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Gender and alcohol moderate caregiver reported child behavior after prenatal cocaine☆

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Abstract

Objective: The concurrence of prenatal alcohol exposure with other drug exposure, low socioeconomic status and environmental risk factors may obscure associations, if any, between prenatal cocaine exposure and child outcomes. This study evaluates the effects of prenatal cocaine exposure on child behavior in analyses stratified by gender and prenatal alcohol exposure status.
Methods: Maternal alcohol, cigarette, and illicit drug use were prospectively assessed by interview during pregnancy and postnatally. Maternal and neonatal urine were tested for drug exposure as clinically indicated. Caregiver report of child behavior was assessed with the Achenbach Child Behavior Checklist (CBCL). Dichotomous cocaine exposure was characterized as no (negative history and biologic markers), and any (positive history and/or biologic markers during pregnancy and/or positive urine screen at delivery from either mother or infant).
Results: Prenatal cocaine exposure was associated with adverse effects on offspring behavior that were moderated by the gender of the offspring as well as prenatal alcohol exposure. For girls without prenatal alcohol exposure, 6.5% of the unique variance in behavior was related to prenatal cocaine exposure. For these girls, the odds of scoring in the abnormal range for Aggression was 17 times control levels (95% confidence limits 1.4 to 203). These findings, though significant, have wide confidence intervals and need to be replicated in larger cohorts and on longitudinal follow-up.

Keywords: Child Behavior Checklist (CBCL); Child behavior; Cocaine; Prenatal exposure delayed effects

1. Introduction

Abuse of cocaine by pregnant women is a major medical and social problem [60]. In the United States, recent reports of cocaine use during pregnancy vary between 2% and 18%. In the mid- to late 1980s at the height of the "cocaine epidemic", as many as 31% of the maternity clients at our center [17,45] had evidence of cocaine use during pregnancy. Because it is lipophilic, cocaine readily crosses the placental barrier by simple diffusion [42,60]. Furthermore, the low levels of metabolic enzymes, cholinesterases, in the fetus, and during

Abbreviations: CBCL, Child Behavior Checklist; HOME, Home Observation for Measurement of the Environment; SCL-90, Symptom Checklist-90; OR, Odds ratio; SES, Socioeconomic status; SCL-GSI, Symptom Checklist—Global Severity Index.

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pregnancy, potentially expose the fetus to relatively higher drug concentrations. Impairment of the reuptake of monoaminergic neurotransmitters by presynaptic nerve endings, a primary mechanism of action of cocaine, leads to accumulation of the neurotransmitters at synapses, activation of the adrenergic system and ultimately depletion of neurotransmitters from nerve endings [26,29,32]. These neurotransmitters have regulatory roles in the development of neuronal circuitry. These disturbances in the monoaminergic systems could adversely affect the developmental outcome of children exposed to cocaine in utero. However, studies on the behavioral teratogenicity of cocaine in animals and humans have produced conflicting results [59]. The ambiguous nature of outcomes may be due to methodological problems typically associated with behavioral toxicology research [4]. These include the potential confounding effects of other substances of abuse and poor maternal health and nutrition, as well as difficulties in obtaining sensitive and valid measurements of prenatal exposure, and of child outcomes. Finally, postnatal factors associated with drug use, including the child-rearing environment and postnatal drug exposure, may alter long-term outcome.

Our research group has previously reported the association of prenatal cocaine exposure and adverse effects on childhood growth, behavior and language development [15,18–20]. We have demonstrated gender moderation of the behavioral effects of prenatal cocaine exposure [21]. In additional analyses, we noted a significant interaction of prenatal cocaine by prenatal alcohol exposure and gender. The aim of the current study was to further examine the nature of this interaction and child behavior. Distinguishing features of this study include statistical analyses stratified by both gender and prenatal alcohol exposure to control for moderators and address collinearity; and sensitive and valid measurement of the level of prenatal cocaine exposure in a large cohort of urban African American women and children followed prospectively from the first prenatal visit.

2. Methods

The design of this study was historical prospective. Beginning in 1986, women attending the urban university-based maternity clinic were routinely screened at their first prenatal visit for alcohol and drug use by trained research assistants.

2.1. Sample

All mothers in this study received prenatal care in the antenatal clinics at Wayne State University and participated in a prospective pregnancy study approved by the IRB. Women were interviewed at their first prenatal visit to initially ascertain a dichotomous self-report of cocaine use and maternal urine was tested as clinically indicated. A trained research assistant administered a standardized, structured research interview to elicit estimates of amounts of cocaine and other illicit drug use (i.e., times/day, days/month and cost/month). At each subsequent prenatal visit, alcohol and illicit drug (henceforth referred to only as drug) exposure data were obtained by research interview [56]. Tobacco exposure was estimated from maternal report of the number of cigarettes smoked in the peri-conceptional period, as well as across pregnancy. At delivery, hospital policy at the time dictated screening of urine samples from mothers and infants for drug exposure when evidence (history or biologic measures) of past or current drug or alcohol use existed. Over 90% of the known cocaine-exposed pregnancies in this study underwent urine screening at delivery.

