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Increased incidence of intraventricular hemorrhage and developmental delay in cocaine-exposed, very low birth weight infants

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Abstract

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This study sought to determine whether very low birth weight (VLBW) infants (<1500 gm) with fetal cocaine exposure differed from non-cocaine-exposed VLBW infants in incidence of neonatal medical complications and in later developmental outcome. Forty-one cocaine-exposed, VLBW infants, followed in a longitudinal study, were compared with 41 non-cocaine-exposed, VLBW infants of comparable race, social class, age, and incidence of bronchopulmonary dysplasia. Cocaine-exposed infants were identified on the basis of combined findings of maternal and/or infant urine immunoassay and on the basis of maternal self-report. At birth, groups did not differ on medical risk factors except that cocaine-exposed infants had a higher incidence of mild (grades I to II) intraventricular hemorrhage. Cocaine-using women were also more likely to use other drugs, especially alcohol, marijuana, and tobacco. At follow-up, at mean corrected ages of 16.5 ± 8 months for 30 cocaine-exposed infants and 18.5 ± 7 months for 37 non-cocaine-exposed infants, standardized assessments of cognitive (Mental Development Index) and motor (Psychomotor Development Index) development were administered. Cocaine-exposed infants had lower mean cognitive (83 ± 27 vs 91 ± 19), and motor (85 ± 25 vs 96 ± 18) scores; the incidence of developmental delay was significantly higher even after control for the effects of intraventricular hemorrhage and chronologic age. Cocaine-exposed VLBW infants were also more likely to be living with relatives or in foster homes. We conclude that these VLBW, cocaine-exposed infants were at increased risk of intraventricular hemorrhage, were more likely to be placed outside maternal care, and had higher incidences of cognitive and motor delays at follow-up. (J PEDIATR 1994;124:765-71)

BPD	Bronchopulmonary dysplasia
GA	Gestational age
IBR	Infant Behavior record
IVH	Intraventricular hemorrhage
MDI	Mental Development Index
PDI	Psychomotor Development Index
VLBW	Very low birth weight

See related articles, "Prenatal cocaine exposure: Nine years later", "Relation of maternal cocaine use to the risks of prematurity and low birth weight", and "Effects of alcohol use, smoking, and illicit drug use on fetal growth in black infants."

The use of cocaine, particularly "crack," among pregnant women has increased to the extent that 10% to 20% of infants born yearly at major, urban medical centers in the United States have evidence of prenatal exposure.[1, 2] Both animal and human studies suggest that, through mechanisms of vascular disruption and hypoxia, cocaine exposure can have significant negative effects on the developing fetus.[3-6] The majority of studies indicate that fetal cocaine exposure is associated with intrauterine growth retardation and low birth weight,[4, 5, 7, 8] and that the occurrence of pre-maturity is increased in exposed cohorts. A higher incidence of very low birth weight (<1500 gm) has also been noted in samples of cocaine-exposed infants[9, 10]; increasing proportions of VLBW populations are reported to have been exposed to cocaine.[11] Because VLBW infants are already at risk for neonatal medical complications associated with prematurity, we sought to determine whether cocaine exposure was associated with greater vulnerability to neonatal medical complications or poorer developmental outcome, or both, within VLBW cohorts.

Methods

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As part of a longitudinal study of VLBW infants with bronchopulmonary dysplasia, admissions to the neonatal intensive care unit were prospectively reviewed for 2 years for consecutive recruitment of VLBW infants with BPD, and of VLBW infants without BPD who were of comparable race, social class, age, and cocaine status. Cocaine status was determined through prospective urine screening or clinical interview at the time of the infant's birth, or both. A previous study at this hospital indicated that 85% of cocaine-exposed mothers are identified with this combination of methods.[5] Urine samples were obtained immediately before or after labor and delivery in the NICU in which the majority (85%) of infants were recruited. They were analyzed by enzyme immunoassay, using the Syva EMIT method (Syva Co., Palo Alto, Calif.), for the presence of cocaine's primary metabolite, benzoylecgonine, and for heroin, phencyclidine, methadone, opiates, barbiturates, and marijuana. The specificity for benzoylecgonine is 99% at concentrations of 0.3 mg/ml.

