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Fetal Cocaine Exposure: Neurologic Effects and Sensory-Motor Delays

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SUMMARY

Research on animal models demonstrates that fetal cocaine exposure results in neurologic deficits in memory and learning. Although drug effects on human infants are difficult to separate from other environmental influences of a drug-using lifestyle, studies suggest that infants exposed to cocaine in utero have reduced growth, delays in sensory-motor development, attentional deficits, and depressed responsivity to social stimulation. Standard interventions to promote behavioral state regulation in affected infants may be helpful when parents are capable of participating.

The history of research on the effects of in utero cocaine exposure has been both short and turbulent. In the 10 years since the “crack baby” was first identified and birth outcomes reported, findings have been controversial and at times contradictory. Perinatal epidemiologic studies in the late 1980s documented the large numbers of infants born after fetal exposure to cocaine. Estimates of the proportion of babies born in urban teaching hospitals who test positive for cocaine range from 5–45%.^{1–4} Early alarming reports about pronounced neurobehavioral abnormalities in neonates exposed to cocaine in utero^{5–7} raised subsequent concerns about potential long-term neurodevelopmental effects on fetal and infant outcome. Recent reports, however, indicate that the effects may be subtle and could be masked and/or confounded by environmental factors, such as amount of prenatal care⁸ or socioeconomic status.⁹

Part of the ambiguity in results might be attributed to the initial lack of information regarding effects of cocaine on human development. With little else to go on, investigators interested in studying the effects of cocaine on the human fetus had two potential bodies of research on which to draw, the known effects of cocaine on adults and on animals. As the volume of literature grew, several issues central to the further study of prenatal exposure to a potentially neurotoxic agent became evident: (a) whether any pre- or perinatal neurologic effect could be attributed to cocaine, (b) whether identified effects could be related to specific neurobehavioral outcomes, and (c) the long-term consequences. An examination, therefore, of the evidence pertaining to the neurologic development of infants exposed to cocaine follows. Additionally, some considerations concerning intervention are offered.

RATIONALE FOR STUDYING THE NEUROLOGIC EFFECTS OF FETAL COCAINE EXPOSURE

Cocaine's central and peripheral nervous system effects on adults have been widely recognized, thus raising questions regarding a potential teratogenic effect. Cocaine easily crosses the placental barrier during gestation.¹⁰ In particular, central nervous system (CNS) alteration during gestation secondary to cocaine exposure¹¹ could result in long-term functional deficits manifesting in behavioral and cognitive abnormalities.

In adults, cocaine use has been related to cerebrovascular accidents,^{12,13} high blood pressure, and seizures.¹⁴ Cocaine's known actions on several neurotransmitter systems in the mature adult have been well-defined.¹⁵ Cocaine acts to prevent re-uptake of catecholamines presynaptically, resulting in an increased level of these neurotransmitters. Alterations in catecholamine levels during fetal gestation may affect the maturation of fetal neurotransmitter systems.^{16,17} Maternal cocaine use also results in concomitant rise in maternal blood pressure as a result of vasoconstriction and tachycardia, decreasing uterine and placental blood flow.¹¹ This interference with blood flow to the fetus reduces oxygen supply and may cause chronic hypoxia which interferes with normal CNS development.

EVIDENCE FOR NEUROLOGIC EFFECT

Animal Studies

The animal literature to date supports the notion that fetal cocaine exposure has deleterious effects on neurological outcome and subsequent neurobehavioral competence. Disruptions in neuro- and gliogenesis and alterations in brain metabolism, especially in opiate and cholinergic systems, are reported.¹⁸ Gestational cocaine exposure in rats has been associated with cephalic hemorrhages, eye abnormalities, and cortical and brainstem defects.^{19,20}

