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Neonatal Neurobehavioral and Neuroanatomic Correlates of Prenatal Cocaine Exposure:

Problems of Dose and Confounding

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Abstract

Complex methodologic challenges face researchers studying the effects of prenatal cocaine exposure on infant outcome. These include unavoidable imprecision in ascertaining the gestational timing and dose of cocaine to which the fetus was exposed and difficulties in identifying and quantifying the confounding, mediating, and moderating variables. Review of research on neonatal behavioral and cranial ultrasound findings following *in utero* cocaine exposure is used to illustrate these issues. We conclude that there are measurable but not dramatic dose-related effects of prenatal cocaine exposure on infant central nervous system structure and function. The effects of dose of prenatal cocaine exposure on later child development remain to be determined. Such research would be facilitated by a scientific consensus delineating relative doses of prenatal cocaine exposure.

INTRODUCTION

Many complex methodologic issues contribute to scientific uncertainty regarding the effects of prenatal cocaine exposure in free living human populations.^{1,2} Unlike those using animal models, researchers with human samples still struggle to refine methods to ascertain accurately whether cocaine exposure occurred at all as well as to determine gestational timing of exposure and the acute and cumulative doses to which the fetus was exposed. In addition, identification and quantification of pharmacologic, biologic, and social variables that may confound, mediate, or moderate drug effects pose a formidable methodologic challenge. To illustrate how these two methodologic issues influence interpretation of human neonatal neurobehavioral outcome studies, we focus on findings of the Neonatal Behavioral Assessment Scales³⁻¹³ and on neonatal cranial ultrasounds.¹⁴⁻²⁰ These outcomes have been measured in multiple studies for nearly a decade.

IDENTIFICATION OF COCAINE DOSE

Many different methods, all with intrinsic limitations, have been used in research projects to identify human prenatal cocaine exposure. The first is to ascertain substance exposure based on interviews conducted by clinicians and noted in medical records. Clinical ascertainment of the use of illicit substances in pregnancy has repeatedly been demonstrated as inadequate, consistently identifying less than half the users identified by other methods.^{21,22} Under research conditions using trained interviewers with stringent assurances of confidentiality, more respondents will acknowledge cocaine use.^{5,23} However, research has shown that

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without biologic markers, even the most skilled research interviewer will underidentify cocaine-exposed mother/infant dyads.²⁴

The lack of standardization of potency and purity of illegal drugs further detracts from the usefulness of self-report. Even if a respondent is willing, within the limits of memory, to make every effort to provide an accurate account of her illicit substance use during pregnancy, the substance that she has used may vary from day to day, from place to place, and from year to year. By contrast, self-report of the use of legal psychoactive substances such as ounces of wine or beer or number of cigarettes permits more accurate calculations of the average volume of alcohol or nicotine to which child and mother were exposed, regardless of where or when the substance was used. No such standardization exists for purity or potency in lines of cocaine. Moreover, respondents may be completely unaware of potential contaminants that have been introduced into illegal drugs, contaminants that may have active toxic effects of their own.

Self-report, however, should never be omitted from research on prenatal cocaine exposure because it also offers some unique advantages. First, clinical interviewing by a skilled interviewer is more equitable than selective urine screening in clinical settings which may be based on provider expectation of drug use rather than actual drug use.^{22,25} Secondly, maternal report is the only way to ascertain lifetime use before conception or use within the first trimester of pregnancy.²⁶ Self-report also identifies route of drug administration and whether the drug is used in a “binge” pattern.²⁶ Self-report can delineate patterns of simultaneous or sequential psychoactive substance use (e.g., cocaine and alcohol use), which also may have important physiologic implications.²⁹ Furthermore, self-report scales are low in cost, readily available, generally well standardized, and easily administered.

Supplementing interview data with biologic markers enhances ascertainment of newborns exposed to cocaine *in utero*.^{21,22,24,25} Unfortunately, no biologic marker yet developed permits precise quantification of the dose of cocaine exposure throughout all trimesters of pregnancy. Until recently the most widely used biologic marker for cocaine exposure in clinical or research settings was assays of maternal or infant urine, either during pregnancy or at delivery.²⁸ The addition of urine assay does enhance ascertainment of infant effects in pregnancies exposed to cocaine. In fact, in a study conducted by our research group, if maternal urine assay had not been used, the cocaine effect on infant size at birth would not have been identified, because so many users would have been misclassified as nonusers.²⁴

Despite its widespread application and demonstrated usefulness, urine assay for drug metabolites poses difficulties. Cocaine metabolites appear in maternal and infant urine for only 24-72 hours after the last dose; therefore, if a mother does not present to a research or clinical setting to provide urine samples relatively close to the time of drug use, such use may not be identified.²⁸ In addition, urine assays are not useful for identification of dose of drug exposure. The concentration of cocaine metabolites in urine varies with the hydration status of the subject.

