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Level of In Utero Cocaine Exposure and Neonatal Ultrasound Findings

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Abstract

Objective—To assess whether there is an association between the level of in utero cocaine exposure and findings on neonatal cranial ultrasound, controlling for potentially confounding variables.

Study Design—In a prospective longitudinal study, three cocaine exposure groups were defined by maternal report and infant meconium assay: unexposed, heavier cocaine exposure (>75th percentile self-reported days of use or of meconium benzoylecogonine concentration) or lighter cocaine exposure (all others). Neonatal ultrasounds from 241 well, term infants were read by a single radiologist who was masked to the exposure group.

Results—Infants with lighter cocaine exposure did not differ from the unexposed infants on any ultrasound findings. After controlling for infant gender, gestational age, and birth weight *z* scores and for maternal parity, blood pressure in labor, ethnicity, and use of cigarettes, alcohol, and marijuana during pregnancy, the more heavily cocaine-exposed infants were more likely than the unexposed infants to show subependymal hemorrhage in the caudothalamic groove (covariate adjusted odds ratio: 3.88; 95% confidence interval: 1.45, 10.35).

Conclusions—This is the first study to demonstrate that ultrasound findings suggestive of vascular injury to the neonatal central nervous system are related to the level of prenatal cocaine exposure. Inconsistency in previous research in identifying an association between prenatal cocaine exposure and neonatal cranial ultrasound findings may reflect failure to consider dose effects.

Whether in utero cocaine exposure among term infants is associated independently with a higher risk of brain lesions visible on perinatal ultrasound is not clearly established. Dixon and Bejar[1] reported a sevenfold increase of ultrasound lesions in general and a twofold increase of subependymal hemorrhage in the caudothalamic groove at the level of the head of the caudate when term, African-American, cocaine-exposed infants were compared with Hispanic unexposed infants. These findings were partially confirmed by others in samples of unspecified ethnicity.[2,3] Investigators working with predominantly African-American samples have not found increased risk of any ultrasound findings associated with in utero cocaine exposure.[4–7]

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Women who use cocaine during pregnancy are more likely (than those who do not) to use cigarettes, alcohol, marijuana, and other illicit drugs[8] that also may be associated with ultrasound-detected lesions.[9] None of the studies correlating cocaine exposure with neonatal ultrasound-detected lesions have controlled for more than one of these substances;[1–3] therefore, misattribution to cocaine of the effects of other psychoactive substances has not been ruled out.

Before perinatal cocaine use became epidemic, Hayden and colleagues[10] noted that nearly 5% of clinically well, term infants show sonographic abnormalities, of which subependymal hemorrhage in the caudothalamic groove is the most common. Vaginally delivered, small for gestational age, African-American infants were at greater risk for these lesions in that sample. Because illegal drug use during pregnancy is detected disproportionately by clinicians among African-American women[11] and often is associated with infants who are small for gestational age,[12] an increase in lesions associated with cocaine use is difficult to interpret without controlling for ethnicity and birth weight for gestational age.

Finally, the issue of possible effects of the level of prenatal cocaine exposure has emerged recently in work demonstrating a dose-response relationship of heavier exposure to less optimal neonatal anthropometric parameters and infant behaviors.[13–17]

The goal of the current analysis was to assess whether there is an association between the level of in utero cocaine exposure and findings on neonatal cranial ultrasound, when potentially confounding variables are controlled statistically.

Methods

Sample Selection Criteria

The Human Studies Committees of Boston City Hospital (now Boston Medical Center) and of the Boston University School of Medicine approved this study. The sample was recruited by trained interviewers and recruiters who screened maternity and nursery records 7 days a week on the postpartum floor of Boston City Hospital from October 1990 to March 1993. Unexposed dyads, roughly comparable to cocaine-exposed mother–infant dyads in ethnicity (African-American/African Caribbean versus other), were approached preferentially for recruitment soon after delivery. All mother–infant dyads met the following criteria, based on review of mother and infant medical records, confirmed by interviews, biologic markers, and infant physical examinations obtained by study personnel: 1) infant gestational age ≥36 weeks; 2) no requirement for neonatal intensive care; 3) no obvious major congenital malformations; 4) no diagnosis of fetal alcohol syndrome in the neonatal record or on physical examination; 5) no history of human immunodeficiency virus seropositivity noted in the medical record of the mother or infant; 6) maternal ability to communicate fluently in English; 7) no indication by neonatal or maternal urine toxic screen or medical history of maternal use during pregnancy of illegal opiates, methadone, amphetamines, phencyclidine, barbiturates, or hallucinogens; 8) mother ≥18 years of age.