Deficits in classical conditioning, an early form of learning, and difficulties in learning tasks such as maze performance and operant learning trials, have also been reported in animal studies, suggesting that cocaine may function as a behavioral teratogen with long-term effects on functional abilities later in life. Animal studies have demonstrated that cocaine exposure in fetal rats adversely affects areas of the brain important for memory and learning, for the regulation of movement and growth, and for reproductive function.²¹ Learning systems in animals may be differentially affected by cocaine exposure as well. Cocaine-treated rat pups have shown learning and retention difficulties using conditioning models,^{22,23} although not all studies have demonstrated deficits.²⁴

Animal studies allow the isolation of specific effects of fetal cocaine exposure apart from the confounds inherent in human populations, such as polydrug use, poverty, or poor nutrition. Unfortunately, findings from animal studies are not necessarily generalizable to human populations. Spear points out, however, that results of human clinical studies of neurotoxicants generally correspond closely to those of laboratory animal studies when similar outcome behaviors are assessed.¹⁸ Thus, it would be highly atypical if the effects of cocaine exposure found in animal studies did not also occur in humans. Spear's conclusion from a review of available animal studies on the behavioral consequences of gestational

cocaine exposure is that data to date provide “convincing evidence that cocaine is a behavioral teratogen in animal models.”¹⁸

Human Studies

Human studies addressing the neurologic effects of cocaine on the fetus and subsequent development have also been emerging. Volpe²⁵ presented a convincing summary of some of the potential mechanisms of destructive neural effects secondary to fetal cocaine exposure, noting that the genesis of CNS effects is likely to be multifactorial. In any case, the neurologic system is significantly affected by fetal hypoxemia caused by impaired placental blood flow resulting in impaired fetal cerebrovascular autoregulation. Such impairments make the fetal brain highly vulnerable to changes in blood pressure, including hemorrhages in the immediate neonatal period. Constriction of blood vessels after cocaine exposure, a well-documented effect in animals, decreases nourishment to the fetus and reduces brain growth.

Recent reports have suggested significant CNS effects in newborns who were exposed to cocaine during gestation in addition to obstetric complications.^{1,2,26} Microcephaly, an abnormality reflecting impairment in intrauterine brain growth (defined as head circumference more than 2 SD below the mean), has been widely reported in cohorts of cocaine-exposed neonates.^{27,28,29} The prominence of microcephaly, an index of brain size, in cocaine-exposed infants, has been construed as one marker of its CNS effects because of its association with later developmental delay. Reduced head size has been identified as a major predictor of depressed cognitive functioning following cocaine exposure.³⁰ Other electrophysiological alterations have been noted. These include seizure activity,³¹ EEG abnormalities,³² sleep discordance,³³ and abnormal brainstem conduction time.³⁴

Serious destructive lesions suggesting prenatally occurring insults were reported in a series of case studies.³⁵⁻³⁷ A San Diego study reported an 8-fold increase in cranial ultrasound abnormalities in term infants exposed to cocaine, a finding which was replicated in a Boston study.³⁸ The latter study also found a significant increase in risk for caudate echodensities in term infants who had been heavily exposed to cocaine during gestation when compared with lightly exposed or non-exposed infants,³⁸ a finding among the first to suggest a dose-response effect. Neurologic sequelae have also been found in cohorts of very low birthweight (VLBW) infants exposed to cocaine. One prospective study of 323 infants weighing less than 1500 grams at birth³⁹ reported a three-fold increase in the occurrence of seizures, among other medical problems, in infants exposed to cocaine. In our own studies of a sample of 41 infants exposed to cocaine, increased incidence of mild (Grade I and II) intraventricular hemorrhage was found at birth compared to controls matched for race, social class, and presence of bronchopulmonary dysplasia.⁴⁰

Finally, numerous studies have employed the Brazelton Neonatal Behavioral Assessment Scale (BNBAS) to assess the neurobehavioral sequelae in the first month of life. Findings have been widely divergent and sometimes contradictory.⁴¹ Several studies have reported depressed interactive behavior, impaired responses to environmental stimuli, and deficits in orientation, and in motor and state regulation in cocaine exposed cohorts. Other well designed studies, however, found no significant deficits on the BNBAS.

