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Prenatal Cocaine Exposures and Dose-Related Cocaine Effects on Infant Tone and Behavior

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Abstract

Background—In experimental models, prenatal cocaine exposure has been found to perturb monoaminergic development. In humans, numerous studies have sought clinical correlates, but few have focused on dose-related effects, especially as regards neurologic function beyond the neonatal period.

Objective—To assess whether prenatal cocaine exposure has adverse effects on infant neurologic, developmental and behavioral outcomes and whether any effects are dose-dependent.

Design/Methods—Infants (398) were enrolled at birth from an urban hospital. Drug exposure was ascertained with biomarkers in hair (n=395), urine (n=170) and meconium (n=109). Children were followed prospectively and 286 (72%) were evaluated blind to drug exposure at 6 months of age with the Bayley scales, Fagan Scale of Infant Intelligence and a standardized neurological examination.

Results—Certain neurological findings increased significantly by the amount of cocaine detected in maternal hair, e.g. abnormality of tone, as indicated by extensor posture was detected among 28% of cocaine-unexposed infants, 43% of infants exposed to lower and 48% exposed to higher cocaine levels in maternal hair ($p<0.009$). Persistent fisting increased in a similar dose-dependent manner. These associations persisted in adjusted analyses. Prenatal cocaine exposure was not

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associated with developmental scores (mental, motor or novelty preference) but was associated with lower orientation scores in adjusted analyses.

Conclusions—At 6 months of age, prenatal cocaine exposure was associated with abnormalities of tone and posture and with lower orientation scores. Perturbations in monoaminergic systems by cocaine exposure during fetal development may explain the observed neurological and behavioral symptoms. Whether such findings in infancy increase the risk of later neurobehavioral problems requires further study.

Keywords

perinatal; cocaine exposure; drug use; hypertonia; child development

INTRODUCTION

Although cocaine use has declined since the height of the epidemic in the 1980's, it remains a major public health problem in urban centers in the United States, where a high level of use continues. Earlier studies of *in utero* cocaine-exposed infants, which exaggerated risks to exposed offspring, were limited by lack of controlled analyses and by the lack of biological markers that quantified exposure in a cumulative manner (i.e. meconium or hair analyses). Over the last 10 years numerous controlled studies have identified developmental and behavioral differences associated with prenatal cocaine exposure. Developmental delays linked with prenatal cocaine exposure have included cognitive differences (1;2) and language delays (3;4). Motor delays are the most consistently reported finding among cocaine exposed children (5), with (6;7)prenatal cocaine exposure predicting poorer fine motor development skills at age 2, particularly in hand use and eye-hand coordination (5). Others, however, have failed to identify developmental or cognitive effects associated with prenatal cocaine exposure after controlling for confounders (8–13).

From a behavioral perspective, a convergence of experimental and clinical studies suggest that prenatal cocaine exposure disrupts the development of arousal and attention (14). Cocaine-exposed (15)infants exhibit a preference for higher rates of stimuli (15) excessive irritability (14) and dose-related perturbations in orientation and state regulation (16). Exposed toddlers and grade school children show differences in task persistence and sustained attention (17–20), problems with impulse control (21), temperamental differences (22), and aggressive/hyperactive behaviors (23–25).

A handful of studies have prospectively assessed neurological function among cocaine-exposed children beyond the newborn period (26–29) and even fewer have quantified fetal exposure (27;30). Lewis et al describe higher rates of a suspect or abnormal neurological examination among cocaine exposed toddlers, but the authors did not further define the nature of neurological abnormalities (27;28). Other have described muscle tone abnormalities, hypertonia in particular, among cocaine-exposed infants and toddlers (27;27–31). We described hypertonia among infants at risk for HIV with cocaine exposure that resolved by 24 months (28), but were unable to control for confounding exposures, especially tobacco exposure, which has been linked to hypertonus (32).

