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## Original Articles

# Cocaine, Anemia, and Neurodevelopmental Outcomes in Children: A Longitudinal Study

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**ABSTRACT.** This longitudinal study investigated the rates of iron-deficiency (ID) and iron-deficiency anemia (IDA) among prenatally cocaine-exposed and nonexposed two- and four-year-old children and assessed their relationships to neurodevelopmental outcomes. The sample consisted of 143 two-year-old (70 exposed and 73 nonexposed) and 274 four-year-old (139 exposed and 135 nonexposed) low socioeconomic status children recruited from an ongoing longitudinal study. Hematological assessments included hemoglobin, serum ferritin, mean corpuscular volume, transferrin saturation, and blood lead levels. The neurodevelopmental outcomes consisted of the Bayley Mental (MDI) and Motor (PDI) Development indices at two years, and the Wechsler Preschool and Primary Scales of Intelligence (WPPSI) and the Peabody Developmental Motor Scales (PDMS) at four years. The rate of IDA in four-year-old children was significantly greater among the cocaine-exposed compared to the nonexposed group ($p = .026$), while the rates at two years were not significant. Exposure to IDA at two years was associated with a significant decrease in concurrent motor scores ($p = .011$) after adjustment for relevant covariates. Peak exposure to IDA, defined as being anemic at 2 and/or 4 years of age, was associated with a significant ($p < .05$) decrease in Full Scale IQ after adjustment. Cocaine exposure was not a significant predictor of Full Scale IQ with the inclusion of peak IDA and lead in the model. These findings indicate the need for greater pediatric surveillance of IDA and lead in cocaine-exposed infants, in order to reduce long-term neuropsychological deficits. *J Dev Behav Pediatr 25:1–9, 2004.* Index terms: *iron-deficiency, lead, prenatal cocaine-exposure, children, neurodevelopment.*

A number of studies on the effect of prenatal cocaine exposure on child neurodevelopmental outcomes have indicated behavioral abnormalities[1–6] and mental, motor, and language impairments;[7–11] although other studies,[12–14] and a recent systematic review,[15] have not found consistent differences.

In the prenatal period, impaired oxygen and nutrient delivery to the fetus can occur as an indirect consequence of maternal cocaine use during pregnancy.[16] Besides fetal malnutrition, prenatal cocaine exposure is also associated with prematurity[17] and low birth weight.[18] All conditions may place the infant at risk for low iron stores at birth.[19,20] Depressed neonatal fat stores and diminished lean body mass were found in newborn infants even after maternal weight for height at conception and pregnancy weight gain were analytically controlled.[21] In the postnatal period, factors such as poverty and quality of the home environment increase the vulnerability of children to postnatal risks such as iron deficiency without anemia (ID) and with anemia (IDA).[22] These include poor diet,[23–25] pica (eating non-food substances such as dirt), low socioeconomic conditions,[22] maternal (low education and IQ, number of children, stress)[22] and caretaking factors. ID is also thought to enhance gastrointestinal absorption of lead and may even increase cellular transport of lead.[26]

In early childhood, ID and IDA are common problems particularly for disadvantaged children. Data from the National Health and Nutrition Examination Survey III (NHANES III) indicate that ID and IDA are prevalent at 9% and 3%, respectively, among toddlers 1 to 2 years of age; and as 3 and less than 1%, respectively, among children 3 to 5 years of age.[22] Several studies have shown that IDA

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is associated with poorer performance on standardized assessments of mental[27–30] and motor development,[30,31] as well as poorer behavioral outcomes.[32] Iron deficiency without anemia in early childhood does not have conclusive evidence on neurodevelopment.[33] However, a recent study[34] reported lower standardized math scores among ID school-aged children and adolescents. The reversal of IDA does not necessarily improve functional outcomes, suggesting that ID at a critical period of brain growth and differentiation may produce long lasting deficits.[30,31,35,36]

Although previous studies of cocaine-exposed infants have considered other substance use and a number of sociodemographic and maternal variables as modifiers and mediators of the variability in neurodevelopment, other postnatal risks such as ID/IDA that may account for some of the variability in infant neurodevelopmental sequelae have not been evaluated. Iron deficiency in cocaine-exposed children can be acquired pre- or postnatally through biologic, maternal, infant, and environmental factors through the several mechanisms described previously. Therefore, we hypothesized that (1) cocaine-exposed children would have higher a rate of ID or IDA compared to nonexposed children and (2) that ID/IDA would be independently associated with deficits in neuropsychological development after adjustment for cocaine, lead levels, maternal, infant, and environmental factors.

## METHOD

### Study Sample

The sample was recruited from a cohort of children participating in a longitudinal study of the effects of prenatal cocaine exposure on development. The characteristics of the cohort and the method of recruitment have been described previously[6,37] and will only be summarized here.

From October 1994 through October 1996, a total of 415 infants (218 cocaine-exposed, 197 nonexposed) were recruited at birth from a large urban teaching hospital. Cocaine-exposed infants were identified through maternal urine screen, clinical interview, or infant meconium screen. Comparison infants were negative on all parameters and drawn from the same racial and social class population. Groups did not differ in ethnicity, gender, or prevalence of very low birth weight. Exclusion criteria for enrolling women were as follows: primary drug of choice was not cocaine, HIV positivity, history of moderate/severe mental retardation, severe psychiatric disorders requiring medication, or significant medical illness (diabetes, cancer). Approximately 86% of the sample were African-Americans and over 75% belonged to socioeconomic status (SES) category V (Hollingshead). Both groups of infants were also polydrug-exposed with cocaine-using mothers using significantly more marijuana than the nonexposed mothers. The presence of other drugs, such as amphetamine, barbiturate, benzodiazepine, heroin, and phencyclidine, were minimal for cocaine users and virtually nonexistent for noncocaine users. At the scheduled two-year visit, 372 infants returned for follow up testing with a 92% retention rate. At the four-year visit, 387 children returned for testing with a 95% retention rate.