These criteria were established to exclude infants with known major risk factors that might confound or obscure the effects, if any, of in utero cocaine exposure. The sample was restricted at recruitment to mothers with English fluency, because many of the neuropsychologic measures planned for the cohort of infants at preschool and older ages are not standardized for populations whose first language is not English. Additional details about sample characteristics and recruitment are reported elsewhere.[17]

Method of Exposure Classification

Mothers participating in the study were identified as lighter users, heavier users, or nonusers of cocaine. They were identified both by interview and by biologic markers that were obtained by clinicians and study personnel. At intake on the postpartum floor, research assistants, using the Addiction Severity Index[18] (supplemented by study-specific questions), interviewed the mothers about pregnancy and lifetime use of cigarettes, alcohol, and illicit drugs. We sought to collect meconium specimens from all enrolled infants to be analyzed by radioimmunoassay for benzoylecgonine (a cocaine metabolite), opiates, amphetamines, benzodiazepines, and cannabinoids. The radioimmunoassay used was a modification of the method of Ostrea, published in detail elsewhere.[14,19]

At Boston City Hospital during the period of study recruitment, urine testing for metabolites of illicit drugs was not universal but was performed for clinical indications at the discretion of health care personnel. We documented, when available in the medical record, urine drug enzyme-multiplied immunoassay technique results obtained for clinical purposes during prenatal care or labor and delivery from mother or infant. In addition, after recruitment and informed consent, we collected additional urine samples from study mothers for research purposes for analysis for benzoylecognine, opiates, amphetamines, benzodiazepines, and cannabinoids by radioimmunoassy using commercial kits (Abuscreen RIA; Roche Diagnostics Systems, Inc, Montclair, NJ).

Subject Exposure Classification

All mother–infant dyads, exposed or unexposed, had at least one biologic marker (urine from mother or infant obtained clinically or for research purposes or meconium) that confirmed their exposure or lack of exposure to cocaine during pregnancy. In this sample, the mean days of self-reported cocaine use during pregnancy was 20.6 days with a range from 0 to 264 days. The mean meconium concentration was 1143 ng of benzoylecognine to 1 g of meconium, ranging from 0 ng to 17 950 ng/g. Before data were analyzed, a composite measure of heavier use was defined apriori as the top quartile of meconium concentration for cocaine metabolites (>3314 ng of benzoylecognine to 1 g of meconium) and/or the top quartile days of self-reported use (>61 days) during the entire pregnancy. All other use was classified as lighter.[14,17]

Pragmatic as well as scientific considerations influenced this either/or definition of exposure level. Women are more likely to underreport rather than to overreport illicit substance use during pregnancy.[8,19] Therefore, we decided *apriori* that women reporting days of use in the top quartile should be considered heavier users, even if the benzoylecognine levels in meconium were not in the top quartile. Not all infants exposed to cocaine in utero have positive meconium assay results.[19] Moreover, we were not able to obtain meconium samples from 14% of study infants. Therefore, whichever indicator (self-report or meconium assay) demonstrated higher exposure was used to define exposure category.

Physical Examination and Record Review

Within 8 to 72 hours (mean: 48 hours), a study pediatrician, trained to reliability and unaware of exposure status, assessed the infant's gestational age according to the method of Dubowitz et al[20] and measured recumbent length and head circumference. After performing the physical examination, the pediatrician reviewed the infant's neonatal record for birth weight (documented after delivery by nursery nurses on a Detecto scale) and neonatal complications using a list adapted from the Hobel Index.[21] A trained research assistant abstracted the mothers' medical records to document the prepartum, intrapartum, and postpartum Hobel Risk Indices for the mothers.[21] The two categories of increased blood pressure during pregnancy and during labor were loosely defined to include physician notation of eclampsia or preeclampsia in the medical record, as well as a documented increase over baseline of diastolic blood pressure of

15 mm and of systolic blood pressure of 20 mm (a definition clinically in use when the study began in 1990).[22] Those categorized by these criteria showing increased blood pressure in labor had maximum average systolic blood pressures during labor of 153 mm (standard deviation [SD]: 18) and diastolic of 89 mm (SD: 12), compared with 133 mm (SD: 16) and 78 mm (SD: 10) among those not so categorized ($P = .00001$).