SENSORY-MOTOR DEVELOPMENT

The most serious consequences of an association between prenatal cocaine exposure and the many atypical neurologic effects reported may not be the rare cases of dramatic medical outcomes, but rather the insidious and likely much more widespread deleterious effects on long-term behavior and development. Delays in language development,⁴² increased rates of behavior disorders,⁴³ and late acquisition of motor milestones⁴⁴ have all been suspected as possible negative consequences of prenatal cocaine exposure. Among other problems, laboratory studies of rats have found that early exposure to cocaine has later developmental effects on the functioning of the dopamine system,¹⁸ particularly in areas of the brain involved in motor functioning.⁴⁵

The importance of motor skills in any at-risk infant population, particularly one exposed to a possible teratogen, is often inferred from general findings suggesting that motor and perceptual skills, as opposed to verbal and symbolic skills, have a large biologic basis and are related to environmental factors in a less direct manner or to a lesser extent.⁴⁶ Additionally, early reflex and motor behavior is viewed as an early indicator of neurologic maturation. Several investigators chose, therefore, to study early motor development in infants exposed to cocaine.

One of the first studies to describe the development of these infants used the Movement Assessment of Infants (MAI).⁴⁷ The MAI has been employed in several subsequent studies to assess the early motoric development of at-risk infants. This measure provides a detailed and systematic appraisal of motor development during the first year. The MAI assesses muscle tone, primitive reflexes, automatic reactions, and volitional movements. Schneider and associates^{48,49} tested 30 full term 4-month-olds exposed to cocaine and compared their scores on the MAI with scores from 50 infants selected from a convenience sample without drug exposure. The two groups differed significantly on the total risk score and on the muscle tone, reflexes, and volitional movements subscales. Schneider⁴⁹ concluded that, although in utero cocaine exposure does not have a significant effect on the motor development of all exposed infants, it appears to have a profound impact on some.

Rose-Jacobs and colleagues⁵⁰ also reported results using the MAI to compare cocaine-exposed and non-exposed infants at 4 months of age. Term infants participating in this study were classified as either heavier cocaine-exposed ($n = 27$), lighter cocaine-exposed ($n = 61$), or unexposed ($n = 82$). Using a regression model, an overall cocaine effect was found only in the volitional movements subscale. The more heavily exposed infants had significantly poorer mean scores than either the more lightly exposed or the unexposed. The authors concluded that their findings supported the importance of evaluating dose response to cocaine.

Arendt and colleagues⁵¹ reported results of a study of sensory-motor development in 100 4-month-olds, 42 of whom were prenatally exposed to cocaine. Testers were masked as to drug status of infants. Overall scores from the MAI indicated a significant mean group difference, with the infants exposed to cocaine performing less well. The mean total score of

the cocaine exposed group exceeded the high-risk cutoff score, suggesting that a significant percentage of the infants were at risk for motor delays.

In the same study, results from the Test of Sensory Functioning in Infants (TSFI) also revealed a significant difference between the groups. The TSFI is designed to assess sensory processing and reactivity in 4- to 18-month-olds. It evaluates response to tactile deep-pressure, visual-tactile integration, adaptive motor, ocular motor, and reactivity to vestibular stimulation. Again, the exposed group of infants performed significantly below the unexposed group, although mean scores of both groups were within the normal range.

Seventy of the children seen at 4 months (33 cocaine-exposed, 37 non-exposed) have been reassessed at 12 months of age using the Bayley Scales of Infant Development.⁵² Preliminary results indicated that the cocaine-exposed group performed, on average, more poorly on the Motor Scale, but are still, as a group, performing within normal limits. There was no significant difference between groups on the Mental Scale.