The current study was designed to assess the effect of cocaine exposure on neurological, developmental and behavior outcome. The primary hypothesis was that children with prenatal cocaine exposure would exhibit higher rates of neurological, developmental and behavioral impairments compared to cocaine-unexposed children of comparable demographic background after controlling for confounding factors. We also hypothesized that risks would be dose dependent with higher rates of abnormalities observed with higher levels of cocaine exposure. We report on the neurologic, developmental and behavioral outcomes of infants enrolled prospectively at delivery in a longitudinal study, in whom prenatal exposure to cocaine and other drugs of abuse was determined at the time of birth with multiple biomarkers.

2. METHODS

Participants

Beginning in May 2000 through November 2004 we prospectively enrolled women-infants dyads from a municipal New York City hospital at the time of delivery as part of a prenatal drug exposure study. Informed consent was obtained at the time of enrollment. The study was approved by the Columbia Institutional Review Board. Women were eligible if English speaking, non-HIV infected, and had no history of intravenous drug abuse, psychosis or bipolar disorder (as determined by chart review). Infants were eligible if > 33 weeks gestational age, free of major congenital malformation and birth asphyxia (5 minute Apgar > 4). As we were recruiting at the time of delivery, enrollment was confined to a narrow window of opportunity that was contingent on maternal health (i.e. postpartum complications) and early discharge, as well as to staff absences due to vacation or illness. Hence, of women delivering at the hospital (n=3671), we approached 2308 : 675 were eligible and 1633 were ineligible primarily due to language constraints (non-English speaking).

Of eligible women approached for enrollment (N=675), 277 refused. We enrolled 398 women-infant dyads (59%) into the study; of these, two were excluded due to medical factors (HIV and Trisomy 21) and 16 withdrew from the study. The final cohort thus comprises 380 mother-infant pairs. We excluded 10 opiate-exposed children from the controlled analyses.

To assess whether our sample was representative of the targeted population, we compared the group that refused enrollment to our group of enrollees via chart review. Among offspring, we found no differences in gender, birth weight, birth length, or type of delivery (vaginal versus cesarean section) between groups (data not shown). Women who refused enrollment, however, were approximately a year and a half older (25.8 yrs ± 6.6) than women enrolled in the study (24.2 yrs ± 5.8, p=.007).

Procedures

Women were interviewed soon after delivery with a structured protocol that inquired about demographic information, obstetrical and medical history and drug use during and prior to the index pregnancy. The instrument, developed by Kline et al has proven sensitive in quantifying reported drug use during pregnancy (30;33;34). Women were also administered

an IQ test and a depression scale. Biological markers of drug exposure were obtained at time of delivery (hair in all, meconium and urine in a subset).

Women and their infants were invited for follow-up at 6 months of age for neurological and developmental assessment. Two hundred and eighty six infants (75% of those enrolled) were brought in for their 6-month assessment. Of these, 276 were accompanied by their biological mothers, four were accompanied by biological fathers, five by grandmothers and one by a foster mother. Comparisons between those who returned for the 6 month follow-up visit (n=286) and those who did not (n=94) revealed no significant differences in maternal age, race, education, welfare status, marital status, gravity, parity, ectopic pregnancies, stillbirths, alcohol, marijuana or cigarette use (data not shown). Women who did not return were more likely to have used cocaine during pregnacy (42% vs. 28%; p=.005) and to be unemployed (62% vs. 46%; .002) compared to women who returned for the 6 month follow-up.

Measures

Maternal—Caregivers were administered an IQ test that relied upon the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) (35). Because of concerns about the suitability of the measure for use among women soon after delivery, we tested all mothers at enrollment and re-tested biological mothers at the 6 month follow up to obtain a more reliable assessment. Testers were trained by the study psychologist (GW). Reliability between maternal IQ obtained at delivery and at 6 months was high (intraclass correlation coefficient (ICC) r = .88). Our analyses use IQ from the 6-month assessment for 254 biologic mothers. For the remaining 21 infants for whom the 6-month assessment of maternal IQ was unavailable, we used the post-delivery assessment. This includes 13 biological mothers for whom the 6-month IQ basal level was improperly assessed (i.e. testers did not administer previous required items when respondent failed first two consecutive items) and 8 mothers whose infants were accompanied to the 6-month visit by someone else.