The short window of identification and inability to use urine assay as an indicator of dose has led to many studies exploring other biologic tissues, including maternal and infant hair and infant meconium. A few studies have used assays of umbilical cord blood and amniotic fluid, but their collection requires sufficiently controlled conditions in the delivery room as to eliminate their usefulness in large epidemiologic studies.^{29,30} The use of maternal or neonatal hair³¹ to identify drug exposure, whether prenatal or otherwise, has been a matter of controversy. Whereas some researchers suggest that segmenting the maternal hair is a reliable way to identify exposure over time,²² other investigators working with nonpregnant samples found that rates of appearance of radioactive labeled cocaine show wide individual variability.^{32,33} In addition, hair assays may inadvertently create ethnic and age biases in research data, such that dose of exposure is underestimated in fair haired samples. Hair with high

concentrations of melanin binds cocaine metabolites more readily than does blond or white hair.³⁴ Environmental contamination may be reflected in assays of adult hair, contamination that cannot be completely removed by washing techniques.³² Cosmetic treatments of hair also alter drug concentration in that hair.^{32,34} Therefore, the use of maternal hair for identifying the timing and amount of illicit cocaine exposure during pregnancy must be considered approximate at best.

Fetal hair is considered by some to be a more promising medium than maternal hair, because the issues of cosmetic interference and environmental contamination do not apply.³¹ However, in many clinical settings mothers may be reluctant to consent to hair being cut from the head of their newborn.²² Assaying newborn hair does not identify exposure before the second trimester when fetal hair begins to grow and does not have 100% congruence with other measures.^{31,35} However, one study of dose effects of prenatal cocaine use correlated concentration of cocaine metabolites in fetal hair with fetal head growth.³⁵

Meconium is currently a relatively widely used biologic marker for ascertaining prenatal cocaine exposure for research purposes.²¹ Although some investigators have reported that drug metabolites can be excreted into meconium as early as 15 prenatal weeks,³⁶ others have been unable to show any accumulation in infants of known users until 3 weeks prior to delivery.³⁰ Meconium is still a controversial medium for measuring dose of cocaine exposure, because in clinical settings the cocaine concentration may be altered by admixture of infant urine which contains cocaine metabolites from recent maternal use.³⁷ Nevertheless, meconium has in several studies proved useful for a heuristic rank ordering of exposure.^{12,13,38} Neither meconium assay nor other biologic markers currently available permit a precise determination of threshold and dose response or of gestational timing of exposure.

CONFOUNDING AND MODERATING VARIABLES

A second major area of difficulty in research on teratology of illegal drug use in the human population is the problem of confounding and moderating variables.¹ In animal studies, these issues are controlled by pair feeding and by standardizing rearing conditions between exposed and unexposed animals. However, in human samples, pregnant women who use cocaine tend to use multiple illicit substances as well as toxic but not illegal substances such as nicotine and alcohol.^{1,24,39,40} As interest in dose has emerged, it has become clear that those who are heavy users of one substance are also likely to be heavy users of another.¹³ Although cumulative adverse effects on birth weight have been described,⁴¹ little is known about the antagonism or synergy of commonly used psychoactive substances during pregnancy in determining fetal outcome. For example, the teratologic effects of cocaethylene are not yet delineated in humans. Cocaethylene, which is synthesized by the liver with the simultaneous use of cocaine and alcohol, has been found in adults to have enhanced cardiotoxicity and longer duration of action than does cocaine used alone.^{27,42}

In addition to pharmacologic confounding, researchers on human infants must deal with a large array of other potential biologic and social confounders. These include factors preceding conception such as maternal age, education, nutritional status, gravidity, and parity.⁴⁰ Other confounders during gestation include infectious disease (particularly sexually transmitted infections such as HIV and syphilis),⁴⁰ lead exposure,⁴¹ malnutrition, and trauma.⁴⁰

Besides biologic confounding and mediating variables, many psychosocial variables must be assessed repeatedly in evaluating the long-term outcome of cocaine-exposed children. These include parental comorbid psychiatric pathology, homelessness, and exposure to violence.¹ Moreover, the researcher in human populations must account for the possible effects of planned (but not usually randomly assigned) interventions both before delivery (prenatal care, drug treatment)⁶ and after, such as home visiting developmental or educational intervention targeted

to at-risk infants and children,⁴³ maternal drug treatment,⁶ or placement of the child away from the mother.

