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Dose–Response Effect of Fetal Cocaine Exposure on Newborn Neurologic Function

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ABSTRACT. *Background.* **Studies of fetal cocaine exposure and newborn neurologic function have obtained conflicting results. Although some studies identify abnormalities, others find no differences between cocaine-exposed and cocaine-unexposed infants. To determine the effects of prenatal cocaine exposure on intrauterine growth and neurologic function in infants, we prospectively evaluated 253 infants shortly after birth.**

Methods. **Women who delivered a live singleton >36 weeks by dates were eligible for enrollment. Maternal exclusionary criteria were known parenteral drug use, alcoholism, and acquired immunodeficiency syndrome; infant exclusionary criteria were Apgar scores ≤4 at 5 minutes, obvious congenital malformations, seizures, or strokes. A total of 98% of infants were evaluated between 1 to 7 days of age. Newborns were assessed with the *Neurological Examination for Children* (NEC) by a pediatric neurologist (C.A.C.) who was blinded to exposure status. Gestational age was determined by Ballard's examination. Cocaine exposure was determined for the last trimester by radioimmunoassay of maternal hair (RIAH). Exposure values ranged from 2 to 4457 ng/10 mg hair. Infants were excluded if a maternal hair sample was missing (N = 13). The sample comprises 240 woman and infant pairs—104 cocaine-exposed and 136 cocaine-unexposed.**

Results. **Compared with unexposed controls, cocaine-exposed infants exhibited higher rates of intrauterine growth retardation (24% vs 8%), small head circumference ([HC] <10th% percentile) (20% vs 5%) and neurologic abnormalities: global hypertonia (32% vs 11%), coarse tremor (40% vs 15%), and extensor leg posture (20% vs 4%). We found increasing odds (odds ratio) of growth and neurologic impairment with increasing level of cocaine exposure in stratified analyses. The odds ratio associated with three levels of cocaine exposure (no exposure, low exposure = RIAH 2–66 ng/mg; and high exposure = RIAH 81–4457 ng/mg) respectively are: 1.0, 3.3, and 6.1 for small head size (χ^2 for trend); 1.0, 3.3, and 4.3 for global hypertonia (χ^2 for trend); 1.0, 3.4, and 7.4 for extensor leg posturing (χ^2 for trend); and 1.0, 3.8, and 3.8 for coarse tremor (χ^2 for trend). Significant associations between cocaine exposure and neurologic signs were found in logistic regression equations that controlled for 20 or more variables.**

Conclusion. **We conclude that adverse neonatal effects associated with fetal cocaine exposure follow a dose–response relationship: newborns with higher levels of prenatal cocaine exposure show higher rates of impairments in fetal head growth and abnormalities of muscle tone, movements, and posture. Significant relationships between cocaine exposure and these outcomes remain in controlled analyses.** *Pediatrics* **1999;103:79–85;** ***neurologic, in utero, cocaine exposure, neonates, hypertonia, central nervous system, movement disorder.***

ABBREVIATIONS. AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; PCP, phencyclidine; BW, birth weight; HC, head circumference; IUGR, intrauterine growth retardation; SGA, small for gestational age; NEC, *Neurological Examination for Children*; OR, odds ratio; LR, logistic regression.

Although the cocaine epidemic has declined, in urban centers cocaine remains one of the most pervasive drugs used. The consequences of prenatal cocaine exposure to the developing nervous system, especially regarding newborn neurobehaviors, is subject to debate. Some studies have described adverse neurobehaviors, including abnormal organizational response and interactive behavior when tested with the Brazelton Neonatal Behavioral Assessment Scale,[1,2] while other studies have described abnormalities of muscle tone and movements.[3] Yet other studies have not found neurobehavioral abnormalities in the early newborn period.[4,5]

Many of these early studies involved small sample sizes that precluded controlling for extraneous variables affecting outcome and used maternal self-report and urine toxicology to ascertain cocaine use during pregnancy, methods that are prone to misclassification. We present data on fetal growth and neurologic function in a cohort of newborn infants in whom cocaine exposure was ascertained by radioimmunoanalyses of a maternal sample of hair (RIAH, Psychemedic Corporation, Culver, CA). This quantitative method of exposure provides information on cumulative cocaine exposure during pregnancy, enabling us to assess for cocaine-related dose–response effects. To our knowledge, no other prospective study of newborn neurologic function has used RIAH to determine cocaine exposure status.

