The Effects of Intrauterine Cocaine Exposure in Newborns

David A. Bateman, MD, Stephen K. C. Ng, MD, DrPH, Catherine A. Hansen, MD, and Margaret C. Heagarty, MD

Introduction

Maternal cocaine use during pregnancy has been associated with several neonatal problems, including diminished fetal growth and preterm birth, congenital malformations, and vascular and neurobehavioral complications. However, the prevalence and severity of these effects remain uncertain. This report examines the outcome of cocaine use during pregnancy at an inner-city public hospital where surveillance for infant drug exposure included universal toxicologic screening of infant urine at birth as well as maternal history of substance use habits during pregnancy.

Methods

The study population consisted of all mothers and their live-born singleton infants delivered at Harlem Hospital in New York during the 1-year period beginning September 1, 1985, and ending August 31, 1986 (n = 2810). By early 1985, cocaine use among women of childbearing age in Harlem, involving chiefly the smokable alkaloid ("free base") known as crack, had become an established epidemic. At that time, Harlem Hospital adhered to a longstanding policy of routinely testing the urine of all newborn infants for several illicit drugs of abuse, including cocaine, opiates, amphetamines, barbiturates, and methadone.

The cocaine-exposed group consisted of all live-born singleton infants delivered during the study year identified either by maternal history or infant urine assay as having been exposed to cocaine during pregnancy (n = 361). These infants were compared to a group of infants not known to be exposed to cocaine or other illicit drugs (unexposed infants) and consisting of every sixth live-born singleton infant and mother, excluding those with positive urine drug assays and those with known histories of illicit drug exposure (heroin, methadone, phencyclidine, or marijuana) during pregnancy (n = 387).

Maternal demographic data and historical information concerning the delivery, physical examination, and gestational age assessment, and hospital course of the infant were obtained from medical records. Histories of maternal substance use during pregnancy were obtained from several sources, including medical, nursing, and social worker evaluations. Although inhalation of free-base cocaine smoke (crack), as opposed to insufflation or injection of cocaine hydrochloride, could not always be reliably ascertained from the records, a group of 133 women who provided a strong history of crack use was identifiable.

Sixty-six percent of the urine collection for toxicologic analysis was accomplished within 36 hours of birth, and 93% within 96 hours. Urine testing was done in two stages, with urine initially screened for cocaine metabolites by the enzyme-
mediated immunoassay technique; positive results were confirmed by radioimmunoassay.

Statistical analyses were performed using the $t$ test to compare two means of continuous variables and the $\chi^2$ test when variables were discrete. Multivariate analyses using least squares multiple regression for continuous dependent variables and multiple logistic regression for dichotomous dependent variables were conducted, controlling for potential confounding continuous variables (gestational age, maternal age, gravidity) and dichotomous variables (race [Black/non-Black], sex of infant, receipt of prenatal care, maternal positive syphilis serology, and use of tobacco, alcohol, marijuana, and phencyclidine). Opiates (methadone and/or heroin use) were combined into a single dichotomous variable. The $P$ values reported are two-tailed.

Results

Composition of Cocaine-Exposed Group

Infants identified as cocaine exposed either by urine testing or maternal history, or both, constituted 12.8% (361/2810) of all live singleton births during the study year. Ninety-four percent of all infants (2644/2810) had a urine sample submitted for toxicologic testing; of these, 11.2% (295/2644) tested positive for cocaine (282 positive for cocaine alone and 13 for cocaine plus methadone or opiates). Mothers providing a history of cocaine use during pregnancy constituted 10.2% (288/2810) of singleton deliveries; 77% (223/288) of infants identified by maternal drug history tested positive for cocaine. Fifty-one percent (184/361) of all cocaine-exposed infants were born to mothers who used cocaine alone; the remainder (177/361) were born to mothers who used cocaine and other illicit drugs (polydrug exposure), including heroin (53), methadone (33), marijuana (112), and phencyclidine (20). No mother admitted to illicit barbiturate or amphetamine use.