For our study, all VLBW infants with positive findings of maternal cocaine use were compared with an equal number of non-cocaine-exposed VLBW infants of similar race, social class, and age, from the same study population, all of whom were black and receiving public assistance. Groups were balanced for BPD status and did not differ in gender, socioeconomic status, or maternal age, but cocaine-using mothers were less likely to be married (□Table I).[12] Two additional cocaine-exposed infants were identified, one, a white female, middle-class (Hollingshead class II) survivor whose mother declined to participate in the study, and the second, a twin who died at birth and whose sibling entered the study.

Table I. Demographic characteristics of VLBW infants

	Cocaine exposed (n = 41)	Non-exposed (n = 41)	*t*/χ^2	*p*
Race (% black)	100	100	-	-
Sex (%male)	58	46	1.2	NS
Maternal marital status*	85	66	3.2	<0.05
Social class†	4.5 ± 0.7	4.3 ± 0.7	0.9	NS
Maternal age (yr)†	27.1 ± 4	25.6 ± 6	1.2	NS

NS, Not significant.
*Percentage unmarried.
†Mean ± SD.

Procedures

The following medical information was extracted from the NICU chart: infant gestational age (based on a combination of Ballard examination[13] and dates from the last menstrual period),[1] birth weight (in grams), length and head circumference (cm), Apgar scores at 1 and 5 minutes, and the presence or absence of respiratory distress syndrome and BPD (defined as requiring supplemental oxygen more than 28 days, with accompanying radiologic changes indicative of pulmonary disease[14]). Also noted were the presence or absence of patent ductus arteriosus, necrotizing enterocolitis (proved, with or without surgery), retinopathy of prematurity, and abnormal hearing test results; number of days ventilator support was required and number of days supplemental oxygen was used; number of days needed to regain birth weight; peak bilirubin levels; and the presence or absence of seizures, periventricular leukomalacia, and intraventricular hemorrhage. Ultrasound studies were obtained for all VLBW infants during their NICU hospitalization and were interpreted by one of four board-certified pediatric radiologists, who were not informed of infant drug status. For IVH, a rating of severity based on extent of lesion was devised: no hemorrhage on ultrasonography was scored as zero, and lesions received gradings from 1 to 4 by the criteria of Papile et al.[15] All infants had at least one ultrasound study; ratings were based on the most severe lesion diagnosed if more than one study was done.

Attempts were made to enroll all cocaine-exposed VLBW infants and their non-cocaine-exposed, VLBW comparison infants in the follow-up study. Results of assessments from the most recent (i.e., oldest age of the child) follow-up visit are reported. Assessments included administration of the Mental and Motor scales of the Bayley Scales of Infant Development[16] and the Bayley Infant Behavior record.[17] Because normative data on the Bayley Scales yield a standard score range restricted to 50 to 150 (±2 SD), lower or higher scores were extrapolated by means of tables developed by Naglieri.[18] One examiner also administered the IBR after the administration of the Bayley Scales. The IBR is a Likert type of rating instrument reflecting the examiner's appraisal of the infant's orientation to objects and people, emotional state, and developmental level.[16] Scoring was statistically analyzed by a method used by Wolf and Lozoff[17] to enhance clinical interpretation. All examiners were blind to infant cocaine status. At follow-up, groups were again compared on medical and birth history factors to determine whether attrition had differentially affected the groups. Information on child custody, hospitalizations, and deaths was obtained. Our study was approved by the University Hospital Institutional Review Board, and maternal written informed consent was obtained for all subjects.

Analyses

Groups were compared on medical risk variables and developmental outcome measures with the use of t tests for continuous data, chi-square analyses for categoric variables, or *z* tests, with correction for continuity, for proportions. For all tests, we hypothesized that cocaine-exposed infants would have increased medical complications and poorer behavioral ratings and developmental outcomes at follow-up. Thus all tests were one tailed. When cell sizes were too small to use chi-square analysis, the Fisher Exact Test was used. Analyses of covariance were used to compare developmental outcomes, with control for appropriate medical risk factors.

Results

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Medical history of urine screening and of self-report of the use of other drugs was available for 81% of the sample (33 with a positive history of cocaine use; 33 with a negative history). Mothers who used cocaine were more likely to use alcohol, marijuana, tobacco, and other drugs during pregnancy than those who did not (□Table II). Among tobacco users, the number of cigarettes smoked per day was significantly higher for cocaine-using women. Cocaine-exposed infants had a significantly increased incidence of IVH (54% vs 29%; □Table III), but there were no significant differences for any of the other medical conditions documented by chart review.* Infants exposed to cocaine were three times more likely to have a grade I or II lesion than nonexposed neonates. For infants with lesions, the severity of the lesions was not different.

