

ACCURACY IN DETECTING PRENATAL DRUG EXPOSURE

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A basic problem encountered by investigations of prenatal cocaine effects has been the valid identification and quantification of exposure. Based on a combination of sources: (a) medical record review, (b) maternal urine toxicology screen, (c) meconium analysis, and (d) maternal postpartum interview, drug exposure status of 415 infants was established. Using this combination as a benchmark, maternal postpartum interview was found most sensitive, while medical record review was slightly less accurate. Meconium analysis and urine screens both demonstrated miss rates greater than the interview or record review methods. Meconium analysis and postpartum interview, however, each detected cases of cocaine exposure that the other had missed. Correlations between the amount of cocaine found in meconium and in maternal report indicated that the cocaine metabolite benzoylecgonine was the best biological marker. Quantifying heavy versus light exposure required a combination of both meconium analysis and maternal postpartum interview techniques.

INTRODUCTION

As the research on the developmental effects of prenatal cocaine exposure has advanced, one of the more difficult methodological issues has been the accurate detection of children whose mothers used drugs during pregnancy. Initial efforts to identify drug-exposed infants varied from site to site, with heavy reliance on maternal self-report to establish drug exposure (General Accounting Office 1990).

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It became apparent, however, that the illegal nature of cocaine gave users strong reason to deny or minimize their drug use (Frank et al. 1988; Zuckerman, Amaro, Cabral 1989). Consequently, urine toxicology screens from either the mother, the newborn, or both were added as a check on maternal reports. Subsequent studies have indicated that, because of the relatively quick rate at which cocaine is metabolized, urine screens alone are not adequate (Ostrea 1995; Ryan et al. 1994). Analysis of meconium, which is the first stool of a newborn, with the potential to assess cocaine exposure beginning in the second trimester, has, therefore, become a commonly recommend method of identification.

Hazards associated with establishing a women's drug use history and the drug-exposed status of her children have frequently been raised. Misclassification of cocaine users threatens the validity of research findings, since including users in a non-user comparison group may weaken differences (Mayes, Granger, Bornstein, and Zuckerman 1992). Misclassifying users and non-users in epidemiological studies may underestimate the prevalence of drug use and outcome studies may overestimate cocaine effects when identification procedures can only detect heavy, chronic cocaine use (Carmichael Olson, Grant, Martin, and Streissguth 1995). Another serious concern, related to the utilization of clinical services, is the failure to provide appropriate services for a child when prenatal exposure is not correctly identified. To balance the increased level of risk associated with failure to provide appropriate services with the potential harm of labeling a child as a "crack kid" (Coles 1993), health care providers and early intervention specialists must have accurate information.

The current study was designed to investigate the accuracy of four commonly used drug exposure measures: medical records review, maternal urine screen, analysis of meconium, and postnatal interview. Using a combination of information from all four measures as the benchmark, each method was compared for percent of cocaine exposed infants correctly identified. The data were also examined to determine whether quantification of drug exposure level by meconium was related to severity of drug use reported by the mother.

METHOD

PARTICIPANTS

As part of an longitudinal study of prenatal drug exposure effects on infant development, 415 mothers and their newborn infants were enrolled at delivery in a large, urban teaching hospital. A nurse recruiter approached the mothers shortly before or after infant birth. Six hundred and forty-seven mother/infants pairs were identified during a two-year period. Of those identified, 155 declined to participate (49 cocaine positive, 106 cocaine negative), 54 were excluded (20 cocaine positive, 34 cocaine negative), and 23 did not show for the enrollment visit. Exclusion criteria for infants included failure to collect meconium, genetic syndromes, or other significant medical risk conditions. Women were excluded from the study for psychiatric history, HIV positive status or low intellectual functioning, and age less than 19 years. Those women whose drug of choice was PCP, amphetamines, barbiturates, or opiates were also excluded. After accounting for those who either refused to participate, were excluded, or who did not show

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up for any data collection visit, the data on 415 dyads were available for analysis in this study.