At the 6-month visit, caregivers were administered a lifestyle questionnaire, the Center for Epidemiological Study-Depression Scale (CES-D) and the WASI test (35). Because of concerns for the safety our staff in carrying out home visits, we administered a version of the HOME scale (36) that was modified for use in the office following recommendations by Jacobson et al. (37). The modified HOME scale entailed devising a scripted conversation to cover mother-child activities but omitted items that require direct observation (e.g. toys observed in the home).

Biololologic markers—At the time of enrollment, we collected maternal hair samples (n=395) and used segmental hair analyses (proximal 3.9 cm of hair) for radioimmunoassay for metabolites of drugs used during the 3rd trimester (RIAH^{TM}), as this could be measured in all women. Short hair length limited our ability to assess first trimester exposure. No woman with a negative hair result for cocaine, reported using this drug during pregnancy. All tests positive for cocaine in urine and meconium were also positive for cocaine on hair testing. The concordance rate between reported cocaine use and biomarker findings was 74%. Of women who denied using cocaine during pregnancy, 28% had a positive biomarker for

cocaine; while of those testing positive for cocaine only 18% reported using cocaine or crack during pregnancy. Quantitative assays measured metabolites of cocaine, opiates, phenylcyclidine (PCP), amphetamines, and qualitative assays measured marijuana exposure. Hair samples were tested at Psychemedic Corp; Culver City, CA. Cutoff levels for drugs of interest were as follows: cocaine and metabolites, 5 ng/ 10mg hair; opiates, 2 ng/10mg; amphetamines, 5ng/10mg; PCP, 3 ng/10mg; and tetrahydrocannabinol, 2 ng/10mg. Maternal urine specimens were collected from 172 mothers; cutoff levels for cotinine and cocaine and its metabolites were 50 ng/ml for each drug.

We collected meconium in a subset of children for whom meconium specimens could be collected within the first 24 hours (N=109). Meconium cutoff levels for drugs of interest were as follows: cocaine and metabolites, 50 ng/g; opiates, 50 ng/g; amphetamines, 250 ng/g; PCP, 25 ng/g; and tetrahydrocannabinol, 40 ng/g. We also measured fatty acyl alcohol esthers (FAEE, ethanol metabolites, 500ng/g) in meconium. When processed at room temperature FAEE was susceptible to loss by evaporation, thus resulting in negative results early in the study. Subsequent specimens were frozen immediately. These efforts notwithstanding, FAEE correlated poorly with alcohol self-report (e.g. any history during pregnancy ($r = -.18$; $p=.08$), number of drinks during pregnancy ($r = -.12$; $p=.23$), and greater than 0.5 oz. of absolute alcohol AA ($r=-.14$; $p=.16$). Meconium and urine specimens were tested at MecStat Laboratories, Desplaines, IL.

Infant measures—At 6 months of age, children were administered the Bayley Scales of Infant Development II (38) (including the Behavior Rating Scale) and the Fagan Scale of Infant Intelligence (39) by staff trained by the study psychologist (GW). All 6 month assessments were administered by a single examiner. Neurological function at 6 months of age was assessed with the Neurological Examination of Children (40) by a single child neurologist (CAC). The NEC is based on the routine neurological examination (41) and was developed to assess tone and posture among HIV-infected children. Herein we analyzed tone and posture items that we identified as sensitive to cocaine-effects based on our previous studies. (28;30;42). All examiners were blind to exposure status.

