Dose-Response Effect of Cocaine on Newborn Head Circumference

David A. Bateman, MD*§, and Claudia A. Chiriboga, MD, MPH‡§

ABSTRACT. **Objective.** To evaluate the relationship between head circumference, birth weight, and cocaine dose in healthy term and near-term newborns exposed to cocaine in utero.

**Methods.** We used radioimmune assay (RIAH) of cocaine metabolite in maternal hair to quantify third trimester cocaine exposure in 240 healthy newborn infants (gestational age: >36 weeks). Cocaine exposure was categorized into 3 levels: no exposure (n = 136), low cocaine exposure (n = 52; RIAH: 2–66 ng/10 mg hair), and high cocaine exposure (n = 52; RIAH: 81–4457 ng/10 mg hair). We collected information on maternal demographic characteristics, the pregnancy, and the use of substances through a structured interview and from the medical record.

**Results.** Means of birth weight, length, and head circumference of infants with high cocaine exposure differed significantly from those with low exposure and no exposure, but were similar between low exposure and no exposure. We used a multiple linear regression model to assess the association between newborn head circumference and cocaine level, adjusting for the effects of birth weight; gestational age; infant sex; and several maternal factors, including height, weight gain during pregnancy, syphilis during pregnancy, and the use of alcohol, cigarettes, marijuana, and opiates during pregnancy. Only birth weight, sex, and high cocaine exposure were significantly associated with newborn head circumference. The predicted head circumference deficit associated with high cocaine exposure (44 cm) represents 34% of the unadjusted difference (1.28 cm) between mean head circumferences of infants in the high cocaine exposure and no exposure groups.

**Conclusion.** Newborns exposed to a high level of cocaine in utero (RIAH: >81 ng/10 mg hair) exhibit asymmetric intrauterine growth retardation in which the head circumference is disproportionately smaller than would be predicted from the birth weight (head wasting). The deficit in head size associated with cocaine exposure may reflect the effects of a specific central nervous system insult that interferes with prenatal brain growth. *Pediatrics* 2000;106(3). URL: http://www.pediatrics.org/cgi/content/full/106/3/e33; cocaine, infant, newborn, fetal development, head.

**ABBREVIATIONS.** RIAH, radioimmune assay; SE, standard error; PCP, phencyclidine; OR, odds ratio.

Several observational studies have found an association between intrauterine cocaine exposure and diminished fetal growth, but the nature of the relationship between head and body size of exposed newborns remains unclear.1–5 One study concluded that exposure to cocaine and marijuana did not alter neonatal body proportionality.4 Another study found that head circumferences of cocaine exposed newborns were relatively smaller than would be expected at a given birth weight.6 Also unclear is the relationship between cocaine dose and head circumference. Two studies found that head circumference decreased with increasing cocaine dose, but this relationship was not adjusted for birth weight or the influence of other possible insults to intrauterine growth.6–8

We hypothesized that if intrauterine cocaine exposure is associated with symmetric growth retardation, exposed newborns should have head circumference measurements that are indistinguishable from those of unexposed infants of similar birth weight from the same general population, regardless of exposure dose. Alternatively, cocaine-exposed infants may demonstrate asymmetric intrauterine growth, with head circumferences that are either disproportionately larger or smaller than would be expected at a given birth weight.9 In the former case, the growth retardation could be considered head sparing, often interpreted as reflecting the effects of late-onset placental insufficiency. In the latter case, the residual deficit in head size (head wasting) might reflect the effects of a specific central nervous system insult. To test this hypothesis and to control for cocaine dose as well as for other factors that might influence the relationship between head circumference and birth weight, we used the results of maternal hair analysis for cocaine metabolite, combined with lifestyle and medical information, to identify the determinants of fetal growth in cocaine-exposed and cocaine-unexposed healthy newborns.10–12

