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REVIEW ARTICLE

Neurobehavioral and Neuromotor Long-Term Sequelae of Prenatal Exposure to Cocaine and Other Drugs: An Unresolved Issue

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When the cocaine epidemic began, predictions were made that the children of cocaine users would demonstrate devastating negative developmental sequelae. In infants and young children prenatally exposed to cocaine most frequently the neurobehavioral and neuromotor systems have been studied. Although clinically described as irritable, difficult to console, and jittery as infants, research findings have not been able to clearly describe a pattern of long-term developmental sequelae. The mechanisms of action of drug exposure on developmental outcome have shown to be more complex than originally suspected. Many factors, other than the drug use, can influence developmental outcome. In most studies of prenatal cocaine exposure, family and environmental factors rarely have been measured, although their influence on developmental outcome has been well documented in other populations. This review of literature summarizes the research on the early effects of prenatal exposure to cocaine and other drugs on neurobehavioral functioning and neuromotor development in an attempt to provide objective and scientifically based information to clinicians working with this population. **(Pediatr Phys Ther 1999;11:140–146)** *Key words: child development/drug effects, cocaine/adverse effects, infants*

INTRODUCTION

Over the past 10 years, physical therapists have assessed and provided developmental services to infants and young children prenatally exposed to cocaine and other drugs.[1,2] These infants are described clinically as very irritable and difficult to console.[3] When the cocaine epidemic began, predictions were made that the children of cocaine users would demonstrate negative developmental sequelae. A fair amount of research has been conducted to document the effects of prenatal drug exposure, primarily on the neurobehavioral and neuromotor systems. In most of this research, it is very difficult to isolate the effects of cocaine because most drug users use a combination of drugs such as cocaine with tobacco, alcohol, and/or marijuana. For this reason, the term "cocaine and other drugs" is often used. This review of literature summarizes the early effects of prenatal exposure to cocaine and other drugs on neurobehavioral functioning and neuromotor development to provide objective information to physical therapists and other clinicians providing services to these children and their families.

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PHARMACOLOGY AND NEUROPHYSIOLOGY OF COCAINE

Cocaine comes from the leaves of *Erythroxylon coca* and other species of *Erythroxylon* trees indigenous to Peru and Bolivia.[4] After extraction, cocaine is converted to a hydrochloride salt and diluted for oral, nasal or intravenous use.[5] After dissolution in an alkaline solution and recrystallization as freebase cocaine or "crack," the drug is smoked typically.[6] Freebase cocaine was named "crack" for the crackling sound the powder makes when heated and vaporized into smoke inside glass containers.[7] The street market availability of a unit dose of crack has removed the price barrier in obtaining cocaine and has contributed to its becoming a drug of choice by escalating numbers of street drug users. Unfortunately, women of childbearing age are

also increasingly using cocaine and crack.[8] Reported incidences of prenatal cocaine use vary from eight percent to 18%,[9-12] with a study conducted in Detroit revealing an incidence as high as 31% on meconium testing.[13] Accurate estimates of the incidence of prenatal cocaine use are difficult to obtain because of the limitations of screening tests (eg, urine testing), difficulties in testing throughout pregnancy, and reliance on maternal self-reports. These estimates are influenced additionally by prevailing ethnic and socioeconomic prejudices regarding drug use during pregnancy.[14,15] In fact, Chasnoff and colleagues[14] have shown that clinicians are 10 times more likely to identify and report drug use among black and low-income women than among white private patients, although the actual rates of drug use do not differ between groups.