Children in this study were the singleton infants delivered between September 1, 1989 and August 31, 1991 to women extensively screened for in-pregnancy drug and alcohol use as described above. Block sampling, which over sampled alcohol- and cocaine-exposed pregnancies, was employed to reduce collinearity between drug and alcohol use, because an unselected sample would likely inadequately identify women using drugs, but not alcohol. Over 2400 pregnancies were screened yearly for this sample selection. Because more than 90% of antenatal patients were African American, the study was limited to this racial group. Additional exclusion criteria were very limited and included multiple gestation, children with major congenital malformations, and known positive maternal HIV status. Mothers with no prenatal care could not be evaluated prospectively in the clinic and were also excluded. The need for this exclusion was unfortunate because drug and alcohol abusing mothers are more likely to avoid prenatal care. However, this design decision was made to reduce the risks of misclassification of cocaine exposure status and inadequate assessment of other prenatal exposures (alcohol, tobacco and other drugs) that would be inherent among women who delivered with no prenatal care.

At follow-up 6–7 years later, families were intensively sought by telephone, mail or by home visit to the last known address. Client files of all Detroit-based University-affiliated hospitals and the pediatric and internal medicine ambulatory services were searched for updated contact information. Telephone numbers were also searched. Additionally, children were sought through the private and public school system. Families who could be contacted represented the potential study sample.

2.2. Instruments and procedure

At age 6–7 years, following informed consent, the child and caregiver (usually the biological mother when available, or, if not available, the primary caregiver) were tested

in our research facility. The caregiver completed the Achenbach Child Behavior Checklist CBCL] [2]. Child testing included the child's self-report of exposure to violence ("Things I Have Seen and Heard [TISH]") [50], whole blood-lead levels (μg/dl) assayed by the institutional laboratory (Polarized Zeeman Furnace Atomic Absorption Spectrophotometer Z8200, Hitachi) and growth. The TISH, a 20-item instrument, assesses the frequency of children's self-report of exposure to violence-related activities in the home and community using a likert scale [50]. Higher total scores indicate more exposure to violence. Raw scores can be examined individually or added to create a summary score. We assigned point values to each item from 0 to 4. Scores for three items relating to positive environmental outcomes were reversed, thus giving a possible range of 80 for this instrument. Additional testing included caregiver's self-reported psychopathology (SCL-90) [22], social support [44], an assessment of home environment (modified HOME assessment) [12], family socioeconomic status (SES) (Hollingshead, unpublished data), and a structured interview to assess postnatal drug, alcohol, and cigarette use in the home. The modified HOME assessment is an investigator-adaptation of the Elementary Version of the Home Observation for Measurement of the Environment (HOME) [12]. This semi-structured interview assessed cognitive and affective dimensions of stimulation provided by caregivers but eliminated HOME questions that required direct observation of the actual home. Research assistants who were trained and masked to prenatal exposure status independently interviewed the child and caretaker.

2.3. Measures

2.3.1. Independent variable: prenatal cocaine exposure

Dichotomous prenatal cocaine exposure was defined based upon history and laboratory tests to identify two exposure groups: "none" or "any". Women were considered to have no cocaine exposure if they had no positive biologic tests and denied use at all prenatal visits, at delivery, and retrospectively at the 6- to 7-year follow-up. Cocaine exposure was considered positive from any of the following sources: maternal history from prospective research interviews during pregnancy or at the age 6–7 assessment; prenatal or neonatal medical histories; maternal urine from antenatal clinic visits; maternal or infant urine at delivery; or when available, infant meconium. Urine testing was performed with the Syva Emit method (Syva, Palo Alto, CA). Sensitivity for cocaine and its metabolites (ecgonine, benzoylecgonine) was <35 ng/ml (given the 95% CI, 35 ng/ml is the lowest concentration that can be detected as reliably different from 0). Urine samples were collected by nursing staff and sent directly to the hospital toxicology laboratory for analysis. The cutoff level for a positive screen was 300 ng/ml. All positive screens were verified with a second Emit procedure. This hospital policy of maternal/infant urine testing at delivery resulted in screening more than 90% of our exposed sample.