**METHODS**

**Study Sample**

The study protocol, including institutional review board approval, consent, selection, and exclusion criteria, and the structured interview were described in a previous publication.13 The study sample consisted of 240 mother–infant pairs recruited at a single inner-city municipal hospital from January 1992 to November 1995, and included only healthy live-born singleton infants with estimated length of gestation >36 weeks by dates, cared for...
in the well-baby nursery, whose mothers furnished maternal hair for toxicological testing. Mothers who had a history of parenteral drug use, alcoholism, documented human immunodeficiency virus positivity; or whose infants had an Apgar score \( \leq 4 \) at 5 minutes, obvious congenital malformations, seizures, and strokes, were excluded from the study. During the hospital stay each mother was interviewed by an experienced interviewer who used a structured questionnaire to collect detailed information about the pregnancy, socioeconomic status, and drug and alcohol use. We used information from the structured interview to estimate the quantity of alcohol and tobacco used by the mother during pregnancy. For tobacco, we used the stated number of cigarettes smoked per day. For alcohol, we estimated the total alcohol consumption during the pregnancy as a product of the frequency of intake of a given drink, its alcohol content, and the duration of pregnancy.

Identification of Cocaine Exposure

The hair sample consisted of a pencil-thick clump of hair removed from the vertex scalp of each study mother; the proximal 3.9 cm of which (corresponding to the expected length of third trimester hair growth) was analyzed for the presence of cocaine metabolite (benzoylcygonine) by radioimmune assay (RIAH, Psychemedics Corp, Cambridge, MA). Detection of metabolite concentration \( > 2 \text{ng} / 10 \text{mg} \) of hair was considered presumptive evidence of cocaine use during the third trimester of pregnancy. We focused on the third trimester because this is the period during which most of fetal growth occurs.

Of the 240 mothers who provided hair samples for RIAH cocaine analysis, 104 tested positive and 136 negative. RIAH in the positive samples ranged from 2.3 to 4457 ng/10 mg of hair (median: 73.5 ng; mean: 676.5 ± 1037 ng); because of their skewed distribution, the results were transformed to their natural logarithms (logRIAH). The log-transformed values had a distinctly bimodal distribution that we empirically divided into low-dose cocaine exposure \( (0 < \text{logRIAH} \leq 4.3) \) and high-dose cocaine exposure \( (\text{logRIAH} > 4.3) \), using the sample median (which corresponded roughly to the trough between the 2 peaks) as the dividing point; the cocaine status was treated in the analyses as a categorical variable with 3 levels: no cocaine exposure \( (\text{no exposure}, n = 136) \), low-dose cocaine exposure \( (\text{low exposure}, n = 52; \text{RIAH}: 2.3–66 \text{ng}) \), and high-dose cocaine exposure \( (\text{high exposure}, n = 52; \text{RIAH}: 81–4457 \text{ng}) \). Within each exposure group, the mean ± standard error (SE) and median logRIAH values were similar: 2.52 ± .11 ng and 2.40 ng for low exposure and 6.69 ± .14 ng and 6.96 ng, respectively, for high exposure.

Concurrent Measures of Maternal Substance Use

Forty of 104 RIAH cocaine-positive mothers (38%) and 1 of 136 RIAH cocaine-negative mothers (7%) admitted using cocaine during pregnancy. All 104 infants born to RIAH cocaine-positive mothers met the hospital’s criteria for evaluation for intrauterine drug exposure (these criteria consisted of maternal risk factors for or a history of drug use or physical signs and symptoms of drug exposure in the infant and/or mother) and had urine specimens submitted for toxicological analysis. Twenty-three specimens tested positive for cocaine; 20 of these were from infants of the 40 RIAH-positive mothers who admitted cocaine use. Only 44 of 105 mothers (42%) whose cocaine use was identified by history and/or hair analysis would have been identified by routine hospital surveillance (consisting of either admitted maternal history of drug use or positive urine toxicology screen result in the infant). However, nearly all of these (41 of 44; 93%) were in the high-exposure group; routine surveillance would have identified 41 of 52 infants (79%) in the high-exposure group.