Exposure ascertainment—Because of the exponential range of cocaine exposure measures in hair (5–3,764 ng/10mg hair; mean 31 ng/10mg), we used the log transformed (base 10) amount of cocaine metabolite quantified in maternal hair samples in statistical analyses to assess associations between prenatal cocaine exposure and infant outcomes. For quantitative analyses we grouped children into a cocaine unexposed (CU) group (n=206) if cocaine metabolites in maternal hair were below the threshold of detection (<5ng/10mg), a low cocaine exposure (CE1) group if metabolites were ≤1.5 log ng/10mg of hair (n=56) and a high cocaine exposure (CE2) group if metabolites were detected >1.5 log ng/10mg (n=27). The median log cocaine of exposure in CE1 group was 1 and the median of CE2 was 2. For dichotomous yes/no exposure data we classified exposure if any biological sample tested positive for cocaine at delivery (urine from infant or mother meconium). Cocaine measured in meconium was not used in quantified analyses because compared to maternal hair measures, meconium measures (n=107) had low sensitivity (11%) to detect cocaine.

Based on the delivery interview, we estimated alcohol intake from reported number of drinks per day or greater than 0.5 AA oz/day. FAEE measures were not used to control for alcohol exposure. Cigarette exposure was ascertained by biomarkers (cotinine) in meconium or maternal urine in 220 subjects (77%). Based on self-report and biomarkers exposure was defined as light (< 5 cigarettes/day or < 50^{th} percentile on biomarker) and heavy (≥ 5 cigarettes/day and ≥ 50^{th} percentile on biomarker). When discrepancies were noted between self-report and level of exposure found on toxicology, analyses were based on toxicology results, given maternal under-reporting of drug and cigarette use during pregnancy (30;43). Marijuana toxicology measures were qualitative. Heavier marijuana users were defined as those who tested positive on biomarkers or who reported using marijuana more than twice a week.

Statistics

Contrasts between cocaine-unexposed children (CU) and children exposed to low (CE1) and high (CE2) cocaine levels were determined by one-way analysis of variance for continuous variables and either the χ^2 test or Fisher's exact test for categorical variables. Stepwise multiple regressions were used to evaluate associations with cocaine exposure after adjusting for potential confounders. We excluded 10 opiate exposed children from all multivariate analyses. Covariates were selected on the basis of empirical and theoretical criteria. Using empirical criteria, from the pool of potential covariates, variables from Table 1 were retained in models when they differed significantly between exposure groups, were associated with a given outcome at $P \leq .2$, and were not highly correlated ($r > .70$) with other covariates. For theoretical reasons, birth weight, prematurity, alcohol, tobacco, and marijuana exposure were also used as covariates in least square models. Because of high levels of shared variance between different covariates and outcomes, covariates were removed from a model when they did not add significant variance to the model. The remaining covariates were included with the exposure effect of interest in linear regression models. Level of cocaine exposure was entered into the model at the final step to assess the impact of cocaine on overall mental, motor, novelty preference and behavioral scores while controlling for the other covariates.

We used logistic regression analyses to examine factors associated with neurological outcomes. Theoretical variables included in the initial model included birth weight, prematurity, child age, tobacco, alcohol, and marijuana exposure. Sociodemographic variables were not associated with neurological outcomes and were excluded from further analyses. Theoretical variables and variables that correlated with outcomes were entered into the initial model and were retained if associated with neurological outcome ($p < .2$). Level of cocaine exposure was included into the model last, either as ordinal exposure (level 0,1 2) or quantitative log cocaine hair.

Results

The cohort comprised a homogenous population of women, mostly African-American (90%) and of low socioeconomic status. The biological mother was the primary caregiver for 280 children at 6 months of age. Cocaine-using mothers were significantly more likely to be

unemployed, older and less educated (Table 1). Comparisons between the cocaine unexposed (CU) and each level of cocaine exposure (CE1 and CE2) showed higher rates of tobacco and alcohol use (Table 1). Comparisons of rates of marijuana exposure were similar between CU and CE1 and CE2 children.

Comparisons of cocaine-unexposed (CU) children with cocaine-exposure level (CE1 and CE2) children showed no differences in age, gender, z-scores of weight, height and head circumference at the time of the 6-month visit (Table 2). Cocaine-exposed children showed significantly lower birth weight, when compared to CU children. Differences in gestational age accounted for this association in controlled analyses.