2.3.2. Dependent variable measure: caregiver reported child behavior

The Child Behavior Checklist (CBCL) [2], was designed for use in the clinical assessment of behavior of children 4–16 years old [3]. Designed at a fifth-grade reading level, the CBCL has high test–retest reliability [2] and can be completed in 15–20 min. Achenbach derived eight syndrome scales from the 118 CBCL items [2]. These scales are further grouped into Externalizing or under-controlled (Aggressive and Delinquent) behaviors, and Internalizing or over-controlled (Anxious/Depressed, Somatic Complaints, and Withdrawn) behaviors. Three syndromes (Social, Thought and Attention Problems) fit neither group (Neither Externalizing or Internalizing). A Total Problem score is also computed by summing all problem items. Higher scores are associated with more problem behaviors. Raw scores are assigned *T* values providing a metric that is similar for all scales. Statistical analyses using *T* scores have less power because of data truncation, but have the added advantage of distinguishing between scores in the normal range compared to the clinical range. Achenbach has proposed *T* scores of 60 and 67 as cutoff points for the syndrome/total and problem subscales, respectively [2]. In this report, CBCL raw scores are used in *t*-tests, ANOVAs and regression analyses (as continuous data); and CBCL *T* scores are used for crosstabulation, computation of odds ratio, and logistic regression (categorical data).

2.3.3. Control variables

Data were collected on a broad range of control variables known to influence childhood behavior and/or to be associated with prenatal cocaine exposure. These included perinatal factors of maternal age, education, HIV status, use of alcohol, cigarettes, and other substances of abuse and child's gestational age at delivery. Postnatal control factors studied included maternal psychopathology, current alcohol and drug use, family structure including custody status, SES, children's lead level, and exposure to violence.

2.4. Statistical analyses

All variables were checked for possible normality violations, and bivariate relations were assessed with two-tailed *t*-tests, chi-squares, and correlations. All analyses were stratified by gender and dichotomous prenatal alcohol exposure status (yes, no). Multivariate analyses were performed with the least-squares multiple regression for continuous dependent variables and with binary logistic regression for dichotomous dependent variables. Potential confounders were identified from zero-order correlations

with exposure and outcome variables in all analyses. Selected control/confounder variables correlated ($p<0.10$) with exposure outcome(s). Control variables were entered stepwise, followed by the forced entry of prenatal cocaine group.

3. Results

Fifty-seven percent of the women denied any cocaine use during pregnancy. There was no difference in the percentage of children exposed to cocaine prenatally by gender.

3.1. Sample characteristics

Six percent of the original cohort of 665 participants refused to participate in the evaluation at 6–7 years. Additional 40 dyads missed multiple testing appointments, and 28 had incomplete data for the variables of interest. Additional exclusions were four children who had major congenital malformations. As mental retardation alone also can be associated with behavior problems, children with an IQ of >2 standard deviations from the sample mean were excluded. As a result, 47 children who had a performance IQ of <65 (n=31) or for whom IQ testing was not available also were omitted from analyses presented in this article. However, statistical analyses performed with and without these low IQ children yielded similar results. In all, 506 parent–child dyads constituted the sample for this study. The mothers of participating subjects were significantly older and had more children than those who did not participate. However, the two groups of children did not differ significantly on any newborn characteristics, and mothers did not differ on prenatal use of cigarettes, alcohol, or cocaine.

Demographic characteristics were similar for boys and girls in the sample described.

3.1.1. Maternal and pregnancy

Maternal age, cigarette and alcohol exposure during pregnancy as well as current drug use (all p's <0.005) were increased with prenatal cocaine exposure. (Table 1) Marital

Table 1
Demographic characteristics by prenatal cocaine exposure group

	No prenatal alcohol		With prenatal alcohol	
	Prenatal cocaine		Prenatal cocaine	
	None (N=95)	Any (N=22)	None (N=197)	Any (N=192)
Child				
Birth weight (g)	3217 (578)	2718 (629)**	3090 (595)	2846 (650)**
Gestational age (weeks)	38.8 (2.3)	37.8 (3.7)	39.1 (2.2)	38.3 (3.0)*
Current lead (μg/dL)	4.8 (2.9)	4.9 (2.7)	4.8 (2.6)	5.2 (3.3)
Maternal				
Age (years)	22.0 (6.3)	28.3 (6.1)**	24.4 (6.5)	28.4 (4.9)**
Education (years)	11.5 (2.0)	11.3 (1.7)	11.6 (1.5)	11.7 (1.6)
Married (%)	29	9	27	25
Prenatal alcohol (oz AA/day)[a]	0.0	0.0	0.1 (0.2)	0.3 (0.6)**
Cigarettes (% use)	12	91**	57	87**
Cigarettes (#/day)	2 (6)	13 (12)**	7 (9)	12 (10)**
Current drugs (% use)	0	0	0	4*
Current alcohol (% use)	21.5	31.6	63	55
Current alcohol (oz AA/day)[a]	0.04 (0.1)	0.05 (0.1)	0.4 (0.6)	0.4 (0.7)
Family				
Custody (biological mom %)	94	59**	90	73**
Custody changes ever (% yes)	9	52**	12	35**
Paternal alcohol during pregnancy (%)	44	52	85	79
Paternal drugs during pregnancy (%)	16	48*	27	51**
SES[b]	31.2 (10.7)	28.7 (8.0)	29.6 (10.2)	28.7 (9.9)
HOME inventory[c]	33.0 (6.1)	32.0 (7.8)	31.2 (6.5)	31.7 (6.5)
Violence exposure scores	14.1 (8.1)	14.0 (8.2)	13.2 (7.9)	13.6 (8.5)
SCL-GSI[d]	0.5 (0.5)	0.5 (0.7)	0.5 (0.5)	0.5 (0.5)

