The Search for Congenital Malformations in Newborns With Fetal Cocaine Exposure

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ABSTRACT. Context. The association between prenatal cocaine exposure and congenital anomalies is not definitive.

Objective. To determine whether prenatal cocaine exposure results in an increased number or identifiable pattern of abnormalities.


Setting. Rural public health population delivering at a regional tertiary medical center.

Patients. Two hundred seventy-two offspring of 154 prenatally identified crack/cocaine users and 154 nonusing controls were matched on race, parity, location of prenatal care (that related to level of pregnancy risk), and socioeconomic status. Drug use was determined through repeated in-depth histories and urine screens. Infants not examined within 7 days of birth were excluded.

Outcome Measures. Assessments were made by experienced examiners masked to maternal drug history. Included were 16 anthropometric measurements and a checklist of 180 physical features defined and agreed upon in advance.

Results. There were no differences on major risk variables between the included and excluded infants. There were significantly more premature infants in the cocaine-exposed group. Cocaine-exposed infants were significantly smaller in birth weight, length, and head circumference but did not differ on remaining anthropometric measurements. There was no difference in type or number of abnormalities identified between the exposed and nonexposed groups. There was no relationship between amount or timing of exposure and any of the outcomes.

Conclusions. This prospective, large-scale, blinded, systematic evaluation for congenital anomalies in prenatally cocaine-exposed children did not identify an increased number or consistent pattern of abnormalities. Pediatrics 2001;107(5). URL: http://www.pediatrics.org/cgi/content/full/107/5/e74; prenatal cocaine use, pregnancy outcome, congenital anomalies.

A search for congenital malformations related to prenatal cocaine exposure has been underway since physicians became aware of the epidemic of prenatal use in the mid-1980s. Concern has been aroused because of a variety of case reports, small patient series, and retrospective studies reporting abnormalities of the skull, heart, skeleton, gastrointestinal tract, and genitourinary tract in infants born to women who used cocaine during pregnancy.1–13 Over the years, the results of prospective studies have yielded somewhat conflicting outcomes.14–28 Methodologic concerns in many of these studies have precluded widespread acceptance of their findings, either positive or negative, leaving unanswered the question regarding the association between prenatal cocaine exposure and congenital anomalies.

The most commonly identified mechanism of the effects of prenatal exposure involves the vasoconstrictive properties of cocaine. The proper growth and development of the fetus depend on a well-functioning vascular system. Vasoconstriction resulting in disruption of blood flow to the fetus could result in the development of structural abnormalities throughout gestation.29,30

The purpose of this study was to determine whether prenatal cocaine exposure was associated with an increased number or an identifiable pattern of congenital anomalies when using a study design that included a detailed, standardized, clinical examination of the newborn; examiners masked to the drug exposure status of the infant; a large sample; systematic identification of prenatal drug use to define more clearly the exposed and nonexposed groups; and prospective prenatal enrollment of participants. It was our hypothesis that more infants prenatally exposed to cocaine would have congenital anomalies than would infants who were nonexposed.

METHODS

This study was part of a longitudinal, prospective study of the medical and developmental effects of prenatal cocaine exposure approved by our institutional review board. Confidentiality of research data was protected by a Certificate of Confidentiality from the National Institute on Drug Abuse, US Department of Health and Human Services (DA-91-45). When a woman enrolled in prenatal care at the county public health unit and was at least 15 weeks pregnant or when she presented for delivery in the case of little or no prenatal care, she was approached for informed consent by a project staff member.

Study Design

A complete, detailed description of the longitudinal study has been previously published.31 In summary, to minimize bias in participant enrollment and to obtain the earliest drug history possible, we prospectively enrolled a full range of cocaine users and matched controls when they first contacted the health care facilitator.
CONGENITAL MALFORMATIONS AND FETAL COCAINE EXPOSURE

Identification/Documentation of Drug Use

Whenever possible, drug history interviews were performed at the end of each trimester of pregnancy to cover the previous 3 months. Forty-one percent of the sample was interviewed at the end of the first trimester and 34% at the end of the second trimester. If prenatal interviews were not possible because of limited or no prenatal care, women were interviewed after birth about drug use in each of their trimesters of pregnancy. This group included the remaining 25% of the sample. The drug history interview was adapted from Day et al32 and included the use of pregnancy calendars to prompt memory and always asked about the amount, frequency, and pattern of past drug use, which is thought to be more threatening and probably more accurate data. Interviewers were trained to be supportive and nonjudgmental and to establish rapport. Because illiteracy is common in our population and we wished to standardize data collection conditions, interviewers read and explained all portions of the interview. Questions were asked about each of a number of categories of commonly used drugs using street or slang labels.

