NEURODEVELOPMENTAL EFFECTS OF COCAINE

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The United States has recently been compelled to acknowledge and to cope with an alarming increase in incidence of drug exposure in newborns owing to a new cocaine epidemic. Perhaps because of the sudden onset of national recognition of the problem, the lack of a firm knowledge base regarding the mechanisms of the effects of cocaine on child development, and the sheer magnitude of the problem in urban areas of the United States, the issue of cocaine exposure in children has been characterized by medical, legal, and social policy controversies. This article focuses on elucidating what is and what is not known about cocaine's neurodevelopmental effects and aims to inform perinatologists about the complex issues associated with understanding and caring for the cocaine-exposed newborn.

INCIDENCE

There is widespread agreement that cocaine, especially in its "crack," or smoked, form, has become a pervasive presence in newborn nurseries and neonatal intensive care units in urban areas nationwide. Studies indicate that 10% to 15% of major urban newborn births are affected by maternal cocaine use.10 The National Association for Perinatal Addiction Research and Education (NAPARE) has estimated that over 100,000 infants annually are born with drug exposure. Data from one teaching hospital indicated a 15-fold increase in prenatal cocaine exposure in a 12-year period compared with previously obtained data.100 Incidence rates may be higher within lower socioeconomic status and minority groups, however. In Ohio, for example, at a major university's obstetrics hospital, cocaine exposure affected 20% of minority, indigent newborns and from 25% to 30% of all very low birth weight (VLBW) births in 1990 (Robert Kleigman, MD, personal communication, June 1992).
can be treated effectively in neonates if discovered early. 20% to 40% of infants prenatally exposed to the acquired immunodeficiency syndrome (AIDS) virus will contract the disease. Approximately 80% of all HIV infections in children in the United States and European countries are acquired perinatally.

SCREENING FOR DRUG EXPOSURE

Identification of cocaine use is most often based on maternal drug interview, urine toxicology screen, or both. An investigation of marijuana and cocaine use on fetal growth highlighted the importance of using biologic markers in combination with self-reports to identify drug use during pregnancy. Because cocaine is metabolized and cleared from an adult woman in 3 to 6 days, however, the most commonly used marker, urine screening, has serious limitations.

Several other biologic markers, including meconium, amniotic fluid, and newborn dried blood specimen, have been investigated. Meconium testing has the advantage of detecting cocaine exposure from as early as the first trimester. Recent reports comparing different methods of cocaine exposure suggest that meconium testing is superior to urine, but these reports also emphasize the need to combine biologic screens with clinical interviews.

Neither urine nor meconium assessment provides a way of assessing maternal pattern of use. One other experimental method of detecting cocaine use, hair analysis, may prove useful in answering questions about maternal pattern of drug use during pregnancy. The question still remains whether a woman used small amounts of cocaine on a regular basis during her pregnancy or used large amounts in binges. Such information is currently obtainable only through clinical interview. Interviews can be highly unreliable owing to the denial common in women who use drugs and alcohol. A large prospective study found that 24% of pregnant women who used cocaine would have been undetected if urine assays were not performed. Simultaneously 47% of women who had negative urine assays admitted cocaine use during clinical interview.

Because maternal prenatal or newborn screening for cocaine is not done universally, identification and treatment of cocaine-using women and their infants are riddled with controversy. Controversy stems from a number of factors, including racial and social class variation in preference for differing illegal drugs; a probable racial and social class bias in detecting maternal drug use in public versus private care hospitals; and racial, social class, and drug-related differences in referral to social service and legal systems.

The few anonymous screening studies of maternal drug use in pregnancy that have been reported all indicate a markedly similar range (10% to 20%) of illegal drug use in poor, minority, and white middle-class groups. White, private-care women, however, tend to use marijuana, whereas minority, lower social class women tend to use cocaine.

Criteria for doing a toxicology screen vary greatly from hospital to hospital and from physician to physician. Commonly used criteria include infant withdrawal symptoms, lack of prenatal care, a family history of child neglect or abuse, and a history of maternal drug use. Few if any private care hospitals screen for maternal drug use. Even in large public hospitals, screening is rarely universal and affects primarily on poor or minority women who use cocaine. As detection of neonatal cocaine exposure in some states initiates referral to legal or social service agencies for investigation of child abuse or neglect, potential racial and social class biases and ethical implications become evident. In the only study to investigate the conse-
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Two large prospective studies, however, have not resolved this issue. In one, a higher, but not significant, incidence of three minor congenital anomalies were found in newborns of cocaine users versus nonusers. In another study, controlling for confounding factors of maternal age, smoking, alcohol, and other drug use, cocaine-exposed infants were found to have more genitourinary anomalies than a comparison sample.