Numbers in parentheses represent standard deviations.
[a] Ounces of absolute alcohol/day.
[b] Socioeconomic status—Hollingshead.
[c] Home Observation for Measurement of the Environment.
[d] Symptom Checklist—Global Severity Index.
* Indicates p values < 0.005 from corresponding t or χ^2 analyses.
** Indicates p values <0.001 from corresponding t or χ^2 analyses.

status and current alcohol use were comparable across groups.

3.1.2. Child

The mean birth weights were lower with any prenatal cocaine exposure ($p<0.005$). Children with prenatal alcohol exposure had a significantly lower gestational age in the presence of prenatal cocaine.

3.1.3. Family

Household composition was related to prenatal cocaine exposure (Table 1). Specifically, at age 6–7 years, children with any prenatal cocaine exposure were less likely to have consistently been in the custody of their biologic mother ($p<0.001$). Paternal drug use at the time of pregnancy was also highly related to prenatal cocaine exposure. Paternal drinking during pregnancy, family SES, HOME scores, exposure to violence and maternal psychopathology were not different between the cocaine exposure groups.

3.2. Child behavior outcome. Prenatal cocaine as a dichotomous variable considering alcohol exposure

Complete data for the CBCL were available for 499 subjects. Bivariate analyses of CBCL raw scores by dichotomous prenatal cocaine exposure revealed higher scores for Externalizing (Aggression, Delinquent), Internalizing, Attention Problems and Total Problem Score (Table 2) in the subgroup of girls without prenatal alcohol. Only scores for Aggression reached statistical significance at the 0.05 level ($p=0.047$). Boys with both prenatal alcohol and cocaine exposures had higher scores on Delinquent ($p=0.032$). There was no difference in CBCL scores by dichotomous prenatal cocaine exposure for girls with prenatal alcohol or for boys without prenatal alcohol exposure. Fig. 1 shows boxplots for the raw scores on Aggression for boys and girls. Girls without prenatal exposure to alcohol or cocaine have lower scores than girls with either or both prenatal exposures.

3.3. Results of stepwise regression

Regression analysis was performed to determine the degree to which prenatal cocaine exposure predicted childhood behavior problems after controlling for covariates and confounders. Dichotomous prenatal cocaine exposure during pregnancy was entered into the regression model after all significant control variables including maternal age, primary caretaker, custody changes, prenatal exposure to cigarettes, paternal use of drugs at conception, and current use of drugs by the primary caretaker. Prenatal marijuana exposure was not entered as a potential confounder because of a lack of substantial univariate relations with outcomes. After control, prenatal cocaine exposure remained a significant predictor of adverse behavioral outcome on Aggression for the subgroup of girls without prenatal alcohol exposure. The amount of variance uniquely accounted for by prenatal cocaine exposure was 6.5%. In the presence of prenatal alcohol, prenatal cocaine exposure was not a significant predictor of CBCL scores for either girls or boys.

3.4. Results of logistic regression (dichotomous cocaine exposure)

Logistic regression was performed to determine the degree to which a dichotomous prenatal cocaine exposure variable predicted CBCL scores in the clinically significant range using the recommended *T*-score cutoffs [2]. Dicho-

Table 2
Mean (SD) CBCL scores by dichotomous prenatal cocaine exposure-stratified by prenatal alcohol and gender