Table II. Other maternal drug use

	Cocaine exposed		Nonexposed			
	n	**%**	**n**	**%**	***t*/χ^2**	***p***
Alcohol	15	46	2	6	13.3	<0.001
Heroin	0	-	0	-	-	-
Methadone	0	-	0	-	-	-
Marijuana	12	36	0	-	14.7	<0.001
Opiates	1	3	0	-	1.0	NS
Barbiturates	4	12	3	9	0.2	NS
PCP	1	3	0	-	1.0	NS
Cigarettes	26	78	11	33	13.6	<0.001
(Cigarettes/day)*	(17 ± 10)		(12 ± 5)		2.1	<0.05

NS, Not significant; *PCP*, pentachlorophenol.
*Mean number ± SD.

Table III. Neonatal neurologic complications and distribution of IVH lesions by severity level

	Cocaine exposed	Nonexposed

	n	%	n	%	χ^2/Zc	p
	Complication					
Seizures*	1	2	2	5	0.4	NS
Periventricular leukomalacia*	2	6	2	6	0.2	NS
Intraventricular hemorrhage	22	54	12	29	2.1	<0.02
(IVH-group mean grade)†	(1.1 ± 1.2)		(0.6 ± 1.2)		1.7	<0.05
	IVH category (severity)					
No IVH	19	46	29	71		
Grades I-II	17	42	8	20		
Grades III-IV	5	12	4	9		

Overall χ^2= 5.4, *p* <0.07; χ^2 (0 - grades I-II × cocaine status) = 5.3, *p*<0.02.
Zc, Statistical test of proportions with the continuity correction; *NS*, not significant.
*Based on the Fisher Exact Test.
†Mean ± SD.

Of 41 surviving cocaine-exposed infants, 3 had died, the parents of 6 refused follow-up, 1 was lost to follow-up, and 1 was visually impaired and could not be tested. Of the 41 nonexposed infants, 1 died, 1 was adopted, the parents of 1 refused, and 1 was lost to the study. Thus the attrition was higher in the cocaine-exposed cohort, as were out-of-home placements (□Table IV).

Table IV. Custody outcomes

	Cocaine exposed (n = 43)		Nonexposed (n = 41)			
	n	%	n	%	Zc	p
With biologic mother	27	63	39	95	3.6	<0.01
Died	3	7	1	2	0.9	NS
Relative placement	7	16	0	0	2.7	<0.01
Foster placement	4	9	0	0	2.0	<0.02
Adopted	2	5	1	2	0.5	NS

Zc, Statistical test of proportions with the continuity correction; *NS*, not significant.

To assess potential effects of attrition, we subjected all medical and demographic variables documented at birth to a series of t tests to determine whether the groups differed at follow-up. The groups did not differ on any medical variable (all *p*values not significant) except IVH; the cocaine- exposed group had a mean (±SD) severity level of 1.2 ± 1.3 versus 0.51 ± 1.0 for the nonexposed group (t [*df* = 64] = 2.3; *p* <0.02), consistent with the findings based on the total sample at birth.

Because children were seen at several assessment points within groups and the trajectory of developmental recovery in VLBW infants may differ, mean Mental Development Index and Psychomotor Development Index scores were analyzed, with covariance for chronologic age. Cocaine-exposed infants performed more poorly in cognitive and motor skills when mean scores were compared; mean MDI and PDI scores were in

the low normal range for cocaine-exposed infants, whereas the mean scores were in the average range for the nonexposed group. Motor development outcomes were significantly lower for cocaine-exposed infants. When the incidence of developmental delay was compared, there was a significantly higher incidence of disability in both motor and mental domains in the cocaine-exposed group. For cognitive measures, almost half (47%) of the cocaine-exposed group were in the at-risk range (MDI <80), in comparison with only 24% of the nonexposed group. Thirty-three percent of the cocaine group had PDI scores in the risk range, versus 8% of the nonexposed group (□Table V).