Maternal Demographic Comparisons

As shown in Table 1, the mean maternal age of cocaine users was similar to that of admitted nonusers; however, there were fewer teenaged mothers among the cocaine users and nearly twice the number of prior pregnancies and spontaneous pregnancy losses. Cocaine-using mothers were four times more likely to test positive for syphilis at delivery and seven times more likely to experience placental abruption.

Univariate Comparisons

Table 2 displays, for cocaine-exposed and unexposed infants, the crude mean values of gestational age, birthweight, birth length, and birth head circumference and the rates of low birthweight (birthweight $< 2500$ g; 31% and 10%, respectively), preterm delivery (gestation $< 37$ completed weeks; 32% and 14%, respectively), and very low birthweight (birthweight $< 1500$ g; 3.6% and 1.6%, respectively).

The rate of admission to neonatal intensive care differed between cocaine-exposed and unexposed infants (24% and 15%, respectively), but reasons for admission in both groups were mainly related to low birthweight. The rates of mortality (1% in both cases) and of minor congenital malformations (8% vs 7%) did not differ significantly between groups. Three cocaine-exposed and three unexposed infants had major malformations. Neurobehavioral symptoms (irritability, feeding difficulty, tremors) were uncommon among cocaine-exposed infants who were not also exposed to methadone or heroin: 86% (312/361) of exposed infants had no symptoms; 10% (36/361) had brief tremors lasting less than 24 hours, requiring no treatment and not interfering with feeding or other vital function; and 2% (7/361) required pharmacologic treatment.

Multivariate Analyses

Multiple linear regression analyses characterizing the overall effects of cocaine exposure and the effects of exposure among subgroups of maternal cocaine use were conducted using as separate dependent variables gestational age, birthweight, length, and head circumference (Table 3). For infants whose exposure was ascertained by either a positive maternal drug history or a positive urine screen (cocaine overall), mean deficits were 154 g (birthweight), 1.02 cm (length), and 0.69 cm (head circumference). Deficits were smaller for infants whose mothers used cocaine alone. Deficits were larger for infants born to mothers who used cocaine in combination with other drugs (marijuana, opiates, and polydrugs) and for infants whose mothers specifically admitted using crack. The gestational age deficit for all cocaine-exposed infants (cocaine overall) was 0.74 weeks.

Mean deficits (not tabulated) for cocaine exposure identified by maternal history were similar to those for exposure identified by infant urine drug screen (birthweight deficits of 170 g and 167 g, respectively). Deficits were smaller for infants with a positive urine screen but negative maternal history (birthweight deficit $= 80$ g). Table 4 displays the effect on birthweight of potential confounding variables in a multiple linear regression analysis for cocaine use overall.

In multiple logistic regression analyses using low birthweight ($n = 111$) as the dichotomous dependent variable, the risk of low birthweight in the cocaine-exposed group (cocaine overall) was more than doubled (OR = 2.10, 95% CI = 1.23, 3.67). The risk of low birthweight was similar for infants exposed to cocaine plus polydrugs (OR = 2.57, 95% CI = 1.31, 5.03), and the risk of preterm delivery for cocaine-exposed infants was nearly doubled (OR = 1.94, 95% CI = 1.21, 3.11).
The number of very-low-birthweight infants (n = 19) was too small for similar analysis.

**Discussion**

The univariate estimates of reduced fetal growth in our study corroborate the findings of several other investigators who found mean reductions in birthweight, length, head circumference, and gestational age of cocaine-exposed infants ranging from 300 to 600 g, 2 to 3 cm, 1 to 2 cm, and 1 to 2 weeks, respectively. The adjusted birthweight deficit attributable to cocaine (154 g) in our study is approximately one third the magnitude of the univariate estimate (461 g), supporting the observations of Zuckerman et al. in a cohort of cocaine-exposed infants in which the multivariate and univariate birthweight deficits were 93 g and 407 g, respectively.