Because of its low molecular weight and its water and lipid solubility, cocaine readily crosses the placenta and the fetal blood brain barrier.[16] Liver and plasma cholinesterases metabolize cocaine to norcocaine, an active, water-soluble metabolite that easily penetrates the central nervous system.[17] Cocaine affects the monoaminergic neurotransmitter system (dopamine, norepinephrine, and serotonin) in the central nervous system through its action on neurotransmitter release, reuptake and recognition at the synaptic junction.[16,18,19] In humans, these neurotransmitters are present in neural pathways that project to brain areas involved in neurologic and behavioral functions including arousal, regulation of attention, response to sensory stimuli, and the modulation of mood states.[20,21]

Cocaine blocks the reuptake of dopamine, norepinephrine, and serotonin by the presynaptic neuron, which in turn prevents the inactivation of the postsynaptic neuron.[22] In the case of dopamine, cocaine impairs its reuptake by binding to the transporter that mediates dopamine reuptake.[23] The excess dopamine and norepinephrine in the synaptic space is responsible for the exaggerated alertness, hypervigilance, tachycardia, and hypertension seen among cocaine users.[4]

Dopaminergic cells are grouped in clusters in the brainstem and are also found in the midbrain and substantia nigra with projections to the corpus striatum, hypothalamus, limbic system, and prefrontal cortex area.[22,24] Effects of cocaine on these neural pathways are responsible for the enhanced reward mechanism through self-administration of cocaine, and hyperkinesia and stereotypic behavior observed in rats.[22] Neural pathways using norepinephrine neurotransmitters also project to the thalamus, hypothalamus, and limbic system.[24] The effects of cocaine on the norepinephrine neurotransmitter system are associated with increased arousal and euphoria.[22] Cocaine reduces the turnover and rate of synthesis of serotonin resulting in decreased sleep and increased aggressiveness.[22]

PRENATAL EFFECTS OF COCAINE

Volpe[21] suggested two types of effects on the fetus exposed to cocaine prenatally: destructive neural effects and teratogenic effects. Destructive neural effects include cerebral lesions that are related to cocaine's effect on the cardiovascular system of the mother and the fetus, whereas teratogenic effects are related to the direct effects of cocaine on the development of the fetal brain. Fetal or neonatal cerebral vascular lesions secondary to cocaine exposure can be induced through two mechanisms: direct or indirect. The direct mechanism of cocaine action is related to the increase of postsynaptic neurotransmitters in the fetal brain. Via their effect on tachycardia, vasoconstriction and increase in blood pressure, the increased number of circulating catecholamines can contribute to fetal hypoxemia and hemorrhage. Cerebral infarctions,[25,26] ultrasound abnormalities in the lateral ventricle, basal ganglia, subependymal germinal matrix and frontal white matter,[27] seizures,[28] intraventricular hemorrhage,[27] and periventricular leukomalacia[29] have been reported in infants exposed to cocaine. The particular distribution of the cerebrovascular lesions is believed to be related to the state of maturation of the cerebral vessels and their responsiveness to cocaine at the time of the lesion.[21] Other researchers, however, have compared the prevalence of abnormal cranial ultrasounds and the occurrence of intraventricular hemorrhage between cocaine exposed and control infants and have found no differences between groups.[30-33] Frank and her colleagues[31] have recently reanalyzed a data set in which no differences were found in ultrasound lesions if infants were categorized as either exposed or unexposed. They found that an increased risk for grade I intraventricular hemorrhage was found among infants most heavily exposed to cocaine when compared with infants who were lightly exposed or unexposed[34,35] thus showing a dose-related effect of prenatal cocaine exposure.

The indirect mechanism of action on fetal or neonatal cerebral vascular lesions after cocaine exposure occurs when catecholamine-mediated vasoconstriction of the uterine arteries causes reduced blood flow to the fetus with resulting hypoxemia.[36] Intrauterine hypoxia and malnutrition induced by vasoconstriction can also cause growth retardation, microcephaly, and congenital anomalies.[36-39]

