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Neurobehavioral sequelae of fetal cocaine exposure

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The biosocial consequences of the crack-cocaine epidemic are being seen in the growing number of cocaine-exposed infants. Approximately 10% to 15% of women of lower socioeconomic status in urban hospitals use cocaine, sometimes in combination with other drugs, during their pregnancies.^{1–3} More than 100,000 babies born in the United States annually are believed to have been exposed to cocaine or other drugs during the critical period of fetal brain development,⁴ representing an increase in incidence of twofold to tenfold between 1983 and the present time.⁵ However, there are no reliable national estimates of maternal prenatal cocaine use because of the lack of systematic and random screening efforts.

Concern has been raised about the potential for cocaine to damage the developing central nervous system permanently. This effect may be similar to that observed for fetal alcohol syndrome, in which fetal exposure to a drug leads to persistent neurodevelopmental abnormalities. Because these abnormalities can be expressed as behavioral and learning disabilities, research and intervention efforts have focused on understanding the effects of maternal cocaine use on the subsequent development of the infant. Pediatricians should have an understanding of the possible developmental problems associated with maternal cocaine use as they encounter these mothers and their children in their practices. Although no information about long-term development is currently available, emerging data on neonatal behavior of cocaine-exposed infants can enhance understanding of the risk status of these infants.

Cocaine is a powerful stimulant drug that has become increasingly popular and available because of decreased price, particularly in its “crack,” or freebased, form. Smoking cocaine results in short periods of intense euphoric feelings, during which energy and self-esteem are enhanced and anxiety is decreased.⁶ However, within hours of use, cocaine’s rebound effects result in anxiety, exhaustion, and depressive feelings. The dependent person takes cocaine repeatedly to avoid these “crash” rebound effects. Chronic use can result in psychologic and physical symptoms, including paranoid and mood disorders, weight loss, and decline in judgment. Thus, in adults, the acute and chronic effects of cocaine are demonstrated through significant alterations of central nervous system function.^{7, 8}

Because of cocaine’s low molecular weight and its water and lipid solubility, it readily crosses the placenta and the fetal blood brain barrier.⁹ Plasma cholinesterase, which

inactivates cocaine, is relatively deficient in the mother and fetus, possibly resulting in a greater time of exposure to the active drug. One adverse effect of cocaine on the fetus is uterine vessel vasoconstriction with reduced uterine blood flow and oxygen transfer.¹⁰ Experiments in animals have also suggested a teratogenic effect,¹¹ and permanent degeneration of nerve terminals in adult animals.^{12, 13} Thus cocaine may have direct neurotoxicity or indirect effects via vasoconstriction on the developing nervous system. Neuspiel and Hamel¹⁴ reviewed the neurobehavioral effects of prenatal cocaine exposure on animal models. Increased spontaneous motor activity and impaired learning behavior in exposed animals support the vulnerability of the developing brain to fetal cocaine exposure.¹⁴

EPIDEMIOLOGIC STUDIES

Epidemiologic studies have provided a partial description of the demographic and life-style characteristics of the cocaine-using pregnant woman. One important weakness of many epidemiologic studies has been the nonrandom selection of subjects. Most studies have been from large, urban hospitals primarily serving indigent and minority women, and have used selective urine toxicology screening to identify some but not all patients. Other methodologic problems have included the use of urine toxicology screening only at the time of labor, or the use of only maternal interview, which is often unreliable; the failure to account for maternal use of other substances, such as alcohol, opiates, marijuana, nicotine, and caffeine; the use of small samples of women who are already involved in drug treatment programs^{15, 16}; and the exclusion of women who received no prenatal care, which may represent as many as 60% of the mothers.¹⁷ In some states, where maternal cocaine use during pregnancy is a legal offense punishable by jail, voluntary informed consent for urine or interview screening is difficult to obtain (and may involve selection biases) unless confidentiality and protection of the mother are guaranteed.¹⁸

One recent study suggested that poor, urban black and Hispanic pregnant women are no more likely to use illegal drugs than their white middle-class counterparts in private care during pregnancy²; approximately 15% of black and white women used some illicit drug while pregnant. Minority women were more likely to use cocaine, whereas white women in private care were more likely to use marijuana.²