	No prenatal alcohol			With prenatal alcohol		
	Prenatal cocaine			Prenatal cocaine		
	None	Any	*p*	None	Any	*p*
Boys	*(n=49)*	*(n=7)*		*(n=103)*	*(n=96)*	
Externalizing	10.4 (9.1)	10.7 (3.4)	NS	10.9 (8.0)	13.1 (11.5)	NS
Aggression	8.6 (7.5)	8.6 (2.6)	NS	8.9 (6.7)	10.3 (8.5)	NS
Delinquent	1.8 (2.3)	2.1 (1.2)	NS	2.0 (1.8)	2.8 (3.4)	0.032
Internalizing	6.9 (7.5)	6.0 (3.6)	NS	6.3 (6.1)	6.8 (6.4)	NS
Attention Problems	4.3 (4.3)	4.3 (1.6)	NS	3.8 (3.6)	4.4 (4.2)	NS
Total Score	30.0 (26.7)	31.4 (9.4)	NS	28.4 (19.6)	32.2 (26.1)	NS
Girls	*(n=45)*	*(n=14)*		*(n=91)*	*(n=94)*	
Externalizing	5.4 (4.9)	10.7 (9.4)	0.061	11.5 (8.5)	10.2 (8.2)	NS
Aggression	4.3 (3.7)	9.0 (8.0)	0.047	9.3 (7.0)	8.5 (6.6)	NS
Delinquent	1.1 (1.7)	1.6 (1.7)	NS	2.2 (1.9)	1.7 (2.0)	0.094
Internalizing	3.1 (3.2)	5.1 (4.7)	0.079	6.7 (5.8)	6.3 (6.6)	NS
Attention problems	1.6 (2.4)	3.9 (4.3)	0.073	3.6 (3.3)	3.5 (3.7)	NS
Total score	15.1 (12.1)	24.9 (18.6)	0.080	30.1 (20.6)	27.5 (21.8)	NS

SD indicates standard deviation.
NS indicates not significant.

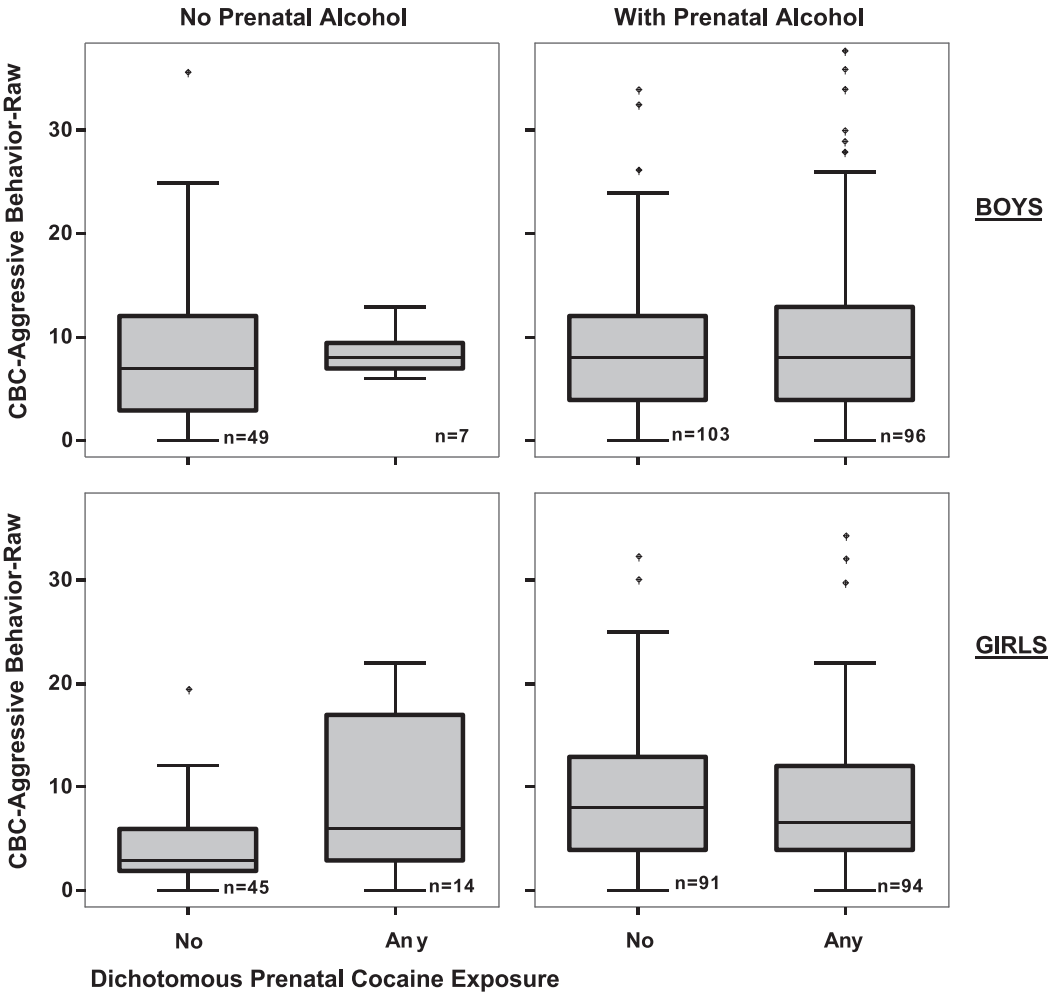

Fig. 1. Boxplots show significant differences between No and Any prenatal cocaine exposure for Aggressive behavior in girls without prenatal alcohol exposure. Between group differences were not significant for girls with prenatal alcohol exposure and for boys regardless of prenatal alcohol exposure. Small solid circles represent outliers.

tomous prenatal cocaine exposure during pregnancy was entered into the regression model after all significant control variables evaluated by stepwise regression (see above). In the subgroup of girls with any cocaine but no alcohol exposure, the odds of scoring in the clinical range for aggression were increased 17-fold (95% confidence limits 1.4 to 203). These findings, though significant, need to be interpreted with caution considering the wide confidence intervals.