To verify the accuracy of information about drug use obtained from the questionnaire, hair specimens from a subsample of mothers \( (n = 91; \text{the 43rd through the 133rd enrollees}) \) were also tested for the presence of phencyclidine (PCP) and opiates. None of the specimens tested positive for PCP; 5 were positive for opiates (including methadone, morphine, and codeine). These 5 were among the 6 RIAH cocaine-positive mothers who admitted using opiates during pregnancy. Thirteen RIAH cocaine-positive mothers and 3 RIAH cocaine-negative mothers admitted using marijuana during pregnancy; none of them had evidence of having used opiates or methadone. Altogether, 5 of 136 mothers in the no exposure group (4%) had historical or urine toxicologic evidence of having used cocaine, opiates, methadone, or marijuana during pregnancy. Birth weight, length, and head circumference measures of the 5 infants did not differ significantly from those of other unexposed infants.

Infant and Maternal Measures of Growth and Body Size

Infant anthropometric measures (birth weight, length, and head circumference) obtained by the pediatric staff at birth were used in the data analysis. Small birth weight for gestational age and small head circumference for gestational age were defined as being below the 10th percentile according to the growth standards of Miller and Hassanein. The second or third day of life, a pediatric neurologist blinded to the cocaine status of each study infant confirmed or corrected the head circumference measurement and determined the observed gestational age for each infant by a standard, scored examination.15 We obtained measurements of maternal height and weight gain during pregnancy from the obstetrical record.

Comparison of Sample to Reference Population (Table 4)

Because the study sample was not selected randomly from the well-baby nursery, we attempted to assess the likelihood of selection bias. We compared anthropometric measures of cocaine-exposed and cocaine-unexposed study infants with those of subsets of exposed and unexposed infants selected from a reference population consisting of all singleton newborns born at the same hospital \( (n = 3038) \) during a single calendar year (1989).16 Maternal demographic and other characteristics and the criteria for collection of infant urine toxicology specimens did not differ between the reference period and the study period. The unexposed reference subset \( (n = 1928) \) consisted of all newborns with gestational age \( > 36 \) weeks in the well-baby nursery whose mothers had no evidence of having used cocaine or other illicit substances during pregnancy and whose infants did not have positive urine toxicologic testing. The cocaine exposed reference subset \( (n = 585) \) consisted of all newborns with gestational age \( > 36 \) weeks in the well-baby nursery whose mothers had evidence of having used cocaine during pregnancy and whose infants did meet criteria for urine toxicologic testing. Newborn anthropometric measurements did not differ between reference subsets and study groups \( (P > .1) \).

Statistical Analysis

Using no exposure as a reference, we calculated the odds ratios (ORs) of dichotomous maternal and infant characteristics cross-tabulated against cocaine levels. We evaluated these ORs for homogeneity using the Mantel-Haenszel \( \chi^2 \) test for trend. We compared means of birth weight, length, and head circumference using 1-way analysis of variance. Posthoc comparisons of paired mean differences among the 3 cocaine levels infant were evaluated for significance using the Tukey method.17,18 To explore the effect of cocaine level and other possible predictors on head circumference, we constructed a regression model with head circumference as the dependent variable and with terms possibly related to intrauterine head growth (including birth weight) as independent variables. Independent variables with nonsignificant coefficients were eliminated one by one until we obtained the final model (Table 3). Birth weight can be considered a mediator of the influence of other covariates on head circumference; that is, inclusion of birth weight in the model alters or eliminates the effect of many variables that might otherwise be associated with head circumference. The final model was tested for the significance of first-order interactions among the remaining terms. We repeated the regression analysis, replacing birth weight by a combined measure of length and birth weight \( (\text{ponderal index} = 100 \times \text{birth weight} / \text{birth length}^3) \). The results of this analysis were similar to what was obtained using birth weight alone, and are not reported. We also repeated the regression analyses using continuous estimates of the quantity of alcohol and tobacco consumed by the mother during pregnancy. The results of these analyses are similar to what was obtained using binary estimates of tobacco and alcohol use and are also not reported.
RESULTS