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METHODS

The Sample

We recruited two hundred sixty-six mothers shortly after giving birth from a single urban hospital between January 1992 and November 1995. Informed consent was obtained from all women agreeing to participate in the study protocol, which was approved by the Harlem Hospital and Columbia University Institutional Review Board. Infants were included in the study if born singleton, if their gestational age by dates was >36 weeks, and if maternal hair was furnished at birth for toxicology testing. Maternal exclusionary criteria were: known parenteral drug abuse, alcoholism, and acquired immunodeficiency syndrome (AIDS); infant exclusionary criteria were: Apgar scores ≤4 at 5 minutes, obvious congenital malformations, seizures, or strokes. No infant required exclusion because of congenital malformations or low Apgar scores. We initially used poor level of prenatal care as a criterion for maternal inclusion, but because of cocaine-positive women were overrepresented in this group (76%), to increase enrollment of cocaine-negative women we expanded the inclusion criteria early in the course of the study to include women with all levels of prenatal care and controlled for level of care in the analyses.

Two of the 266 mothers delivered twins and were excluded from the sample. Of the 264 mothers, 11 had infants who were unavailable for examination either because the infant was in the neonatal intensive care unit or because the mother had changed her mind about participating; of these 11 infants 1 mother reported cocaine use during pregnancy. Of the remaining 253 cases, 240 (121 boys and 114 girls) had maternal hair cocaine toxicology results available. By design, women with known parenteral drug use and AIDS were excluded; however, at interview 2 women in the cocaine-exposed and 1 in the cocaine-unexposed group admitted to using heroin or methadone and 7 in the cocaine-exposed and 3 in the cocaine-unexposed group admitted to human immunodeficiency virus (HIV) infection at the time of delivery, although this was not documented in their hospital chart.

Charts were reviewed to determine maternal infection with HIV, pregnancy complications, level of prenatal care, treatment for syphilis during pregnancy, and urine toxicology results. The mothers were interviewed during their hospital stay by experienced interviewers using a structured protocol that queried the women about their pregnancy, including drug and alcohol use, as well as socioeconomic factors. Infants were examined in the early newborn period by a pediatric neurologist (C.A.C.), who was blinded to exposure status; the mean age of infants at examination was 54.7 hours. To diminish the influence of infant behavioral state on neurologic findings, every effort was made to carry out examinations 2 to 3 hours after the last infant feeding; the mean time since last feeding was 2.4 hours. Thirty-one infants were examined <2 hours after feeding because of scheduling difficulties and unforeseen feeding practices.

RIAH was used to determine cocaine exposure.[6,7] Hair processing followed a strict cleaning protocols of five consecutive washes to avoid external contamination.[8] Hair that is chemically treated may bind cocaine metabolites less avidly and thus underestimate true level of exposure. Maternal RIAH is a valid method of assessing gestational cocaine exposure, that has been found to be more sensitive than urine toxicology and meconium analyses.[9] RIAH is well-suited for dose–response analyses as correlations between drug dose and levels of drugs in hair have been documented.[7,8] RIAH assessments are not racially biased, as increased rates of cocaine-positive RIAH is mirrored by higher levels of cocaine used identified by self-report and urine toxicology analyses, reflecting the preference for urban blacks to use cocaine over other drugs of abuse.[10]

Analyses were conducted on the proximal 3.9 cm of maternal hair, which reflects exposure during the last trimester of pregnancy. A specimen was reported as positive if the cocaine metabolite detected was >2 ng per 10 mg of hair. Herein cocaine-exposed infants refers to infants in whom RIAH results proved positive for cocaine at the minimum of 2 ng/10 mg hair. Unexposed infants refers to infants for whom RIAH results showed no evidence of cocaine. Only 1 woman with a negative RIAH test reported using cocaine during pregnancy. A subsample of the hair specimens were tested for phencyclidine (PCP) and opiates in addition to cocaine. Seven women were positive for opiates: 2 of these were ascertained through self-report of heroin use during pregnancy; and the remainder were ascertained through positive RIAH for opiates, which includes methadone, morphine, and codeine. All opiate-exposed infants except 1 were also cocaine-exposed. These infants were included in the analyses and opiate exposure was controlled for in the analyses.