To supplement histories and maximize the accuracy of the classification of participants as users or nonusers, drug screening of urine specimens was required on 2 occasions that participants could not anticipate: the day study consent was obtained and the day of delivery. Toxicology screening was performed that included testing for barbiturates, benzodiazepines, cocaine, marijuana, methamphetamine/amphetamines, opiates, phencyclidine, and propoxyphene, using fluorescence polarization immunoassay. Positive screens were confirmed with gas chromatography/mass spectrometry.

Infant Evaluations

Each infant was assessed by an experienced examiner who was masked to the drug history of the mother and any information about the infant. The examiners included 6 experienced neonatal nurses overseen by 1 neonatology investigator (N.P.B.). Infants were included in the anomalies study if they were examined by 1 of the 7 members of the research team at birth, defined as within the first 7 days of life. Examinations were conducted in the Clinical Research Center or in a few cases in the nursery if the infants were unable to be transported. Birth weight was obtained by the clinical nursing staff immediately after admission to the nursery. Research examiners obtained the remaining 15 anthropometric measurements. Standard measurements of overall body size were included as well as standard facial and genital measurements. The latter measurements were chosen because of both the increased alcohol exposure in the cocaine-exposed group and previous reports of facial and genitourinary abnormalities occurring in cocaine-exposed infants. A method of Dubois and Dubois16 was used to determine gestational age. Ponderal Index was calculated using the standard formula of weight (g) × 100/length (cm). Size for gestational age (including weight, length, and head circumference) was based on the norms of Lubchenco et al,36 which use the 10th percentile as the lower cutoff. In addition, the examiners used a modified checklist of 180 physical features adapted from Simpson et al37 to note the presence or absence of specific abnormalities, each of which was defined in advance and reviewed and agreed upon by the examiners. Examiners were randomly available for testing according to each of their clinical schedules. Each examiner completed nearly identical numbers of assessments within the cocaine-exposed and nonexposed groups. A copy of the complete examination is available on request. Presence or absence of abnormalities was determined solely based on physical examination.

In an attempt to determine any differences in the identification of congenital anomalies among the excluded infants who did not undergo detailed physical examinations by research staff, 4 items from the Hobel38 risk scale specifically dealing with the issue of congenital anomalies were analyzed.

Statistical Analyses

For purposes of data analyses, the complete list of 180 abnormalities was divided into 27 items referred to as major abnormalities and 153 items referred to as minor as originally described.32 Additional analyses were undertaken with individual items grouped together by organ systems: skull, heart, skeleton, gastrointestinal, and genitourinary. Simple comparisons of continuous outcomes were made using Student’s t test or the Wilcoxon rank sum test. Fisher’s exact or χ² test was used for comparisons of categorical data. Analysis of variance was used to determine whether there was a relationship between amount of cocaine use and the outcome measures. We decided a priori to use an arbitrary but absolute definition of high use, which is ≥$10.00 or 1 rock/day on average throughout pregnancy. During the period of participant enrollment, crack sold for ~$10.00 a rock in our community. Participants were grouped into the following user categories: unexposed controls (n = 135); heavy users, defined as mean daily use of cocaine throughout pregnancy ≥$10.00/day (n = 23), and less heavy users, defined as mean daily use of cocaine throughout pregnancy of <$10.00/day (n = 94). To investigate the relationship between timing of cocaine exposure and outcome, analyses were performed comparing infants with first-trimester exposure (n = 97) to nonexposed controls (n = 135). Eliminated from the analyses for amount and timing were the infants of 20 participants who had positive urine screens for cocaine metabolites but denied cocaine use by history.

RESULTS

Of the 154 cocaine users originally enrolled in the study and their 154 matched controls, 81% were black, 87% were multiparous, and 77% were from the lowest level of the Hollingshead Index39 of socioeconomic status. The cocaine users were significantly older than were controls (27.6 ± 4.8 vs 23.8 ± 5.5 years; P = .001), even after controlling for tobacco, alcohol, and marijuana use. Both groups had 1 mother over age 40 years. Of those reporting cocaine use, 80% indicated that they used crack, and only 6% of the women reported being in drug treatment programs during pregnancy. There were significantly more cocaine users than controls who used tobacco (80% vs 24%; P = .0001), alcohol (77% vs 31%; P = .0001), and marijuana (44% vs 7%; P = .0001).