Neurotransmitters play an important role in fetal brain development through their influence on neuronal migration and differentiation, synaptic proliferation, and on the development of receptor sites.[40,41] Although full scientific support for the suspected cocaine-induced changes in the human fetal neurotransmitter system and the ensuing neurodevelopmental consequences is still lacking, preliminary research has shown results suggestive of such a relationship. In a recent study with newborn infants, Mirochnick and colleagues[42] showed plasma norepinephrine concentrations were higher in infants who had been prenatally exposed to cocaine and marijuana than in infants who were unexposed. Among the infants exposed to cocaine, plasma norepinephrine concentrations were associated with a decreased responsivity to social and nonsocial auditory and visual stimuli and higher levels of depressed behavior on the Neonatal Behavioral Assessment Scale (NBAS). Of note, these associations remained significant even when controlling for the effects of prenatal marijuana

exposure. Needlman and his colleagues[43] examined the relation between prenatal cocaine exposure and the presence of monoamine precursors and metabolites in the central nervous system. Relative to infants who were not exposed, infants who had been prenatally exposed to cocaine had decreased levels of homovanillic acid, the principal metabolite of dopamine, in their cerebrospinal fluid. These findings suggest that prenatal cocaine exposure may result in changes in central dopaminergic systems in the neonate.[43]

The potential effects of cocaine exposure on the fetus are not limited to the neurotransmitter system. Spear and Heyser[44] reported that prenatal cocaine exposure also results in transient alterations in whole brain levels of gangliosides and glycolipids, which play important roles in the regulation of cell growth. The effects of these changes on the developing nervous system of the fetus remain to be identified. Because of the immaturity of the arterial system, fetuses exposed to cocaine earlier in gestation might be more at risk for neural developmental effects whereas infants exposed to cocaine later in gestation might be more at risk for cerebral vascular lesions.[21] Early in gestation, the brain areas are not yet differentiated or organized into complex association areas. Early disturbances of the neurotransmitter system could result in diffuse neurobehavioral manifestations whereas later exposure to cocaine could result in more specific neurological and neurobehavioral deficits.[45]

Documented Effects on Neurobehavioral Functioning

Over the past decade, researchers have made numerous attempts to document the effects of prenatal exposure to cocaine and other drugs on the young infant's neurobehavioral and neuromotor functioning. The identification of prenatal effects of cocaine on the fetus is complicated because women who use drugs during pregnancy do not necessarily limit their intake to a particular time during pregnancy or to cocaine alone. Multiple drug use including marijuana, alcohol, tobacco, and/or heroin is the typically observed pattern of use.[46] Precise knowledge of maternal cocaine use during pregnancy, timing of exposure, quantity, and frequency are measures that are difficult to obtain and control in research with humans. Other confounding variables include other medical risk factors, such as lead poisoning or factors related to the home environment such as poverty, violence, and maternal depression.[47] For these reasons, the true effects of cocaine on the developing fetus have been and remain difficult to ascertain.

Although scientific evidence has been available for 10 years, some of the early research is flawed with methodological difficulties suggesting that conclusions be drawn with reservation. For example, some studies have failed to differentiate between cocaine and opiate exposure,[8] whereas others have failed to control for potential confounding variables such as exposure to other illicit drugs, alcohol or tobacco, maternal nutrition, prenatal care, birth weight and gestational age.[6] Even in those studies where the use of opiates during pregnancy was absent, results on the NBAS are inconsistent and not fully replicated.[3,37,48,49] Despite these limitations, many investigators have reported that prenatal cocaine and other drug exposure is significantly related to compromised infant neurobehavioral performance on the NBAS, although specific findings vary across studies.[3,37,49-53] Clinically, full-term infants who have been exposed prenatally to cocaine and other drugs have been described as being easily over-stimulated and requiring increased examiner intervention to maintain control of their hyperexcitable nervous systems.[50] This hypersensitivity and need for examiner intervention is still described at one month of age.[50] Some infants exposed to cocaine and other drugs are unable to tolerate even low levels of stimulation and quickly reach an agitated crying state. Compared with neonates who have not been exposed, neonates with a history of prenatal cocaine and other drug exposure exhibit poorer state regulation,[50-52] motor maturity,[50] orientation,[50] habituation,[3,53] and greater excitability.[52] In some studies,[51,52] these findings remained significant even when the effects of confounding variables such as birth weight and prenatal exposure to other drugs were controlled analytically. Moreover, significant dose-related effects of prenatal cocaine exposure have been related to infant NBAS performance.[51,52] It has to be mentioned, however, that researchers using the NBAS have not been able to replicate each other's findings, but rather have shown effects on different items of the NBAS.