Outcome in Neonates

Anthropomorphic Measures

Birth weight (BW), length, and head circumference (HC) were obtained at birth by the obstetric and pediatric staff. HC was also measured at the time of the neurologic examination. Gestational age was estimated using Ballard's simplified gestational maturity rating scale.[11] Maternal dates of gestational age in 55 infants were reported to be >36 weeks; however, when these infants were assessed with Ballard's scale, their gestational ages were in fact between 33 and 37 weeks. We included these infants in the sample and controlled for gestational age in the analyses. Intrauterine growth retardation (IUGR) was classified using growth standards developed by Miller et al[12] based on a representative sample of newborns with diverse racial composition. Norms are stratified by gender for gestational ages 36 to 42 weeks and by gestational age only in infants <36 weeks. Infants below the 10th percentile for gestational age in intrauterine growth (weight and HC) were classified as growth retarded or small for gestational age (SGA).

Neurologic Evaluation

A modified version of the *Neurological Examination for Children* (NEC) was used to assess neurologic integrity in newborns.[13] This version of the NEC omits age-inappropriate items and emphasizes movement and tone abnormalities.

Urine Toxicology Analysis

A subset of infants and women (N = 104) also had urine toxicology submitted at the time of birth. The Antigen Antibody Complex Immunoassay (Abbott Laboratories, Pasadena, CA) was used to detect the presence of the following substances: marijuana, barbiturates, opiates, PCP, and cocaine and its metabolites. Urine toxicology was negative for cocaine in all cocaine-unexposed women and infants, but was positive for barbiturates in 2, for opiates in 1, and for marijuana in 1. Urine toxicology was positive for cocaine in 23 cocaine-exposed women and infants. It was also positive for barbiturates in 1, for opiates in 4, and for unspecified substances in 3 infants.

Statistical Methods

Results for continuous measures (eg, BW) are expressed as means ± standard deviation. Differences between cocaine-exposed and cocaine-unexposed infants were tested for significance with use of the 2-tailed Student's t test and by odds ratio (OR) for strength of association. For dichotomous or categorical variables differences between proportions for both groups were analyzed by either the 2-tailed χ^2 test or Fisher's exact test. Pearson's correlation coefficient (r) was used to evaluate the relationship between specific variables. We used the quartile distribution of RIAH to develop two tiers of cocaine exposure for dose–response analyses: the low level comprises the sum of the two lower quartiles and reflects cocaine measures ranging from 2 to 66 ng/mg; the high level comprises of the sum of the two upper quartiles and reflects cocaine exposure ranging from 81 to 4457 ng/mg. Stratified trend analyses based on these three levels of exposure—no exposure, low exposure, and high exposure—were then computed.

We used analysis of variance to determine association between cocaine and angle measurements while controlling for independent factors and covariates (gestational age, gender, and race); we used logistic regression (LR) models to identify OR estimates of independent correlates of hypertonia of all types, coarse tremor, extensor leg posturing, and small head size, entering into the equations variables believed to be confounders. To avoid colinearity, birth measures were centered. The full LR model included 21 variables: gestational age, BW, birth head size, SGA, small head size, gender, race, HIV infection, diagnosis of congenital syphilis (positive rapid protein reagin), poor prenatal care opiate (RIAH, urine toxicology, and self-report), and cocaine exposure and maternal report of alcohol (number of drinks/day during pregnan-

cy), marijuana, and cigarette smoking (number of cigarettes smoked/day during pregnancy), low Apgar (<8), preeclampsia, fetal distress, poor prenatal care (≤5 visits), number of previous pregnancies, maternal age, and infant age (hours) at time of examination. Ordinal alcohol and cigarette smoking variables (ie, light versus heavy), as well as dichotomous exposures (yes/no), were not significantly associated with neurologic outcomes. The final model used dichotomous variables for drug exposures, including cocaine, as these were more highly correlated with outcomes. Second- and third-order interaction were tested and not found to be significant and were thus omitted from the final model. The variables associated with a P value <.1 in the full model were: for hypertonia—Apgar score; poor prenatal care; race; SGA; small head size; gestational age; gender; marijuana; opiate; alcohol; cocaine and congenital syphilis; for coarse tremor—gender; cocaine and HIV; for extensor posture—gestational age; maternal age; small head size; and cocaine; for small head size—BW; gestational age; cocaine; alcohol; and infant age at time of examination.

