Direct and Indirect Interactions of Cocaine With Childbirth Outcomes

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Objective: To evaluate neonatal sequelae of maternal cocaine use during pregnancy.

Methods: One hundred women positive for cocaine use during pregnancy were compared with 100 matched controls who did not use cocaine. Maternal characteristics and infant neonatal outcomes were compared. We used t tests, χ², and multiple regression analyses to evaluate the contributions of cocaine vs other drugs to outcome.

Results: Cocaine was the best predictor of increased incidence of abortions, higher maternal gravidity, and poorer prenatal care. Cocaine was also the best predictor of preterm birth and of lower birth weight, after controlling for prematurity. Maternal use of cocaine and alcohol in combination was the best predictor of decreased linear growth, after controlling for prematurity.

Conclusions: Maternal cocaine use predicts negative birth outcomes directly, as well as through obstetric risk factors of abortion history and less prenatal care. Interactive effects of cocaine and alcohol should be considered in future studies of birth outcomes.


Recent studies have highlighted the adverse perinatal and neonatal sequelae of maternal cocaine use during pregnancy. The use of "crack" cocaine in conjunction with other drugs has reached epidemic proportions among pregnant women in urban medical centers in the United States.1,2 Research efforts have focused on elucidating the spectrum of maternal and infant morbidity associated with cocaine use and on understanding the contribution of other medical, socioeconomic, and environmental variables associated with cocaine use to perinatal and neonatal outcome. Obstetric complications of cocaine use by pregnant women have included increased occurrences of preterm labor,3,4 spontaneous abortions,5,6 and meconium-stained amniotic fluid,7 but these problems are not consistently noted. Intrauterine growth retardation in affected infants is the most salient finding.8-10

The purpose of the present report is twofold: (1) to broaden the description of the adverse consequences of maternal cocaine use during pregnancy by documenting maternal health and infant birth outcomes in a large sample of cocaine-using women and (2) to assess the contribution of cocaine relative to other drug, medical, obstetric, and social variables to identify indirect mechanisms by which maternal cocaine use can influence infant outcome.

RESULTS

Prenatal Data

Maternal demographic, prenatal, and substance use data for study and comparison groups are summarized in Table 1 and Table 2. All women were African-American, of low socioeconomic status, and receiving public assistance. The groups dif-
SUBJECTS, MATERIALS, AND METHODS

A retrospective chart review over a 1-year period of the medical characteristics of cocaine-using women and their offspring was conducted.

LABORATORY PROCEDURES

Urine samples were obtained immediately before or after labor and delivery. Samples were analyzed by enzyme immunoassay using a specific method (Syva Emit). Assays were performed for cocaine's metabolite, benzoylecgonine, and for barbiturates, marijuana, and heroin. The specificity for benzoylecgonine is 99% at concentrations of 0.3 mg/mL. Follow-up gas chromatography analyses were not performed. The hospital performs urine toxicology screens for drugs on all women who receive no prenatal care, appear to be intoxicated or taking drugs, who have histories of involvement with the Department of Human Services in previous pregnancies, or who self-admit or appear to be at high risk for drug use after interview by a clinical social worker. Women who met these criteria were asked to undergo a urine screening, with 93% agreeing to do so. When compared with the total number of women identified in an anonymous comprehensive screening of hospital deliveries, 95% of cocaine-positive women were identified by the combination of interview, historical findings, and voluntary drug testing conducted as part of the normal procedures during the same period.

STUDY GROUPS

From this population of identified high-risk women, study group 1 was formed by randomly selecting 100 charts of women prospectively identified as cocaine using, either through urine toxicology screen or clinical interview. From the same race and social class population, a comparison sample (group 2) was formed by randomly selecting 100 charts of women who had given birth and who had both negative urine toxicology screens for cocaine and negative drug history interviews for cocaine. Use of both urine screen and clinical history allowed maximum identification of cocaine-using women and minimized the number of women who might be misidentified.