4. Discussion

In this study of urban African American children, a dichotomous measure of prenatal cocaine exposure was associated with adverse behavioral outcomes on caregiver-reported child behavior among girls without prenatal alcohol exposure. This study differs from earlier reports in that it evaluates the moderating effects of both gender and prenatal alcohol exposure status by stratified analyses. For girls without prenatal alcohol exposure, after controlling for covariates, prenatal cocaine exposure was associated with higher Aggression scores (i.e., more problem behaviors) accounting for 6.5% of unique variance in the scores.

Use of multiple drugs of abuse is common during pregnancy. Kandel et al. [36] reported a strong link between cigarette smoking and alcohol use and the use of illicit drugs among pregnant women [36]. Among those women who used both cigarettes and alcohol, 20.4% also used marijuana and 9.5% took cocaine. Conversely, of those women who said they had not used cigarettes or alcohol, only 0.2% smoked marijuana and 0.1% used cocaine. Because of the abuse of multiple drugs during pregnancy, unselected samples may not adequately demarcate a group of women who used cocaine, but not alcohol [51]. When control variables are highly correlated with the exposure, they may obscure the toxic effects of one or both exposures [33]. In recognition of the strong relation between the use of prenatal alcohol and cocaine, the design of this pregnancy study included over-representation of low-alcohol, high-

cocaine users by block sampling. This design increased the study's ability to distinguish alcohol from cocaine effects. Block design reduced the zero-order correlation between prenatal alcohol exposure and prenatal cocaine exposure from 0.42 to 0.19 [33]. Because prenatal alcohol has been found to alter childhood behavior [56,59], we stratified our analyses by prenatal alcohol exposure to observe the effects of prenatal cocaine alone. Additional stratification by smoking would have decreased the number of observations in each cell markedly. Therefore, although less desirable, smoking was controlled in the statistical analysis rather than through stratification.

The CBCL has gender-specific normative data for raw scores with higher scores for boys. Because the scores are normed by gender, main effects of gender were not expected in analyses using raw scores [57]. Without stratification any differential effects by gender are likely to be diluted and potentially missed.

An additional concern in pregnancy studies of drugs of abuse is how to quantify the exposure status. The difficulties associated with establishing a woman's drug use history and the drug-exposure status of her children has previously been discussed [5]. Underreporting of drug use by pregnant women because of fear of consequences or recall inaccuracy has been well documented [27,40,45]. The importance of using both self-report and a biomarker was illustrated by Frank et al. [27] who found that self-report misclassified 24% of cocaine users identified by urine toxicology. In addition, 51% of those who admitted cocaine use had urine tests that were negative for cocaine. Although not consistently available during our study period, a meconium assay is currently the most widely accepted and recommended procedure to detect prenatal cocaine exposure [5]. In our study, the use of both self-report and biological measures (urine drug screen) to categorize exposed infants has enhanced reliability and allowed detection of important differences [55]. Similarly, there is a potential for misclassification of alcohol users as no alcohol users because there was no available biological marker for alcohol use to confirm or refute maternal reports. This has been discussed in a previous publication from our group [56].

Studies in animals and humans suggest that transplacental exposure to cocaine alters programs for brain development and may be associated with lasting alterations in brain structure and function [16,18,34,38,39,54]. While neonatal human behavioral changes have been demonstrated [9,14,16,24,43,48,54], reports of the long-term neurobehavioral effects of prenatal cocaine exposure are limited and inconsistent [1,6,30,48,49]. A limited number of reports have examined caregiver report of emotional and behavioral problems in prenatally cocaine-exposed children with mixed results [1,6,17,30,31,46,48]. Behaviors characterized as "fussy/difficult," "unadaptable," and "excessively persistent" were predicted by prenatal cocaine exposure at 1 year of age [48]. First trimester cocaine use was a significant predictor of CBCL ratings on the Total Score and Internalizing syndrome scale at age 3 years [31]. Hawley et al. [31] found that preschool children exposed to cocaine in utero showed significantly higher CBCL *T* scores on Internalizing problems and were more likely to score in the clinical range compared to controls. Griffith et al. [30] reported that after controlling for other exposures, intrauterine cocaine was a significant predictor of externalizing behaviors accounting for 5% of the variance at 3 years of age. Gender differences (but not gender-by-exposure interactions) were tested with factor analysis. Additionally, Chasnoff et al. [13] reported greater internalizing problems and externalizing difficulties through age 6. Conversely, Phelps et al. [46] reported no difference in the CBCL between similar groups of cocaine- and nondrug-exposed preschoolers. Azuma et al. [6] did not find any group differences on CBCL Externalizing scores at age. More recently, Accornero et al. [1] showed that prenatal cocaine exposure was not related to parent-reported child behavior assessed by the CBCL at age 5 in their cohort of 140 cocaine-exposed children.