RESULTS

Women

Cocaine-exposed women were significantly more likely to be older, black, of low socioeconomic status, to have poor prenatal care, syphilis, and a higher number of previous pregnancies, live births, and miscarriages. They were also more likely to use alcohol, tobacco, marijuana and either hydrochloride or alkaloidal cocaine (crack). By design, women with known parenteral drug use and HIV were excluded; however, at interview 2 women in the cocaine-exposed and 1 in the cocaine-unexposed group admitted to using heroin or methadone and 7 in the cocaine-exposed and 3 in the cocaine-unexposed group admitted to HIV infection at the time of delivery, although this was not documented in their hospital chart. As they were asymptomatic (ie, non-AIDS) they were included in the analyses. No significant differences in complication of pregnancy were observed between the two groups of women. Cocaine-exposed and cocaine-unexposed women exhibited similar rates of preeclampsia, meconium stain, fetal distress, and birth trauma (Table 1).

Infants

The sample comprised 104 cocaine-exposed (57 boys) and 136 cocaine-unexposed infants (69 boys). (Table 2). There were no differences between cocaine-exposed and cocaine-unexposed infants in gestational age (38.8 weeks ± 2.2 vs 29.0 weeks ± 2.4) or Apgar score at 5 minutes (8.8 ± .5 vs 5.8 ± .5). One infant exposed to 75 mg/d methadone prenatally exhibited neonatal abstinence signs and required treatment.

Anthropomorphic Measures

Cocaine-exposed infants exhibited lower mean BW, birth length, and HC than cocaine-unexposed infants (Table 2). Intrauterine growth retardation (BW <10th percentile) and small HC (<10 percentile) were more frequent among cocaine-exposed infants than among cocaine-unexposed control infants. The ponderal index (BW/birth length^3 × 100) and the proportion of children with ponderal indices <10th percentile according to Miller et al[12] was not significantly different between cocaine-exposed and cocaine-unexposed infants.

TABLE 1. Maternal Characteristics According to Cocaine Exposure Status

Maternal Characteristics	Exposed N = 104	Unexposed N = 136	P Value
	N (%)	N (%)	
Demographic information			
Mean age ± SD	27.4 ± 6.1	25.5 ± 6.8	.028
Black	82 (78.8)	67 (49.3)	<.001
High school graduate	40 (40.4)	67 (50.4)	.13
Income <$5000	57 (61.3)	80 (63.5)	.74
Poor prenatal care (≤5 visits)	39 (37.5)	14 (10.3)	<.00001
Syphilis at delivery	12 (11.5)	3 (2.2)	.003
HIV-infected	7 (6.7)	3 (2.2)	.11
Obstetric history			
Gravida ± SD	4.1 ± 3.1	2.1 ± 2.0	<.001
Parity ± SD	2.6 ± 2.3	1.3 ± 1.3	<.001
Miscarriages ± SD	0.6 ± 1.0	0.2 ± 0.4	<.001
Obstetric complications			
Gestational diabetes	4 (3.8)	7 (5.1)	.63
Birth trauma	4 (3.8)	5 (3.7)	.95
Meconium stain	12 (11.5)	14 (10.3)	.76
Preeclampsia	4 (3.8)	3 (2.1)	.66
Fetal distress	5 (4.8)	7 (5.1)	.90
Drugs reported during pregnancy			
Alcohol use	31 (30.1)	9 (6.6)	<.001
Cigarette smoking	55 (52.9)	13 (9.6)	<.001
Cocaine/crack	40 (38.5)	1 (0.7)	<.001
Marijuana	13 (12.5)	3 (2.2)	.0029
Opiate (heroin + methadone)	2 (1.9)	1 (0.7)	.5803

TABLE 2. Characteristics of Cocaine-Exposed and Cocaine-Unexposed Newborn Infants