NEONATAL BEHAVIOR AND CRANIAL ULTRASOUNDS

To illustrate how variability in measurement of dose and of confounding or mediating variables contributes to inconsistencies in studies evaluating whether prenatal cocaine exposure exerts independent negative neurobehavioral and neuroanatomic effects on human neonates, we focus on findings on neonatal behavioral assessment scales and neonatal cranial ultrasounds, which have been measured in multiple studies for nearly a decade.

As Table 1 shows, Brazelton's Neonatal Behavioral Assessment Scale³ (NBAS) was performed in seven independent samples without regard to dose.^{4,6,11} No consistent behavioral profile emerged in the immediate neonatal period. Two of these studies which assessed both newborn behavior and behavior at 2-4 weeks of life found no effects in the first 3 days of life, but detected effects later in the first month.^{8,10} Table 2 summarizes three^{5,12,13} studies using the NBAS to assess outcome after some estimation of dose of prenatal cocaine exposure. Each study uses a different method. For example, Delaney-Black *et al.*¹² perform continuous correlation with concentration of cocaine metabolites in meconium; Tronick *et al.*¹³ ordinal rank exposure by a combination of meconium metabolites and the number of self-reported days of cocaine use; and Richardson *et al.*⁵ by the use of one or more lines of cocaine a day during the first two trimesters of pregnancy. Again, although all of these studies attempt to address dose, no cocaine effect is found in all three studies, although state regulation is less optimal following *in utero* cocaine exposure in two samples out of three.^{12,13} In addition, the Delaney-Black *et al.*¹² and Richardson *et al.*⁵ studies do not follow up children beyond the first week of life, although the Richardson study showed washout of the negative effects found on Day 2 by Day 3.

The data on cranial ultrasound outcome after prenatal exposure to cocaine is even more difficult to interpret, because in many studies covariates are not controlled. In published studies correlating cocaine exposure with neonatal ultrasound lesions, only one controlled for *in utero* cigarette or marijuana exposure¹⁶; two controlled for *in utero* opiate exposure^{16,18} and one for alcohol.¹⁹ Thus, misattribution to cocaine of the effects of other psychoactive substances on ultrasound findings cannot be ruled out from published data.

Despite case reports of catastrophic central nervous system infarction and malformations following *in utero* cocaine exposure,^{44,45} the findings in large controlled samples with comparison groups are much less striking, with three studies finding an increase in low grade intraventricular hemorrhage among cocaine-exposed children of various gestational ages,^{14,18,19} whereas four did not.^{15,17,20} (Table 3). None of these studies controlled for maternal cigarette use; the other variables controlled varied from study to study. We recently reanalyzed a dataset in which no differences were found among 241 term infants in ultrasound lesions if they were categorized only as cocaine exposed or unexposed.⁴⁶ The increased risk for grade I intraventricular hemorrhage was found only among the most heavily cocaine exposed (top quartile by days of self-reported use or concentration of cocaine metabolites in meconium), in whom the odds of such a hemorrhage were 3.88 (95% CI 1.45, 10.35, two-tailed $p = 0.007$) compared to those of unexposed after covariate control (including cigarettes, alcohol, and marijuana).⁴⁷ The more lightly exposed did not differ from the unexposed. This lesion is clinically silent at birth and has unknown long-term implications for developmental outcomes.