A series of standard multiple regressions were conducted to determine whether early sensory-motor scores would predict later mental and motor scores. Results of these analyses suggested that the MAI total score, but not the TSFI total score, accounted for a significant portion of the variance in both Bayley Mental and Motor scores, even after accounting for gestational age. Further analysis revealed that the relationship between Bayley and MAI scores was consistent when only the non-exposed group data was analyzed, but this relationship was not significant for the cocaine exposed group data analyzed separately, suggesting a greater degree of variability in the development of the latter.

Frank and her colleagues³⁸ reported that the fine and gross motor movements of 6-month-old infants exposed to cocaine were rated as less optimal than unexposed infants on the Infant Behavior Record (IBR) portion of the Bayley Scales of Infant Development. They also reported a trend for lower scores on the Psychomotor Development Index scores. Statistical modeling indicated that cocaine had a direct effect on IBR motor coordination and an indirect effect through birthweight. PDI scores were also significantly related to the motor coordination scores.

Overall, findings indicate that 4-month-old infants who were exposed to cocaine in utero demonstrate delays in sensory-motor development. A significant delay remains at 12 months when an exposed group is compared to a similar group of non-exposed infants. Findings of no group difference on the Bayley Mental Scale comparisons suggest that, at 12 months of age, motor development may be a more explicit domain in which to discern developmental effects related to cocaine exposure. Failure to predict motor development in the exposed group suggests that individual subjects may demonstrate recovery or the influence of other effects during the period between 4 and 12 months.

LONG-TERM BEHAVIORAL AND COGNITIVE OUTCOMES

Given the animal literature's findings of deficits in conditioning, a basic form of learning, similar studies in human infants are of particular interest. Instrumental responses and emotional expression were assessed in a task that required infants to pull a string to elicit a

visual display and musical accompaniment.⁵³ Infants exposed to cocaine did not master the contingency learning task as well as non-exposed infants and showed decreased arousal and lower emotional responsivity. For example, the infants exposed to cocaine failed to show frustration during the extinction phase or change in interest when the extinction phase of the experiment was discontinued.

Recent findings from one of our on-going studies⁵⁴ using 16 rating scales from the Bayley IBR indicated a significant overall group difference at 12 months of age between infants who were exposed versus non-exposed infants. Ten of the scales showed significant univariate differences. On four scales (Responsiveness to Mother, Goal Directedness, Activity, and Level of Energy), analyses suggested that a significantly greater percentage of infants exposed to cocaine fell into the suspect range. A Test Orientation and a Summary Risk score also revealed significant negative correlations with Bayley performance scores. In general, the infants appeared less socially oriented, less responsive to task and people, and less motorically coordinated than control infants. Although not matching the stereotype of hyperactivity following drug-exposure, a hesitant or inattentive child is at risk for delays.

One consistently reported association between prenatal cocaine exposure and birth outcome is intrauterine growth retardation and/or low birthweight.⁵⁵ Because low birthweight infants, especially those below 1500 grams (VLBW), are already at increased medical and developmental risk,⁵⁶ Singer and colleagues⁴⁰ investigated whether cocaine exposure was associated with greater vulnerability to neonatal medical complications or poorer developmental outcomes in very low birthweight babies. At an approximately one and a half year follow-up, 30 infants exposed to cocaine were compared to 37 control infants. Bayley Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores were significantly lower in the cocaine exposed group. The authors also reported that a significantly greater percentage of the exposed infants, 33% as compared to 8% of the non-exposed infants, obtained standardized motor scores below 80. This result suggests that motor development was delayed in many of the infants exposed to cocaine. Behavioral development was also more deficient in the cocaine-exposed group, even though the VLBW comparison group was of equivalent medical risk. On a sub-sample rated on the IBR, cocaine exposure was related to increased bodily tension, less sustained interest in and less responsivity to test material, and less imaginative play. About one-third of the cocaine-exposed group was ranked as having “fleeting to easily distracted” attention span and as “unreactive and unresponsive.”

