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ORIGINAL ARTICLE

Testing for fetal exposure to illicit drugs using umbilical cord tissue vs meconium

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Objective: We assessed the agreement of testing for fetal exposure to illicit drugs contrasting paired specimens of meconium vs umbilical cord tissue.

Methods: We obtained paired samples of meconium and umbilical cord tissue from 118 pregnancies with high suspicion of illicit drug use by the mothers. Each specimen was tested for amphetamines, opiates, cocaine, cannabinoids, and phencyclidine using drug class-specific immunoassays.

Results: The agreement of drug screening results between cord and meconium was above 90% for all drugs tested. Meconium identified 21 cases as positive for amphetamines. The paired cord identified 20 of these, and in addition identified three other positives that the meconium labeled as negative. Gas chromatography–mass spectrometry confirmed these three cord samples as methamphetamine positive. Meconium identified 97 samples that were negative for amphetamines, while the cord identified 94 of these as negative but three as positive. Agreement of cord with meconium for amphetamines was 96.6%. The concordance for opiates was 94.9%, for cocaine was 99.2%, and for cannabinoids was 90.7%.

Conclusions: Umbilical cord tissue performs as well as meconium in assessing fetal drug exposure to amphetamines, opiates, cocaine, and cannabinoids. Results of studies using the cord may have a more rapid return to the clinician, because waiting for meconium to be passed sometimes requires several days. Moreover, in some cases the meconium is passed *in utero* making collection impossible, whereas cord should always be available for drug testing.

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Introduction

Healthy People 2010 is a framework of health goals for the nation.[1] Objective 16–17 of this framework is, 'to increase abstinence from alcohol, cigarettes, and illicit drugs among pregnant women.'[2] As a step toward meeting this goal, accurate data are needed on the incidence of illicit drug use in pregnancy. Urine testing and maternal reporting underestimate the incidence. Ostrea *et al.*[3] reported that meconium testing could detect drug intake during pregnancy. They subsequently showed that meconium testing has advantages over urine testing, particularly when maternal drug administration occurred several days prior to delivery.[4–6] However, sometimes meconium testing is not possible, or is not timely. For instance, sometimes the meconium is passed *in utero* making it unavailable for testing, and in other cases meconium is not passed for several days, particularly among preterm infants. Kintz and Mangin[7] reported neonatal hair testing as an alternative to meconium. However, hair testing may not be as acceptable, because sufficient hair must be cut such that it is noticeable to parents, and some neonates have too little hair for accurate testing.

We hypothesized that cutting a 10 cm segment of umbilical cord at delivery, and homogenizing this tissue for drug testing, would give results comparable to that obtained with meconium. To test this, we obtained paired samples of meconium and umbilical cord from pregnancies with a high suspicion of illicit drug use by the mothers. Each of the pairs was tested for amphetamines, opiates, cocaine, cannabinoids, and phencyclidine (PCP), and the results obtained with cord tissue vs meconium were compared.

Methods

During an 18-month period (August 2003–February 2005) a segment of approximately 10 cm was cut from each umbilical cord of a delivery at McKay-Dee Hospital. The segment was lightly rinsed with sterile saline and placed in a sterile container in a laboratory refrigerator. If the neonatologist or pediatrician ordered MecStat™ testing on meconium of that neonate, the meconium and the umbilical cord segment were both submitted to the laboratory for testing. If no meconium testing was ordered after 1 week, the umbilical cord segment was discarded in the usual manner. MecStat™ testing was carried out if any of the following were

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present; history of a previous pregnancy where drug abuse was proven, maternal report of drug abuse during this pregnancy, no prenatal care, no permanent address, sexually transmitted diseases, mother or father appearing intoxicated, 'high,' or abusive or inappropriate.