PROCEDURES

For all deliveries, the following information was extracted from the medical chart. Maternal history of alcohol, cigarette, and other medication use was assessed through medical interview. Maternal age, height, delivery weight and labor length, race, low-income status, and gravidity were noted. Numbers of previous neonatal deaths and numbers of elective and spontaneous abortions were noted. Additional medical illnesses, such as hepatitis, colonization with group B streptococcus, vaginitis, urinary tract infection, and sexually transmitted diseases, were documented. Number of prenatal care visits attended was recorded. Preterm labor was defined as occurring at less than 37 weeks' gestation based on history of last maternal menstrual period and infant Ballard score. For infants, birth weight (grams), length (centimeters), gestational age based on Ballard score, and Apgar scores at 1 and 5 minutes were obtained. Infants were identified as low birth weight (<2500 g) and very low birth weight (VLBW; <1500 g).

Bivariate statistical comparisons were performed with $X^2$ tests of significance for categorical data and with $t$ tests for comparisons of two means for continuous data. Reported $P$ values are two tailed. Where differences between cocaine and noncigarette groups were significant, a series of multiple regression analyses were used to assess the relative impact of cocaine vs other confounding variables in predicting outcome.

OBSHETRIC DATA

Table 3 summarizes comparisons of the obstetric and perinatal outcomes for the current pregnancy. Both cocaine and control groups had similar lengths of labor. For infants, several neonatal measures were also comparable for the cocaine and control groups, namely Apgar scores at 1 and 5 minutes. Infants of cocaine-using mothers, however, were of lower mean gestational age at delivery and lower birth weight and length. The incidence of low birth weight (<2500 g) and VLBW (<1500 g) was increased in the cocaine group. Preterm labor, designated as occurring at less than 37 weeks' gestational age, occurred in 40% of cocaine-exposed births vs 22% in non–cocaine-exposed births.
CORRELATIONS BETWEEN DRUG USE AND OBSTETRIC AND BIRTH OUTCOMES

Table 4 outlines correlations between substance use and obstetric and neonatal variables. In addition to cocaine, maternal use of other substances related to several maternal prenatal risk conditions. For all mothers, the number of cigarettes smoked per day correlated with a higher rate of prior neonatal deaths and lower maternal delivery weight. Alcohol use was associated with more prior abortions and higher gravidity. Marijuana use was significantly related to more prior abortions, pregnancies, and fewer prenatal visits.

Similarly, as shown in Table 5, infant birth outcomes were also related to the use of substances other than cocaine. Increased tobacco and marijuana use was related to lower gestational age and birth weight. Alcohol use was reliably related to lower gestational age, lower birth weight, and reduced length.

PREDICTION OF OBSTETRIC OUTCOME

Because the cocaine and the comparison groups differed on several factors also known to affect maternal obstetric and infant outcomes, a series of standard, hierarchical, and stepwise multiple regressions were computed (Table 6). Standard regression analyses indicated the variance in outcome predicted independently by cocaine and other substances. Hierarchical regression analyses allowed us to control for the effects of other covariates prior to assessing the effect of cocaine per se. In stepwise analyses, all variables that differed between cocaine- and non–cocaine-using samples were entered into the equation, allowing the computer to statistically choose predictors that best accounted for the outcomes. As cocaine-using women also differed on their use of other drugs, marijuana, alcohol, and tobacco, two interaction terms (cocaine×marijuana and cocaine×alcohol) were allowed to enter the equations. Because gestational age was lower in the cocaine-exposed group, analyses of maternal delivery weight, number of prenatal care visits, and neonatal birth weight and length were conducted after controlling for gestational age. Likewise, analyses of abortion history, gravidity, and neonatal deaths were conducted using maternal age and/or gravidity as covariates.