Only one published study of long-term outcome has examined the effects of prenatal cocaine exposure on development at age 3.⁸ In that report, 93 children exposed to cocaine performed more poorly than non-exposed children on the Verbal Reasoning subtest of the Stanford Binet Intelligence Scale. The majority of the children exposed to drugs, however, scored within the average range in this sample, a “best-case scenario” in which mothers received medical care and drug treatment early in their pregnancies and children were followed with intensive intervention services.

ENVIRONMENTAL CONSIDERATIONS

Our own studies in Cleveland⁵⁷ have followed a more typical cohort of infants exposed to cocaine prenatally. Identified largely at birth, the infants' mothers generally did not receive adequate prenatal care but did bring the babies for well-child care to a special interdisciplinary clinic for high-risk infants. Infants, 98% of whom were African-American and poor, were administered the Bayley Scales at 6-month intervals. The most recent follow-up included 90 cocaine-exposed and 30 non-exposed infants at mean corrected ages of 17 ± 8 months.⁵⁸ Consistent with our earlier findings, infants exposed to cocaine persisted in lagging behind the comparison group on both Mental and Motor Scale average standard scores. In this study we also assessed mothers as soon as possible after infant birth with the Brief Symptom Inventory (BSI), a standardized normative self-report of psychological symptoms (examiners were not masked as to drug status). We have found in previous work that post-partum women who were cocaine users showed an increased incidence of psychological distress, particularly paranoid ideation and phobic anxiety. When MDI scores were regressed on a summary score of the BSI and cocaine status, after controlling for infant prematurity, both variables independently predicted MDI outcome. For PDI scores, maternal psychological symptoms were not significant predictors, but the variable for cocaine use remained marginally significant ($p < .06$). These findings provide support for cocaine's direct effects on infant development and highlight the need for further studies on the effect of cocaine use on maternal psychological status because psychological status can affect maternal caregiving behavior and subsequent infant development.

METHODOLOGICAL DIFFICULTIES IN STUDYING NEUROLOGIC DEFICITS IN COCAINE-EXPOSED COHORTS

Although a growing number of published research studies and abstracts have documented a negative effect of cocaine on child neurological and developmental outcome, caution should be used when applying research findings in clinical practice. A substantial number of methodologic limitations exist in the available research literature.⁵⁹ Whether cocaine, per se, is responsible for the negative effects reported continues to be a matter of debate because the majority of samples studied have been of poor, urban women who are polydrug users. In particular, women who use cocaine tend to use alcohol, a known teratogen, more frequently than members of comparison groups, and many of the deleterious sequelae attributed to cocaine are similar to those noted in follow-up studies of fetal alcohol exposure or tobacco exposure. Scientifically, it remains important to determine cocaine's specific effects versus its confounded or synergistic effects with other substances. Pragmatically, however, infants exposed to cocaine are likely to be polydrug-exposed, and outcome or intervention studies that aim for real world validity will need to be generalizable to children as they present to clinicians.

Other methodological difficulties with the extant research literature include small sample sizes and differentially higher attrition rates in cocaine-exposed cohorts. Differential attrition may bias the sample toward those infants who are most affected and who remain in follow-up because of an identified need for service, or, alternatively, who are born at-risk and remain in follow-up because of better maternal care.

Numerous confounding factors related to maternal cocaine use continue to make it difficult to establish cocaine as a teratogen apart from associated risks of a drug-using lifestyle, including poverty, poor caretaking, poor nutrition, infections, lack of prenatal care, and premature delivery. These confounds may never be fully extricable in studies on humans.

PRACTICAL CONSIDERATIONS IN INTERVENTION

Several authors have repeated the therapeutic recommendations of Schneider⁴⁹ that delineate a programmatic effort of identification, assessment, intervention, and parent education. Identification is made most frequently on the basis of an interview. Early identification of drug exposure is difficult, however, because of the illicit nature of the drug and the mother's fear that she might go to jail and/or lose custody of her baby. Although drug screening of all pregnant women may be unfeasible and/or unwarranted, urine or, preferably, meconium testing should be considered when there is a history of inadequate prenatal care, incarceration, or previous involvement with human services agencies related to either removal of children from the home or family violence. It should be remembered that although a positive drug screen may do nothing to prevent initial drug exposure in the fetus or newborn, the information can be useful in the future when counseling the mother to quit drug use for the remainder of her current pregnancy or during future pregnancies.

