above borderline/clinical cut-off scores.

1Aggression: The OR for age was 0.99 (0.54-1.82), p < 0.98

2Internalizing: The OR for age was 1.21 (1.09-1.34), p < 0.0003

†Externalizing: There was a significant (p < 0.05) interaction between average prenatal tobacco exposure and child's age, indicating that 2nd trimester tobacco exposure's affect on externalizing varies by age.

Table 7

Among cocaine-exposed children, odds of being rated above borderline/clinical cut-off if placed in adopted/foster care vs. biological/relative care

CBCL Outcome	OR	95% CI		p-value
		Low	High	
Somatization	0.70	0.16	3.01	0.63
Social Problems	4.24	1.16	15.55	0.03
Thought Problems	2.57	0.89	7.46	0.08
Attention Problems	7.48	3.13	17.85	<.0001
Delinquency	2.92	1.32	6.43	0.01
Aggression	4.70	2.08	10.64	0.0002
Internalizing	4.87	1.97	12.04	0.0006
Externalizing	8.80	3.72	20.81	<.0001
Total Problem	9.70	4.08	23.04	<.0001

* Fully adjusted models