In Table 1, ORs of risk factors for poor neonatal outcome, small birth weight for dates, and small head circumference for dates increased with increasing level of cocaine exposure. This dose–response effect is confirmed by the results of a Mantel-Haenszel χ² test for trend. In Table 2, the mean values of birth weight, length, and head circumference differed little between the low-exposure and no-exposure groups but were significantly lower in the high-exposure group compared with either of the other 2 groups.

The regression model displayed in Table 3 shows that high cocaine level is independently associated with smaller head circumference (P < .015). The first column of Table 3 displays the coefficients for all main effect terms that were entered into the linear regression model. The second column of Table 3 shows the coefficients for the terms that were retained in the final model after sequential removal of nonsignificant terms. In the final model, only birth weight, female sex, and cocaine level were found to be related to head circumference. Between the initial and final model, these coefficients were stable in direction, magnitude, and variability.

Table 1 displays the relationship between head circumference and birth weight according to cocaine level. Separate plots are shown for males and females. Each of the regression lines represents a simple linear regression line through its own subset of points. The fact that first-order interaction terms (cocaine level with birth weight, cocaine level with sex, birth weight with sex) had no significant effect on head circumference when included in the model implies that the slopes of the 3 regression lines (within the limits of the study’s power) did not change significantly over the range of birth weight examined by the study.

DISCUSSION

Our results demonstrate that the head circumferences of healthy term and near-term cocaine-exposed infants are disproportionately smaller than would be predicted from their birth weight. This effect is seen only among infants exposed to a high level of cocaine (ie, to a value arbitrarily designated as being above the median value of cocaine metabolite concentration in our samples of maternal hair). Low cocaine exposure had no significant effect on head circumference when adjustment was made for the effect of birth weight and sex of the infant. Female infants, independent of birth weight and cocaine exposure status, also had smaller head circumferences. The predicted head circumference deficit associated with high cocaine exposure (.44 cm) represents approximately one third (34%) of the unadjusted difference between mean head circumferences of infants in the high-exposure and no-exposure groups.

According to the model of Cooke et al, a head circumference differential of this magnitude (.44 cm) represents ∼15 g of brain mass or 4% of the total expected brain mass for an infant whose head circumference is 34 cm. A head circumference differential of 1.28 cm (the unadjusted difference between no and high cocaine mean head circumferences) represents a 40-g decrement in brain weight, 11% of the total expected brain mass. Frank et al found decreased subcutaneous tissue in newborns with intrauterine cocaine exposure, raising the possibility that the smaller head circumference may be attributable to decreased scalp thickness rather than a decrease in the volume of the brain. However, the magnitude of the effect of cocaine on subcutaneous tissue is very small (fat decrement = .3 mm after adjustment for confounders) and would be expected to be even smaller after adjustment for birth weight. Frank et al also observed a decrease in the nonfat area of the arm associated with cocaine exposure, but it is not clear what a change in this parameter might mean in terms of scalp thickness. Thus, it is very unlikely that cocaine alters scalp thickness rather than brain volume in a way that has not been accounted for by the analysis.

TABLE 1. Maternal and Infant Characteristics According to Level of Cocaine Metabolite in Maternal Hair (Categorical Variables)

