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Agreement of umbilical cord drug and cotinine levels with maternal self-report of drug use and smoking during pregnancy

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Abstract

Objective—We undertook this study to assess the agreement between fetal umbilical cord drug levels and maternal self-report.

Study Design—Cord samples were collected from 103 placentas after delivery as a sub-project of the larger Pacific Research Center for Early Human Development (PRCEHD) study. These cord samples were then processed to obtain cord lysates and enzyme-linked immunosorbent assay (ELISA) performed for cotinine and illicit drugs. Levels of each of these substances were compared with clinical information.

Results—We found fair agreement between self-reported smoking and cotinine levels (kappa = 0.26 (0.07–0.5)) as well as slight agreement with current drug use and positive drug levels (kappa = 0.19 (−0.05–0.4)). Compared with maternal self-report, sensitivity of cotinine levels was 27% and specificity was 98%. Sensitivity of positive cord illicit drug levels was 32% and specificity was 85%.

Conclusion—Umbilical cords provide another independent measure of maternal drug use and are readily available. To our knowledge, this is the first study to measure cotinine levels in the umbilical cord tissue.

Keywords

Methamphetamines; marijuana; tobacco; ELISA; cocaine; opiates; substance abuse

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Introduction

Maternal illicit drug use continues to be a significant problem, contributing to many obstetrical and neonatal/pediatric complications(1). Many of these complications can be ameliorated by good obstetric care(2–4) and developmental interventions(5, 6), however, it is often difficult to obtain an accurate assessment of maternal drug usage, given the legal and social difficulties women face upon disclosing their drug use. Previous biological means to detect maternal drug use have relied on maternal urine, blood and hair and fetal urine, meconium, and hair. These methods are all limited in their ability to reliably detect drug usage, especially given collection issues and a relatively narrow window of positivity. Conflicting reports exist on the sensitivity and specificity of biologic testing, specifically meconium, vis a vis maternal self-report(7). Clearly better methods are needed to reliably detect maternal drug usage.

Montgomery et al (8)described using a segment of umbilical cord and correlated the values obtained by this means with those obtained with meconium, finding good correlation using mass-spectrometry. In addition, they found that ELISA-based tests (9) can be used to assess fetal exposure to drugs of abuse, with extremely high negative predictive values (>98%) compared with mass-spectrometer.

Many complications of maternal drug usage may be also due to concomitant use of tobacco by the mother. No studies to date have reported this method of umbilical cord testing to confirm and quantify maternal tobacco use.

The aim of this paper was to correlate self-reported drug use during pregnancy with umbilical cord ELISA of five drugs of abuse in addition to quantifying cotinine levels, a stable metabolite of nicotine.

Methods

Sample collection

Cord samples were collected as a subproject of the larger Pacific Research Center for Early Human Development study (PRCEHD). PRCEHD is a cohort study, which banks de-identified placental and blood samples from women at delivery, and links these samples with a database of prenatal, delivery and infant outcome information derived from medical record data. Approval was obtained from the University of Hawaii Institutional Review Board for the subproject as well as Western IRB for the larger PRCEHD study. Informed consent was obtained from the women for participation in the larger PRCEHD study. The subproject was deemed exempt as the clinical information and tissues were de-identified. 10-cm portions of each cord were collected from each placenta within 8 hours of delivery, rinsed with phosphate-buffered saline and frozen at −80 degrees c until processing.

Subjects

Women were identified as drug users if they either self-reported drug use during the course of their prenatal care or if they had a positive toxicology screen at any time during pregnancy. Screening for substance abuse was done by the treating physician, the admitting

resident and the admitting nurse, and was noted in the prenatal record, which was then downloaded into the database. Women were classified as smokers if they admitted to smoking within a week of delivery. Controls were chosen randomly from the women in the database with no noted pregnancy complications or substance use.

Processing of Umbilical Cord Tissue Samples

Prior to use, tissue pieces were thawed, wet weight recorded and tissues homogenized 1:4 (w:v) in Tris-HCl buffer containing 5 mM $MgCl_2$ and 2 mM PMSF (pH 7.4). Homogenization was performed using a mechanical T10-Basic Laboratory Homogenizer at 6,500 RPM for ~30 sec per sample (IKA Labortechnik, Wilmington, NC). After processing, whole umbilical lysates were aliquoted (8–10 aliquots/sample) then stored frozen at −80 °C until analysis. Immediately prior to assay, umbilical cord lysates were thawed and measured for protein content using the Bicinchoninic acid method with Bovine Serum Albumin (BSA, free fatty acid fraction V, Sigma Chemical Co. St Louis, MO) as a the standard (10).