The cerebral blood flow velocity of 20 full-term, newborn, cocaine-exposed infants and 18 nonexposed infants was studied on the first 2 days after birth. Increased mean arterial blood pressure and cerebral blood flow velocity on the first day of life suggested the existence of a hemodynamic effect that puts cocaine-exposed infants at increased risk for intracranial hemorrhage.

In an interesting pilot study with implications for long-term development, cardiovascular effects of prenatal cocaine exposure in a small group of newborns were compared with a group of normal controls. Results from a complete echocardiographic study indicated that the left ventricular (LV) posterior wall and septum were significantly thicker in the exposed group. In addition, the exposed group had significantly larger LV mass, suggestive of the LV hypertrophy found in adult cocaine users.

Neurologic Abnormalities

Cranial ultrasound was used to detect the presence of central nervous system injury in 74 generally healthy, term neonates exposed to cocaine, methamphetamine, or cocaine and a narcotic. The incidence of cranial abnormalities was significantly greater in the drug-exposed infants compared with a group of well infants. Lesions in the drug-exposed infants included intraventricular hemorrhage, echodensities, and cavitory lesions focused in the basal ganglion, frontal lobes, and posterior fossa. Echodensities and echolucencies in the frontal lobe and basal ganglia may result in morphologic alterations that affect specific functions such as affect or information processing. Recently a large-scale study of infants in Boston, however, failed to replicate these findings.

Although striking, findings of congenital neurologic abnormalities have been limited to a few cases. It is unclear whether local hemorrhages, leading to infarcts and limb reduction defects, are directly responsible or whether vasoconstriction-produced anoxia results in a generalized inhibition of growth and differentiation in the developing embryo and fetus. In any case, if similar to other teratogens, prenatal cocaine exposure can potentially produce a continuum of anomalies—from mortality to possible noncranial congenital abnormalities, to more subtle forms of morbidity and behavioral deficits—depending on the extent of diminished blood flow as well as the time during gestation when the insult occurs.

It appears that cocaine is a relatively weak teratogen that produces toxicity to both the mother and the fetus. What remains uncertain are the implications of findings from animal studies for the development of human infants. Animal studies, although more controlled, must be considered with great caution when applied to understanding of human development. Although it is possible to develop models that reconstruct fetal cocaine exposure, animal studies have not addressed the interaction of the numerous postnatal environmental factors that also influence developmental outcome. Unfortunately, animal research as well as some earlier studies with human infants failed to take postnatal factors into account. This led to exaggerated perceptions concerning the negative impact of prenatal cocaine exposure.
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There are now seven published studies investigating the neurobehavioral sequelae of cocaine-exposed newborns in the first month of life using the Brazelton Neonatal Behavioral Assessment Scale (BNBAS).\textsuperscript{15,17,27,34,78,87,108} The BNBAS, the most widely used neonatal behavioral assessment, groups individual item scores into six behavioral clusters: habituation, orientation, motor performance, range of state, state regulation, and autonomic regulation. These clusters are conceptualized to describe autonomic, motor, state, and social attention systems that influence the infant's capabilities and limits in contributing to the caregiving environment.

All seven investigators administered the Brazelton within 1 to 7 days after birth on term, healthy infants but with widely divergent findings. Two separate studies of cocaine-exposed and comparison infants\textsuperscript{15,17} found depressed interactive behavior, impaired responses to environmental stimuli, and deficits of orientation, motor, and state regulation in cocaine-exposed cohorts. In a matched, stratified design,\textsuperscript{24} cocaine-exposed infants were less likely than a nonexposed comparison group to show adaptive habituation to repeated stimulation in the first week of life. In contrast, four other studies,\textsuperscript{27,78,87,108} some with larger sample sizes and some of which controlled testing bias by ensuring examiners were blinded to drug status, found no significant deficits in cocaine-exposed infants on BNBAS dimensions in the early neonatal period.