When assessing infants exposed to drugs it is important not to attribute every neuromotor abnormality to cocaine. To date, many descriptions of exposure effects in infants and pre-school children are similar to those of other at-risk children. Several authors have warned against the dangers of labeling a young child.^{60,61} The dangers of identifying a child as cocaine-exposed, however, should be weighed against the need for services. Unfortunately, because no specific crack-cocaine syndrome has yet been identified, labeling the "crack" baby provides no unique blueprint for intervention and may erroneously bias practitioners and educators.⁶²

None of the studies published so far have suggested that standard interventions aimed at improving sensory-motor development in other at-risk infant populations would have any less success on the functioning and development of infants and young children exposed to cocaine. Consequently, therapeutic interventions commonly used to promote behavioral state regulation in children at risk as a result of prematurity, failure to thrive, or fetal alcohol exposure should be considered. Forrest⁶³ made several recommendations that included swaddling the infant in a semiflexed position to reduce extensor muscle tone, using slow vertical rocking and a pacifier to prompt self-calming, and hydrotherapy. In addition, as the infant grows older, Forrest recommended avoiding placing the child in a sitting or standing position. Rather, the infant should be carried on the caregiver's hip in a flexed position facing away from the caregiver to improve trunk control and encourage reaching and grasping.

Field and her colleagues⁶⁴ reported on an intervention used with infants exposed to cocaine that was based on work with premature infants and on findings suggesting that infants exposed to cocaine display diminished performance on the response decrement items of the Brazelton Neonatal Behavioral Assessment Scale. Response decrement to repetitive external

stimulation reflects the ability to shut out stimulation and is related to dopaminergic functioning in the brain. The intervention consisted of tactile-kinesthetic stimulation in the form of a slow and relatively deep pressure massage, performed in a highly specific manner. Results indicated that massage facilitated weight gain. In addition, response decrement scores approached normal.

Although a direct program of physical therapy and/or occupational therapy will not be required in most cases, Schneider⁴⁹ described several areas of parent education applicable to at-risk infants that could be applied to those exposed to cocaine. Parents can be taught to be attentive to their infant's motor behavior, noting strengths and weaknesses, and to be responsive to the individual needs of their infant. When deemed appropriate following a complete assessment, early intervention specialists should demonstrate developmentally appropriate stimulation activities and teach parents handling, range of motion, and positioning techniques that foster state regulation and normalization of muscle tone.⁶⁵

Parent education, however, presents special challenges when adults are using drugs. Parents who use drugs may have difficulty regulating their own behavior, often relying on drugs to maintain their functioning. Parents with such problems will certainly have difficulty promoting their child's self-regulation. Attending to the infant's development and providing the appropriate activities require management of time and other resources. A drug-using lifestyle requires a person to devote much time, energy, and finances to acquiring and using the drug.⁴³ Without help, a parent who uses drugs may not be able to resolve the conflicting demands created by the child and the drug. The best parent education program will not benefit the child if it is not implemented. Following directions of a therapist requires compliance and acceptance of authority that is frequently absent among drug users.

CONCLUSION

The data supports the conclusion that infants exposed to cocaine in utero are at risk for delays in motor development. The extent of the risk, however, varies greatly. Developmental outcome is the product of multiple determinants, including a host of postnatal factors interacting with neurologic insults and biologic impairments. Early intervention is, therefore, both possible and often necessary. It is also important to remember that both the caregiver and the infant contribute to the developmental course. Coordinated and multifaceted efforts from numerous health care and human service disciplines are required to prevent drug exposure and, when that fails, to provide appropriate intervention.

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