Neurological outcomes

In univariate analyses, cocaine exposed children showed significantly higher rates of hypertonia, extensor posture, and persistent fisting compared to CU children; rates of tremor, excessive startle, microcephaly was not significantly different between CE and CU children (Table 3). The odds of hypertonia, extensor posture, and persistent fisting showed a significant increasing trend according to higher levels of cocaine exposure as compared to CU children (Table 4). After adjusting for potential confounders associations between level of cocaine exposure remained significant for extensor posture and persistent fisting (see footnote Table 4); while a trend was noted with hypertonia (p=.06). Cocaine-exposed infants were more likely to be unable to sit independently and to have poor prehensile skills compared to unexposed infants (Table 3). Association with not sitting remained after controlling for age and prematurity (i.e. corrected age) (OR=1.8 [95%CI 1.05–3.1]) but not for poor prehensile grasp [OR=1.6 [95%CI .96–2.7].

Developmental outcome

Novelty preference was unrelated to exposure with or without adjustment for maternal IQ, Apgar 5 minutes, marijuana exposure and infant head size z-score (F= 3.245; p=.0007; R^2 =. 061) (*P* = .84) (Table 5). Prenatal cocaine exposure was unrelated to Bayley mental development scores (MDI) with or without adjustment for significant factors (maternal IQ, HOME scale, and infant gender; F= 3.556; p=.008; R^2 =.051) (Table 4). Cocaine exposure was also unrelated to PDI scores, with or without adjustment for maternal IQ, high school education, age > 30 yrs, birth weight, marijuana and level of tobacco exposure (F= 3.687; p=.002; R^2 =.101) (*P* = .52; .6 PDI points; Δ R square .002).

Behavior (BRS)

Cocaine exposure was associated with differences in the Bayley Total Behavior Scale score in univariate analyses (p=.04) that remained significant upon adjustment with birth weight (*P* = .04; . −3.8 points; Δ R square .014). Level of cocaine exposure was also associated with significantly lower orientation scores in univariate analyses (p=.01), that persisted after controlling for significant covariates (maternal IQ and maternal age > age 30 ; F= 4.654; p=. 01; R^2 =.033) (*P* = .06;. −6.8 points; Δ R square =.013) (Table 5). Cocaine exposed infants received lower emotion scores (on the Bayley scales) than CU infants but findings were not significant in univariate (p=.12) or multivariate analyses (p=.37).

Children with abnormalities of tone and posture had significantly lower Bayley scale behavioral scores. Orientation scores were highly correlated with adverse neurological outcomes: hypertonia, rho = −.135 (p = .02) extensor posture, rho= −.145 (p = .015) and persistent fisting, rho= −.171 (p =.004).

DISCUSSION

We describe neurologic, developmental, and behavioral outcomes at age six months associated with prenatal cocaine exposure in an urban cohort in whom drug exposures have been carefully ascertained with a variety of biomarkers. Insofar as over 40% of women approached refused enrollment, our cohort may not be representative of the population at large. Comparisons, however, between enrollees and refusals showed no differences in mode of delivery, offspring gender, birth weight or birth length suggesting no significant bias in infants enrolled. Women refusing enrollment, however, were older than enrollees. Enrolled women who were lost to follow-up showed no sociodemographic differences when compared to women who were seen in follow-up, but were older and more likely to have used cocaine during pregnancy. Our study, thus, may have underestimated cocaine exposure and may be biased toward the null.

Misrepresentation of drug use is well documented during pregnancy (30;44) and has been ascribed to the stigma surrounding potential harm to the fetus and possible loss of infant custody to the authorities. In the present study, the number of women who denied using cocaine during pregnancy but had a positive biomarker result was comparable (28%), though slightly lower, to proportions obtained in a large recent study (38%) (44) and to a similar earlier study of ours (38%) that drew patients from the same population source, employed similar research protocol and identical pregnancy questionnaires and hair analyses. The main difference between these two studies is the lower mean level of cocaine measured (38 ng/10mg) in the current study compared to mean levels obtained over a decade ago (81 ng/10mg). It is possible that women in this cohort who are “light” users or use cocaine more sporadically are less likely to view themselves as “cocaine users” when questioned. As we ascertained cocaine exposure based on toxicology results, maternal misrepresentation of cocaine use will not affect magnitude of associations.