Ultrasound Methods

Within the first 72 hours of life, real time cranial ultrasounds were performed using Advanced Technology Laboratories Ultramark 4 or Ultramark 8 equipment with a 7.5-MHz transducer. Using the anterior fontanel as the acoustic window, 12 sequential images were obtained from anterior to posterior in the coronal plane. In the sagittal plane, images were obtained in the midline with 5 to 6 parasagittal images on each side from just adjacent to the midline to the Sylvian fissure. One axial view was obtained. There were no images through the posterior fontanel.

In reading cranial ultrasounds, note was made of any variation from the normal echotexture, as well as any asymmetry no matter how subtle. Using these study-specific criteria, a single radiologist (K.M.M.), who was unaware of exposure history, read all 241 ultrasounds and coded them in standard format. Using the same criteria, a second radiologist (C.D.R.) who was unaware of exposure history and of the readings of the first radiologist independently coded 40 ultrasounds that were selected randomly from the total sample of 241. Percent agreement for subependymal cysts was 88%, and percent agreement for caudothalamic groove subependymal hemorrhages was 85% with a κ of .68. ($P < .001$) for both. For linear echodensities in the basal ganglia, percent agreement was 80% with a κ of .4 ($P < .04$). The readings of the first radiologist were used in the analysis.

Statistical Methods

Associations of potentially confounding variables with the three categories of cocaine exposure (none, lighter, and heavier) and with selected ultrasound findings were evaluated by one way analysis of variance for continuous variables and χ^2 and Fisher's exact test for categorical variables. Multiple logistic regression analyses to control for potential confounding variables were performed if a bivariate association by χ^2 and Fisher's exact test was found between the category of cocaine exposure and the ultrasound finding. In these analyses, in utero cocaine exposure was modeled as 2 dummy variables: heavier exposure versus none and lighter exposure versus none. Choice of covariates reflected both theoretical and statistical considerations. Maternal parity, infant gender, gestational age, and birth weight *z* score for gender were included because of their importance in other studies of ultrasound findings in term infants.[10] Prenatal exposure to cigarettes, marijuana, and alcohol were included as covariates in the final model because they were germane to the research question of the present study. Other covariates were included in the final model if their inclusion one at a time altered the unadjusted association between cocaine exposure and outcome by >10%.

Results

Sample Characteristics

Of the 252 infants enrolled, 241 underwent ultrasound evaluation. The 11 infants who were not evaluated (because of logistic reasons such as early discharge or malfunctioning equipment) were exposed to a lower average daily volume of alcohol in the 30 days before delivery than were those who were evaluated (.002 vs .22; $P < .001$) but did not differ in level of cocaine exposure or in any other obstetric or demographic characteristics.

Table 1 shows that unexposed women were more likely to be primiparous. The three exposure groups did not differ significantly ($P < .05$) in ethnicity. Table 1 also shows that during the index pregnancy, women who were heavier users of cocaine were more likely than light users or nonusers to use marijuana, cigarettes, and alcohol. Despite selection criteria, which limited the sample to well term or near term infants, cocaine-exposed infants had a slightly lower gestational age than did unexposed infants. As the level of cocaine exposure increased, all anthropometric parameters, standardized for gender, decreased. There were no significant differences among the three groups in rates of cesarean sections, positive Venereal Disease Research Laboratory tests or in the proportion of those with clinically important elevations of blood pressure noted during pregnancy or delivery. The infants from the three groups did not differ in gender or 5-minute Apgar scores.

Because study exclusion criteria restricted this sample to clinically healthy newborns, some established correlates of neonatal ultrasound abnormalities in term infants, such as breech (4%), forceps or vacuum delivery (1%), infant polycythemia (0.5%), and hypoglycemia (4%),[23] were too infrequent to analyze.