Mothers/foster parents of these infants tested at two and four years were approached to participate in the study of iron deficiency with and without anemia. Venous blood samples were drawn by trained pediatric phlebotomists at the two time periods. Blood samples could not be obtained from some children at each assessment time due to parental refusal, inability to draw blood without undue stress, child sickness, or logistical difficulties. The numbers of subjects with valid blood measures at age two and four years were 143 and 274. A subgroup of 122 children had measures at both 2 and 4 years of age. Evaluation of selection bias between the participants and nonparticipants of this study indicated that a significantly greater percentage of African-American and married women, and a lower percentage of foster parents, consented for blood collection. Other maternal and infant characteristics did not differ between the groups.

This study was approved by the Institutional Review Boards of the participating hospital, and written informed consent was obtained from the mother/foster parent prior to infant's participation.

## PROCEDURES

### Maternal Assessments

As part of the parent study, the biologic mother was interviewed soon after delivery regarding her drug use and other substances during pregnancy using the structured interview format of the maternal postpartum questionnaire.[8,38] Cocaine and marijuana exposure were characterized by frequency of use, ranging from six (several times a day) to one (once a month), and duration of use during pregnancy. The number of marijuana joints smoked weekly and the number of cocaine rocks used were also calculated. Alcohol exposure was obtained by multiplying the number of drinks described as taken on each occasion by the number of drinking occasions per week. Each drink (12 ounces of beer, four ounces of wine, cocktail with shot) was considered 0.5 ounces of alcohol. Cigarette exposure was quantified by counting the number of packs smoked per week and multiplying by 20. Maternal IQ was estimated using the Peabody Picture Vocabulary Test-Revised (PPVT-R) Scale.[39] Mothers and caregivers were also administered the Brief Symptom Inventory[40] which yielded an overall measure of self-reported severity of psychological distress, the Global Severity Index (GSI). Other characteristics such as maternal race, age, SES, gravida, parity, and number of prenatal care visits were obtained at the time of infant birth from the medical records.

### Infant Measures

Infant measures were taken at the time of birth from the hospital record and included infant birth outcomes, and Apgar scores. The Hobel Neonatal Risk Index[41] was computed as a measure of the severity of medical complications and illness for the period immediately after birth.

### Hematologic Assessments

Hematologic assessments included hemoglobin (Hb), mean corpuscular volume (MCV), % 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[23] and previous studies.[27,30] They were as follows: the cutoff values for two year olds (Hb < 11.0 g/dl, MCV $\leq$ 70 $\mu m^3$, TS $\leq$ 10%, SF $\leq$ 12 $\mu$g/liter); and for four year olds (Hb < 11.2 g/dl, MCV $\leq$ 73 $\mu m^3$, TS $\leq$ 12%, SF $\leq$ 12 $\mu$g/liter). For estimating rates, elevated blood lead values were defined as $\geq$ 10 $\mu$g/dL.

Iron status was defined as follows: (1) nonanemic (normal Hb levels) and all three iron measures (SF, MCV, TS) in the normal range (iron sufficient), (2) nonanemic (normal Hb levels) and any two of three iron measures (SF, MCV, TS) in the abnormal range (iron deficiency [ID]), (3) anemic (abnormal Hb levels) and any two of three iron measures (SF, MCV, TS) in the abnormal range (iron deficiency anemia [IDA]). Using this definition we had 3 and 7 children with ID and IDA, respectively, at two years; and 8 and 5 children with ID and IDA, respectively, at four years. To provide the most powerful possible test of exposure, a peak IDA index was defined as having IDA at any of the assessments at ages 2 and/or 4 years. The peak analysis included children who had hematology measures at both 2 and 4 years, so that the children could be correctly classified as being either nonanemic or anemic within the defined time interval. By this criterion, 11 children had IDA at some point in the preschool years. A peak ID index was not used in the analysis because the differences in mental and motor outcomes of ID and iron sufficient children were minimal.

## Neurodevelopmental Examinations

Examinations were conducted at the research laboratory by trained observers blinded to the cocaine, iron, and lead status of the child. The Bayley Mental Development Index (MDI)[42] was used to assess overall cognitive development and the Bayley Psychomotor Development Index (PDI)[42] was used to assess gross and fine motor development at two years of age. The MDI and PDI were adjusted for infant prematurity. At four years, a prorated version of the Wechsler Preschool and Primary Scales of Intelligence (WPPSI)[43] was used to assess overall Full Scale IQ, as well as Verbal (subscales: arithmetic, vocabulary, information) and Performance IQ (subscales: block design, object assembly, picture completion). The Peabody Developmental Motor Scales[44] were used to assess gross (PDMS-GM) and fine (PDMS-FM) motor abilities at four years.

## Environmental Measures

The Home Observation of the Environment (HOME)[45] was administered to the caregiver in an interview format as a measure of the quality of the caregiving environment at the time of their follow-up visit to the research laboratory.

## Statistical Analysis

The comparison of demographic, maternal, infant, and hematology measures between cocaine-exposed versus nonexposed children were analyzed using t-tests for continuous data and chi-square for categorical data. The prevalence of ID, IDA, and high lead levels was also calculated and compared for the cocaine-exposed and nonexposed groups. Due to the minimal differences in neurodevelopmental scores between ID and iron sufficient children, they were collapsed into the nonanemic group for all analyses. Therefore the anemic (IDA) status of the child was the exposure of interest. Additionally, since the majority of the children belonged to the cocaine-exposed group (only 1 child with IDA was in the nonexposed group), the interaction effect of cocaine with IDA was not considered due to the problem of precision in the estimated coefficients from the regression models.

