Prenatal Cocaine Exposure: Drug and Environmental Effects at 9 Years

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Objective To assess school-age cognitive and achievement outcomes in children with prenatal cocaine exposure, controlling for confounding drug and environmental factors.

Study design At age 9 years, 371 children (192 cocaine exposure [CE]; 179 non–cocaine exposure [NCE]) were assessed for IQ and school achievement in a longitudinal, prospective study from birth. An extensive number of confounding variables were controlled, including quality of caregiving environment, polydrug exposure, blood lead level, iron-deficiency anemia (IDA), and foster/adoptive care.

Results Prenatal cocaine exposure predicted poorer perceptual reasoning IQ, with a linear relationship of the concentration of the cocaine metabolite benzoylecgonine to the degree of impairment. Effects were mediated through birth head circumference, indicating a relationship with fetal brain growth. Negative effects of alcohol, lead, and marijuana exposure and positive effects of the home environment were additive. The CE children in foster/adoptive care had better home environments and lower lead levels. School achievement was not affected.

Conclusions Persistent teratologic effects of CE on specific cognitive functions and additive effects of alcohol, lead, and marijuana exposure; IDA; and the home environment were identified. Documenting environmental factors in behavioral teratology studies is important, because in this sample, CE was associated with better home environment and lower environmental risk in a substantial number of children. *(J Pediatr 2008;153:105-11)*

Hundreds of thousands of children exposed prenatally to cocaine in the 1980s and 1990s have now reached school age, but there is little information on their cognitive outcomes.[1] Animal studies document significant negative effects of fetal cocaine exposure, including alterations in brain structure and function and deficits in cognitive processes, especially attention, spatial working memory, and the ability to acquire new learning.[2,3] Conducting human studies is more difficult because of variability in timing, dose, and duration of exposure, as well as numerous confounding factors, including low socioeconomic status; maternal psychological distress, lower IQ, and low education level; polydrug exposure; poor prenatal care; iron-deficiency anemia (IDA); and lead exposure.[4] Out-of-home placement is common, and there often is significant, selective attrition in longitudinal studies.

Recent large, well-controlled studies with high retention rates have demonstrated negative effects of prenatal cocaine exposure on fetal growth, birth weight, and infant behavior.[5,6] Specific language and cognitive deficits have been reliably found in preschool assessments;[7-10] however, there are few methodologically adequate reports on children at school age, when earlier problems may resolve or may become more pronounced in response to greater cognitive demands, and the findings are inconsistent.[11,12] The present study investigated cognitive outcomes and school achievement in a large sample of children followed from birth after prenatal cocaine exposure, controlling for confounding factors.

CE	Cocaine exposure	OR	Odds ratio
CI	Confidence interval	PPVT-R	Peabody Picture Vocabulary Scale–Revised
df	Degrees of freedom	SE	Standard error
Hb	Hemoglobin	SF	Serum ferritin
HOME	Home Observation of the Environment	TS	Transferrin saturation
IDA	Iron-deficiency anemia	WAIS-R	Wechsler Adult Intelligence Scale–Revised
MANCOVA	Multivariate analysis of covariance	WISC-IV	Wechsler Intelligence Scale for Children–Fourth Edition
MANOVA	Multivariate analyses of variance		
MCV	Mean corpuscular volume	WJTOA-III	Woodcock-Johnson–III Tests of Achievement
NCE	Non–cocaine exposure		

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METHODS

Subjects

The study subjects included 9-year-old children enrolled in a longitudinal study from birth (September 1994 to June 1996). Mothers were recruited at a large urban county teaching hospital from a high-risk population screened for drug use. Women at high risk for drug use due to lack of prenatal care, behavior suggesting intoxication, a history of involvement with the Department of Human Services, or self-admitted use underwent toxicology screening. Maternal and infant urine samples were obtained immediately before or after labor and delivery and analyzed for cocaine metabolites, cannabinoids, opiates, phencyclidine, and amphetamines, using the Syva Emit method (Syva Co, Palo Alto, CA), followed by gas chromatography. Meconium collected from infants' diapers was analyzed for drug metabolites, including benzoylecgonine, meta-hydroxybenzoylecgonine, cocaethylene, cannabinoids, opiates, phencyclidine, amphetamines, and benzodiazepines. Screening assays were conducted using polarization immunoassay reagents (fluorescence polarization immunoassay; US Drug Testing Laboratories, Inc, Des Plaines, IL). Cutoff levels were as follows: cocaine and metabolites, 25 ng/g; opiates, 25 ng/g; amphetamines, 100 ng/g; phencyclidine, 25 ng/g; tetrahydrocannabinol, 25 ng/g. Confirmatory assays were conducted. Specificity for both urine and meconium cutoffs was 99%.