Despite these methodologic limitations, epidemiologic data have consistently documented multiple interrelated socioeconomic and health risks with cocaine use in the populations studied. Poor, inner-city minority women who use cocaine have health and life-style characteristics that differentiate them from comparison groups of pregnant women of similar race and social class. These characteristics are also known to affect perinatal outcome adversely. Available studies uniformly indicate that cocaine-using women are likely also to be heavy users of other drugs, particularly alcohol, marijuana, cigarettes, opiates, amphetamines, phencyclidine, barbiturates, lysergic acid diethylamide, and diazepam. Rates of use of these other substances can be up to three or four times higher than in comparison groups.^{1, 18a} Cocaine-using women obtain less prenatal care and weigh less at the time of delivery¹ (unpublished observations), and they may gain less weight during pregnancy.^{1, 18a} Cocaine-using pregnant women are more likely to be single and to have high rates of

sexually transmitted diseases^{1, 3} and, in some areas of the country, human immunodeficiency virus infection.³ Increased gravidity is also likely^{18a, 19} (unpublished observations). These multiple risk factors make it difficult to isolate the effects on infant neurodevelopmental outcome of cocaine use from that of other drugs or social problems. Because of these multiple risk factors, the impact of maternal cocaine use during pregnancy may not be considered as a unitary variable; its interactions with other drugs or the presence or absence of other health or social risks may potentiate or mitigate the adverse sequelae of maternal cocaine use.

PERINATAL MEDICAL COMPLICATIONS

Numerous reports have described significant obstetric and neonatal complications associated with maternal cocaine use during pregnancy. Among the most compelling findings are consistent descriptions of increased rates of spontaneous abortions, abruptio placentae, and meconiumstained amniotic fluid.^{1, 14, 15, 20, 21} Intrauterine growth retardation has been found in all studies of reasonable size in which cocaine-exposed neonates were compared with non-drug-exposed neonates.^{1, 18a-25}

Increased rates of prematurity^{15,21} and lowered gestational age in cocaine-exposed pregnancies^{16, 26} have been found, suggesting that prematurity or its complications may be indirect mechanisms by which cocaine's neurodevelopmental effects are expressed. Alternatively, premature birth may be a marker for mothers with greater dependency on drugs, a heavier use of drugs, or significant socioeconomic disadvantages. Furthermore, some, but not all, investigations of newborn infants have suggested a higher rate of congenital malformations in the form of cardiac, cranial, and genitourinary tract anomalies.²⁷⁻²⁹ The central nervous system and cardiorespiratory systems may be especially vulnerable to in utero exposure to cocaine.³⁰ Abnormal neonatal cerebral ultrasonographic abnormalities, transiently abnormal visually evoked brain-stem responses, decreased brain-stem transmission time, and electroencephalographic abnormalities have been identified in some cocaine-exposed infants during the first 2 weeks of life.³¹⁻³³

Thus the use of cocaine by pregnant women has been associated with a range of significant adverse sequelae in the immediate period after birth. All of these reported abnormalities are consistent with cocaine's known pharmacologic actions on the vascular and central nervous systems in adult human beings, and are also consistent with the neurochemical alterations identified in the emerging, better-controlled animal studies.¹¹⁻¹⁴ It is currently uncertain whether these observed but transient effects noted immediately after birth are due to the remaining presence of cocaine in the infant's central nervous system, to the associated adverse neonatal problems (prematurity, growth retardation, fetal distress), or to a permanent alteration of brain development after gestational exposure to cocaine.

In a large epidemiologic study, cocaine use in pregnancy was established as an independent adverse factor resulting in a specific perinatal abnormality also known to be associated with developmental delay (i.e., intrauterine growth retardation²²). Lower birth weight in cocaine-exposed infants is a consistent clinical finding and has been found in studies even when very low birth weight and sick infants have been excluded^{24, 25} and when other drug effects have

been considered.²⁵ Marijuana use, alcohol use, and cigarette use have also been shown to be significant independent or interactive contributors to reduced fetal growth in samples of poor, urban, minority pregnant women.^{22, 25} Other available studies have had methodologic problems that prevent clear attribution of the poor medical outcomes of cocaine-exposed pregnancies to cocaine use alone. These problems include small sample sizes, lack of comparison groups, and retrospective sampling.

INFANT BEHAVIOR AND DEVELOPMENT

Health professionals working with cocaine-exposed neonates have been impressed with the behavioral differences in some of these infants. Lethargy, poor social responsivity, irritability, tremulousness, hypertonicity, and disorganized patterns of feeding and sleeping are among the most commonly reported behaviors.³⁴ Neonatal differences in neurobehavioral function are important because they may be early signals of the possible long-term effects of cocaine on neuropsychologic functioning. Alternatively, if these differences are not permanent sequelae of in utero exposure to cocaine, they may make early caretaker-infant interaction difficult, adversely affecting developmental outcome in an indirect manner. Despite widespread publicity about the neurodevelopmental problems of cocaine-exposed infants and children,^{35, 36} only a handful of studies currently are available that have attempted to assess the neurobehavioral sequelae of fetal cocaine exposure in a scientific manner.