Maternal medical history and prenatal care variables that differed between groups were examined first; ie, maternal age, gravidity, weight, number of prenatal visits, history of abortions, and prior neonatal deaths. With maternal age controlled, cocaine status still had a significant effect on gravidity, indicating that cocaine-using women had more prior pregnancies than nonusers. Cocaine status also was the best predictor of level of prenatal care and of increased incidence of abortions. In fact, for these risk factors, cocaine predicted risk independently, ie, even when all other drugs and interaction terms were controlled. However, no drug predicted maternal delivery weight or history of neonatal deaths once
Interactions of cocaine with alcohol and marijuana on neonatal outcomes. These analyses indicated that cocaine, when compared with other substances, was the best predictor of prematurity, and that, after controlling for gestational age, cocaine was the only significant predictor of infant birth weight. For prematurity and birth weight, cocaine predicted poorer outcome even after controlling for all other drugs and interactions. Maternal use of the combination of cocaine and alcohol was the best predictor of reduced infant length, even after controlling for prematurity. The interaction effect of cocaine and alcohol on infant length is illustrated in Table 8 and indicates that mothers who used both cocaine and alcohol while pregnant had infants who were smaller in length than infants of mothers who did not use cocaine or alcohol or who reported using only either cocaine or alcohol.

Finally, we also examined the contribution of maternal obstetric risk variables to birth outcomes (Table 8). None of the obstetric risk variables predicted birth weight once gestational age was controlled; however, the number of prior abortions predicted infant length at birth. Prematurity was predicted best by the number of prenatal care visits and by the number of abortions a mother experienced prior to this pregnancy. In addition analyses, gravidity did not predict birth outcomes, after controlling for abortion history. However, a history of increased incidence of abortions predicted prematurity, even after the effects of gravidity were considered.

PREDICTION OF NEONATAL OUTCOME FROM DRUGS AND OBSTETRIC RISK

Table 7 presents the results of regression equations assessing the effects of the individual drugs and the other factors accounted for. Thus, lack of appropriate levels of prenatal care, increased gravidity, and higher incidence of prior abortions are potentially contributing factors to the obstetric sequelae associated with maternal cocaine use.

The present findings document that maternal cocaine use can affect pregnancy and neonatal outcome on at least three levels: i.e., prenatally, through reduced prenatal care and increased obstetric risk; through prematurity at birth; and beyond the effects of prematurity, through reduced somatic and linear growth.

In this study, corroborating others, infants of women who used cocaine during pregnancy were of lower birth weight, shorter length, and had reduced gesta-
Table 7. Stepwise Regressions for the Prediction of Neonatal Outcome (N=200) From Drug and Obstetric Variables

<table>
<thead>
<tr>
<th>Predictor and Obstetric Predictor</th>
<th>R² Change</th>
<th>F Change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight</td>
<td>0.44</td>
<td>144.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gestational age</td>
<td>0.46</td>
<td>77.7</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Gestational age</td>
<td>0.04</td>
<td>3.8</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Gestational age</td>
<td>0.20</td>
<td>40.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gestational age</td>
<td>0.03</td>
<td>4.6</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Birth weight</td>
<td>0.44</td>
<td>144.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gestational age</td>
<td>0.49</td>
<td>19.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total prenatal visits</td>
<td>0.14</td>
<td>11.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Abortions</td>
<td>0.23</td>
<td>5.4</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

Table 8. Length (in Centimeters) of Infants by Cocaine and Alcohol Exposure *

<table>
<thead>
<tr>
<th></th>
<th>Cocaine +</th>
<th>Cocaine -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>45.5</td>
<td>48.1</td>
</tr>
<tr>
<td>Alcohol</td>
<td>47.9</td>
<td>49.3</td>
</tr>
</tbody>
</table>

*Plus sign indicates exposure; minus sign, nonexposure. Combined exposure to alcohol and cocaine vs alcohol only or cocaine only, F=3.6; P<.001; t=1.8; P<.05, one tailed.

nential age at birth, when compared with the infants of non-cocaine-using women of similar race and social class. The incidence of low birth weight and VLBW was also increased in the cocaine-exposed group. The present data also indicate that maternal cocaine use can interact with other drugs in affecting outcome differentially.

Mothers who used both cocaine and alcohol had shorter infants than mothers who used only cocaine or alcohol. Cocaine's significant effects on intrauterine growth are important, as undernutrition at birth has been related to learning difficulties at school age. Since most cocaine-using women are polydrug users, potential interactive effects would be important to assess. Two recent articles have suggested that prenatal exposure to the drug combination of cocaine and alcohol had more negative effects than either drug alone on the growth and physical maturation of rat samples and on the reflex behavior of human infants early in life. Interactions may be due to specific effects of new substances generated through the combination of certain drugs, eg, cocaethylene, or may serve as measures reflecting more severe or long-term use.