From the neurological perspective, we have identified abnormalities of tone and posture associated with cocaine exposure in a dose-dependent manner, that remained associated with prenatal cocaine exposure in analyses that adjusted for prematurity, birth weight, cigarette smoking and alcohol use during pregnancy. We reported similar dose-response associations with hypertonia and postural abnormalities in newborns (30), but in those analyses we were limited in our ability to control for cigarette exposure with biomarkers, which others have linked to hypertonia (32). Beyond the neonatal period Hurt et al. report no neurological findings associated with prenatal cocaine exposure in 30 month-old infants (10) while Belcher et al. described similar postural anomalies in this age group (29). In an earlier report, we also described high rates of hypertonia associated with prenatal cocaine exposure among children at risk for HIV infection (infected and seroreverters (exposed to maternal HIV but uninfected)) (28). Hypertonia peaked at 6 months and disappeared over the first 2 years of life. The present study, however, excludes children of HIV-infected mothers. The

lack of association between cocaine exposure and developmental scores found in this study has mirrored that found in other studies involving toddlers (8;13;45;46) and older children (9;12)

Behaviorally, cocaine-exposed infants have been described as exhibiting excessive irritability (14) and changes in both arousal modulation (15) and impulse control (21). The orientation behaviors tapped by the BRS are consistent with these findings. Several developmental studies using the BSID have failed to identify behavioral differences related to cocaine (46). Discrepancies across studies may be a function of the method of cocaine ascertainment, as other reports have not used hair analyses.

Hair analysis is an extremely sensitive marker of cocaine use over a period of time dependent on the length of hair analyzed (47).(34;48;49) There has been concern, however, that passive exposure to cocaine may lead to a false positive result for hair analysis. In order to distinguish between ingested cocaine and passive environmental exposure to the drug, the hair specimen is washed repeatedly (5 times) prior to analyses. Moreover, if there were any false positive results these would be equally distributed between the two groups and would thus decrease the magnitude of estimates (50). Meconium also provides a cumulative measure of exposure, yet in this study meconium was less sensitive than hair in detecting and quantifying cocaine exposure. Incomplete meconium collection or meconium staining at delivery (resulting in either absent or incomplete meconium collection) may have influenced the accuracy of this measure.

This study has strived to address the limitations encountered in earlier studies which included problems with study design, exposure ascertainment, and confounding. The strengths of this study are its prospective study design, careful ascertainment of cocaine exposure, as well as other illicit drugs, and the comprehensive environmental and perinatal variables for which we control. In addition, cocaine ascertainment is enhanced by the use of segmental analyses (cumulative exposure during last trimester) and by quantification of exposure that facilitates determining dose effects. Finally, the use of a structured neurological protocol provides us with a distinct perspective by which to assess cocaine effects.

The main limitation encountered in this study is the differential loss of follow-up of women who used cocaine during pregnancy, which, as noted, may have biased our results toward the null. Insofar as cocaine-exposed children have higher rates of exposure to multiple drugs, both licit and illicit, it is possible that our findings reflect synergy of polydrug exposure. We have endeavored to control for such exposures by employing a variety of biomarkers. Nevertheless, given the imperfect non-experimental conditions of clinical studies our findings could have been confounded by polydrug exposure.