	Cocaine-exposed N = 104	Cocaine-unexposed N = 136	P Value
	N (%)	N (%)	
Male sex	57 (54.8)	69 (50.7)	.53
Age at examination (h)	57.4 ± 37.9	52.7 ± 30.9	.30
Gestational age (wk)	38.6 ± 2.2	39.0 ± 2.4	.16
SGA*	20 (19.2)	9 (6.6)	.003
Small head size*	20.2 (20)	7 (5)	.0003
Low ponderal index*	18 (18.6)	33 (26.2)	.18
Preterm (<37 wk)	22 (21.2)	32 (23.5)	.66
Birth weight (g)	3098 ± 526	3368 ± 471	<.001
Birth length (cm)	49.6 ± 3.1	51.4 ± 2.6	<.001
Birth head size (cm)	33.8 ± 1.5	34.6 ± 1.4	<.001
Ponderal index†	2.54 ± .36	2.47 ± .29	.14
HC/BW* 100	1.11 ± .1	1.04 ± .1	<.001
5-Minute Apgar score	8.8 ± .51	8.8 ± .50	.84

Abbreviations: SGA, small for gestational age; HC, head circumference; BW, birth weight.
* Less than 10th percentile based on norms by Miller and Hassanein.[12]
† Ponderal index = (birth weight/birth length) × 100. Birth length and ponderal index are based on 224 measures.

Neurologic Findings

Tone

Hypertonia, characterized by a uniform increase in resistance of muscle tone, was significantly more frequent among the cocaine-exposed infants (32% vs 11%; P = .000007) (Table 3). Of 33 cocaine-exposed infants who were hypertonic, 30 exhibited general-

TABLE 3. Neurologic Findings and Individual Items of the Neurologic Examination for Cocaine-Exposed and Cocaine-Unexposed Newborn Infants

Neurologic Items	Exposed RIAH >2 NG	Unexposed RIAH = 0	*P* Value
	N (%)	*N* (%)	
Does not regard examiner	35 (35.0)	14 (10.7)	.00001
Does not follow face	30 (29.7)	23 (17.3)	.025
Tone abnormality any kind	39 (37.5)	22 (16.2)	.0002
Hypertonia	33 (31.7)	15 (11.0)	.00007
Hypotonia	6 (5.8)	7 (5.1)	.83
Tremor			
Fine tremor	11 (10.6)	21 (15.8)	.24
Coarse tremor	42 (40.4)	20 (15.0)	.00001
Extensor leg posture	20 (19.6)	6 (4.4)	.00022
Axial tone			
No head lag (axial hypertonia)	54 (51.9)	40 (29.4)	.0004
Head erect upon pull	29 (28.2)	23 (17.4)	.049
Ventral suspension, head below trunk	22 (21.2)	33 (24.4)	.549
Support under axilla-does not slip	35 (33.7)	32 (23.5)	.083
Exaggerated deep tendon reflexes*			
Biceps	65 (62.5)	72 (52.9)	.138
Patella	67 (64.4)	83 (61.0)	.590
Ankle	68 (65.4)	73 (53.7)	.068
Sustained ankle clonus*	11 (10.6)	13 (9.6)	.794
Transient ankle clonus*	45 (43.3)	45 (33.1)	.106
Crossed adductor reflex*	74 (71.8)	79 (58.1)	.028
Extensor plantar response*	1 (1.0)	1 (0.7)	1.00
Mean adductor angles ± SD	21.9 ± 6.4	23.629 ± 6.791	.052
Mean popliteal angles ± SD	94.7 ± 14.9	97.1 ± 16.0	.239

Abbreviations: NG, nanogram of cocaine per 10 mg protein; SD, standard deviation.
* Only right-sided results are shown, because of right and left correlations. *N* varies across items from 100 to 104 for cocaine-exposed infants and from 131 to 136 for unexposed infants.

ized hypertonia consistent with a diagnosis of hypertonic tetraparesis and 3 exhibited predominant leg hypertonia (hypertonic diparesis). A diagnosis of hypertonia was inversely correlated with fetal growth: birth HC (r = -.16; P = .012), BW (r = -.18; P = .005) and birth length (r = -.19; P = .004). Although univariate analyses demonstrated minimal increase in adductor and hamstring muscle tone (popliteal angle) among cocaine-exposed infants, analyses of variance that controlled for gestational age, and assessed for the main effects of male sex, cocaine exposure and race with 2- and 3-way interactions, found a significant main effects of cocaine exposure on adductor and popliteal angles (P value for adductor angle = .006 and for popliteal angle = .006). Fifty-two percent of cocaine-exposed infants compared with 30% of cocaine-unexposed infants (P = .0004) showed axial hypertonia, as indicated by the absence of head lag.