Ultrasound Findings—There was no significant difference in total number of ultrasound findings among the groups. The most frequently encountered ultrasound findings were subependymal cysts, linear echogenic foci in the basal ganglia, and caudothalamic subependymal hemorrhage. The frequency of subependymal cysts did not differ among the groups (none: 21%; lighter: 16%; heavier: 24%; $P = .47$). In bivariate analyses, cocaine exposure was associated significantly in a dose-related manner ($P < .05$) with decreased likelihood of linear densities in the basal ganglia (none: 12%; lighter: 5%; heavier: 2%), but this effect was no longer found after control of covariates. In contrast, higher cocaine exposure was associated with increased likelihood ($P = .005$) of caudothalamic groove subependymal hemorrhage in both bivariate (none: 24%; lighter: 22%; heavier: 47%) and multivariable analyses. Elevated blood pressure during labor and African-American/African Caribbean ethnicity were associated significantly in bivariate analysis with caudothalamic groove subependymal hemorrhage. The overall Hobel risk scales were not associated with these findings. Table 2 shows the odds ratios for subependymal hemorrhage in the caudothalamic groove by level of cocaine exposure, controlling for these and other potential confounders. This analysis indicates that the increased risk for subependymal hemorrhage at the level of the head of the caudate resides in the most heavily (top quartile) cocaine-exposed infants, whereas the more lightly exposed infants do not differ from the unexposed infants. There was no interaction effect found on subsequent analyses between the level of cocaine exposure and elevated blood pressure in labor or between level of cocaine exposure and maternal ethnicity on risk of subependymal hemorrhage in the caudothalamic groove (our analyses are available by request).

Discussion

This is the first study to show in multivariable analyses ultrasound changes suggestive of vascular injury to the central nervous system related to the dose of prenatal cocaine exposure. The inconsistency in other research in identifying prenatal cocaine effects on neonatal cranial ultrasound findings may reflect lack of consideration of possible dose effects. If we had analyzed prenatal cocaine exposure only as present or absent, we would have found no significant difference between exposed and unexposed groups on subependymal hemorrhage in the caudothalamic groove ($P = .26$) or on any other ultrasound findings.

Our definition of dose, using a composite of self-report and meconium concentration of cocaine metabolite and using top quartile levels of either to define heavy exposure, should be interpreted as a heuristic rank ordering of exposure rather than as a precise determination of threshold and

dose response. This definition does not address the issue of timing of exposure by pregnancy trimester or peak exposure on a single occasion. Our subjects were all recruited after delivery, so timing of cocaine use by pregnancy trimester could not be confirmed by biologic markers and was not used in the analysis. Meconium is still a controversial medium for measuring cocaine exposure, because, in clinical settings, the cocaine concentration may be altered by admixture of infant urine, which contains cocaine metabolites from recent maternal use. Moreover, in this sample, we analyzed a sample from a single stool of each infant, which may be less accurate than analysis of the infant's pooled output of meconium.[19] In contrast to cocaine, marijuana metabolites are deposited preferentially in maternal fat and are not found consistently in meconium, even when there is positive self-report of use.[19] Therefore, our findings must be interpreted with caution with regard to marijuana, because we are able to classify infants only as exposed or unexposed without estimating dose.

Concerns may be raised that the data reported here represent overreading because of the high rates of findings, such as subpendymal cysts and linear echodensities, found in all study groups. Criteria for identifying ultrasound echodensity or echolucency in a term infant as a lesion may differ among settings. The lack of scientific consensus on ultrasound reading criteria for term infants of various ethnicities does not invalidate our finding of cocaine dose-related differences among groups in this sample, because ethnicity was controlled. In this study, a single radiologist, who was unaware of the cocaine exposure status and ethnicity of the infant, read all ultrasounds by uniform criteria that were more stringent in noting any variation from normal than are those used in clinical settings. These criteria, established for research purposes, were able to be applied reliably in ultrasound readings by a second radiologist. They are available from the authors on request. More stringent reading criteria than those applied in usual clinical practice may account for an apparently higher incidence of findings in all subjects than in other, more clinically based, studies. Although the absolute incidence of ultrasound findings differ between this study and others, these data, nevertheless, are consistent with those of Hayden et al,[10] which show that apparently healthy African-American/African Caribbean term infants have higher rates of subependymal hemorrhage at the level of the head of the caudate than do infants of other ethnic groups. We do not know what unmeasured variables may account for the apparent association of prenatal cocaine exposure and lower rates of linear echodensities in the basal ganglia, which are thought to represent a nonspecific mineralizing vasculopathy, associated with multiple possible etiologies.[24,25] The effect is statistically marginal and does not persist after control for covariates measured in our sample. King et al[6] also reported that infants, who were not exposed to cocaine, manifested increased ultrasound findings, other than subependymal hemorrhage, compared with cocaine-exposed infants.