Detection and quantification of Cotinine, Amphetamine and Methamphetamine in umbilical cords

All umbilical cord samples were assayed by blinded bench scientists using only 4-digit numbers as identifiers. Each patient sample was quantified in triplicate using commercial ELISA kits for cotinine and methamphetamine as per the manufacturer's instructions (Immunalaysis, Pomona, CA). Spectral detection was performed at $\lambda = 450$ and 650 ± 2 nm (SpectraMax Plus, Molecular Devices, Sunnyvale CA).

Cotinine levels in umbilical cords were quantified by comparison to a standard curve of cotinine (0, 5, 10, 25, 50, 100, 500 ng/mL) supplied by the manufacturer (Immunalaysis, Pomona, CA). Standard curves were constructed by fitting sigmoidal dose-response models (4-parameter logistic functions) to pure cotinine standards and interpolating the absorbance units (AU) of unknown samples. Results were subsequently normalized to mg of umbilical cord protein (results expressed as ng cotinine/mL/mg protein) allowing comparison between tissue samples.

Methamphetamine results were quantified using a standard curve of pure d-methamphetamine (Sigma Chemical Co. St Louis, MO) constructed in-house by serial dilution. Standard curves were performed with 7 concentrations, each in triplicate: 1, 5, 10, 25, 50, 75 and 100 ng/mL and within the manufacturer's recommended linear range for the methamphetamine ELISA kit (1–50 ng/mL). Again, the sigmoidal dose-response model was fitted to AU from the methamphetamine standards, then concentrations of unknown samples interpolated. Following quantification, kit results (ng/mL) were normalized to mg of umbilical cord protein (ng/mL/mg protein) to facilitate comparison between tissue samples.

Both assay blanks (buffer used to dilute samples, "0 ng/mL") and true negative samples (synthetic urine negative for the drug, manufacturer supplied) were included in each assay and these negative controls were used alongside the standard curves to assign results. To be considered "Positive" (P), an unknown sample had to satisfy two conditions: each must have AU greater than that of both the assay and true blanks combined:

$$AU\ sample = \left[\left(\frac{AU_{blank} + AU_{negative}}{6}\right) + 3 * S.D.\right] \quad \text{Equation 1}$$

Secondly, unknown samples had to return a quantifiable number derived by interpolation from the standard curve and were above the limit of detection for the curve (1 ng/mL). Samples that met both criteria were termed “Positive” and those results are reported in ng/mL/mg protein. Samples with AU higher than Equation 1 criteria, but which could be quantified (i.e. where sample AU was above the limit of sensitivity of the standard curve at 1 ng/mL) the absorbance reading was not more than 3SD below assay blanks termed “Negative” but were re-assessed on a separate day by a different scientist. Those with AU below the blanks and outside the standard curve were termed “Negative” (N). Additional re-runs were performed for any sample with where the coefficient of variation (CV, Equation 2) for the triplicate was ≥ 15 %.

$$Coefficient\ of\ Variation\ (CV) = \left(\frac{\text{Standard Deviation}}{\text{Mean}}\right) * 100 \quad \text{Equation 2}$$

Qualitative detection of Amphetamine, Cannabis, Cocaine and Opiates in umbilical cords

Because standard curves were not available for these latter four assays, samples were designated “Positive”, “Potential Positive” or “Negative” as follows: triplicate wells for both an assay blank (buffer used to dilute samples) and a true negative (synthetic urine negative for drug, provided by manufacturer) were included in each assay. Kit results were considered valid when both the assay blank and negative control returned absorbance readings with a CV ≤ 15 %. To be considered “Positive” an unknown sample had to return an absorbance reading of greater than three SD above the average absorbance of assay and true blanks combined (n = 6 wells, equation 1 above).

Since the SD for triplicates averaged less than 5% for all ELISAs, a high degree of precision and accuracy for the assays was inferred. This allowed us to use a very stringent measure for assigning positive results, namely Average AU + 3 SD which vastly reduces false positive (Type I statistical error). However; since Average + 3 SD is such a stringent measure, any “Negative” patient samples with absorbance greater than 2 SD from the negative control averages were called “likely negative” but were repeated on a separate day by a different scientist. This was in an attempt to mitigate type II error (false negative) caused by either samples being close to the limit/s of detection of the commercial kits. Whilst we wished to take a conservative position on assigning “positive “ samples without a standard curve (the use of + 3SD and insistence on at least 2 independent confirmations of positive status), we did not wish to artificially exclude any borderline positive samples, so these borderline samples were also re-assayed for stringency. If a second assay confirmed the initial trial, “Positive”, or “Negative” were assigned. Where second results contradicted the first this sample was designated “Potential Positive”.