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Cocaine Exposure n = 136 (%)</th>
<th>Low Cocaine Exposure n = 52 (%)</th>
<th>High Cocaine Exposure n = 52 (%)</th>
<th>OR [95% CI] (No Cocaine Versus Low Cocaine)</th>
<th>OR [95% CI] (No Cocaine Versus High Cocaine)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor prenatal care (≤5 visits)</td>
<td>14 (10)</td>
<td>9 (17)</td>
<td>30 (58)</td>
<td>1.82 [6.26, 5.35]</td>
<td>11.9 [5.62, 25.2]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Black race</td>
<td>67 (49)</td>
<td>37 (71)</td>
<td>45 (87)</td>
<td>2.54 [1.44, 4.48]</td>
<td>6.62 [3.89, 11.3]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Syphilis‡</td>
<td>3 (2.2)</td>
<td>1 (1.9)</td>
<td>10 (19)</td>
<td>.87 [0.04, 17.4]</td>
<td>10.6 [2.50, 4.46]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cigarettes‡</td>
<td>13 (10)</td>
<td>14 (27)</td>
<td>41 (79)</td>
<td>3.49 [1.37, 8.89]</td>
<td>35.3 [17.2, 72.4]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Alcohol‡</td>
<td>9 (6.6)</td>
<td>9 (17)</td>
<td>22 (42)</td>
<td>2.95 [94, 9.26]</td>
<td>10.35 [4.22, 25.4]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heroin and/or methadone‡</td>
<td>1 (7)</td>
<td>0 (0)</td>
<td>6 (12)</td>
<td>—</td>
<td>17.6 [1.82, 1.70]</td>
<td>.001</td>
</tr>
<tr>
<td>(admitted or RIAH-positive)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marijuana‡</td>
<td>3 (2.2)</td>
<td>5 (10)</td>
<td>8 (15)</td>
<td>4.72 [87, 25.5]</td>
<td>8.06 [1.79, 36.4]</td>
<td>.001</td>
</tr>
<tr>
<td>Cocaine§ (admitted or urine-positive)</td>
<td>1 (7)</td>
<td>2 (4)</td>
<td>41 (79)</td>
<td>5.40 [34, 86.8]</td>
<td>503 [67, 3771]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female newborn</td>
<td>67 (49)</td>
<td>21 (40)</td>
<td>26 (50)</td>
<td>.70 [35, 1.39]</td>
<td>1.03 [54, 1.95]</td>
<td>.81</td>
</tr>
<tr>
<td>Preterm birth (&lt;37 wk gestation)</td>
<td>32 (24)</td>
<td>10 (19)</td>
<td>12 (23)</td>
<td>.77 [30, 2.02]</td>
<td>.97 [40, 2.38]</td>
<td>.76</td>
</tr>
<tr>
<td>Small birth weight for dates†</td>
<td>9 (6.6)</td>
<td>5 (10)</td>
<td>15 (29)</td>
<td>1.50 [37, 6.16]</td>
<td>5.72 [21, 15.1]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Small head circumference for dates†</td>
<td>7 (5.4)</td>
<td>8 (15)</td>
<td>13 (25)</td>
<td>3.35 [97, 11.6]</td>
<td>6.14 [20.8, 18.1]</td>
<td>&lt;.001</td>
</tr>
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CI indicates confidence interval.
* P value, χ² test for trend (Mantel-Haenszel extension).
† <10th percentile for gestation according to standards of Miller and Hassanein.14
‡ Occurrence or use during pregnancy.

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Several mechanisms by which cocaine exposure might impair fetal brain growth have been postulated. These include the indirect effects of compromised nutrition and oxygenation resulting from cocaine-induced vasoconstriction of placental vessels, as well as direct effects of cocaine on cell division, cell migration and neurotransmitter function within the developing brain. The latter possibility is supported by findings of microcerebral dysgenesis in rodents exposed to cocaine, who also exhibit decreased head growth. Our finding that impaired fetal head growth is independent of effects on somatic growth supports the hypothesis that cocaine acts directly to inhibit fetal brain growth.
In infants with intrauterine growth retardation, small head size at birth is an important predictor of subsequent adverse neurodevelopment.25,26 A study of school-aged children found a twofold increase in rate of microcephaly (head circumference <5th percentile) among cocaine-exposed children, compared with cocaine-unexposed children.27 Several follow-up studies comparing cohorts of cocaine-exposed and unexposed infants in early childhood and at school age have found compromised behavioral and cognitive development in association with small head circumference.28–31 Further investigation is needed to clarify the relationship between cocaine dose, head circumference, and long-term neurodevelopmental outcome.