Movement Disorders

Cocaine-exposed infants exhibited a significantly higher proportion of coarse tremor (40% vs 15%; P = .00001) and extensor leg posture (20% exposed vs 4% unexposed; P = .0002) compared with cocaine-unexposed infants. Fine tremor was equally distributed among cocaine-exposed and cocaine-unexposed infants (11% exposed vs 16% unexposed; P = .24).

Other Signs

Cocaine-exposed infants showed higher rates of pyramidal tract signs, but these were significant only for positive cross-adductor reflex (see Table 3). Similar rates of tonic down-gaze of the newborn were found among cocaine-exposed and cocaine-unexposed infants. A higher proportion of cocaine-exposed infants as compared with cocaine-unexposed infants could not be engaged to regard the examiner's face (35% vs 11%; P = .0001) or to briefly follow the examiner's face (30% vs 17%; P = .025). Only 1 cocaine-exposed infant had an overtly depressed sensorium and was unarousable at the time of the examination.

Dose–response Effects

In analyses stratified by level of exposure (Table 4), we found that infants with higher levels of exposure had higher rates of small head size (HC<10th percentile) and IUGR/SGA (BW <10th percentile). With regard to neurologic findings, the OR associated with three levels of cocaine exposure (no exposure, low exposure = RIAH 2–66 ng/mg and high exposure = RIAH 81–4457 ng/mg), respectively were: for small head size, 1.0, 3.4, and 6.1 (χ^2 for trend

TABLE 4. Odds of Impaired Fetal Growth and Neurologic Function Associated With Increasing Levels of Cocaine Exposure Based on RIAH*

	Cocaine-unexposed	Level I Exposed 2–66 NG	Level II Exposed 81–4457 NG	χ^2 Linear Trend‡
	OR [95% CI]	OR [95% CI]	OR [95% CI]	*P* Value
Fetal growth				
IUGR/SGA†	1.0 [.4–2.6]	1.5 [.5–4.7]	5.7 [2.3–14.3]	.00011
Small head size†	1.0 [.34–2.9]	3.4 [1.15–9.8]	6.1 [2.2–16.5]	.0001
Neurological findings				
Hypertonia	1.0 [.47–2.1]	3.3 [1.5–7.3]	4.3 [2.6–20.7]	.000003
Extensor leg posture	1.0 [.31–3.2]	3.4 [1.1–10.7]	7.4 [2.6–20.7]	.000009
Coarse tremor	1.0 [.51–2.0]	3.8 [1.8–7.9]	3.8 [1.8–7.9]	.00002

Abbreviations: NG, nanogram of cocaine per 10 mg protein; OR, odds ratio; CI, confidence interval; SGA, small for gestational age; IUGR, intrauterine growth retardation.
* Cocaine measures with radioimmunoanalyses of hair. Level I (low exposure) represents two lower quartiles; level II (high exposure) represents two upper quartiles.
† Less than 10th percentile based on norms by Miller and Hassanein, 1971.
‡ Adjusted Mantel-Haenzel χ^2 for trend.

TABLE 5. Odds Ratio Estimates of Independent Correlates of Hypertonia, Coarse Tremor, Extensor Leg Posture, and Small Head Circumference Using Multiple Logistic Regression Models