The effect of IDA on neurodevelopmental outcomes at age 2 and 4 years was evaluated using multiple regression analysis for exposure measured at ages 2 and 4 years, respectively. For these two regression models, nontime variant covariates and covariates specific to the age were used for adjustment of data. For the multiple regression analysis of peak IDA on neurodevelopmental outcomes at age 4 years, the time-dependent covariates were replaced by the means of the measures made at the two time periods.

The regression models included cocaine exposure for all assessments. Other candidate covariates to be included in the final regression model were selected on the basis of their relationship to neurodevelopmental outcomes and to IDA, and those that were related to selection bias. These variables were grouped according to maternal factors at birth (ethnicity, SES, maternal age, parity, prenatal visits, maternal education, marital status, maternal IQ, GSI, severity of alcohol, tobacco, and marijuana use), infant characteristics at birth (birth weight, birth length, head circumference, APGAR scores, Hobel risk score, gestational age, and gender), and environmental (lead, HOME, and nonmaternal care). The HOME scores were not available for the entire two-year cohort and hence were not used for the two-year analysis. Time dependent variables included the GSI and lead levels. The covariates were entered into the model in the order listed above.

Pearson's product moment and Spearman correlations were computed between the outcome and other risk factor variables at each age. Due to the large number of potential covariates, several levels of checking were used to select the most parsimonious model. First, covariates were considered for the model if they were significantly different between cocaine exposed and nonexposed groups and/or related to the outcome at $p < 0.10$. Second, the covariates were entered stepwise into the model and were retained only if they contributed to at least a 10% change in the estimated regression coefficients for the exposure (IDA). Third, collinearity statistics using tolerance was used to further screen the variables entered into the model. Covariates with tolerance values close to zero were eliminated. These included infant birth outcome variables (mediating) that were highly collinear with cocaine status. Interaction terms of IDA with cocaine/other covariates were not included due to the limited size of the IDA group. The forced-entry procedure was utilized for the final

regression model. For all analyses significance was assessed at $p < 0.05$.

## RESULTS

### Sample Characteristics

A total of 143 two-year-old (70 cocaine-exposed and 73 nonexposed) and 274 four-year-old (139 cocaine-exposed and 135 nonexposed) children participated in this study. The mothers of 2- and 4-year-old cocaine-exposed children (Table 1) were significantly older, of higher parity, had greater psychological distress, had fewer prenatal visits, and increased use of substances such as alcohol, tobacco, and marijuana. The cocaine-exposed infants (Table 1) had significantly lower birthweight, birth length, and head circumference, with a higher proportion placed in non-maternal care at both assessment periods.

### Rates of ID/IDA/Lead Levels

The rates of IDA in the two-year cohort were 7.1% among the cocaine-exposed compared to 1.4% among the nonexposed children, but this difference was not significant. In the four-year cohort, a total of five children with IDA were found only in the cocaine-exposed group and were significantly different from the nonexposed group (3.6% versus 0%, $p = 0.026$). The ID rate in the two-year-old children was not different (1.4% in cocaine-exposed versus 2.7% in nonexposed). The rate of ID in the four-year group was also not different (3% in cocaine-exposed versus 3% in nonexposed). Blood lead exposure ($\geq$10 μg/dL) was not different between the cocaine-exposed and nonexposed groups at both ages 2 years (28% versus 36%) and four years (21% versus 17%).

### Tests of the Hypothesis

The ID and iron sufficient children were collapsed into the nonanemic group due to the minimal neurodevelopmental differences for all analyses. The differences between ID and iron sufficient children for the peak ID index were not significant ($p > 0.05$) for Performance (88.6 ± 15.0 versus 93.7 ± 16.5), Verbal (81.9 ± 12.3 versus 80.2 ± 11.3) and Full Scale IQ (83.5 ± 13.4 versus 85.2 ± 13.1), respectively. These differences were also not significant for the concurrent two- and four-year analyses. Therefore the two categories used were anemic (IDA) and nonanemic (ID and iron sufficient) children.

Variables that were significantly different between the cocaine-exposed and nonexposed groups (Table 1), and those that were related to neurodevelopmental measures (Tables 2 and 3) were considered as potential covariates. Inclusion of ethnicity, prenatal care, maternal education, GSI, alcohol, cigarette, and marijuana use did not