It is difficult to draw specific conclusions from these neonatal studies for a number of reasons. Although all used the BNBAS as a measure of infant behavioral functioning, the populations sampled varied markedly. Mothers varied as to whether or not they were enrolled in drug treatment programs versus whether they were from urban or rural communities, and whether they were light versus heavy users. They also differed in level of prenatal care; extent of use of other drugs, especially alcohol and tobacco; and mode of use (smoked versus snorted). Snorted cocaine results in a significant increase in potency of the drug compared with snorted cocaine; thus differentiation of mode of use is important. Studies also differed as to whether or not urine samples were available for comparison groups, and sample sizes ranged from inadequate to large. For studies in which comparison groups did not have urine samples, null results could have stemmed from the undetected presence of cocaine exposure in the comparison sample. Only one study reported on the use of obstetric medications in cocaine versus noncocaine-using women. This study found cocaine users to be more likely to receive anesthesia during delivery.\textsuperscript{97} Because obstetric medication or anesthesia could be expected to influence infant behavioral performance within the first 3 days of life, their confounding effects need to be evaluated in studies of infants undertaken immediately postpartum.

Three of the investigators also readministered the BNBAS within a month's follow-up after birth, presumably when effects of other drugs would not influence test results. One study\textsuperscript{108} found no differences between groups at the later assessment, whereas two\textsuperscript{27,78} found differences at follow-up. Cocaine-exposed infants in these two studies had increased abnormal reflexes\textsuperscript{27} and deficits in motor function at 1 month.\textsuperscript{78} In a study with a sample adequate to control for other drug use, neonatal complications, and tester factors, cocaine was found to have independent effects on infant motor behavior, state regulation, and abnormal reflexes at 28 days.\textsuperscript{27} Despite these differences, none of the studies reported that the behavior of cocaine-exposed infants was clinically aberrant. Also, by 1 month of age, the environmental impact of living with a drug-using caregiver may have already exerted a negative effect on infant behavior.

Another difficulty limiting interpretation of these studies is the use of the BNBAS as the sole indicator of behavioral functioning. The BNBAS, similar to other
revealed significant differences in muscle tone, reflex, and volitional movements. Rather than using only measures that strictly assess differences between cocaine-exposed and drug-free infants in motor milestones, the authors recommended using measures that are sensitive to qualitative differences.

One recent study produced an unforeseen result. Cocaine-exposed infants had higher scores on a global measure of motor skills than a nonexposed comparison group. The authors suggested that the better performance was primarily in gross motor development and may be related to increased muscle tone. No data are yet available to replicate this finding or to support the position that cocaine-exposed infants have persistent, increased muscle tone.

Long-Term Follow-Up Studies

Because prenatal cocaine exposure has only recently become a major concern, longitudinal studies are relatively few. Although the development of drug-exposed infants beyond the neonatal period has major implications for health, education, and social services, it also raises many difficult scientific issues.

In one of the few published, follow-up studies of prenatally drug-exposed infants, standardized scores from the Bayley Scales of Infant Development were reported on a group of cocaine-exposed children. The Mental portion of the Bayley Scales assesses sensory-perceptual acuity, visual and auditory discrimination, and verbal ability. The Psychomotor portion provides a measure of gross and fine motor abilities and coordination.

At 2 years of age, cocaine-exposed children did not differ on the scales from a nonexposed comparison group. Cocaine and other drug-exposed infants did, however, show an increased proportion of infants with Mental and Psychomotor Index Scores greater than 2 SD below average on the scales.

The same study also reported that the mean head size, a correlate of brain growth, of the drug-exposed infants was smaller at birth and remained smaller through 2 years of age compared with the control infants. When all groups were combined, there was a significant correlation between head size and developmental score. The authors noted that postnatal head growth may be an important biologic marker in predicting development of prenatally drug-exposed children.

A recent follow-up report on the same subjects suggested that differences in head growth were still evident at 3 years. Although mean score at 3 years of age of the drug-exposed children was within the normal range, the children were more likely to be perceived by their mothers as displaying behavior problems. The 3-year-old, drug-exposed children also scored significantly lower on verbal and reasoning tasks.

A preliminary report from another ongoing study found that the mean scores of cocaine-exposed infant groups were below those of a nonexposed comparison group on the Bayley Mental Scale, but not on the Motor Development Scale, at 6 and 12 months of age. Additionally, when compared with the nonexposed infants, a disproportionate number of cocaine-exposed infants had scores below average on the Mental Scale. Differences were still present after accounting for group differences in gestational age.

Other investigators have assessed visual recognition memory in 36 healthy, full-term infants prenatally exposed to drugs with the Fagan Test of Infant Intelligence (FTII) at 67 and 92 weeks' conceptional age. The FTII is an alternative infant assessment measure based on differential visual fixation to novel over familiar pictures. The infants were born to mothers who used several drugs, frequently in
between desired treatment and scheduled treatment, and lack of adequate care for children while the mother is receiving treatment. Additionally, most traditional drug treatment programs were designed for white, middle-class, male populations and may not generalize to other populations. A consequence of these significant barriers to treatment is that many drug-exposed infants are raised by mothers who continue to use drugs.