Hypertonia				
Variable	OR	(CI)	R	*P* Value
Male	8.3	(3.0–23.0)	.20	.0009
Birth weight	.99	(.99–.99)	−.17	.0026
Gestational age	1.7	(1.4–2.2)	.24	.0001
SGA	.10	(.01–.40)	−.10	.04
Poor prenatal care	4.4	(1.5–12.5)	.16	.006
Cocaine exposure	6.3	(2.3–17.3)	.19	.0012
Opiate exposure	14.3	(1.8–113.2)	.13	.0152
Alcohol exposure	1.3	(1.0–1.6)	.10	.04
Cigarette smoking	.98	(.95–1.0)	−.06	.10
Apgar score <8	.25	(.10–.89)	−.11	.03
Coarse Tremor*				
Variable	OR	(CI)	R	*P* Value
Male	2.7	(1.4–5.4)	.15	.004
Small HC	2.9	(1.0–7.4)	.10	.04
Birth weight	.99	(.99–.99)	−.06	.02
SGA	.40	(.20–4.2)	−.05	.10
Cocaine exposure	3.0	(1.5–5.8)	.17	.002
Human immunodeficiency virus	.20	(.14–8.0)	−.03	.2
Extensor Leg Posture†				
Variable	OR	(CI)	R	*P* Value
African-American	3.0	(.8–11.4)	.06	.10
Poor prenatal care	2.4	(.8–6.1)	.07	.09
Birth HC	.44	(.26–.75)	−.21	.09
Gestational age	1.2	(1.0–1.6)	.19	.006
Small HC	.10	(.02–.6)	−.17	.01
Cocaine exposure	3.2	(1.1–9.4)	.12	.055
Small Head Circumference‡				
Variable	OR	(CI)	R	*P* Value
Birth weight	.99	(.99–.99)	−.15	.0173
Gestational age	1.6	(1.3–2.1)	.27	.0001
Infant age at examination	.98	(.96–1.0)	−.08	.08
Alcohol exposure	1.2	(.98–1.4)	.08	.07
Cocaine exposure	3.7	(1.2–10.8)	.14	.02

Abbreviations: HC, head circumference; SGA, small for gestational age (<10th percentile).
Variables remaining in model using back step elimination maximum likelihood method with criterion of $P < .1$. Original model includes 21 maternal and infant variables. Variables excluded from equation because of instability: * Apgar score; and † opiate exposure and eclampsia. ‡ Excludes head size (cm) and small head size from model.

$P = .000002$); for global hypertonia, 1.0, 3.3, and 4.3 (χ^2 for trend $P < .001$); for extensor leg posturing, 1.0, 3.4, and 7.4 (χ^2 for trend $P < .001$); and for coarse tremor, 1.0, 3.8, and 3.8 (χ^2 for trend $P < .001$).

Controlled Analyses

Table 5 shows the variables remaining in the model based on logistic regression equations that started with 21 variables (see "Methods" section) and used a backward elimination procedure (significance level .1). We found a significant association between cocaine exposure and the odds of small HC (OR = 3.7; $P = .02$) and adverse neurologic outcomes: hypertonia (OR = 6.3;.003), coarse tremor (OR = 3.0; .002), and extensor leg posturing (OR = 3.2; $P = .6$) Male infants were over 8 times more likely to exhibit hypertonia ($P = .0046$) and nearly 3 times more likely to have coarse tremor than female infants. SGA was inversely associated with hypertonia. Opiate exposure (by self-report, toxicology, and RIAH) was strongly linked to hypertonia.

DISCUSSION

The results of our study indicate that neonates with prenatal cocaine exposure exhibit higher rates of IUGR and neurologic abnormalities than unexposed infants. The advantages of this study include its prospective design, careful assessment of perinatal factors that affect neonatal outcome, quantitative method of assessing prenatal drug exposures, and its relative paucity of confounding with heavy illicit drugs. The sample is primarily weighted toward cocaine users, with few women identified who used other heavy drugs (barbiturates, PCP, and opiates). Only 30% percent of cocaine-exposed women report alcohol use, while 53% reported cigarette smoking.

The benefit of using RIAH to assess cumulative cocaine exposure is that it greatly diminishes the level of misclassification of cocaine otherwise expected, as evidenced by our finding that 60% of women who tested cocaine-positive on RIAH denied using cocaine during pregnancy. Because hair measurements were limited to exposures occurring during the last trimester of pregnancy, our study does not reflect findings among the offspring of sporadic cocaine users or women who quit in early pregnancy, but of those chronically exposed throughout pregnancy.

A study limitation was that smoking and alcohol ascertainment relied only on self-report and lacked a gold standard against which to test veracity of self-report on use. Rates of cigarette smoking among cocaine-exposed women (53%) in our study were lower than that found (67%) in larger series,[14] suggesting that these measures underestimated actual level of use and that our findings may be partly confounded by them.