**Table 1. Maternal and Infant Comparison of the Cocaine-Exposed and Nonexposed Children**

| | 2 yr Cohort | | | | | | 4 yr Cohort | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cocaine + (n = 70) | | | Cocaine − (n = 73) | | | Cocaine + (n = 139) | | | Cocaine − (n = 135) | | |
| Variables | Mean | | SD | Mean | | SD | $p^a$ | Mean | | SD | Mean | | SD | $p^a$ |
| Maternal at birth | | | | | | | | | | | | | | |
| Ethnicity (non-white) | | 61% | | | 62% | | 0.703 | | 84% | | | 85% | | 0.816 |
| Socioeconomic (low) | | 68% | | | 71% | | 0.966 | | 98% | | | 98% | | 0.978 |
| Maternal age | 30.0 | | 5.0 | 26.0 | | 5.0 | 0.000* | 29.7 | | 5.0 | 25.5 | | 4.6 | 0.000* |
| Parity | 3.6 | | 2.0 | 2.8 | | 2.1 | 0.039* | 3.5 | | 1.8 | 2.8 | | 2.0 | 0.002* |
| Prenatal visits | | 13% | | | 8% | | 0.350 | | 15% | | | 8% | | 0.073 |
| Maternal education | 11.9 | | 1.5 | 11.9 | | 1.3 | 0.964 | 11.7 | | 1.7 | 12.0 | | 1.5 | 0.138 |
| Married | | 9% | | | 18% | | 0.071 | | 10% | | | 19% | | 0.045* |
| Maternal IQ | 77.8 | | 19.1 | 78.0 | | 5.7 | 0.950* | 74.4 | | 16 | 78.0 | | 15 | 0.063* |
| Global severity index | 0.6 | | 0.6 | 0.4 | | 0.5 | 0.050* | 0.8 | | 0.7 | 0.5 | | 0.5 | 0.000* |
| Alcohol use | | 56% | | | 42% | | 0.002* | | 87% | | | 66% | | 0.000* |
| Cigarette use | | 58% | | | 26% | | 0.001* | | 87% | | | 37% | | 0.000* |
| Marijuana use | | 35% | | | 9% | | 0.001* | | 49% | | | 12% | | 0.000* |
| Infant at birth | | | | | | | | | | | | | | |
| Birth weight (g) | 2718 | | 31 | 3112 | | 49 | 0.000* | 2730 | | 70 | 3078 | | 15 | 0.000* |
| Birth length (cm) | 47.0 | | 49 | 49.0 | | 3.4 | 0.005* | 47.5 | | 3.4 | 48.9 | | 3.9 | 0.002* |
| Head circumference (cm) | 32.6 | | 3.0 | 33.7 | | 2.5 | 0.013* | 32.4 | | 1.7 | 33.5 | | 2.5 | 0.000* |
| Apgar (5 min) | 8.8 | | 0.7 | 8.8 | | 0.6 | 0.804 | 8.8 | | 0.6 | 8.7 | | 0.8 | 0.377 |
| Hobel risk score | 8.2 | | 17.8 | 5.6 | | 13.6 | 0.317 | 6.1 | | 11.8 | 6.6 | | 17.1 | 0.779 |
| Gestational age (wk) | 3.78 | | 2.5 | 38.3 | | 2.6 | 0.250 | 37.9 | | 2.2 | 38.3 | | 3.0 | 0.141 |
| Gender (% male) | | 31% | | | 32% | | 0.957 | | 45% | | | 51% | | 0.281 |
| Environmental | | | | | | | | | | | | | | |
| Lead | 8.3 | | 4.7 | 8.9 | | 5.5 | 0.490 | 6.7 | | 4.0 | 7.4 | | 4.2 | 0.137 |
| HOME | | | | | | | | 42.3 | | 5.6 | 40.9 | | 7.0 | 0.066 |
| Non-maternal care | | 35% | | | 4% | | 0.001* | | 57.4% | | | 7% | | 0.000* |

[a]$p$ was calculated using $t$-test for means and $\chi^2$ for frequencies.
*Significant at $p < 0.05$.

**Table 2. Correlations of Maternal, Environmental, and Infant Characteristics with Cognitive Outcomes at Each Follow-up Period**

| Variables | 2 yr MDI | 4 yr Verbal IQ | 4 yr Perform IQ | 4 yr Full Scale IQ |
|---|---|---|---|---|
| Maternal at birth | | | | |
| Ethnicity | −0.19** | −0.14** | −0.09 | −0.12** |
| Maternal age | 0.02 | 0.02 | 0.01 | 0.02 |
| Parity | −0.18** | −0.17* | −0.20** | −0.18** |
| Prenatal visits | −0.06 | −0.01 | 0.14** | 0.07 |
| Maternal education | 0.09 | 0.05 | 0.18** | 0.14** |
| Marital status | 0.08 | 0.08 | 0.15** | 0.13** |
| Maternal IQ (PPVT-R) | 0.05 | 0.06 | 0.16** | 0.13** |
| Global Severity Index | −0.07 | −0.07 | −0.09 | −0.10 |
| Alcohol use | −0.13 | −0.03 | −0.01 | −0.02 |
| Cigarette use | −0.06 | 0.01 | −0.04 | −0.02 |
| Marijuana use | 0.11 | 0.01 | −0.03 | −0.02 |
| Cocaine exposure | −0.20** | −0.01 | −0.07 | −0.04 |
| Infant at birth | | | | |
| Birth weight | 0.12 | 0.07 | 0.18** | 0.14** |
| Birth length | 0.14* | 0.10* | 0.20** | 0.18** |
| Head circumference | 0.18** | 0.12** | 0.20** | 0.18** |
| Apgar (5 min) | −0.06 | 0.07 | 0.06 | 0.07 |
| Hobel risk score | −0.06 | −0.08 | −0.18** | −0.15** |
| Gestational age | −0.09 | 0.09 | 0.19** | 0.16** |
| Gender | −0.18** | −0.14** | −0.08 | −0.11* |
| Environmental | | | | |
| Lead | −0.22** | −0.17** | −0.32** | −0.27** |
| HOME | | 0.27** | 0.26** | 0.29** |
| Nonmaternal care | −0.10 | −0.03 | −0.05 | −0.03 |

MDI, mental development index; PPVT-R, Peabody Picture Vocabulary Test-Revised; HOME, Home Observation of the Environment.
*Significant at $p < 0.10$.
**Significant at $p < 0.05$.

contribute to a 10% change in the coefficient values for IDA or cocaine. Further, some independent variables were highly collinear with the other variables in the model and thus required elimination. Variables such as parity, marital status, maternal age, birth weight, birth length, head circumference, HOBEL score, and nonmaternal care that had lower tolerance values were collinear with cocaine status. The covariates thus selected for the final model were maternal IQ, infant gender, lead levels, and HOME scores (only for four-year assessments).