Mother-Infant Interaction

A caregiver’s ability to respond through talking, eye contact, and tactile stimulation to the infant’s behavioral cues is necessary for optimal intellectual and emotional infant development. Although it has been suggested that drug-dependent mothers are impaired in the ability to respond to their infants, the specific interactional behavior of cocaine-using mothers is still under investigation.

It has been suggested that maternal psychologic status and her interactions with infants may be impaired through drug intoxication or withdrawal. A few studies have focused on psychologic or personality characteristics of cocaine-using mothers in relation to interactional style and caregiving. One study found decreased responsivity and lower social involvement of the cocaine-using mother to her infant’s cues in the neonatal period. Another examined the relationship of maternal psychopathology, evaluated by a personality inventory, to scores on the infant orientation subscale of the BNBAS. It was found that the infant’s orientation score at 1 month of age was significantly negatively correlated with clinically elevated maternal scores. The conclusion was that maternal psychologic distress in cocaine-using women affects interaction with her infant.

Maternal Psychologic Characteristics

Cocaine dependence has been associated with increases in psychopathology, such as depression, psychoticism, anxiety, and personality disorders, although a consistent pattern of symptoms has not emerged. Additionally, it is not clear whether psychologic distress precedes the onset, or is a result of, cocaine use.

Depression in cocaine-using women is a concern because maternal depression has been demonstrated to have adverse effects on infant development. Investigations of depression in cocaine-using mothers have produced inconsistent results. Although some studies have found a relationship between cocaine use and level of depression, other studies have not.

For example, Singer et al. recently surveyed cocaine-using postpartum mothers with a self-report, measuring depression and other symptoms of psychologic distress. Symptoms of depression were no more prevalent in the cocaine-using sample than the control group. Cocaine-using mothers did report more symptoms of paranoid ideation, phobic anxiety, somatic complaints, and psychosocial compared with noncocaine-using women.

A group of cocaine-dependent and alcohol-dependent women receiving drug treatment were assessed for personality disorders according to DSM III-R criteria. Significantly more cocaine-dependent women (75%) versus alcohol-dependent women (32%) met the criteria for personality disorder in this study. Specifically paranoid, borderline, and histrionic personality disorders were most prevalent for cocaine-dependent women.

In another study of cocaine-using mothers, treatment seekers were found to
surveyed drug-exposed infants born in 1989 were placed in foster care. The increased need for foster care placement indicates that parental abandonment, abuse, and neglect of children are associated with increases in maternal drug use.¹⁰³

Maternal Drug Use Patterns

In light of the fact that cocaine-using women are much more likely also to use other drugs, the relevance of studying the isolated effect of cocaine use comes into question. A recent survey of psychologic distress among cocaine-using mothers indicated that as a group, the best predictor of psychologic distress was the combined use of both cocaine and alcohol.⁶ In addition to the interaction effect of cocaine and alcohol on psychologic distress in mothers, consideration of specific detrimental effects to the developing fetus has begun to be investigated in mammals. The interactive effect of alcohol and cocaine was found to affect birth weight, postnatal mortality, and delayed physical maturation more adversely in rats than the use of either drug alone.⁹¹

The unique effects of specific combinations of drugs may produce a uniquely different outcome for a developing fetus. Additionally, maternal use of a combination of drugs may affect parenting behavior in a unique way. The explosive increase in the use of “crack” cocaine in pregnant women has placed an emphasis on the search for specific sequelae of its use on infant development. Because cocaine rarely seems to be used in isolation but is characteristically used in combination with other harmful drugs, it may be useful to expand research endeavors in this area.

SUMMARY

How and to what extent fetal cocaine exposure produces specific, negative, long-term effects on infant neurodevelopmental competence has not yet been determined. We have argued previously that results from animal studies, the findings of intrauterine growth retardation in human studies, and the markedly higher incidence of numerous associated risk factors in cocaine-exposed cohorts herald significant clinical risk to the developing infant.⁴⁴ Recognition of infant risk status should not imply condemnation of a group of children but, as with preterm infants, lead to aggressive, national, social, and scientific efforts to delineate and intervene with potential sequelae of drug exposure.

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References

3 Anisfeld E, Cunningham N: Project 0 to 2: A comprehensive intervention with cocaine-