The meconium was tested and the results reported to the physician as with any clinically ordered specimen. However, the umbilical cord specimens were batched for periodic research analysis, and the results of these were not reported to the attending physician, but rather were treated as a deidentified, anonymous dataset. The umbilical cord segments were stored at −20°C and were batched for analysis. No specimens were stored for more than 12 months. The aim of the study was to obtain 100–120 paired samples for testing from pregnancies at high risk for maternal drug abuse. The McKay-Dee Hospital Institutional Review Board approved the study protocol.

The umbilical cord specimens were extracted by the procedures reported by Le *et al*.[8] for meconium, and the extracts were analyzed for amphetamines, opiates, cocaine, cannabinoids, and PCP by ELISA assays (Immunalysis Corp, Pomona, CA). Gas chromatography–mass spectrometry (GC–MS) confirmations were made following procedures modified from Le *et al*.[8]

To arrive at the agreement values between meconium and cord screening data it was necessary to determine cutoff values for the umbilical cord screening assays. This was carried out by using receiver-operating characteristic (ROC) plots to assign a screening cutoff value for amphetamines, opiates, cocaine, and cannabinoids.[9]

Results

A total of 118 paired samples of umbilical cord and meconium were obtained. For the umbilical cord specimens, ROC plots were generated for amphetamines, opiates, cocaine, and cannabinoids, but could not be constructed for PCP because no PCP-positive samples were detected during this study. From the ROC plots, cutoffs were chosen that yielded the best sensitivity and specificity for each drug screening assay and these cutoffs then yielded the cord data for the agreement tables with meconium.

The agreement between results of cord and meconium testing ranged from 90.7 to 100% concordance, with sensitivity ranging from 75 to 95.24% where calculations were possible, and specificity from 91.18 to 100% where meconium samples were considered the *Gold Standard*. For instance, as shown in Table 1, 21 meconium samples screened positive for amphetamines while 20 of the matched umbilical cords also screened positive. Of the 97 meconium samples that screened negative for amphetamines, 94 of the matched cords also screened negative, but three screened positive. The three samples screening as positive for amphetamines in cord, but negative in meconium, were confirmed as methamphetamine-positive specimens using GC–MS. We observed 94.9% concordance for opiates, 99.2% concordance for cocaine, 90.7% for cannabinoids.

Table 1 Agreement between paired meconium (MEC) and umbilical cord (UC) specimens in drug screening assays

Amphetamines	MEC	
	+	−
UC	+20	3
	−1	94
	Agreement = 96.6%	
	Sensitivity (95% CI): 95.24 (76.18, 99.88)	
	Specificity (95% CI): 96.91 (91.23, 99.36)	
Opiates	MEC	
	+	−
UC	+7	4
	−2	105
	Agreement = 94.9%	
	Sensitivity (95% CI): 77.78 (39.99, 97.19)	
	Specificity (95% CI): 96.33 (90.87, 98.99)	
Cocaines	MEC	
	+	−
UC	+3	0
	−1	114
	Agreement = 99.2%	
	Sensitivity (95% CI): 75.00 (19.41, 99.37)	
	Specificity (95% CI):100.00 (96.82, 100.00)	
Cannabinoids	MEC	
	+	−
UC	+14	9
	−2	93
	Agreement = 90.7%	
	Sensitivity (95% CI): 87.50 (61.65, 98.45)	
	Specificity (95% CI): 91.18 (83.91, 95.89)	

Discussion

In 1980, Ostrea *et al*.[3] reported tissue distribution of morphine at autopsy of six addicted monkey fetuses and two neonates of drug-dependent mothers. They observed significant drug concentrations in meconium and suggested that meconium screening might be a useful way to detect fetal morphine exposure. Ostrea later reported meconium specimens from 20 neonates of drug-dependent mothers and five control neonates, as analyzed by radio immunoassay for metabolites of heroin, cocaine, and cannabinoids.[4] They reported that meconium of the controls had no drugs detected while that from neonates of drug-dependent mothers invariably showed the presence of at least one drug metabolite. Larger studies followed,

showing that the meconium was a useful way to detect maternal drug use, and that meconium could be positive even if the urine tested negative.[10–14]