The analysis (Table 4) of two-year psychomotor development index (PDI), with two-year IDA exposure and covariates, predicted a mean decrease of 12.9 points ($p = 0.012$). The analysis of four-year Full Scale IQ, with peak IDA exposure and covariates, predicted a mean decrease of 8.1 points ($p = 0.047$).

The contribution of the independent variables to the cognitive outcomes are listed in the order of importance and are as follows: For the two-year mental outcomes with concurrent two-year IDA exposure and covariates, the significant predictors were cocaine exposure, lead levels, and gender. For the four-year Full Scale IQ measures with concurrent four year IDA exposure and covariates, the significant predictors were HOME scores and lead levels. For the concurrent four-year Performance IQ analysis with exposure and covariates, the significant predictors were lead levels, HOME scores, and cocaine status. For the concurrent four-year Verbal IQ analysis with exposure and covariates, the significant predictors were HOME scores and gender.

The results of the peak analysis (Table 5) indicated that four-year Full Scale IQ was significantly predicted by IDA and lead levels, verbal IQ was explained by HOME scores, and performance IQ was explained by maternal IQ, cocaine exposure, and lead. There was not a significant trend ($p < 0.10$) for peak IDA exposure to explain both Verbal and Performance IQ.

For the analysis of two-year PDI with concurrent two-year IDA exposure and covariates, the significant contributors to the model were gender and IDA. The models predicting four-year gross and fine motor outcomes were not significantly explained by any of the independent variables in the model.

## DISCUSSION

The present study is the first to report rates of ID, IDA, and lead levels among cocaine-exposed children and provides insight into the extent of the problem among these high-risk children. Higher rates of IDA were found in the cocaine-exposed group at both ages and were significantly higher in the exposed versus the nonexposed in the four-year-old children. The rates of IDA in the two- and four-year-old cocaine-exposed groups was higher than the national averages reported by the NHANES III survey, while the rates in the nonexposed group was similar to the

**Table 3. Correlation of Maternal, Infant, and Environmental Risk Characteristics with Motor Outcomes at Each Follow-up Period**

| Variables | 2 yr PDI | 4 yr gross motor | 4 yr fine motor |
|---|---|---|---|
| Maternal at birth | | | |
| Ethnicity | −0.17** | 0.06 | 0.01 |
| Maternal age | 0.06 | 0.11* | 0.09 |
| Parity | −0.02 | 0.13** | 0.12* |
| Prenatal visits | −0.04 | 0.03 | 0.01 |
| Maternal education | 0.17** | 0.02 | 0.08 |
| Marital status | −0.01 | 0.09 | 0.10* |
| Maternal IQ (PPVT-R) | 0.01 | −0.14** | −0.05 |
| Global Severity Index | 0.01 | −0.04 | −0.07 |
| Alcohol use | −0.04 | −0.05 | −0.03 |
| Cigarette use | −0.11 | −0.04 | −0.01 |
| Marijuana use | 0.09 | 0.05 | −0.05 |
| Cocaine exposure | −0.1 | −0.05 | −0.06 |
| Infant at birth | | | |
| Birth weight | 0.03 | 0.16** | 0.05 |
| Birth length | 0.01 | 0.12 | 0.02 |
| Head circumference | 0.07 | 0.13** | 0.04 |
| Apgar (5 min) | −0.04 | 0.09 | 0.07 |
| Hobel risk score | −0.08 | −0.16** | −0.09 |
| Gestational age | 0.09 | 0.13** | 0.07 |
| Gender | −0.21** | −0.03 | −0.14** |
| Environmental | | | |
| Lead | −0.02 | 0.10 | 0.04 |
| HOME | | −0.02 | 0.10 |
| Nonmaternal care | −0.03 | −0.09 | −0.15** |

PDI, psychomotor development index; PPVT-R, Peabody Picture Vocabulary Test-Revised; HOME, Home Observation of the Environment.
*Significant at $p < 0.10$.
**Significant at $p < 0.05$.

national rates.[22] The fact that the majority of children who had IDA belonged to the cocaine-exposed group suggests that there may be some mechanism by which these exposed children were at higher risk. One speculation is that the iron stores of cocaine-exposed children may be lower at birth, possibly due to maternal malnutrition or preterm delivery. During infancy, the lower iron stores may become depleted faster because of the increased need for iron during early childhood thus placing these children at higher risk for IDA. This increased need is also common with preterm and low birth weight infants.[19,20] In this study we found no correlation between IDA and infant birth outcomes. Both cocaine-exposed and nonexposed children from this cohort were from equally disadvantaged homes, indicating that environmental factors and diet may not be entirely responsible for the differential rate of IDA in these groups.