A wide range in amount of drug use was reported by the study participants with 20% of the cocaine users reporting, on average, spending $10.00 or more a day for cocaine for the entire length of their pregnancy (high use). The reported daily drug usage by trimester and throughout the entire pregnancy has been reported previously in detail.31 In summary, cocaine users reported significantly more use of each drug during each trimester and throughout the entire pregnancy. On average, over the entire preg-
nancy, cocaine users and noncocaine users, respectively, reported smoking 8.3 ± 8.7 cigarettes per day compared with 2.1 ± 5.8 cigarettes per day (P < .0001); smoking 0.16 ± 1.02 joints of marijuana per day compared with 0.01 ± 0.11 joints of marijuana per day (P < .0001); and drinking 0.23 ± 0.20 oz of absolute alcohol per day compared with 0.01 ± 0.03 oz of absolute alcohol per day (P < .0001).

Of the 308 women originally enrolled in the study, 272 delivered infants who were examined within the first 7 days of life (137 cocaine-exposed and 135 controls). Excluded were perinatal deaths (n = 7) and those not examined in depth by 7 days of age because of illness (n = 5) or breaks in protocol (n = 24). The 272 participants included in the sample did not differ from the 36 excluded participants on any of the following variables: cocaine exposure status, race, parity, socioeconomic status, maternal age, or amount of prenatal tobacco, alcohol, marijuana, or cocaine exposure. In addition, there were no differences between the excluded and included infants on the 4 items from the Hobel risk scale designed to identify major anomalies through postnatal chart review of clinical assessments performed either prenatally or during the birth hospitalization. The 4 items from the Hobel risk scale were: 1) Were there major anomalies visible at birth? 2) Were there anomalies of the respiratory tract? 3) Were there major anomalies of the heart that required/did not require intervention? and 4) Were there chromosomal abnormalities identified by blood analysis?

There were a significantly higher proportion of premature infants in the cocaine-exposed group (14% vs 6%; P = .028). Although not significant at the traditional level of .05, there were also a higher percentage of small for gestational age infants observed in the cocaine-exposed group (8% vs 3%; P = .06). There was no significant difference between groups in the Ponderal Index (2.62 ± 0.36 vs 2.63 ± 0.34, respectively; P = .87).

The 27 premature infants were excluded from the analyses for the anthropometric measurements so that unadjusted data could be presented. The 118 cocaine-exposed term infants (63 females and 55 males) had lower mean birth weights, lengths, and head circumferences than did the 127 term controls (53 females and 74 males). These growth results have been presented previously for the entire birth cohort.29 There were no differences between the exposed and nonexposed term infants for the remaining anthropometric measurements (Table 1).

The remaining analyses include the entire sample of infants, unless otherwise specified. Overall, there were 16 infants identified with 1 major anomaly (10 cocaine-exposed and 6 controls) and 1 infant with 2 major anomalies (cocaine-exposed). No infant had >2 major anomalies identified. All infants had at least 1 minor abnormality identified on detailed physical examination. The mean number of major and minor abnormalities identified per child did not differ significantly between the cocaine-exposed and nonexposed groups (7.3 ± 3.0 vs 6.7 ± 3.0, respectively; P = .35). In addition, there was no difference in the number of children within each group identified with a major or minor anomaly.

The types of major abnormalities identified are listed in Table 2 by group. The most common problem identified was microcephaly. Based on the physical examination, no pattern of abnormalities was identified, and when items were grouped by organ systems, there was no increase in abnormalities of the skull, heart, skeleton, or gastrointestinal or genitourinary tract that could be related to cocaine exposure.

Analyses regarding amount of cocaine exposure did not reveal any relationship between heavy use and any of the anthropometric measurements or the identification of major or minor anomalies. Likewise, the analyses regarding the timing of exposure did not indicate a relationship between first-trimester cocaine usage and any of the outcomes.

### DISCUSSION

The primary goal of our study was to determine whether prenatal cocaine exposure was associated with an increased number or distinctive pattern of
congenital anomalies that could be identified by means of a clinical examination. Although the exposed infants had lower mean birth weight, shorter mean length, and smaller mean head circumference than did the nonexposed infants, we were unable to identify any other anthropometric differences or any increase in the number of major or minor anomalies or in the number of children with major or minor anomalies in the cocaine-exposed group. In addition, we could not identify any distinctive pattern of anomalies among the cocaine-exposed infants or an increase in anomalies of the skull, heart, skeleton, or gastrointestinal system or genitourinary tract as previously reported. Finally, attempting to determine whether the amount of cocaine used during pregnancy or whether the time during gestation that it was used affected outcome yielded negative results.