Lester and colleagues,[55] using cry analysis, identified two neurobehavioral profiles among newborns exposed to cocaine: excitable and depressed. Whereas the excitable profile seems to be related to primary effects of cocaine exposure, the depressed profile is believed related to the secondary effect of cocaine on intrauterine growth retardation. A potential confounding variable such as intrauterine growth retardation has rarely been controlled for and might explain some of the variability reported in earlier studies.[15]

Early detection of neurobehavioral abnormalities such as those revealed on the NBAS is important for infants prenatally exposed to drugs and for other high-risk infants. These behaviors may represent early manifestations of potential insult to the nervous system that may contribute to later compromised developmental outcome. Unfortunately, few developmental assessments designed to capture neurobehavioral organization beyond the newborn period are available for infants exposed to drugs prenatally.[56] Most of the research efforts to study neurobehavioral functioning beyond the newborn period use a variety of instruments and procedures designed to meet the needs of their particular research.

Blanchard, Suess, and Beeghly[57] conducted a longitudinal study of prenatal cocaine and other drug exposure. Twenty-six infants exposed to cocaine and other drugs and 23 control infants from low socioeconomic backgrounds were compared on measures of neurobehavioral functioning during neuromotor assessment at one, four, and seven months of age. None of the measures of neurobehavioral

functioning showed any significant group differences. Interestingly, some maternal and infant demographic variables showed more effects on neurobehavioral functioning than group exposure status. The age of the infant, calculated as the number of days since birth, at the seven-month testing session significantly predicted the need for examiner intervention at seven months but drug exposure did not. This relationship indicated that slightly older infants had higher scores on examiner persistence, ie, they required less examiner persistence or intervention during testing than did slightly younger infants regardless of drug exposure status, although the actual difference in age was a mere few days. At one month of age, a significant interaction was also found between parity and group exposure status on the numbers of interruptions during kinematic testing. The number of interruptions per minute was an indicator of the number of additional or unplanned handling procedures introduced during testing. For example, interruptions occurred to reposition the infant for testing. At one month of age for the infants in the exposed group, an increase in one child in the family caused the number of interruptions to increase. In the control group, an increase in two children was needed to cause an increase in the number of interruptions during kinematic testing. The results from this study suggest that infants with more siblings were more demanding (ie, required more assistance) during kinematic testing at one month and that among the infants exposed to cocaine and other drugs, the effects of parity occurred with fewer siblings in the family. The reason why parity influenced the number of interruptions at one month during kinematic testing is difficult to interpret. Possibly mothers who use drugs differ in their handling of their infants when multiple children are in the home and perhaps they are less able to divide their attention and respond to their infant's needs for consoling. Mothers who use drugs may also be more stressed by an additional child, which could also lead to difficulties in the development of organized behavior.

In a study conducted by Bendersky and Lewis,[54] arousal modulation was examined using a modified still-face procedure in four-month-old exposed and unexposed infants. The infants were seated on a table facing their mothers. The mothers were then asked to interact with their infant for a duration of two minutes, after which they were told to stop interacting and to drop their heads for 45 seconds. The mothers then resumed playing with their infants for a period of one minute. In this study, Bendersky and Lewis[54] found that a greater percentage of four-month-old infants heavily exposed to cocaine, compared with those who were not exposed, showed less enjoyment during face play with their mothers. Those exposed to cocaine continued to show negative expressions when their mothers attempted to reengage them in pleasant interaction.[54]