The present study found that peak IDA was significantly associated with Full Scale IQ deficits at four years, even after adjustment for cocaine and other variables related to early child development. These results suggest that chronic exposure to IDA may have long-term cognitive implications. Several other studies have also shown that IDA in early infancy may affect subsequent cognitive development at later years.[30,34,36,46,47] One recent study[48] indicates that umbilical cord iron status (fetal iron status) was associated with diminished mental performance at five years of age. In the present study, history of exposure to IDA was also weakly related to lower Verbal and Performance IQ. An interesting finding was that IDA was not a mediator of cocaine exposure effects but had independent effects on cognition at later years. Although prenatal cocaine exposure may be a potent neuroteratogen for postnatal mental outcomes,[11] our results indicate that factors such as IDA must be considered in future studies. In this study cocaine-exposed children with IDA had a two-fold decrease in Full Scale IQ scores when compared with children with cocaine-exposure and no IDA. Independently, both cocaine and IDA alter dopamine neurotransmission,[49,50] a major factor in learning and cognition. Therefore we speculate that the greater deficit in cognitive outcomes for children with both cocaine and IDA exposures may be through the dopaminergic

**Table 4. Adjusted Association Between Iron Deficiency Anemia (IDA) and Neurodevelopmental Outcomes Based on Multiple Regression**

| Assesments[a] | Estimated Effect Size | Standard Error | $p$ | $R^{2c}$ |
|---|---|---|---|---|
| 2-yr IDA with MDI | −3.6 | 5.2 | 0.488 | 0.15 |
| PDI | −12.9 | 5.1 | 0.012* | 0.11 |
| 4-yr IDA[b] with 4-yr full scale IQ | −6.2 | 5.7 | 0.280 | 0.14 |
| Verbal IQ | −5.1 | 5.5 | 0.352 | 0.10 |
| Performance IQ | −5.8 | 6.2 | 0.352 | 0.15 |
| Gross motor | −7.9 | 6.2 | 0.202 | 0.04 |
| Fine motor | −2.4 | 4.5 | 0.591 | 0.05 |
| Peak IDA[b] with 4-yr full scale IQ | −8.1 | 4.0 | 0.047* | 0.20 |
| Verbal IQ | −6.9 | 3.9 | 0.078 | 0.14 |
| Performance IQ | −7.9 | 4.3 | 0.068 | 0.23 |
| Gross motor | −3.8 | 4.7 | 0.415 | 0.04 |
| Fine motor | −4.5 | 3.4 | 0.187 | 0.06 |

MDI, mental development index; PDI, psychomotor development index.
[a]For all the assessments the core model included cocaine status, gender, maternal IQ, and lead.
[b]For the 4-yr and peak assesments, the variables included the core model plus HOME scale.
[c]$R^2$ values given are for all the variables in the model.
*$p < 0.05$

**Table 5. Regression Model of Peak Iron Deficiency Anemia Exposure and Covariates with Four-Year Cognitive Outcomes**

| | Verbal IQ (n = 122) | | | Performance IQ (n = 122) | | | Full Scale IQ (n = 122) | | |
|---|---|---|---|---|---|---|---|---|---|
| Predictor variables | β | SD | *p* | β | SD | *p* | β | SD | *p* |
| Maternal IQ | 0.004 | 0.07 | 0.952 | 0.2 | 0.07 | 0.016* | 0.10 | 0.07 | 0.130 |
| Cocaine exposure | −1.2 | 2.2 | 0.581 | −5.4 | 2.4 | 0.027* | −3.5 | 2.3 | 0.128 |
| Gender | −3.2 | 2.2 | 0.141 | −3.7 | 2.4 | 0.133 | −3.6 | 2.3 | 0.109 |
| Lead | −0.4 | 0.3 | 0.172 | −1.0 | 0.3 | 0.0001* | −0.7 | 0.3 | 0.012* |
| IDA | −6.9 | 3.9 | 0.078 | −7.9 | 4.3 | 0.068 | −8.1 | 4.0 | 0.047* |
| HOME | 0.5 | 0.2 | 0.012* | 0.2 | 0.2 | 0.438 | 0.4 | 0.2 | 0.066 |
| Intercept | 64.3 | 9.8 | 0.000* | 79.1 | 10.9 | 0.000* | 67.6 | 10.2 | 0.000* |

IDA, Iron Deficiency Anemia; HOME, Home Observation of the Environment.
*Significant at $p < 0.05$.

pathway. Animal studies[51,52] have shown significant dopaminergic alterations in ID rats that resulted in decreased motor behavioral activity compared to non-ID rats despite high doses of cocaine administered postnatally to both groups. The animal studies do not provide exact parallels of the effects of the relationship between cocaine exposure and ID in humans, but do provide a framework for understanding the possible role of altered dopamine neurotransmission theory. It is important that future studies of the neurodevelopmental outcomes of cocaine-exposed children include measures of IDA from birth to assess the contribution of various risk factors to development. Iron deficiency without anemia (ID) did not seem to have a similar association with mental outcomes in this sample of children, consistent with prior observations.[49] Despite this finding, chronic ID has been found in other studies to have detrimental effects on the developing brain and with long term consequences.[36]

The exposure to IDA at two years was significantly associated with lower motor outcomes at the same age. Early motor outcomes may be predictive of later cognitive performance through maturation of motor behaviors as suggested previously.[53] This was further supported by the significant correlation that was found between the two-year motor scores and the four-year cognitive outcomes. An association of IDA with motor outcomes at four years was not found and, in fact, none of the covariates in the model were significant predictors for these motor outcomes. We also did not find an association of IDA with concurrent two-year MDI or four-year cognitive scores, possibly due to the small number of IDA cases. Our results should be explored further with a larger sample of IDA cases.

Elevated blood lead levels are a potential confounder in the association between IDA and cognitive outcomes, but the finding was that lead exposure independently predicted poorer cognitive outcomes (MDI, Performance and Full Scale IQ) at both ages in this sample. Lead exposure was higher than NHANES III prevalence rates[54] (two years: 6%; four years: 4%) but was not different between cocaine-exposed and nonexposed children, indicating that socioeconomic disadvantage (approximately 75% belong to SES category V) can increase the exposure for both groups of children. The finding that higher lead levels predicted lower cognitive outcomes at both ages is consistent with prior studies[55–57] and should be investigated further in cocaine-related studies.