The results of our study may be biased in several ways. Study enrollment depended on the willingness of mothers to submit to an interview and to yield a hair specimen for cocaine analysis. Because some mothers did not wish to participate in the study, infants included in the cocaine-exposed and cocaine-unexposed groups were not random samples of cocaine-exposed and cocaine-unexposed newborns in the well-baby nursery, and the risk factors for exposure, pattern of cocaine use, and outcomes are not necessarily typical of such infants. However, we compared the growth measurements of RIAH-positive and RIAH-negative infants with those of healthy term cocaine-exposed and cocaine-unexposed infants chosen by the same criteria from a reference population born at the same hospital, and we found them to be the same. Thus, selection bias probably exerts a small effect on the study results.

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Second, the study included only term and near-term infants admitted to the well-baby nursery. In our hospital, cocaine-exposed infants are more than twice as likely as unexposed infants to require care in the neonatal intensive care unit.3 Because such infants are also more likely than normal to be prema-

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**TABLE 4.** Mean (± Standard Deviation) Anthropometric Measures of Study Infants Compared With Those of Newborns Selected From a Reference Population*

<table>
<thead>
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<th>Birth Weight (Grams)</th>
<th>Length (cm)</th>
<th>Head Circumference (cm)</th>
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<tbody>
<tr>
<td>No cocaine exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study (n = 136)</td>
<td>3369 ± 471</td>
<td>51.4 ± 2.6</td>
</tr>
<tr>
<td>Reference (n = 1928)†</td>
<td>3339 ± 455</td>
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<tr>
<td>t value§</td>
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* All singleton newborns born at the same hospital during calendar year 1989 (n = 3038).
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‡ All newborns with gestational age >36 weeks in the well-baby nursery whose mothers had evidence of having used cocaine during pregnancy and whose infants met criteria for urine toxicologic testing (n = 585).
§ Differences between study and reference groups are not significant (2-sample t test, P > .10).

---

**Fig 1.** Head circumference versus birth weight by cocaine exposure level. Lines represent separate independent regression lines for each subset of points according to cocaine level.

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ture and growth retarded, their exclusion would be expected to cause an apparent attenuation of the true effects of cocaine. The results of our study should be interpreted as applying only to healthy term or near-term newborns.

Third, we looked at the aggregate effects of exposure during the third trimester only. If the degree or pattern of insult to growth associated with cocaine varied according to the timing of exposure, we may be incorrectly estimating the dose–response effect. Until the intrauterine growth of a large sample of cocaine-exposed infants is studied longitudinally in relation to the timing of exposure (the social situation of most cocaine-using mothers makes such an assessment very difficult) the extent of this kind of bias cannot be assessed.

Two other findings deserve mention. The separate regression lines for each cocaine level for both boys and girls shown in Fig 1 seem to converge as head circumference and birth weight increase. Although Fig 1 suggests that the impact of cocaine exposure on head circumference decreases as the birth weight increases, this trend is not statistically significant, perhaps because the sample included a relatively narrow birth weight range and because the power of the study to detect this trend was reduced within subsets of the data.

Finally, we note the near concordance between the group of infants identified by the hospital’s routine methods of surveillance for neonatal drug exposure and the group who had exposure to high-dose cocaine. This, plus the fact that fetal growth impairment was seen only in the high-exposure group, suggests that routine practices of surveillance and detection (history of maternal drug use, positive urine toxicology, physical or behavioral signs of exposure) should be adequate to identify most infants with clinically evident growth impairment attributable to cocaine. It also suggests that the size estimates of growth impairment based on routine methods do not require drastic revision, as long as it is understood that such effects are probably a product of relatively heavy exposure at least during the third trimester.

REFERENCES
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