MEASURES

BIOLOGICAL MARKERS

Urine toxicology screens were performed by the hospital on all women who received no prenatal care, appeared intoxicated or under the influence of drugs, who had a history of involvement with the Department of Human services, or who self-admitted or appeared to be high risk for drug use after interview by a social worker or medical resident. In addition, women enrolled in this study who had not been previously required to give a urine sample for the clinical reasons just listed, were also asked to give a voluntary urine sample. A single urine sample was obtained from the mother within 24 hours before or after delivery. Urine analysis was done by the Syva Emit (Enzyme-Multiplied Immunoassay Technique). Follow-up thin layer chromatography or gas chromatography were performed for confirmation. The published specificity of this measure for benzoylecgonine (BZE), the most common metabolite of cocaine in adults, is 99 percent at a concentration of 300 ng/ml.

Meconium is a sticky, dark green waste product that collects in the fetal intestines from swallowed amniotic fluid, starting around the 16 week of gestation until birth, and is excreted within the first few days after birth. Meconium specimens were collected in the hospital from the infants' diapers. The meconium was scraped from the diaper with a wooden spatula and placed into a plastic container. In order to maximize the amount collected, stool specimens from multiple diapers of the same newborn, when available, were accumulated and kept refrigerated. The entire sample was then stirred for five minutes to insure homogeneity.

Meconium analysis was conducted using Gas chromatography—Mass spectrometry (GC-MS). In addition to the parent compound, cocaine (COC), meconium analysis identified the presence of three cocaine metabolites, i.e., benzoylecgonine, cocaethylene (COCETH), and meta-hydroxybenzoylecgonine (m-OH-BZE). Analysis also quantified the amount of tetrahydrocannabinol (THC), the primary psychoactive agent in marijuana, in the sample and identified the presence of cotinine, the major urinary metabolite of nicotine. The published specificity of this measure for cocaine or any of the cocaine metabolites is 99 percent at a concentration of 5 ng/g. Specificity of the GC-MS is also 99 percent at concentration of 2 ng/g. Cotinine detection was done using enzyme immunoassay (EIA) techniques with a cutoff of 50 ng/g. Because our primary goal was to correctly identify infants who had been exposed to cocaine, special effort was made to collect a sample from those infants who by prenatal and delivery records were thought to be drug free.

CLINICAL MEASURES

In addition to demographic and medical characteristics, clinical records of the mothers and infants were reviewed for any information regarding a history of substance abuse during the pregnancy or at the time of delivery.

The postpartum interview was adapted from Streissguth (1986) and included the TWEAK (Russell 1994) alcohol screening measure. It was administered to the biological mother, usually at the first infant assessment point, within five weeks postpartum. Although 34 percent of the drug using mothers and 1 percent of the comparison mothers did not have custody of the infant at two weeks, every attempt was made, to obtain information from all biological mothers. Efforts included conducting a maternal interview separately from the time of the infant assessment and conducting interviews in treatment and incarceration facilities. Informed consent was obtained and all mothers received \$35 and cab/transportation fare after the interview. This study was approved by the Institutional Review Boards of the participating institutions.

The post-partum interview quantifies maternal drug use for the month prior to and during each trimester of pregnancy (Singer, Arendt, Farkas, Minnes, Huang, and Yamashita, 1997). In addition to asking about prescription drug use during pregnancy, for each time period mothers were asked to recall frequency and amount of tobacco, alcohol, marijuana, and cocaine use. The frequency of use was multiplied by the amount of use per day to compute a severity of use score for the month prior to pregnancy and for each trimester.

Because there is no "gold standard" by which the various measures of prenatal cocaine exposure status can be assessed, we chose to use a combination of all four methods to categorize each newborn as either cocaine exposed or unexposed. Cocaine use was identified by a positive result on any one of the four measures. In order to be considered as non-exposed, all four indicators had to be negative.

DATA ANALYSES

This method assumes that no unexposed infant would be identified as exposed, e.g. no false positives and that the specificity of the combination was 100 percent. Specificity is defined as the number of true negatives divided by true negatives plus false positives. In terms of the present context, specificity is the percentage of infants who were not exposed to cocaine who are classified as having not been exposed.