Struthers and Hansen[69] reported that infants exposed to cocaine and amphetamines performed significantly worse than unexposed infants on the Fagan Test of Infant Intelligence, a motor-free standardized test of visual attention and recognition. Alessandri and colleagues[70] found that infants who had been exposed to cocaine prenatally expressed less interest and joy during a learning task and less anger and sadness when the stimulus was removed than infants who were not exposed. Mayes and her colleagues[71] reported that three-month-old infants with a history of prenatal cocaine and other drug exposure were more likely to cry and exhibit negative affect during a novel stimulus-presentation task and show greater decrements in calming down to repeated presentations than same-age infants who were not exposed.

In a related study, Mayes and colleagues[72] found that infants in the exposed group were more likely to fail to start an habituation procedure and were more irritable during the early part of the procedure than infants in the unexposed group. Among the subset of infants who successfully completed the habituation paradigm, however, no group differences were observed in habituation performance between children who were and were not exposed. Given the comparable performance between the two groups on the habituation task, Mayes et al.[72] suggested that the early effects of drug exposure may be particularly evident in qualitative dimensions of infant behavior such as arousal modulation and attention regulation, rather than in early cognitive abilities.

Documented Effects on Neuromotor Development

Effects of prenatal cocaine exposure have also been shown on neuromotor functioning. In the neonatal period, infants exposed to cocaine present increased tremors and startles on the NBAS when compared with controls.[8,58] One of the early studies examining neuromotor functioning in infants prenatally exposed to cocaine reported significant effects of cocaine exposure and may have influenced clinicians' expectations about neuromotor performance of these young children.[1,59] Schneider[59] reported significantly higher risk scores on the Movement Assessment of Infants (MAI) in infants exposed to cocaine in comparison with infants who were not exposed. The infants' performances were particularly poor in the areas of muscle tone, primitive reflexes, and volitional movement. Forty-three percent of the infants exposed to cocaine fell into the high-risk category in comparison with two percent of the control group. The infants exposed to cocaine presented tremors, especially in the upper extremities; increased extensor muscle tone, especially in the lower extremities; and persistence of primitive reflexes.[59] At eight months, preliminary results indicated that the infants exposed to cocaine were slow in crawling and demonstrated weight-bearing on their toes with stiff extension of the lower extremities.[1] Close examination of the data collection procedure, however, revealed major weaknesses in the design of their study, thus limiting the generalizability of their findings. For example, the examiner was not blind to the group status of the infants being tested and the exposed group included four infants born preterm, whereas the control group did not.[59]

More recently, Fetters and Tronick[60] reported their

findings on the neuromotor development of 28 infants exposed to cocaine and 22 control infants from birth to 15 months. Cocaine exposure was associated with poor motor performance at four and seven months. At four months, a significantly larger proportion of the infants exposed to cocaine and other drugs fell below the 50th percentile on the Alberta Infant Motor Scales and had a greater proportion of suspicious risk scores on the Movement Assessment of Infants. At seven months, infants in the exposed group had significantly lower scores on the Movement Assessment of Infants. This difference among infants who were exposed or not exposed, however, was no longer evident at 15 months. Additional examination of these data showed that the areas of motor performance most compromised in the exposed group were observed in the prone and standing subscales of the Alberta Infant Motor Scale at seven months and in the primitive reflex section of the MAI at seven months.[61]