Most earlier published studies of the neurobehavioral capacities of the cocaine-exposed neonate suggested statistically significant abnormalities across a variety of tasks at birth. Cocaine-exposed neonates have been found to have inferior visual and auditory orienting skills, poorer motor abilities, decreased interactive behavior, decreased consol-ability, less adequate state regulation, and more abnormal reflexes.^{15, 16} Attempts to assess withdrawal symptoms at birth have yielded inconsistent results,^{23, 25, 26, 31, 32} perhaps because these scales were designed to characterize narcotic withdrawal symptoms rather than the effects of stimulant withdrawal. Studies of fetal behavior monitored through serial ultrasound assessments have described cocaine-exposed infants as having abnormal, delayed in utero behavior that correlated with deficient neonatal functioning.^{37, 38}

Comparability of these earlier behavioral studies is complicated by the use of differing and frequently less-than-optimal methods. For example, such studies have varied in subject sampling (mothers in drug treatment vs general care), type of population (urban vs rural), age of infant at test administration, standardization of neonatal neurobehavioral measures, blindness of assessors, and use of appropriate comparison groups. Additionally, the spectrum of other illicit drugs taken by the cocaine users, which were ascertainable by urine screenings, differed across studies. Furthermore, the studies differed in the maternal use of alcohol or cigarettes, other drugs, and the use of analgesics during delivery, all of which may affect immediate neonatal performance if these substances are present at birth. Infants also differed in the degree of intrauterine growth retardation, illness, and prematurity. Generally, the sample sizes were too small to assess or to control confounding variables statistically.

A longer follow-up of cocaine and other drug-exposed infants has received considerable publicity in the national press.^{35, 36, 39, 40} Eighteen drug-exposed toddlers who varied in degree of prematurity, maternal drug use, and placement in foster care were compared with a high-risk preterm group on play and attachment behaviors.^{39, 40} Although drug-exposed children were found to be more disorganized and to have more insecure attachments, the small sample size and other significant methodologic problems preclude drawing any conclusions from these studies. Even though the maternal drug of choice in these samples was not cocaine, the findings have been widely misrepresented as characteristic of cocaine-exposed children.^{35, 36}

Several recent studies with improved methods have sought to assess the behavior of cocaine-exposed infants and to account for some of the confounding factors identified in previous studies.^{23–25} These three studies used similar scoring systems of the Brazelton Neonatal Behavioral Assessment Scale⁴¹ in the first week of life and assessed only apparently healthy, term cocaine-exposed infants. The NBAS evaluates the infant's performance on 20 reflex and 27 behavioral items, summarized in these studies according to seven cluster scoring criteria: habituation, orientation, motor behavior, range and regulation of state, autonomic stability, and abnormal reflexes.⁴¹ All three studies controlled experimentally or statistically the confounding factors of maternal age, ethnicity, prematurity, and polydrug use. All used multivariate analyses to assess the effects of cocaine relative to other drugs or confounders on infant behavioral outcome. Consistent results were noted in all studies with regard to intrauterine growth. Despite careful matching procedures and exclusion of preterm and low birth weight infants, cocaine-exposed infants had significantly reduced growth. Although one study used a random stratification design to match birth weight and gestational age, head circumference was smaller in the cocaine group.²³ In the other two studies, all measures of growth were reduced.^{24, 25} With regression analyses, cocaine exposure was found to contribute 18% of the variance in birth weight, and cocaine and alcohol in interaction to contribute 18% of the variance in head circumference. Nonetheless, maternal obstetric and health status also contributed significantly to all growth outcomes at birth in this study.²⁵

Results across these studies were not consistent with regard to the specific infant neurobehavioral abnormalities noted, however. One study found that cocaine-exposed infants showed impaired habituation skills on the NBAS in the first week of life.²³ Habituation, which involves the infant's ability to adapt to or shut out aversive or redundant stimulation, is considered an early form of learning. A stepwise regression analysis indicated that cocaine exposure was the only significant variable contributing to habituation performance.²³ However, the other two studies did not confirm this finding.^{24, 25} An important methodologic difference may have affected the ability of the two studies that failed to detect differences on NBAS performance neonatally; these studies restricted assessments to the infant's first 3 days of life, when the lingering effects of analgesics and anesthetics may have obscured differences between cocaine-exposed and comparison infants. One study²⁴ also did not include urine screens on control infants and their mothers, which may have further diminished group differences because cocaine-using women may have been inadvertently placed in the control group. This study also used only women who had received some prenatal care, perhaps limiting the cocaine sample to the least affected

mothers.²⁴ The other study²⁵ did not consider habituation scores because of a small sample size on that dimension. In these latter two studies, infants were also followed beyond the immediate postpartum period for up to 30 days.^{24, 25} Group differences were found at follow-up, but on differing NBAS subscales, with one study²⁴ finding deficits in motor functioning and the other²⁵ finding a higher incidence of abnormal reflexes.