Sensitivity is the primary index of test performance under investigation in the present study. It is defined as the number of true positives divided by true positives plus false negatives. In other words, sensitivity is the proportion of cocaine exposed infants in the study who were correctly identified as cocaine exposed. The first set of analyses was designed to determine sensitivity of the various measures, i.e. how well each measure identified infants who were exposed to cocaine in utero. The second set of analyses were separate correlations to determine level of agreement between the amount found in the meconium and the severity of use reported by the mother in the postpartum drug interview. The final analysis examined agreements and disagreements between the meconium and interview methods for determining heavy and light exposure within the cocaine group.

RESULTS

Mothers were primarily poor, minority women who were the single head of household (See Table 1). Mothers who used cocaine were older, had delivered

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more children, and had fewer prenatal visits. They also used more alcohol, cigarettes and marijuana during pregnancy than did the cocaine free mothers.

TABLE 1
MATERNAL CHARACTERISTICS

	Cocaine (n=218)	Non-cocaine (n=197)	χ^2
Maternal age (M \pm SD)	29.6 \pm 5	25.7 \pm 5	8.3***
Parity (M \pm SD)	3.5 \pm 2	2.7 \pm 2	4.5***
Prenatal visits (M \pm SD)	5.2 \pm 5	8.7 \pm 5	-7.4****
Marital status			
Married	7%	17%	13.0*
Single	78%	72%	
Divorced/Separated	15%	11%	
Widowed	1%	0%	
Ethnicity			
Black	81%	79%	
White	15%	19%	
Hispanic	2%	0%	
Other (Mixed/Oriental)	2%	2%	
Maternal Education			
Less than high school	48%	31%	11.5**
High school	33%	42%	
Some college	17%	25%	
College graduate	2%	2%	
Annual Income			
\$0 - \$10,000	97%	80%	
\$10,000 - \$20,000	2%	13%	
> \$20,000	1%	7%	

Other drug use (M \pm SD)			
Tobacco ¹	11.7 \pm 10.8	4.4 \pm 8.1	-7.4****
Alcohol ²	1.3 \pm 4.4	9.9 \pm 18.5	-6.2****
Marijuana ³	0.6 \pm 3.4	1.3 \pm 3.5	-2.1*

¹ # cigarettes/day² # drinks/day x # days/week³ # joints/day x days/week

*p<0.05

**p<0.01

***p<0.001

****p<0.0001

Table 2 indicates that, when compared to the benchmark, the interviews and questionnaires had greater sensitivity than the biological measures. When the measures were looked at in the order collected, e.g. prenatal information in medical records, maternal urine screen at delivery, meconium collected after birth, and, finally, postpartum interview, all 218 mothers identified as cocaine users could have been found by use of just the combination of medical records and urine screens. By way of comparison, if just the two postpartum measures, meconium and interview, were used, 24 of the cocaine exposed infants would have been identified as unexposed.

TABLE 2
SENSITIVITY OF MEASURES

Self-report/medical records	80.6% (414)
Maternal urine screens	61.1% (405)
Meconium analysis	60.5% (341)
Postpartum interview	89.2% (391)

Parentheses indicates number collected

Because it is a relatively inexpensive and easily administered instrument, a maternal drug interview is still commonly used to determine prenatal drug exposure. It may, therefore, be instructive to compare the drug interview to the current primary biological marker of infant cocaine exposure, e.g. meconium. Of the 323 mother/infant dyads for which both interview and meconium data were available, there was a total of 91 cocaine positive meconium samples. This compares to the 131 mothers who admitted in the drug interview that they used cocaine, either during the pregnancy or immediately before it. Positive evidence of cocaine was found both in meconium and by interview in 82 pairs. Both forms of drug use detection were negative in 183 cases. This left 58 cases in which the results were inconsistent. Looking at these inconsistent cases, there were nine cases in which a mother denied cocaine use in an interview but the meconium

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results were positive for cocaine or its metabolites. This compares to 49 cases in which meconium results were negative but the mother reported using cocaine.