Neurochemically, cocaine is highly active as it inhibits monoaminergic reuptake resulting in increased postsynaptic concentrations of norepinephrine, dopamine and, through tryptophan, of setotonin. Perturbations in the ontogeny of receptors of these systems resulting from cocaine teratogenesis is postulated to underlie neurobehavioral findings linked to cocaine (51). It is interesting to note that in our cohort of cocaine-exposed children, neurological and

behavioral abnormalities were highly correlated. These findings would be consistent with embryopathic perturbations in monoaminergic systems. For instance, perturbations in dopaminergic (DA) systems could account for tone and posture abnormalities as DA systems serve extrapyramidal systems, which in turn are likely to influence motor development, thus explaining the associations found in many studies between prenatal cocaine exposure and motor delays. Changes in norepinephrine and dopamine system could also affect arousal modulation (52). Perturbations in serotoninergic systems are likely to account for behavioral irritability but could also adversely influence neurological function as suggested by the embryopathy exhibited by infants exposed prenatally to serotonin re-uptake inhibitors (SSRI) (tremor and hypotonia) (53;54) (55) that mirrors the neurological findings described among cocaine exposed infants. Thus, perturbations in fetal serotonin systems could influence both muscle tone and behavior in offspring. Whether neurologic or behavioral abnormalities are markers or risk factors for subsequent neurobehavioral sequelae is not known and requires further study.

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Table 1

Maternal demographic, obstetrical and drug use characteristics grouped by any cocaine use during pregnancy.

	Cocaine-unexposed CU (N=206)	Cocaine 1 CE1 (N=53)	Cocaine 2 CE2 (N=27)	P value[!]
Demographic Information	N (%)	N (%)	N (%)	
	Mean ± SD	Mean ± SD	Mean ± SD	
Mean Age ± sd	24.2 ± 5.5	23.1 ± 5.2	28.4 ± 8.5	.001
Education (yrs)	11.9 ± 1.6	11.2 ± 1.7	11.0 ± 1.8	.005
African-American	197 (94)	47 (89)	22 (92)	NS
Income <$5,000	126 (61)	36 (68)	17 (71)	NS
Unemployed	83 (40)	32 (60)	16 (67)	.003
Welfare	104 (50)	30 (57)	12 (50)	NS
Married	24 (12)	8 (15)	6 (25)	NS
Obstetric History				
Gravida ± sd	2.4 ± 2.2	2.5 ± 3.0	4.1 ± 2.9	.002
Parity± sd	1.2 ± 1.4	1.2 ± 1.3	2.6 ± 2.4	.000
Drug and Alcohol Use During Pregnancy	N (%)	N (%)	N (%)	
Alcohol	31 (15)	14 (26)	9 (36)	.01
Tobacco	59 (28)	24 (45)	13 (52)	.008
Marijuana	64 (31)	20 (38)	7 (28)	NS

CE1 = Log riah <1.5; CE2 = Log riah ≥ 1.5.

[!]ANOVA or Chi-square using ordinal level of cocaine exposure (O,1,2).

NS, non-significant

Table 2

Infant characteristics by level of cocaine exposure during pregnancy.

	Cocaine - UNEXPOSED CU (N=206)	Cocaine 1 CE1 (N=53)	Cocaine 2 CE2 (N=27)	P VALUE[!]
	N (%) Mean ± SD	N (%) Mean ± SD	N (%) Mean ± SD	
Male	109 (52)	30 (57)	12 (48)	NS
Corrected Age in ms	6.6 ± .8	6.6 ± .9	6.6 ± .8	NS
Weight z-score	.54 ± 1.1	.66 ± .9	.66 ± .9	NS
Height z-score	.47 ± 1.1	.43 ± 1.0	.43 ± 1.0	NS
Head size z-score	.27 ± 1.1	.16 ± 1.0	.16 ± 1.0	NS
Neonatal measures				
Birth weight (grams)	3273 ± 492	3291 ± 493	2987 ± 559	.02
Birth length (cms)	50.8 ± 2.5	51.0 ± 2.2	49.6 ± 2.4	NS
Birth HC (cms)	34.2 ± 1.4	34.1 ± 1.5	33.5 ± 1.8	NS
Gestational age	39.2 ± 1.8	38.9 ± 2.5	38.8 ± 2.9	NS
Apgar 5	8.9 ± .4	8.7 ± 1.3	8.5 ± 1.8	.04
Premature (≤ 37 wks)	15 (7)	8 (15)	8 (20)	.04

[*] N=255 CE1 = Log riah <1.5; CE2 = Log riah ≥ 1.5.