When all these studies are reviewed together, the perinatal effects of prenatal cocaine exposure on human central nervous system structure and function, once confounding variables are considered, appear to be small but detectable. Unlike the narcotic abstinence syndrome,

prenatal cocaine exposure is not associated with a clinically obvious, consistent neurobehavioral profile; however, subtle adverse effects on state regulation have been described in more than half the published studies, both those measuring dose effect^{12,13} and those analyzing cocaine exposure as an all or none variable.^{4,6,9,10} Structural alterations in the neonatal central nervous system are also inconsistent from sample to sample.¹⁴⁻²⁰

CONCLUSIONS

The popular preception is that *any* prenatal exposure to cocaine is almost certainly associated with devastating effects on the neonate. However, these data suggest that most potentially detrimental effects (including neonatal size,³⁸ neonatal behavior,^{12,13} and central nervous system lesions⁴⁷) of prenatal cocaine exposure occur disproportionately among the heaviest users, a phenomenon also noted for alcohol and cigarette exposure.²³ This dose effect requires further replication, because it has only been explored in a few samples.

To enhance the field of investigation into *in utero* exposure to illicit drugs in general and cocaine in particular, a consensus must evolve in defining what is heavy use. Currently, it is not clear whether the heavy users in one population are comparable to the heavy users in another, given the geographic variability in potency and routes of administration and the different modes of ascertainment of dose of prenatal cocaine exposure. Moreover, some of the current interview criteria for quantifying heavy dose (using more than 2 days a week²³ or more than one line a day⁵) conflate frequency and quantity. In alcohol research, because of the standardization of alcohol content under government supervision, the problem of comparative dose has been addressed more systematically, although imprecision for the purpose of teratologic studies remains. There is consensus that more than five drinks on a single occasion constitute a "binge." The most familiar type of index of substance use has been used to quantify drinking behavior. One measure is the Quantity-Frequency index of Strauss and Bacon⁴⁸ which was modified by Mulford and Miller.⁴⁹ This tool used the average amount per drinking occasion as the measure of quantity, thus making no distinction between the person who achieves a certain average quantity by drinking extremely large amounts on some occasions and very small amounts on others and the one who achieves the same average quantity through drinking the same amount on each occasion. A second index, developed by Cahalan and Cisin,⁵⁰ is the Volume-Variability Index which attempts to compare massed versus spaced drinking which holds volume constant. The basic technique of this index entails a two step operation: (1) to classify each respondent according to his average daily volume and (2) to divide each of several daily-volume groups into subgroups according to how variable the person is in his/her intake from day to day. The latter scale can differentiate people who drink only medium amounts of alcoholic beverages in terms of total consumption, depending on whether they drink in a massed or spaced-out pattern.⁵⁰ There is as yet no comparable consensus in cocaine research.

In addition, the precision of dose quantification in humans for cocaine is not yet adequate for statements to be made regarding whether the pattern of the effect is continuous or whether there is an actual threshold beyond which effects occur. Great caution must be exercised in drawing health education and public policy conclusions from available information regarding dose. For instance, several studies define heavy users as those who use more than twice a week,^{13,23} but this is not a true threshold. One cannot be sure that less frequent use would not have detrimental effects. In addition, dose may vary throughout pregnancy; most investigators find that women's use decreases as the pregnancy progresses.⁵ It is not yet known whether the primary determinant of adverse outcome is cumulative dose, which is only approximately reflected in meconium²¹ or neonatal hair,³¹ or maximum dose used on a single occasion, which usually occurs earlier in pregnancy and may not be reflected in available biologic markers.

Even if a standardized mode of quantifying prenatal cocaine exposure develops, the phenomenon of dose response is not always straightforward. Simple linear models (the more exposure, the worse the outcomes) may not be adequate to describe the actual relationships, which may be nonlinear or even paradoxical (some is worse than none or a lot).⁵³ Moreover, the possible explanations for such paradoxical effects vary and include biologic and social mechanisms. For example, a larger cocaine dose may produce greater placental vasoconstriction with less metabolite transferred to the fetus.⁵¹ One could speculate that repeated use might upregulate enzymatic pathways of detoxification, decreasing effects with higher cumulative use.⁵² There is also the question of a “healthy user” effect, with women with better overall health tolerating higher doses than women with other adverse health conditions which may place the fetus at risk.⁵³

There are also potential social mediators of possible paradoxical dose effects, if women with better education or more economic resources obtain more doses of an illicit drug. This phenomenon has been described in Jamaica where compared to infants of nonusers, infants of heavy marijuana users had more optimal behavioral findings at 1 month of age.⁵⁴ In the United States, because heavier users and their infants may be more readily detected by clinicians, they may be given preferential access to compensatory services such as maternal drug treatment or infant developmental intervention, leading to a more optimal long-term outcome than that of infants exposed to a lower dose who receive no compensatory care.^{6,43,55}