In all studies, maternal cocaine use, either independently or in interaction with other drugs, accounted for significant portions of variance in infant behavioral outcome even when group differences were not reported. Cocaine effects were more pronounced with increasing infant age,^{24,25} affecting motor behavior, state regulation, and abnormal reflexes. Nonetheless, with a large sample size, independent effects of maternal health, tester, prenatal care, and other drugs on behavioral outcome were also noted.²⁵ Additionally, it cannot be determined whether these negative effects are directly attributable to the biologic vulnerability caused by prenatal cocaine exposure or are due to long-term dysfunctional interactions and caretaking by the cocaine-using mother.

In these studies, cocaine did not produce clinically aberrant behavior, despite statistically significant effects. Additionally, currently available neonatal assessments are poorly predictive of later development, so it is difficult to assess the meaning of the observed group differences. Growth retardation, however, does relate to poorer developmental outcome,^{42, 43} and the emerging evidence of cocaine's independent impact on intrauterine growth, especially head circumference,⁴⁴ provides strong impetus for continued investigation of these potential interactions as they produce neurobehavioral deficits.

Cocaine-exposed neonates thus have growth, behavioral, and neurologic abnormalities that are associated with later developmental problems. Whether or not a drug-exposed infant has adequate parenting postnatally will also have an impact on later performance, as will an impoverished socioeconomic environment. Although the chaotic life-style and chronic psychosocial problems of cocaine-using mothers have been noted clinically, there are few data on how maternal care-giving behavior and attachment are altered with cocaine use. Much more needs to be learned about the life-style, behavior, and perceptions of cocaine-using mothers, because impaired maternal care giving and psychologic status have direct effects on infant development. There is little information regarding perinatal outcome among middle-class or rural women who use cocaine. Furthermore, little is known about the implications of the health and drug habits of fathers of cocaine-exposed infants, even though they have important biologic and social roles in the infant's development. The influence of fathers should be considered in future studies related to development in cocaine-exposed infants.

SUMMARY

The number of infants born to cocaine-using mothers has continued to rise during the past 5 years. Maternal cocaine use during pregnancy is associated with medical and life-style characteristics detrimental to fetal and infant development. Cocaine exposure has been independently linked to growth retardation and impaired fetal oxygenation even when polydrug use and other confounding factors are considered. Neurologic and neurobehavioral

abnormalities noted in the immediate neonatal period have also been associated with fetal cocaine exposure. The direct and indirect toxic effects of cocaine, per se, have not yet been independently linked to specific behavioral outcomes because of small sample sizes, confounding factors, and lack of long-term follow-up. The impoverished environments and increased risk for out-of-family placement of cocaine-exposed infants are known independent correlates of negative developmental outcomes. Poor maternal nutrition, lack of prenatal care, and other health and life-style factors related to maternal cocaine use during pregnancy also appear to be factors mediating the developmental problems of cocaine-exposed infants. The cocaine-using mother often uses other drugs, particularly alcohol, independently known to be linked to growth and behavioral impairments similar to those proposed for cocaine-exposed infants. Accounting for these multiple confounding variables in studies of the specific effects of cocaine on neurobehavioral outcome may be scientifically appropriate, but in clinical practice these factors cannot be “isolated,” and their statistical consideration in studies does not diminish clinical risk.⁴⁵ Finally, currently available studies of behavioral outcome have restricted their samples to term infants. It is possible that preterm infants may be less affected by prenatal cocaine exposure because of decreased exposure. However, because epidemiologic studies suggest that prematurity is a sequela of maternal cocaine use,^{17, 19, 22, 27} restriction of samples to term or appropriately sized infants may underestimate the spectrum of morbidity associated with cocaine exposure.

We believe that maternal cocaine use during pregnancy is a “marker” variable for early impairments in infant growth and behavioral functioning that have long-term implications for later developmental outcome, especially for learning disabilities and behavioral disorders. Critically assessing the independent contribution of cocaine to negative developmental outcome and determining whether early neonatal abnormalities are permanent or modifiable may allow clinical intervention and improved social policy. Assessing the independent effects of cocaine on child developmental outcome will require carefully designed, long-term, longitudinal, population-based studies with samples large enough to allow multivariate data analyses and statistical control of confounding medical and social variables.

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