Health care practices, cultural attitudes related to sexual activity and pregnancy, and prior obstetric history were also significantly different for cocaine-using women. Cocaine-using women showed increased use of marijuana, alcohol, and cigarettes, and were older, with higher gravidity. They received less prenatal care and had lower delivery weights. Controlling for confounding variables, cocaine use was the only significant predictor of other maternal risk factors that predicted pregnancy outcome in this sample, including lower levels of prenatal care and increased incidence of prior abortions.

Presumably, women who received less or no prenatal care, who were cocaine using and older, with increased history of abortions, would represent a more severe, chronic pattern of drug abuse. Considered together, these data suggest that maternal cocaine use may have an impact on neonatal outcome through these mediating obstetric variables that are also predicted by cocaine use.

Abortion history, as a risk factor, may be more prominent in severe cases of cocaine use, in which women may be so preoccupied by addiction that they receive no birth control or prenatal care when pregnant. The present study suggests that there is reason to consider increased history of abortions as an independent, mediating, or potentially additive risk factor in studies of perinatal outcome in cocaine-using populations. High gravidity has been demonstrated as a consistent risk factor for low birth weight, independent of cocaine, in prior studies. However, the present data suggest that it is the history of abortions, rather than gravidity per se, that is related to increased prematurity, since increased abortions predicted prematurity after accounting for the effects of gravidity, but not vice versa. This risk may relate to biologic interactions of internal functions but more likely represents cultural attitudes about birth control, increased sexual activity, or both.

Another finding from this study is that increased rates of low birth weight and VLBW were associated with maternal cocaine use. The incidence of VLBW among the infants born to women in the cocaine use group was double that in the comparison sample, but it did not reach statistical significance in this study. Because of its low population incidence, larger sample sizes are necessary to evaluate population differences in the rate of VLBW infants. Low-birth-weight and VLBW infants are at increased developmental risk for brain injury, infection, and growth retardation due to the sequelae of prematurity. As fetal cocaine exposure may impact differentially on very small, preterm infants, this group warrants further study.

Limitations of the present study should be considered in evaluating these findings. Subjects were all poor, minority women, living in an urban environment. Thus,
results are not generalizable to middle-class, white, or rural women who use cocaine. Independent effects of cocaine may have been underestimated owing to limitations in sample size. Also, some women who used cocaine may not have been identified by either urine screen or interview, thus masking differences between the cocaine-using and the comparison sample. However, if such misclassification occurred, it would serve to underestimate rather than overestimate the effect of cocaine. The present study was also not able to assess the severity or duration of cocaine use or other drugs in this sample, with the exception of tobacco. These aspects of maternal drug use also need further evaluation. Although women were prospectively identified, data were extracted retrospectively from the medical charts, increasing the chances of incomplete data or biases in information. However, information extracted included variables routinely collected by medical or nursing staff, and missing data were negligible. There are problems inherent in asking drug-using women to recall past events reliably. However, it is unlikely that they would uniformly exaggerate the number of prior pregnancies, births, and abortions in their history.

Nevertheless, the proximate causes of the adverse effects noted in pregnancies associated with cocaine use are more complicated and possibly less direct than previously thought. While recent studies have highlighted that racial, social class, and health care differences in populations are related to low birth weight outcomes, as yet there has been limited exploration of what impact maternal cocaine use may have on these risk factors. Cocaine interacts in combination with maternal demographic factors such as age, obstetric history, and possibly cultural factors, and results in multiple adverse pregnancy variables, including low maternal weight and low infant birth weight. Cocaine also acts in interaction with other drugs, creating additional risk. The precise mechanisms of interaction among maternal obstetric risk factors, premature birth, intrauterine growth, and cocaine use are undetermined and should be investigated in future studies.

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Reprint requests to Rainbow Babies and Childrens Hospital, 2101 Adelbert Rd, Cleveland, OH 44106 (Dr Singer).

REFERENCES