In contrast to the variable behavioral effects of the previously described studies, prenatal cocaine exposure has been consistently associated with problems in attention processing. Richardson et al. [49] reported that children prenatally exposed to cocaine had deficits in their ability to sustain attention on a computerized vigilance task. Similarly, Bandstra [8] reported a stable cocaine-specific effect on indicators of sustained attention processing in the early childhood years. Bandstra's results indicated a gradient of influence, with each standard deviation increase in the level of prenatal cocaine exposure relating to a 16% standard deviation increase in omission scores at age 7. Interestingly, the results contrast with our study results in two ways. Cocaine-associated problems were greater among children whose mothers had concomitantly used alcoholic beverages heavily during pregnancy, and there was no gender difference in the strength of the association between prenatal cocaine exposure and attention task performance over time.

A recent systematic review of 36 selected studies by Frank et al. [28] concluded that no independent cocaine effects have been shown on standardized parent and teacher reports of child behavior scored by accepted criteria. These authors noted that experimental paradigms and novel statistical manipulations of standard instruments do suggest an association between prenatal cocaine and decreased attentiveness and emotional expressivity, as well as differences on neurophysiological and attention/affective findings. Many of the studies included in the review had small sample sizes and lacked the statistical power necessary to detect a cocaine effect, particularly with designs that require control for numerous confounders and risk factors, while other studies had low follow-up rates [52]. However, some large studies with significant results were excluded from the systematic review because they did not meet the stringent inclusion criteria [28].

Our finding of an independent effect of prenatal cocaine exposure in the absence of alcohol intake during pregnancy

in girls suggests that neurochemical pathways mediating the effects of both prenatal alcohol and cocaine may be shared and saturable. Fetal exposure to alcohol and cocaine simultaneously has been hypothesized to produce synergistic effects on cocaine's actions on the dopamine transport site [47,54]; however, such a synergism on CBCL scores was not observed in the current study. An alternative hypothesis is that the measurable effect of prenatal alcohol or cocaine exposure, i.e., altered behavior is the final expression of alterations in different neurochemical pathways which may be differentially affected by the two exposures; however, no data are available to address this hypothesis.

Gender differences in behavioral and neurochemical response to prenatal exposure have been reported [23–25,41], though little systematic work has been done to date on the mechanism for such differences. Differences in neuroendocrine systems as well as neurotransmitter systems, including the serotonin system, have been identified in male and female pre-weanling rats [25]. For example, estrogen may be influential in aspects of the genetic expression of enkephalin, a neuropeptide involved in D_2 dopaminergic receptor systems that are potentially critical to some of the behavioral profiles observed in cocaine-exposed animals [41]. Cocaine administration to rat pups in the 1st or 2nd postnatal week (corresponding to later third-trimester gestation in humans and a period of rapid synaptogenesis) is associated with widespread increase in glucose metabolic activity across several different regions of the brain, including cortex, but with particular increases in regions that are highly innervated by dopamine. These effects were most dramatic in the female adult rats. For both fetal and adult male rats, there were no substantial areas of increased metabolism, and the nucleus accumbens continued to show decreased activity as was true prenatally. Moreover, female rats remained sensitized to subsequent cocaine doses; sensitization was not seen, however, in males [24].

The CBCL was the instrument used in this report for assessing childhood behavior. However, similar effects were observed from this cohort when teachers were asked to rate the child's behavior [7]. Caregivers are usually the most knowledgeable about their child's behavior across time and situations [2]. Caregiver involvement is required in the evaluation of most children, and caregivers' views of their children's behavior are often crucial in determining what will be done about the behavior. The CBCL has a screening sensitivity of 61% [10]. In their two-phase epidemiological survey of 4- to 16-year-old Puerto Rican children, Bird et al. [10] reported that parent information was most informative in screening for childhood psychopathology. In the first stage of their study, the CBCL was used as a screening instrument and child psychiatrists evaluated children clinically during the second stage. Similarly, Verhulst and van der Ende [58] reported substantial agreement between CBCL scores and clinical severity ratings of psychopathology by psychiatrists for 14-year-old children. Agreement was higher for externalizing than for internalizing behaviors. The correlation coefficient between the CBCL total problem score and the psychiatrists' rating of the severity of problem behaviors was 0.63. In the present study, the CBCL raw scores were used for the ANOVA and linear regression analysis while *T* scores were used for categorical analyses. The raw scores directly reflect differences between individuals without any truncation or transformation and hence have greater statistical power [2]. Statistical analyses using *T* scores yields similar results as raw score analysis with less power and have the added ability of distinguishing between scores in the normal range compared to those in the clinical range.