To assess agreement between different ways of quantifying cocaine use, we calculated correlations between the amount of drug found in meconium and the severity of use reported by the mother. There was a reasonable correlation between the severity of drug use reported by the mother in the postpartum drug interview and the amount found in the meconium (See Table 3).

TABLE 3
CORRELATIONS BETWEEN BIOLOGICAL AND SELF-REPORT SEVERITY MEASURES

Interview	Meconium	
Marijuana	THC	0.45***
Alcohol	Cocaethylene	0.29***
Cocaine	Cocaine	0.46***
Cocaine	Cocaethylene	0.32***
Cocaine	Benzoylcegonine	0.57***
Cocaine	m-OH-Benzoylcegonine	0.51***

*** $p < 0.001$

The final analyses investigated the agreement between level of exposure, heavy or light, as determined by interview and by meconium analysis. We designated the 70th percentile as the break point between light and heavy use. As seen in Table 4, 20 of the infants who would have been categorized as lightly exposed based on meconium results would be classified as heavily exposed based on maternal report. In contrast 52 of the infants whose mothers reported only light use were categorized as heavy users based on the amount of cocaine metabolites in their meconium.

TABLE 4
SEVERITY OF COCAINE USE BY MEASURE

		Meconium	
		Light	Heavy
Interview	Light	59	52
	Heavy	20	14

When the interviews of the 20 mothers classified by interview as heavy users but light by meconium were reviewed, 13 of the cases reported that they had used heavily in the month prior to conception or in first trimester, but had abstained or greatly reduced their use of cocaine in the second and third trimesters. This decrement in use over the first two trimesters may account for the light amount of cocaine detected in the meconium. A pattern of diminishing use of cocaine over the course of pregnancy has been frequently reported (Eyler, Behnke, Colon, Woods, and Wobie 1998; Jacobson, Jacobson, Sokol, Martier, and Chiodo 1996; Richardson, Hamel, Goldschmidt, and Day 1996; Singer, Arendt, Farkas, Minnes, Huang, and Yamashita 1997). To the extent that such a pattern occurs in any particular research sample, meconium analysis will not determine either a qualitatively exact incidence of fetal cocaine exposure or a more quantitatively accurate level of exposure.

DISCUSSION

Results indicate that, at present, no one cocaine detection technique used alone is a completely accurate marker of prenatal exposure. Each assessment technique identified cocaine exposed infants that other measures had missed, but each also missed some exposed infants identified by other means. Each method has both relative advantages and disadvantages. Investigators must consider time expenditure, monetary cost, collection difficulty, and, especially for the biological markers, the point or points in the pregnancy when information can be obtained. The best results appear to be generated by use of multiple measures, preferably one biological and one behavioral.

The high degree of accurate identification of cocaine use from medical records and post-natal interviews contrasts with other reports of poor reliability for maternal self-reports. It is important to keep in mind that data collected for these analyses were part of a research protocol. Interviewers were extensively trained and highly skilled and the interview itself was more sophisticated and contained more detailed information than typically collected by clinical staff in obstetric units. Additionally, because the study was voluntary, potential participants who felt they should conceal drug use could refuse to be included. This bias likely inflated the specificity of the medical records/prenatal interview results.

Currently, meconium assay is the most widely accepted and recommended procedure to detect prenatal cocaine exposure. This method is not, however, without shortcomings. Meconium results were either unavailable ($n=61$) or negative ($n=62$) in 56 percent of the 218 cases that were positive according to the combined measures. In this regard, however, it is important to note that, because meconium is difficult to collect, store, and analyze, the greatest efforts were made to collect specimens from infants who were thought to be unexposed. This meant that, while the raw number of children identified as cocaine exposed by meconium was likely to be low, the results would have been biased in favor of meconium accurately identifying a greater, rather than lower, percentage of cocaine exposed infants than the self-report measure if mothers falsely denied use. It is also worth noting, however, that the sensitivity of the meconium analysis (60.5 percent) reported in the current study falls below that reported in other studies (Callahan et al. 1992; Mirochnick, Frank, Cabral, Turner, and Zuckerman 1995).