The Bayley Scales of Infant Development (BSID) are frequently used in research with infants and young children exposed to cocaine. In the majority of these studies, prenatal cocaine exposure was not significantly related to infants' performance on either the Mental Developmental Index (MDI) or Psychomotor Developmental Index (PDI).[32,62,63] A study conducted by Chasnoff and colleagues[50] found significant differences between infants in cocaine exposed and control groups on the Mental and Psychomotor Scales at six months, but not at three, 12, 18, or 24 months. It is interesting that in this study the alcohol/marijuana exposure showed more significant effects on the BSID than cocaine exposure at the tested ages. Another study reported differences on the Mental Developmental Index at 12 months, favoring the control group[64] whereas another reported significantly higher Psychomotor Developmental Indexes for infants exposed to cocaine.[65] Billman and colleagues[66] reported that the PDI scores varied according to infant exposure status, but only when infant ethnicity was considered. That is, infants who are black and who had been exposed to cocaine and other drugs had higher PDI scores than control infants who were black. No significant difference was reported for infants who were white.[66] Kaiser and colleagues[63] suggested that the BSID may be too limited in sensitivity and specificity to consistently detect neuromotor or psychomotor abnormalities in infants exposed to cocaine. In support of this argument, Rodning et al. [67] and Howard and colleagues[68] suggested that children exposed to drugs perform within the normal range when tested on assessments that are task-specific and highly structured by the examiner (ie, the BSID).

CONCLUSIONS

In most studies of prenatal drug exposure, families are from low socioeconomic backgrounds. This bias in the studied populations was found in a study examining the prevalence of substance use during pregnancy.[14] In this study, although no racial or social class differences were noted among pregnant women using the identified substance, women who were black and poor were more likely to be reported for substance abuse while pregnant than their white and middle class counterparts. Frank and colleagues[15] have proposed that long-term negative effects of prenatal cocaine exposure might be more representative of outcome in a population of poor children living in difficult and chaotic home environments. In a long-term follow-up study of children prenatally exposed to drugs, Chasnoff and colleagues[50] suggested that children of low income families, regardless of their prenatal drug exposure status, are at risk for developmental delays early in life. In this study, children from both groups of drug exposure scored below national norms on the Bayley Scales of Infant Development. Fetters and Tronick also found neuromotor scores that were below average on the Movement Assessment of Infant and the Alberta Infant Motor Scales for both groups of infants, cocaine exposed and control.[60] To examine the effects of prenatal drug exposure without the co-morbid influences of poverty, future studies would need to include groups of exposed and control subjects from higher socioeconomic levels. In fact, socioeconomic status and mother's level of education have long been recognized as significant predictors of developmental outcome in infants born prematurely.[73,74]

In most studies, detailed information on the family home environment was not collected. Postnatal environmental factors such as consistent, sensitive caregiving or early intervention services may significantly moderate the toxic effects of prenatal cocaine exposure and help promote healthy adaptation in children exposed to drugs prenatally.[75,76] In one longitudinal study, increased maternal sensitivity and maternal psychological adaptation during the first year of life predicted higher Bayley scores in infants prenatally exposed to cocaine and other drugs.[77] In other research,[78] mothers using drugs who received support services were more likely than other mothers to provide a developmentally supportive environment for their infants and to have infants whose developmental skills were age-appropriate at one year of age. Similarly, Frank and colleagues[79] showed that, among infants heavily exposed to cocaine in utero, BSID scores during the first two years of life were significantly higher if the infants or their caregivers had received early intervention services. In future studies with drug-exposed samples, the moderating effects of these environmental variables should be assessed.

Whereas early neurobehavioral and neuromotor dysfunctions have been reported for infants exposed to cocaine and other drugs, these findings have not been consistently replicated, and have not, so far, been found to predict long-term motor or neurobehavioral negative sequelae. As these signs of dysfunction have not been readily demonstrated beyond the newborn period, they might reflect only transient effects of prenatal exposure that are not present later in development. Determining the effects of cocaine and other drug exposure on infants' and young children's developmental outcomes is very complex. Cocaine and drugs themselves may or may not be sufficient, given other factors present in a child's life, to cause significant and permanent changes in developmental outcome.

Clinicians must keep an open mind when working with children exposed to drugs and their families and consider a wide range of possible reasons to explain their clinical observations. In future studies, infants and children from all subgroups of drug users, including middle-class mothers, should be examined to separate the effects of prenatal cocaine exposure from the potential effects of suboptimal rearing environments.

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