Numerous studies have been undertaken in both humans and animals to identify malformations in offspring exposed to cocaine in utero. Some studies report no increases in congenital abnormalities in rats or mice.40–42 Other studies in both species, however, have indicated that prenatal cocaine exposure may be teratogenic in a dose-dependent manner, resulting in abnormalities of the limbs,43–45 cardiovascular,46,47 genitourinary,53,44,47,48 and central nervous systems.43,44,46,47,49

Some human reports have likewise noted anomalies of the genitourinary53,10,11,13,20,21 and cardiovascular systems,1,8,14–16 skull defects,14 limb defects and intestinal atresias,6,13,20,21,56 and a variety of central nervous system lesions5,7,9,13,51–56 in infants exposed to cocaine in utero. Two additional studies report mild facial abnormalities in exposed infants.2,12 However, within the reported literature no consistent pattern of congenital anomalies has been observed and no increased incidence of malformations substantiated.17–19,22–28,57–60

The reasons for these divergent findings in the human literature could be related to a variety of methodologic issues. For example, there is the problem of separating cocaine effect from the confounding effects of such things as other drug exposures, infectious diseases, and nutritional differences, all of which have known fetal effects. Samples should be large enough to statistically control for confounding variables if group differences are found. Conflicting findings could also be related to other methodologic issues, including retrospective study designs; sample selection biases; lack of inclusion of appropriate, nonexposed comparison groups; and lack of masking of examiners. Potential problems related to retrospective samples, lack of comparison groups, and the use of nonmasked examiners are obvious. In addition, relying on nonsystematic drug screening, using drug histories obtained retrospectively from patients who are referred for evaluation of an abnormality, or using the drug history recorded in the clinical record are all ways of introducing potential biases into the sample.

Using a detailed, standardized examination as a common outcome is also important when comparing studies. Some investigations that have found anomalies related to cocaine exposure have relied on advanced technologies, such as cranial or renal ultrasound, echocardiography, magnetic resonance imaging, and doppler flow measures. Although these outcomes are interesting and important, they cannot be compared with the outcomes from studies that rely solely on physical and dysmorphology examinations, which answer different but equally important questions.

Also of concern is whether anomalies are related to the amount of drug reaching the fetus or to the developmental stage of the fetus at the time of drug exposure. This is a particularly difficult question to answer when studying illegal drugs, because amounts used are not readily known, the purity of the drug can be variable, and recall among all participants is difficult, with the reliability of the memory of a drug user perhaps more questionable. Although animal studies point to potential dose-dependent teratogenic effects of cocaine, few human studies have yet dealt with the issues of amount and timing of exposure in the area of congenital abnormalities.

Our study was designed to build on the work of previous investigators with improved methodologies to avoid some of these earlier shortcomings. We prospectively enrolled a sample of prenatal cocaine users when they first entered the prenatal care system and matched them to a control group of nonusers. By enrolling in this way, we reduced sample selection bias and included a wide range of drug use from no known use to very high use. Our study was designed to have a sample size large enough to statistically control for confounding variables in data analyses, if necessary, and our examiners were masked to the drug status of the mothers and infants. The outcome measures that we used were standardized for this protocol and were extensive, providing a detailed look at each infant. In addition, our detailed drug histories that were obtained repeatedly throughout pregnancy afforded us the opportunity to examine issues related to the amount and timing of drug exposure.

Despite some advances, however, we were not able to adequately address all of the methodologic issues of concern. For example, our sample size was several-fold larger than most previously reported studies that found differences related to cocaine exposure, thus, being large enough to show differences in outcomes of the magnitude previously reported. However, it might not have been large enough to identify abnormalities occurring at very low rates under various conditions of amount and timing of the exposure. Thus, these remaining issues will need to be addressed by future research.

**CONCLUSION**

Our study found no evidence for cocaine contributing to the development of gross abnormalities in humans, as have been previously reported. If cocaine does produce human malformations, it seems to do so at a very low rate or only under certain conditions, perhaps related to such events as the amount and timing of the exposure or to the simultaneous inges-
tion of other substances, or it requires advanced technologies for identification.

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