The data presented here support the presence of a dose–response relationship between increasing levels of chronic cocaine exposure and infant outcome (fetal growth and neurologic function). Such a relationship was observed in each exposure strata for all main neurologic outcomes, except coarse tremor. The plateau in these effects could be explained by a lower effect threshold for coarse tremor. To our knowledge, only one previous study using quantitative cocaine assessment has reported a dose–response effect on newborn state regulation and excitability at age 3 weeks, but only among the heavily exposed infants. No neurobehavior abnormalities were found, however, at age 3 days.[5] Although such a report lends credence to the existence of a late-emerging excitable phase that has been postulated to occur among cocaine-exposed infants,[15] the finding from our present study would indicate that neurologic impairments can be detected shortly after birth.

Because cocaine-using women tend to use many other drugs, it is possible that heavier cocaine-using women also used other drugs more heavily as well, so that the increasing trend of impaired neurologic

outcomes reflect the excessive use of other substances of abuse instead of cocaine. This interpretation is, however, unlikely in light of the significant association cocaine had with both neurologic abnormalities and impaired head growth, which remained significant in logistic regression models that controlled for numerous risk factors for adverse neonatal outcome. Nevertheless, the argument can be made that because cocaine was more accurately ascertained than cigarette smoking and alcohol use, to some degree our findings may still be confounded by these exposures, especially cigarette smoking, which as reported by Fried et al,[16,17] exerts effects on neurologic outcome that overlap with those reported with cocaine.

We adjusted for gender based on animal studies showing that girls suffer greater adverse cocaine effects on behavior and dopaminergic pathways than boys.[18] However, we found that boys were more than 8 times as likely to manifest hypertonia than girls. Higher rate of hypertonia among cocaine-exposed boys was also reported in toddlers at risk for HIV infection.[19] The biologic reason(s) for this gender finding is unclear; greater male susceptibility may be attributable to a differential effect of in utero hormonal exposure on monoaminergic systems, a mechanism akin to that invoked to explain male overrepresentation among children with attention deficit disorder, learning disorders, autism, and developmental pervasive disorders.

We also found a significant association between fetal cocaine exposure and IUGR of the symmetrical type (without sparing of fetal head growth). Length and weight were similarly compromised by cocaine exposure as indicated by the similar mean ponderal indices for exposed and unexposed children. IUGR is postulated to result from cocaine-related vasoconstriction on placental vessels, leading to diminished fetal perfusion hypertension, and hypoxemia.[20] If sustained, this effect could lead to diminished fetal growth,including the brain. Whether these growth effects lie in the causal pathway of cocaine effects on neurologic function or represent a common phenotype to high exposures that are produced through parallel mechanisms is not known.

SGA was inversely associated with hypertonia. A similar relationship was previously described in 6-month-old children at risk for HIV.[19] The reason(s) for the protective effect of SGA on hypertonia is not known. Lester et al[21] reported a difference in cry patterns between SGA and non-SGA cocaine-positive infants, which he postulated to result from two distinct modes of action: a direct cocaine mechanism on the central nervous system among non-SGA infants, and an indirect mechanism in SGA infants, perhaps related to hypoxia or malnourishment. The effect of malnutrition on muscle tone appear to have obscured cocaine-related hypertonicity.

The term hypertonic tetraparesis is used here to indicate a uniform pathologic increase in muscle tone more akin to rigidity than to spasticity. The extensor leg posturing resembles dystonic movements, which have been described among cocaine-using adults.[22] The abnormalities of movement (tremor and dystonia) in addition to muscle tone findinds would suggest a direct effect of cocaine on neural circuitry, especially of monoaminergic systems. In support of this hypothesis are findings of reports of changes in dopaminergic and serotoninergic systems in the developing rat brain induced by cocaine exposure.[18,23–25] Whether such neurologic abnormalities in neonates have any impact on subsequent child development and behavior is not known, but findings from one study suggest that neurologic impairments in infancy may be a marker for subsequent developmental impairments.[19] Therefore, additional studies are needed to determine if neurologic findings, even if transient, are helpful in identifying cocaine-exposed children who are vulnerable to subsequent neurodevelopmental or behavioral problems.

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THE CROWDED EXAMINING ROOM

The image of the doctor alone in the examining room with the patient (and with God) gave way [after 1966-1976] to the image of an examining room with hospital committee members, lawyers, bioethicists, and accountants virtually crowding out the doctor.

Rothman DJ. *Strangers at the Bedside.* New York, NY: Basic Books; 1991

Submitted by Student