In this sample, salient factors known to be related to child developmental outcomes were considered, which did not reduce the association of cumulative IDA or lead levels on cognitive outcomes. Further, lower maternal IQ and poorer HOME scores were also associated with lower cognitive outcomes consistent with other child development studies of cocaine[11] and IDA.[36]

In conclusion, the rates of IDA were significantly higher among four-year-old cocaine-exposed children. Overall IDA and high lead levels were higher in this sample than reported national rates, suggesting that current screening and treatment practices may be inadequate or may not be appropriately utilized by at risk populations. In fact, 64% of our sample were receiving Women, Infants, and Children program (WIC) assistance at the time of this study. This suggests that, despite effective programs and services in place, postnatal nutritional and environmental risks are still prevalent. Pediatricians need to increase surveillance efforts for this segment of the population, and especially for cocaine-exposed children. Our data also suggest that exposure to IDA between ages two and four years was detrimental to neurodevelopment. To be effective, intervention for ID/IDA must be timely and coincident with the complex neural changes that take place in the human brain between birth and two years of age.[33] Currently, there is a lack of data on the prevalence of ID/IDA in cocaine-exposed cohorts before two years of age. It is of public health interest to further study these groups with a larger sample size and target appropriate screening and intervention strategies.

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## REFERENCES


1. Chasnoff IJ, Burns WJ, Schnoll SH, Burns KA. Cocaine use in pregnancy. *N Eng J Med*. 1985;313(11):15–18.
2. Chasnoff IJ, Griffith DR, MacGregor S, et al. Temporal patterns of cocaine use in pregnancy. *JAMA*. 1989;261:1741–1744.
3. Griffith D, Chasnoff IJ, Gillogley K, Freier C. Developmental follow-up of cocaine-exposed infants through age three years. *Infant Behavior and Development*. 1990;13:126A.
4. Coles CD, Platzman K, Smith I, et al. Effects of cocaine, alcohol, and other drugs used in pregnancy on neonatal growth and neuro-behavioral status. *Neurotoxicol Teratol*. 1991;13:1–11.
5. Eisen L, Field T, Bandstra E, et al. Perinatal cocaine effects on neonatal stress behavior and performance on the Brazelton Scale. *Pediatrics*. 1991;88:477–480.
6. Singer L, Arendt R, Minnes S, Farkas K, Salvator A. Neurobehavioral outcomes of cocaine-exposed infants. *Neurotoxicol Teratol*. 2000;22: 653–666.
7. Jacobson SW, Jacobson JL, Sokol RJ, Martier SS, Chiodo LM. New evidence of neurobehavioral effects of in-utero cocaine exposure. *J Pediatr*. 1996;129:581–588.
8. Singer L, Arendt R, Farkas K, Minnes S, Huang J, Yamashita T. Relationship of prenatal cocaine exposure and maternal postpartum psychological distress to child developmental outcome. *Dev Psychopathol*. 1997;9:473–489.
9. Singer L, Arendt R, Minnes S, Salvator A, Siegel AC, Lewis BA. Developing language skills of cocaine exposed infants. *Pediatrics*. 2001;107:1057–1064.
10. Arendt R, Angelopoulos J, Salvator A, Singer L. Motor development of cocaine-exposed children at age two years. *Pediatrics*. 1999;103: 86–92.
11. Singer L, Arendt R, Minnes, et al. Cognitive and motor outcomes of cocaine-exposed infants. *JAMA*. 2002;287:1952–1960.
12. Chasnoff IJ, Griffith DR, Freier C, et al. Cocaine/polydrug use in pregnancy: two-year follow-up. *Pediatrics*. 1992;89:284–289.
13. Griffith DR, Azuma SD, Chasnoff IJ. Three-year outcome of children exposed prenatally to drugs. *J Am Acad Child Adolesc Psychiatry*. 1994;33:20–27.
14. Hurt H, Brodsky L, Betancourt L, Braitman LE, Belsky J, Gianetta. Play behavior in Toddlers with in utero cocaine exposure: A prospective, masked, controlled study. *J Dev Behav Pediatr*. 1996; 17:373–379.
15. Frank DA, Augustyn M, Knight WG, et al. Growth, development, and behavior in early childhood following prenatal cocaine exposure. A systematic review. *JAMA*. 2001;285:1613–1625.
16. Volpe JJ. Effect of cocaine use on the fetus. *N Engl J Med*. 1992; 327:399–407.
17. Singer L, Arendt R, Song L, et al. Direct and indirect interactions of cocaine with childbirth outcomes. *Arch Pediatr Adolesc Med*. 1994; 148:959–964.
18. Zuckerman B, Frank DA, Hingson R, et al. Effects of maternal marijuana and cocaine use on fetal growth. *N Engl J Med*. 1989;320: 762–768.
19. Dallman PR, Siimes MA, Stekel A. Iron deficiency in infancy and childhood. *Am J Clin Nutr*. 1980;33:86–118.
20. Earl R, Woteki CE. *Iron deficiency anemia: recommended guidelines for the prevention, detection, and management among U.S. children and women of childbearing age*. Washington, DC: National Academy Press, 1993.
21. Frank DA, Bauchner H, Parker S, et al. Neonatal body proportionality and body composition after in utero exposure to cocaine and marijuana. *J Pediatr*. 1990;117:622–626.
22. Looker AC, Dallman PR, Carroll MD, et al. Prevalence of iron deficiency in the United States. *JAMA*. 1997;277:973–976.
23. Oski FA. Iron deficiency in infancy and childhood. *N Engl J Med*. 1993;329:190–193.
24. Eden AN, Mir MA. Iron deficiency in 1- to 3-year-old children. *Arch Pediatr Adolesc Med*. 1997;151:986–988.
25. Boutry M, Needlman R. Use of diet history in the screening of iron deficiency. *Pediatrics*. 1996;98:1138–1142.
26. Mahaffey KR, Michaelson IA. The interaction between lead and nutrition. In: Needlman HL, ed. *Low level lead exposure: The clinical Implications of current research*. New York: Raven Press; 1980.
27. Lozoff B, Brittenham GM, Viteri FE, et al. Developmental deficits in iron-deficient infants: effects of age and severity of lack. *J Pediatr*. 1982;101:948–952.
28. Walter T, Kavalskys J, Stekel A. Effect of mild iron deficiency on infant mental developmental scores. *J Pediatr*. 1983;102:519–22.
29. Grindulis H, Scott PH, Belton NR, Wharton BA. Combined deficiency of iron and vitamin D in Asian toddlers. *Arch Dis Child*. 1986;61:843–148.
30. Lozoff B, Brittenham GM, Wolf AW, et al. Iron deficiency anemia and iron therapy. Effects on infant developmental test performance. *Pediatrics*. 1987;79:981–995.
31. Walter T, DeAndraca I, Chadud P, Perales CG. Iron deficiency anemia: adverse effects on infant psychomotor development. *Pediatrics*. 1989;84:7–17.
32. Lozoff B, Wolf AW, Urrutia JJ, Viteri FE. Abnormal behavior and low developmental test scores in iron deficient anemic infants. *J Dev Behav Pediatr*. 1985;6:69–75.
33. Pollitt E. Iron deficiency and cognitive function. *Ann Rev Nutr*. 1993;13:521–537.
34. Halterman JS, Kaczorowski JM, Aligne CA, Auinger P, Szilagyi PG. Iron deficiency and cognitive achievement among school-aged children and adolescents in the United States. *Pediatrics*. 2001; 107:1381–1386.
35. Lozoff B, Jimenez E, Wolf AW. Long-term developmental outcome of infants with iron deficiency. *N Engl J Med*. 1991;325:687–694.
36. Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. *Pediatrics*. 2000;105:E51.
37. Singer L, Arendt R, Fagan J, et al. Neonatal visual information processing in cocaine-exposed and nonexposed infants. *Infant Behavior and Development*. 1999;22:1–15.
38. Streisguth AP. The behavioral teratology of alcohol: Performance, behavioral, and intellectual deficits in prenatally exposed children. In: West JR, ed. *Alcohol and Brain Development*. New York: Oxford University Press; 1986:3–44.
39. Dunn L, Dunn L. *Peabody Picture Vocabulary Test-Revised*. Circle Pines, MN: American Guidance Service; 1981.
40. Derogatis L. *The Brief Symptom Inventory: Administration, scoring, and procedures manual (2nd Ed.)*. Baltimore, MD: Clinical Psychometric Research, Inc; 1992.
41. Hobel C, Hyvarinem M, Okado D, Oh W. Prenatal and intrapartum high-risk screening. *Am J Obstet and Gynec*. 1973;114:1–9.
42. Bayley N. *Bayley Scales of Infant Development*. 2nd ed. New York: Psychological Corporation; 1993.
43. Wechsler D. *WPPSI-R Manual*. New York: Psychological Corporation; 1989.
44. Felio M, Fewell R. *Peabody Development Motor Scales & Activity cards*. Allen, TX: DLM Teaching Resources; 1983.
45. Caldwell B, Bradley R. *Home Observation for Measurement of the Environment*. Little Rock, AR: University of Arkansas; 1984.
46. Palti H, Pevsner B, Adler B. Does anemia in infancy affect achievement on developmental and intelligence tests? *Hum Biol*. 1983;55:183–194.