[!] ANOVA using ordinal level of cocaine exposure (O,1,2)

Table 3

Infant neurological outcome by cocaine exposure during pregnancy.

Infant Outcome	Cocaine-Unexposed (N=206)	Cocaine-Exposed (N=80)	P value	OR [95%CI]
Neurologic				
Microcephaly	12	6	.6	1.3 (.5–3.6)
Tremor*	3	3	.2	2.6 (.5–13.2)
Excessive startle*	11	4	.9	.9 (.3–2.9)
Opistotonus	8	4	.7	1.3 (.7–4.5)
Hypertonia	47	28	.04	1.8 (1.02–2.1)
Extensor Posture	57	36	.008	2.0 (1.2–3.5)
Bilateral fisting	11	11	.02	2.7 (1.1–6.6)
Not Sitting	17	12	.08	2.0 (.91–4.4)
Poor Pincer Grasp	26	21	.01	2.2 (1.2–4.3)

* Exact significance two sided;

OR = Odds ratio; 95%CI= 95 percent confidence interval

Table 4

Infant neurological outcome by level of cocaine exposure

	Cocaine Unexposed (N=206)	Cocaine 1 CE1 (N=53)	COCAINE 2 CE2 (N=27)	P VALUE TREND	P VALUE Adjusted	ADJUSTED ODDS RATIO* [95% CI]
Neurologic	N (%) OR	N (%) OR	N (%) OR			
Global Hypertonia	48 (23) 1	17 (32) 1.5	11 (44) 4.3	.0005	.06	1.5 [.97–2.5]
Extensor Posture	58 (28) 1	23 (43) 2.0	12 (48) 2.4	.009	.03	1.6 [1.1–2.4]
Persistent Fisting	11 (5) 1	5 (9) 1.8	5 (24) 4.4	. 009	.02	1.9 [1.1– 3.7]

CE1 = Log riah <1.5; CE2 = Log riah ≥ 1.5. OR= Odds ratio; CI= confidence interval. Adjusted p value controlling for covariates in logistic regression models in which initial model includes gender, 5 minute Apgar score, corrected age, birth weight, prematurity, alcohol exposure, marijuana, and level of tobacco and cocaine exposure.

*Adjusted analyses exclude 10 opiate exposed children.

Table 5

Developmental and Behavioral Outcome by Drug Exposure Status

	Cocaine Unexposed CU (N=206)	Cocaine Low CE1 (N=53)	COCAINE HIGH CE2 (N =27)	P VALUE	P VALUE Adjusted*
BSIDII	Mean ± SD	Mean ± SD	Mean ± SD		
Mental (MDI)	88.5 ± 4.5	88.6 ± 6.2	87.2 ± 4.6	NS	NS
Psychomotor (PDI)	90.9 ± 8.9	92.4 ± 9.7	88.6 ± 9.3	NS	NS
BRS					
Total score	54.7 ± 20.3	47.8 ± 22.9	47.2 ± 22.8	.04	.06
Orientation*	46.0 ± 17.1	39.8 ± 19.0	37.8 ± 20.3	.01	.03
Emotion	68.0 ± 20.2	61.4 ± 25.7	63.9 ± 25.3	NS	NS
FSII! N	58.2 ± 6.7	58.9 ± 6.2	57.5 ± 6.6	NS	NS

Adjusted for maternal IQ, age > 30 years, HOME scale, high school education, maternal depression scores, infant gender, infant head size (z score), birth weight, prematurity, alcohol, tobacco, and marijuana exposure as described in text.

*Adjusted analyses excludes 10 opiate exposed children.

!Fagan Scale of Infant Intelligence (novelty preference).

NS = non-significant.