Table V. Developmental outcomes

	Cocaine exposed (n = 30)	Nonexposed (n = 37)	*t*/Zc/*F*	*p*
Corrected age at follow-up (mo)*	16.6 ± 7	18.5 ± 7	1.1	NS
Bayley MDI*	83 ± 27	91 ± 19	2.7	<0.05†
Bayley MDI <80	47%	24%	1.9	<0.03
Bayley PDI*	85 ± 25	96 ± 18	4.2	<0.02†
Bayley PDI <80	33%	8%	2.6	<0.006

Zc, Statistical test of proportions with the continuity correction; *NS*, not significant.
*Values (except *t/Z*c/F and *p* values) are expressed as mean ± SD.
†Adjusted for chronologic age.

Because groups differed on incidence and severity of IVH, two separate analyses of covariance were run, with MDI and PDI scores as dependent variables and severity of IVH (0 to 4) as a covariate, to assess the effects of IVH on these outcome measures. In neither case was there any covariate effect ($F = 0.04$ and 0.41; p value not significant). Further, because a significant number of cocaine-exposed children were placed outside the care of their biologic mothers, test scores were also compared within the cocaine group on the basis of custody outcomes. Neither MDI scores (79 ± 23 vs 86 ± 29; t [$df = 28$] = 0.7, not significant) nor PDI scores (85 ± 17 vs 85 ± 29; t [$df = 28$] = 0.00, not significant) were significantly different for children placed outside the home versus those who remained in the care of their biologic mothers. However, because of the smaller sample sizes for analyses within the cocaine group, power may have been inadequate to detect the clinically significant higher MDI scores for the group reared by biologic mothers.

The IBR ratings were available for 19 cocaine-exposed and 34 nonexposed infants. Not all infants were rated, because one examiner was not trained to administer the IBR. Cocaine-exposed infants were rated as having more bodily tension (mean ± SD: 4.3 ± 2 vs 3.6 ± 2; t = 1.7; $df = 50$; $p < 0.05$), less sustained interest in test materials (mean ± SD: 5.4 ± 1 vs 5.9 ± 9; t = 1.9; $df = 50$; $p<0.05$), as less imaginative in their play (mean ± SD: 1.8 ± 4 vs 1.5 ± 5; t = 1.9; $df = 50$; $p<0.05$), and as less responsive to presented materials (mean ± SD: 5.7 ± 2 vs 6.4 ± 1; t = 1.8; $df = 50$; $p<0.05$).

When the distribution of scores was examined, a higher proportion (37%) of cocaine-exposed infants were rated as having "fleeting to easily distracted" attention spans versus 15% of nonexposed infants (Zc = 1.75; $p<0.04$). Similarly, 33% of the cocaine versus 3% (Zc = 2.9; $p < 0.005$) of the nonexposed infants were rated as "unreactive and unresponsive." Mean scores for the cocaine group, although consistently more deficient, were not in the clinically "suspect" ranges of the IBR.[17] Many items did not differ between groups, including those measuring infant responsivity to persons, fearfulness, general emotional tone, goal directedness, activity level, and cooperativeness.

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Discussion

Consistent with cocaine's known vascular effects, VLBW cocaine-exposed infants were at increased risk of IVH and developmental delays in this study. Although our findings are limited by the small sample size and by the significantly greater use of additional drugs by cocaine-using women, cocaine use, especially the "crack" form of cocaine that the women used, can plausibly be associated with destructive neural effects, according to findings of prior animal and human studies. Cocaine functions as a central nervous system stimulant, producing increased norepinephrine levels and subsequent vasoconstriction, tachycardia, and hypertension[19] in adults. As cocaine readily crosses the placenta, it may affect the fetus in similar ways. Volpe[6] postulated that fetal hypoxemia caused by impaired placental blood flow[20, 21] results in impaired fetal cerebrovascular autoregulation, analogous to animal findings.[22] Increases in blood pressure and in cerebral blood flow velocity, demonstrated in human studies,[23] could also lead to hemorrhages. Chasnoff et al.[24] originally reported the case of a newborn infant with two cerebral infarcts in the perinatal period after intrauterine cocaine exposure. One study reported ultrasonographic abnormalities, including IVH, in cocaine-exposed neonates versus drug-free, healthy infants,[25] but another found no differences between cocaine-exposed and nonexposed neonates in an inner city population.[26] Caution should be taken, however, in attributing the increased incidence of IVH solely to the effects of cocaine. As in other studies, maternal use of cocaine was accompanied by greater use of alcohol, marijuana, and cigarettes, and the sample size in our study was not large enough to disentangle the effects of cocaine alone from those of other drugs.