An infant was placed in the cocaine exposure (CE) group if the mother reported use during pregnancy or if her urine or her infant's urine or meconium were positive, or in the non–cocaine exposure (NCE) group if maternal self-report, urine, and meconium assays were all negative. Of the 647 mothers and infants identified, 54 were excluded (20 CE, 34 NCE)—15 for no meconium, 2 due to Down syndrome, 16 due to maternal psychiatric history, 2 due to primary heroin use, 5 because of positive human immunodeficiency virus status, 1 due to maternal IQ $<$ 70, 1 due to fetal alcohol syndrome, 2 due to maternal age under 19 years, 3 due to a medical illness in the infant, 4 due to chronic illness in the mother, and 3 for other reasons. A total of 155 women (49 CE, 106 NCE) refused to participate; 23 (9 CE, 14 NCE) did not come to the enrollment visit. Consequently, a total of 415 women and infants (218 CE, 197 NCE) were enrolled.

Approval for human research was received from the Institutional Review Boards of MetroHealth Medical Center and University Hospitals of Cleveland. Compliance with the Health Insurance Portability & Accountability Act of 1996 (HIPPA) was maintained. Written consent was obtained from the parent/guardian of each subject and, when appropriate, from the subject himself or herself. All subjects were protected by a writ of confidentiality (DA-04-03) which prevents the principal investigator from being forced to reveal any subject information from the research, even under court order.

Procedures

After birth, a research assistant interviewed each mother about prenatal drug use.[13] To quantify use, the mother was asked to recall frequency and amount for the month before pregnancy and for each trimester of pregnancy. The number of tobacco cigarettes and marijuana "joints" smoked per day and the number of drinks of beer, wine, or hard liquor consumed per day (with each drink equivalent to 0.5 oz of absolute alcohol) were computed. For cocaine, the number of "rocks" consumed and the amount of money spent per day were noted. For each drug, frequency of use was recorded on a Likert-type scale ranging from 0 (not at all) to 7 (daily use), converted to reflect the average number of days per week that a drug was used, except for cigarettes, which was recorded as the number smoked per day. Frequency was multiplied by the amount used per day to compute an average use score for the month before pregnancy and for each trimester. This score was then averaged to obtain a total score. Measures were updated at each follow-up.

Maternal education level and socioeconomic status (on public assistance vs not) were determined. The Peabody Picture Vocabulary Scale–Revised (PPVT-R),[14] and the block design and picture completion subscales of the Wechsler Adult Intelligence Scale–Revised (WAIS-R)[15] were used to obtain measures of maternal vocabulary and nonverbal intelligence. The General Severity Index, a summary scale of the Brief Symptom Inventory,[16] was used to measure psychological distress. Maternal race, age, parity, and number of prenatal visits and infant gestational age, birth weight, length, head circumference, and Apgar scores were obtained from hospital records. The Hobel neonatal risk score[17] was used to assess neonatal risk.

At age 2 and 4 years, all children participated in a separate study of lead exposure and IDA.[4] Blood samples could not be obtained from some children due to parental refusal, inability to draw blood without undue stress, child illness, or logistic difficulties. The numbers of subjects with valid blood measurements at 2 and 4 years were 143 and 274, respectively. For the 122 children with blood measurements at both times, the values were averaged. A greater percentage of African-American and married women and a lower percentage of foster parents consented to blood collection. Elevated blood lead values were defined as $\geq$10 mg/dL at either 2 or 4 years.

Hematologic assessments included hemoglobin (Hb), mean corpuscular volume (MCV), percent transferrin saturation (TS), serum ferritin (SF), and lead. Abnormal blood values for iron deficiency with and without anemia followed the recommendations of the American Academy of Pediatrics and previous studies[18,19] for cutoff values at 2 years (Hb $<$ 11.0 g/dL; MCV, 70 m^3, TS, 10%; SF, 12 g/L); and at 4 years (Hb $<$ 11.2 g/dL, MCV, 73 m^3; TS, 12%; SF, 12 g/L).

At age 9 years, examiners unaware of the children's cocaine exposure status individually administered the Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV)[19] and the Woodcock Johnson–III Tests of Achievement (WJTOA-III)[20] to assess math, reading, and written lan-