Currently available human research suggests that after confound control, there is a cocaine dose effect on neonatal size at birth, with the more heavily exposed infants in any sample being smaller in all parameters than those less heavily exposed. Dose effects have also been detected on neonatal behavior and on cranial ultrasound findings, but these results must be considered tentative until replicated because they have only been reported in one or two samples. The effects of dose after the neonatal period have been explored in only two samples,^{23,56} one of which found negative effects of higher dose exposure on infant information processing,²³ whereas the other found no effect on cognitive test scores at 4 years.⁵⁶ More information is needed on potential dose effects on long-term outcome such as cognitive test scores, attention, behavior, affect regulation, and physical growth after the first year of life. As these areas evolve, defining dose and documenting mediating and confounding biologic and social variables will continue to pose major challenges.

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Cocaine Effects on Brazelton Neonatal Behavioral Assessment Score in Term Infants Not Exposed to Opiates

TABLE 1

Study	Habituation	Orientation	Motor	State Range	State Regulation	Autonomic Regulation	Abnormal Reflexes
Chasnoff (1989) (n = 79)	0	+	+	0	+	0	+
Eisen (1991) (n = 52)	+	0	0	0	0	0	0
Neuspiel (1991) (n = 111)	0	0	+	0	0	0	0
Coles (1992) (n = 107)	0	0	0	0	+	+	+
Mayes (1993) (n = 86)	+	0	0	0	0	0	0
Scafidi (1996) (n = 60)	0	0	0	+	+	0	0
Phillips (1996) (n = 50)	0	0	0	+	+	0	0

+ 1 to 3 days.
+* 2-4 weeks.

TABLE 2

Cocaine Dose Effects on Brazelton Neonatal Behavioral Assessment Scores

Study	Habituation	Orientation	Motor	State Range	State Regulation	Autonomic Regulation	Abnormal Reflexes
Tronick* (n = 251)	0	0	0	0	+	0	0
Richardson+ (n = 165)	0	0	+	0	0	+	+
Delaney-Black (n = 52)	0	0	+	0	+	0	0

* At 3 weeks only.

+ Present on day 2, not day 3.

TABLE 3
Findings on Neonatal Echsonography after *in Utero* Cocaine Exposure without Regard to Dose

	Dixon & Bejar (1989)	Heier <i>et al.</i> (1994)	Dusick <i>et al.</i> (1993)	Dogra <i>et al.</i> (1994)	Singer <i>et al.</i> (1994)	King <i>et al.</i> (1996)
Cocaine exposed (n)	50	43	41	40	86	39
% African American	50%	84%	100%	NR	93%	63%
Controls (n)	87 19 well	62	41	84	146	39
% African American	94% 0	76%	100%	NR	86%	77%
% Preterm	0	Median GA both groups, 31 weeks	100%	27%	100%	Median GA 39 weeks
Urine toxic screen	100% cases	58%	<1,500 g	100% cases	<1,500 g	100% cases and controls
Meconium cases	NR	No	No	No	30%	No
Controls	No	24%	No	100%	100%	No
Cigarettes %	NR	NR	78% cocaine	NR	NR	NR
Controlled analysis?	No	No	No	No	No	No
Alcohol %	NR	NR	46% cocaine NR controls	47% cocaine	NR	NR
Controlled analysis?	No	6% controls	No	Yes	No	No
Marijuana	NR	No	36% cocaine	No	NR	NR
Opiates	45%	0% controls	None	No	NR	NR
Grade I, II, IVHs	10% cases	35% cases	42% cases	7.5% cases	36% cases	11% cases
	3.4% sick	31% controls	20% controls	0 controls	35% controls	11% controls
	Controls 5.4%					
Other CNS findings increased in cocaine exposed	Well cases White matter cavities; white matter densities; acute infarction; subarachnoid hemorrhage; ventricular enlargement All cocaine exposed in normal nursery	Cortical infarction (17%); congenital CNS abnormality (12%)	None	Echoluencies in basal ganglia (25% vs 0)	Seizures (17% vs 5%)	Increase in cerebral blood flow day 1 to day 2
Notes		All in NICU	All in NICU	All had prenatal care and AGA term with more lesions than preterm	17% cases used alcohol, opiates, marijuana	All in normal nursery