Only a few studies have addressed the issue of medical sequelae in preterm cocaine-exposed infants. In one cohort of 323 VLBW infants, there was no difference in the incidence of IVH between cocaine-exposed and nonexposed infants, although rates of seizure, abruptio placentae, and patent ductus arteriosus ligation were increased.[27] That study differed from ours in that meconium analyses were used in addition to urine screening and interview to determine fetal exposure. One third of their sample were identified through meconium assessment alone, and it is difficult to assess how their addition to the sample may have affected outcome findings. Women identified only by meconium assessment may be more casual, infrequent, or less severe users of cocaine, or they may have used it earlier in pregnancy, and their inclusion in samples may mask the effects of more chronic use. Volpe[6] suggested that IVH might occur only in the latter stages of gestation, or after birth, when the intraventricular musculature is developed. Other reports that found no relation between fetal cocaine exposure and IVH[28, 29] in preterm infants did not control for the confounding factors of BPD, gestational age, race, or social class. Comparison of cocaine-exposed and nonexposed infants within VLBW cohorts would need to account for BPD and lower GA, which are known correlates of increased risk of IVH.

We did not find decreased birth weight or lower GA when comparing cocaine-exposed infants with other VLBW infants, in contrast to strong findings of growth retardation in term samples.[4, 9-11] There may have been a higher rate of stillbirths or neonatal death associated with lower GA or birth weight in the cocaine-exposed infant sample, which would not have been ascertained in our recruitment. Finally, our design required matching for BPD status, and may have masked effects associated with BPD, such as earlier GA and smaller birth weight. The lack of differences on these medical variables between groups, however, strengthens our findings related to increased incidence of IVH.

To date, there has been little information on the developmental outcome of cocaine-exposed VLBW infants. In a sample of preterm infants assessed in the NICU, cocaine-exposed infants had inadequate arousal and attentional organization[30] and a suppressed cortisol response to stressful events.[31] Our findings indicate that, by the second year of life, VLBW infants exposed to cocaine in utero lag significantly in development, in comparison with their nonexposed counterparts, even when the effects of IVH and other medical complications are controlled. Cocaine-exposed infants were also perceived as deficient on dimensions of sustained attention, interest in objects, and play behavior.

Overall developmental scores for cocaine-exposed VLBW infants were in the risk range. The percentage of infants in the cocaine-exposed group with significant cognitive and motor disabilities was high, and could not be attributed to differences in birth complications or assessment age. Differences in outcome cannot solely be attributed to the effects of cocaine, because cocaine-using women were also more likely to use alcohol, marijuana, and tobacco. It is possible that the negative outcomes may relate to the increased use of these other substances, especially alcohol.[1-9] Cocaine-exposed VLBW infants also were less likely to be in the care of their biologic mothers; almost one third were in adoptive, relative, or foster care. Poor caregiving environments may account for some of the developmental deficits of the cocaine-exposed VLBW infants in our study.

The use of global assessments of functioning in this study may limit the ability to detect the impact of minor hemorrhages early in life. Subtle effects of neurologic abnormalities may not be apparent until older ages, when demands are greater and when more specific measures of neuropsychologic functioning can be used. Earlier studies found no effect of minor hemorrhages on child development, but more recent work[32] indicates that preterm children with a history of minor hemorrhages perform less well on some school readiness tasks than those with no history of hemorrhage.

There was also greater attrition in the cocaine-exposed group, which raises the possibility that only more compromised infants returned for follow-up. However, there were no differences in initial social, medical, or demographic variables between those who returned and those lost to follow-up.

Finally, the drug screening techniques used in the current study could have missed some drug-using women in the comparison group. However, this error would have decreased the likelihood of finding group differences.

Currently available follow-up studies suggest that healthy, cocaine-exposed infants born at term may be at risk for only subtle deficits in later outcome.[33] It appears, however, that VLBW infants with prenatal cocaine exposure may be at increased risk for neurologic complications, specifically IVH, and for significant later developmental delays, in comparison with nonexposed VLBW infants. Cocaine-exposed VLBW infants may be at increased risk because of the combined effects of cocaine exposure, other drug exposure, nonoptimal caregiving, and prematurity and its complications. Follow-up studies assessing the developmental correlates of cocaine exposure in VLBW cohorts are necessary to begin to develop appropriate services for this increasing group of children with enormous medical, educational, and social needs.

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