47. Wasserman G, Graziano JH, Factor-Litvak P, Popovac D, et al. Independent effects of lead exposure and iron deficiency anemia on developmental outcome at age 2 years. *J Pediatr*. 1992;121: 695–703.
48. Tamura R, Goldenberg RL, Hou J, et al. Cord serum ferritin concentrations and mental and psychomotor development of children at five years of age. *J Pediatr*. 2002;140:165–170.
49. Parks YA, Wharton B. Iron deficiency and the brain: Clinical significance of behavioral changes. In: Dobbing J, ed. *Brain, Behavior, and Iron in the Infant Diet*. London: Springer-Verlag; 1990:157–176.
50. Holzman C, Paneth N. Maternal cocaine use during pregnancy and perinatal outcomes. *Epidemiol Rev*. 1994;16:315–334.
51. Nelson C, Erikson K, Pinero DJ, et al. In vivo metabolism is altered in iron-deficient anemic rats. *J Nutr*. 1997;127:2282–2288.
52. Erikson K, Jones BC, Beard JL. Iron deficiency alters dopamine transporter functioning in rat striatum. *J Nutr*. 2000;130:2831–2837.
53. Idjradinata P, Pollitt E. Reversal of developmental delays in iron-deficient anaemic infants treated with iron. *Lancet*. 1993;341:1–4.
54. Update: Blood lead levels-United States, 1991–1994. *Morb Mortal Wkly Rep*. 1997;46:141–146.
55. Bellinger D, Leviton A, Waternaux, Needleman H, Rabinowitz M. Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. *N Engl J Med*. 1987;316:1037–1043.
56. Wigg NR, Vimpani GV, McMichael AJ, et al. Port Pirie Cohort Study: Childhood blood lead and neuropsychological development at age two years. *J Epidemiol Community Health*. 1988;42:213–219.
57. Needleman H, Schell A, Bellinger D, Leviton A, Allred EN. The long-term effects of exposure to low doses of lead in childhood. An 11-year follow-up report. *N Engl J Med*. 1990;322:83–88.

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