Several mechanisms by which cocaine might reduce fetal growth have been proposed. In contrast to both marijuana and tobacco smoke, which reduced mean body mass, Frank et al. found that cocaine was associated with reduced fat stores, suggesting that cocaine might alter nutrient transfer or fetal metabolism. Cocaine may act by depressing active placental amino-acid uptake and transfer. These insults to fetal growth may be worsened by the effects of maternal tobacco, alcohol, opiate, and marijuana use and by use of cocaine throughout pregnancy.

The risk of preterm delivery for cocaine-exposed infants (OR = 2.88) in univariate analysis translates into a decrease in the mean duration of gestation of 0.74 weeks after adjustment for confounders. Cocaine may stimulate early labor by blocking extraneuronal uptake of norepinephrine in the uterus. Abruptio placentae associated with cocaine use may also induce labor; however, the rate of placen-
Table 3 shows that fetal growth decrements are larger when cocaine is used in combination with other psychoactive substances during pregnancy (i.e., with marijuana, opiates, or polydrugs) than when it is used alone. When cocaine is used with marijuana, the mean birthweight deficit is 45 g larger than when cocaine is used alone; when cocaine is used with opiates, the birthweight deficit is enlarged by 112 g. Contributions to the additional mean deficits include the individual effects of marijuana or opiates and, possibly, such other effects of multiple drug use as differences in the frequency and duration of illicit substance and tobacco use. Mothers who use multiple substances are more likely to use them heavily.21 Thus, smaller growth deficits in infants born to mothers who use cocaine alone may be the result of less frequent cocaine use; in infants born to polydrug users, larger growth deficits may be due to heavier cocaine use, synergism with other substances, or the effects of these substances themselves.

The data and conclusions of this study are subject to several limitations. Urine drug screening of infants at birth verifies exposure only within 3 to 5 days of delivery; therefore, cocaine-exposed infants born to mothers who denied drug use and who abstained from using cocaine for several days prior to delivery may have been included in the unexposed group, attenuating cocaine’s true effects. Conversely, underadjudication for confounding risk factors for low birthweight (e.g., other substance use during pregnancy) might accentuate effects of cocaine. Against this possibility is our finding of birthweight deficits due to tobacco and alcohol use (Table 4) that are consistent with previous studies on these substances.22,23 The use of illicit “hard” drugs other than cocaine (heroin, methadone, and phencyclidine) may also have been underestimated, but the resulting errors are likely to be quite small since maternal use of these drugs was subjected to the same historical and urinary surveillance as was cocaine.

On balance, therefore, our data probably provide a low estimate of both the rate of cocaine exposure and the strength of cocaine’s effect. However, the degree of underestimation of cocaine’s effect on exposed infants born to mothers who deny cocaine use may be small: mean growth deficits for infants with a negative maternal drug history and positive urine screen are much smaller than mean deficits for infants for whom maternal history is positive (80 g vs 170 g, respectively). A recent study that used toxicologic analysis of meconium to identify drug-exposed infants reported that the rates of low birthweight and prematurity for cocaine-exposed infants born to mothers who denied cocaine use were similar to the rates for unexposed infants.5 The authors suggested that the modest effects of cocaine on growth and gestation in this group (compared with much larger effects when mothers admitted using cocaine) might be due to lighter use by mothers less likely to volunteer an accurate drug history.

In summary, the results of our study provide further evidence that cocaine use during pregnancy shortens gestation and diminishes fetal weight, length, and head size, particularly when cocaine is used as crack or is used in combination with other substances. As measured by the increased need for neonatal intensive care and the infrequency of neurobehavioral symptoms, the morbidity of cocaine exposure apparent at birth appears to be related mainly to low birthweight and the social consequences of maternal drug use (e.g., congenital syphilis). Catastrophic complications of cocaine use, including abruptio placenta, extreme prematurity, and severe neurobehavioral symptoms, were uncommon in our study.

Acknowledgments
The authors are grateful for the assistance of Ruth Clark and the Support Network, without whom the study could not have been accomplished.

References
23. Meredith HV. Relation between tobacco smoking of pregnant women and body size of their progeny: a compilation and synthesis of published studies. Hum Biol. 1975; 47:45-472.