When used as a check against hospital records and diligent maternal interviews to establish cocaine exposure status, the value of meconium analysis in the present study was limited. Although it failed to detect some exposed infants, meconium analysis was useful in assigning level of exposure among those who were identified as exposed.

Several authors have reported findings that are consistent with a cocaine dose response. Mirochnick et al. (1995) reported that there was an inverse relationship between the concentration of benzoylecgonine in the meconium of 95 infants and their birth weight, length and head circumference. Although Jacobson, Jacobson, Sokol, Martier, and Chiodo (1996) failed to detect cognitive differences in a large group of inner-city infants based on the presence or absence of cocaine use during pregnancy, they did find that heavy exposure early in pregnancy was related to subtle neurobehavioral effects. Delaney-Black et al. (1996) reported that as the concentration of cocaine metabolites in the meconium of 23 infants increased, they displayed increasingly negative behavioral effects. Singer et al. (1999) also found heavy cocaine exposure to be associated with poorer visual recognition memory in neonates.

Although the initial design included collecting urine from newborn, difficulties in the collection technique limited the number of specimens obtained. Additionally, contamination of meconium with urine is likely (Lombardero, Casanova, Behnke, Eyster, and Bertholf 1993). These problems, plus the limited support found in the literature for validity of newborn urine screen results (Callahan et al. 1992; Ryan et al. 1994; Wingert, Feldman, Kim, Noble, Hand and Yoon 1994) and the more ready availability of meconium testing, suggests that the practice of collecting urine screens from newborns, especially for the detection of cocaine, is of marginal value. Other authors (Lombardero et al. 1993), however, have suggested that measurement of cocaine and its metabolites extracted from neonatal diapers may be an efficient and valid alternative to collecting urine samples.

The results we report in this article have several methodological attributes that limit their generalizability. The first consideration is the decision made, in the absence of any "gold standard", to use the combination of all measures as the standard and to assume that there would be no false positives. This effectively meant that specificity would be 100 percent. It is important to not confuse specificity with the clinical task of determining the probability that a patient does not have a condition, e.g. cocaine use or exposure, given that he or she obtained a negative test result (Elwood 1993). This clinical decision making rule, called the negative predictive power of a test, involves both true negatives and false negatives and is affected by the base rate of cocaine use in the population.

Another methodological point that limits extrapolation of current results to the accuracy levels that may exist in a clinical setting is that we were able to promise the mothers that the drug use information they voluntarily provided would remain confidential. Because of wide differences in state laws, the right to keep information about maternal drug use during pregnancy confidential may not be available in all cases. It also, however, illustrates the dilemma faced in clinical settings when women are prosecuted for drug use, especially when pregnant. Rather than providing an incentive to misrepresent their drug use or to avoid

medical care and prenatal visits, pregnant women should receive priority for substance abuse treatment, including regular monitoring of use.

Determining that cocaine is a developmental neurotoxicant is an important first step in the risk assessment process. The next requirement is to quantify the amount of drug exposure to determine whether the substance produces a dose response, i.e., increased exposure produces greater teratogenic effects (Vorhees, 1986). Although dose-response assessment may be a straight forward process in risk assessment of some environmental toxins, e.g. thalidomide, researching the risk of a potential neurotoxin is more complex because numerous endpoints, both behavioral and neurochemical, must be considered (Weiss 1995).

It is important to remember that little is currently known about the properties of cocaine in meconium. There are over a dozen metabolites and pyrolysis products of cocaine that can be identified in meconium (Oyler, Darwin, Preston, Suess, and Cone 1996). The source of many of these products, whether fetal or maternal, has yet to be established. Although it is consistent with a dose response, establishing a relationship between one or more of these products in meconium and greater impairments or delays in developmental outcomes does not necessarily constitute the same construct as finding a dose response.

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