Neonatal hair has also been used as a tissue source for detecting fetal drug exposure.[7,14–16] Bar-Oz *et al.* reported a correlation between neonatal hair and meconium concentrations of cocaine, cannabis, and opiates. They found meconium to be slightly more sensitive than hair, but pointed out that collecting meconium may be more acceptable to some parents than cutting hair for testing.[15]

We hypothesized that drug testing could be carried out on umbilical cord tissue. If correct, this might have certain advantages over meconium or hair testing. For instance, cord tissue could be sent for testing immediately after delivery, while for preterm infants sometimes meconium is not passed for several days. Also, fetuses that are stressed often pass meconium *in utero*, making that source unavailable for testing. Testing hair may not be as acceptable to some as is testing meconium or umbilical cord tissue, which are otherwise discarded. Also, for widespread epidemiological testing, obtaining a piece of umbilical cord at delivery might be simpler than collecting meconium or cutting hair, and may be a method better suited to anonymous testing. However, meconium testing might have an advantage over cord testing, if the maternal drug abuse was not suspected at delivery and the cord discarded, yet meconium could still be collected.

Our level of agreement in 118 paired meconium vs umbilical cord samples is similar to the reports comparing meconium vs hair.[14,15,17] Most clinical testing of meconium is carried out with an immunological screening method,[4–6] and false positives can be a problem.[6,17] In the present studies, immunological screening resulted in an area under the ROC plot for amphetamine, opiates, cocaine, cannabinoids greater than 90%, indicating that the umbilical cord screening tests certainly have the ability to distinguish between the presence and absence of drug. GC–MS would be more specific and sensitive than our immunological methods, but they would be much more costly and time consuming.[6,17] When we found samples that were positive for amphetamines in cord tissues, which were negative in the paired meconium, we used GC–MS to resolve the issue of whether the cords gave a false-positive test, or rather, whether the cord was more sensitive than meconium. We observed that in all three cases, the methamphetamine-positive cord samples were confirmed as positive by GC–MS. Therefore, it is possible that umbilical cord tissue is more sensitive than meconium for detecting fetal methamphetamine exposure. Thus, this first study established the feasibility of using umbilical cord specimens for testing of maternal illicit drugs, but future studies will be needed where GC–MS is used for all of the umbilical cord specimens, not just those where a discrepancy between cord and meconium is found. This will be needed to firmly establish cutoff values for the cord specimens.

The question of how recent a maternal drug ingestion must be in order to be detected in meconium, hair, or umbilical cord, has not been settled. Studies of Silvestre *et al.*,[18] using a pregnant rat model, illustrated the complexity of this issue. They observed that the size of the unit dose, the length of drug exposure, and the drug used, were among the variables influencing the drug concentration in meconium. Indeed, whether any given drug of abuse is detectable in meconium longer than it is in umbilical cord or hair is not completely clear. Drugs that are concentrated in bile might likely have higher levels in meconium than in nongastrointestinal tissues. Perhaps these drugs would be detectable in meconium longer than in umbilical cord or hair. For drugs that are not concentrated in bile, perhaps meconium, hair, and umbilical cord would have roughly equivalent concentrations, and would be similarly sensitive to distant exposure.

In this study, we demonstrated the feasibility of using umbilical cord tissue as a means of assessing fetal drug exposure. We recognize that additional confirmatory testing is needed, particularly for opiates, cocaine, and PCP, since so few of the 118 cases were positive for these. We predict that the cost of performing such studies using umbilical cord segments will be similar to meconium testing, and that laboratories now set up to analyze meconium could do these determinations on umbilical cord tissue. We speculate that umbilical cord testing would sometimes have an advantage over meconium testing because it could generally be sent for analysis sooner than could meconium. Moreover, umbilical cord tissue might be a more suitable screening method of anonymous epidemiologic testing, with fewer inherent problems than with hair or meconium collection, in order to acquire the data needed for the Healthy People 2010 goals of reducing illicit drug use during pregnancy.

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