Predicting the relation between prenatal cocaine exposure and child behavior is complicated by multiple prenatal, neonatal and family/environmental factors as well as the accuracy of the measure of exposure. Thus, it is important to control, either by design or statistical analysis, for the large number of confounding variables. If it is known that a particular risk factor for the disease under investigation is unrelated to the exposure of interest, then the risk factor can be ignored without biasing the results [37]. In our study, socioeconomic status, the home environment, maternal psychopathology and exposure to violence were similar across the two prenatal cocaine exposure categories and were excluded from the final analysis. However, prenatal cigarettes, custody status and custody changes, paternal use of drugs at conception, maternal age, and current use of drugs by the primary caretaker were controlled by entering them as covariates in regression analysis. Perinatal marijuana exposure was not entered as a potential confounder because it was unrelated to outcome of interest; this was similar to the findings reported by Singer et al. [53]. The inclusion of control variables unrelated to the developmental outcome is likely to increase the error term, making it more difficult to detect significant toxic effects [33]. For these analyses, birth weight and gestational age were not treated as confounders as they are more appropriately regarded as mediators of cocaine on neurobehavioral outcomes and their treatment as a confounder would potentially reduce the effect of the exposure [33]. In this study, current drug use did not predict the caregiver's report of the child's behavior problems. This is in agreement with finding from Richardson et al. [48].

There are, of course, limitations to this study. First, the subjects were limited to one ethnic group from primarily low socioeconomic status, potentially limiting generalizability. Second, the women enrolled in this study voluntarily sought prenatal care and were available for follow-up. Thus, the results may not be relevant to women whose alcohol and drug use interfered with access to prenatal care. Of the original cohort, 6% refused the evaluation at 6 years and an additional 6% missed multiple appointments and were not included. While no neonatal differences were detected between the children who participated and the group refusing further study, it is

possible that unmeasured differences exist between the sample studied and those lost to follow-up. In longitudinal studies, subject losses over time because of inability to trace, migration or refusal are inevitable [11]. The loss to follow-up may be of the magnitude of 20–30%. Another possible study deficiency is that some women who used cocaine may not have been identified by either interview or urine assay leading to misclassification. This means the results of this study may represent a low estimate of the effects of prenatal cocaine exposure on child behavior. Finally, though an extensive list of possible risk factors was considered in the regression analysis, it is possible that other unmeasured factors may account for the observed differences by alcohol exposure group.

Even after control for other well-known social/environmental variables, the effects of prenatal cocaine exposure remain significant in predicting child behavior in girls without prenatal alcohol exposure. The amount of variance uniquely accounted for by prenatal cocaine exposure in the present study was 6.5%. Other factors that were predictors of childhood behavior in the adjusted analysis were paternal drug use at conception and current alcohol use by the primary caretaker.

The present study had several advantages which may have increased the likelihood of detecting significant drug effects including a large relatively homogenous sample, use of biologic markers to verify exposure status, control in study and statistical design for covariates, prospective case identification, assessments by research assistants masked to prenatal exposure status, longitudinal follow-up, and comparability of those who were unable to be contacted for study participation.

5. Future directions

The findings of the present study as well as those reported by Bailey et al. [7], using the teacher report form emphasize the need for collection of longitudinal data to follow the evolution of the manifestation of effects of prenatal exposures in offspring and to replicate these findings. The manifestations of prenatal cocaine exposure are likely to change with the development of the child and are probably different in adolescents. Previous studies have shown that children prenatally exposed to cigarettes are prone to cigarette use during adolescence, with the effect being much stronger for females [35]. It would be critical to explore the use of cocaine and other substances by this cohort of children as they enter adolescence.

6. Conclusions

Prenatal cocaine exposure was associated with adverse behavioral outcomes on caregiver-reported child behavior in girls without prenatal alcohol exposure in this large African American socially disadvantaged sample. After control for covariates, these girls had higher mean scores on Aggression accounting for 6.5% of unique variance in the scores. On binary logistic regression, girls without prenatal alcohol exposure had an odds ratio of scoring in the clinically abnormal range for Aggression of 17 times control levels (95% confidence limits 1.4 to 203). In boys, a trend of increasing CBCL scores for Delinquent with any prenatal cocaine exposure was observed in the presence of prenatal alcohol exposure; however, this relationship was not significant on regression analysis.

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