The finding of a relationship between high dose in utero cocaine exposure and subependymal hemorrhage, but not subependymal cysts, suggests a biologically plausible mechanism of effect that occurs close to delivery. Subependymal cysts that are present at birth may reflect in utero viral or bacterial infection or represent liquefaction over weeks to months of a previous hemorrhage.[26–27] In contrast, subependymal echodensities in the caudothalamic groove on ultrasound are thought to represent hemorrhages that have occurred within hours or days of the ultrasound study. We speculate that, because of the well described recurring vasoconstrictive effects of cocaine on maternal and fetal circulation,[28] infants exposed heavily to cocaine may show less adaptive vasoregulation in response to the hypoxic–ischemic stress of labor, especially when the stress is increased by elevated maternal blood pressure.

The long-term functional implications of these findings for children exposed heavily to cocaine remain to be determined. Similar neonatal ultrasound lesions are not associated with increased risk of cerebral palsy or mental retardation in preterm infants;[29] more subtle neurobehavioral outcomes have not been assessed. Research with this cohort is continuing into primary school to ascertain whether there are long-term behavioral and cognitive correlates of subependymal

hemorrhage in the caudothalamic groove in term infants with and without in utero cocaine exposure.

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Abbreviation

SD

standard deviation

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TABLE 1

Maternal Parity, Ethnicity, and Psychoactive Substance Use in Pregnancy and Infant Gestational Age and Size by Level of Cocaine Exposure

	Exposure to Cocaine			
	Nonuse ***n*** **= 109**	**Lighter** ***n*** **= 87**	**Heavier** ***n*** **= 45**	***P***
Primiparous	44%	28%	33%	.05
African-American/African Caribbean	91%	82%	84%	.16
Marijuana use	8.00%	35.00%	38.00%	.001
Average daily cigarettes*	0.51 (1.57)	3.22 (2.24)	6.5 (1.96)	.001
Average daily volume of alcohol (oz)*	0.002 (0.01)	0.14 (0.48)	0.37 (0.90)	.001
Mean Dubowitz gestational age (wk)*	40.3 (1.1)	39.8 (1.3)	39.8 (1.1)	.012
Birth weight *z* scores for gender*	0.21 (1.11)	−0.41 (0.90)	−0.65 (0.97)	.0001
Length *z* scores for gender*	−0.37 (0.93)	−0.91 (0.91)	−1.37 (1.10)	.0001
Head circumference *z* scores for gender*	0.02 (1.03)	−0.41 (1.05)	−0.74 (1.00)	.0001

* Mean (SD).

TABLE 2

Logistic Regression: Covariate Adjusted Odd Ratios of Subependymal Hemorrhage in the Caudothalamic Groove Following Heavy In Utero Cocaine Exposure (n = 227)*

Model P = .01	**Odds Ratio**	**95% CI**	***P* Value**
Heavier vs unexposed	3.88	1.45, 10.35	.007
Lighter vs unexposed	1.16	0.51, 2.63	.72
Marijuana use	0.66	0.28, 1.56	.34
Log, average daily cigarette	0.94	0.68, 1.29	.7
Log, average daily volume alcohol	1.04	0.43, 2.52	.94
African-American/African Caribbean	3.05	0.92, 10.17	.07
Birth weight z score for gender	0.93	0.67, 1.28	.66
Female	0.72	0.39, 1.38	.33
Dubowitz gestational age (wk)	0.98	0.74, 1.31	.92
Increase BP during labor	3.12	1.30, 7.48	.01
Primiparous	1.28	0.67, 2.46	.45

* Fourteen subjects were omitted because of missing data (blood pressure in labor and other covariables).