Statistical Analysis and Model Fitting

All quantitative analysis for ELISAs was performed using Prism 5.0 (GraphPad Prism, San Diego, CA). Standard curves were fitted to a 4-parameter logistic function (Hill Curve, Sigmoidal dose-response with variable slope) and fits were iterated to am maximum of 1000, until the equation best-fit the data by moderately strict criteria (successive fits deviate by less than 0.001%). Goodness of fit was assessed by evaluation of Sy.x., R^2 values and 95% confidence intervals. Standard curves were accepted if the fit converged and when both the negative control (supplied by the manufacturer) and the assay control (blank buffer tissue lysates were made in) returned "zero" readings when they were interolated from the standard curve. For triplicate determinations of any single sample, the CV cutoff was 15% for intra-assay precision for the maximum allowable error. Samples with ≥ 15% CV were automatically re-tested.

Correlation with Maternal Drug Use and Smoking

To arrive at the correlation between self-reported behaviors and umbilical cord values, Cohen's kappa values and 95 % confidence intervals were calculated(11). In addition, sensitivity, specificity, positive and negative predictive value were calculated, comparing maternal self-report with drug cotinine and drug levels. Only those women who admitted use during pregnancy were included in these calculations. Only the confirmed positives were used in these calculations, potential positives were considered negative. Univariate analysis of the characteristics of the cohort were done with t-tests using SAS 9.1 (SAS, Cary, NC).

Results

Characteristics of the full cohort studied have been previously reported(12). Cords from 103 women were processed. Of these women, 28 admitted to using street drugs during the pregnancy, of these 28, 71% were smokers, which decreased to 50% by the time of delivery. Thirty-five women were classified as persistent smokers, meaning smoking within one week of delivery, without other drug use. There were 38 healthy controls, women who denied any smoking, alcohol or drug use on routine screening. See table 1 for characteristics and full results of the cohort. Women in both the smoking and drug groups did not differ in age, but did have significantly higher gravidity and parity.

Correlation of cotinine levels and self-reported smoking

Of the self-reported persistent smokers, 13 (27%) had positive cotinine levels. Only one non-smoker had a positive cotinine level (12.5 mg/ml.mg tissue). The calculated agreement between self-reported smoking and cord cotinine levels was fair (kappa=0.26 95% confidence interval 0.7–0.5). Using self-reported smoking as the "gold standard," the sensitivity is 27%, specificity is 98%, positive predictive value is 93%, and negative predictive value 60%. These results are shown in Table 2.

Street Drugs

Of the 28 women who admitted using street drugs, 9 admitted methamphetamine use in the third trimester, 12 admitted methamphetamine use during pregnancy, but quit before the third trimester, 3 of those women also admitted to marijuana use. Three women had a

history of methamphetamine use, but quit before the current pregnancy. Three women admitted to polysubstance use, including marijuana, methamphetamines and cocaine, and one woman admitted to just cocaine use. Interestingly no women were noted to have used solely marijuana.

Cord analysis

Six cords (5.8%) were positive for either methamphetamine or amphetamine, three cords were possibly positive (1 of 2 tests positive). Eighteen cords (17.5%) were positive for marijuana, with an additional six possibly positive. More cords were positive for meth in the control group than in the drug group, but this difference was not statistically different. Three cords each were positive or possibly positive for cocaine. Tables 2–4 show the results, kappa coefficients, sensitivities, specificities, negative and positive predictive values for all drugs, methamphetamines, and marijuana. No women with possibly positive values had noted a history of drug use. Notably, six women who mentioned other drug use were positive for marijuana, but not their drug of choice.

Discussion

These results show that umbilical cord tissue has a slight to fair correlation with self-reported substance use. We showed that umbilical cord ELISA has different sensitivities for different substances: for example, this test is more sensitive at picking up marijuana than methamphetamine and cotinine. This can be explained by the sensitivity of the kits themselves, which is controlled by the manufacturer and thus not under our control; affinity of drugs to various tissues; the pharmacology of drug distribution; and the characteristics of the kappa statistic, which is dependent on the prevalence of the exposures in question(13).

Umbilical cord tissue consists of a polymatrix of Wharton’s jelly, which is made up of mucopolysaccharides. It contains one vein to carry oxygenated blood and nutrients to the fetus and two arteries carrying deoxygenated blood and fetal wastes back to the placenta. These vessels are lined with endothelia (14). Based on these characteristics, and the very fat-soluble nature of drugs of abuse, the umbilical cord would not be expected to function as a good reservoir of drugs in the way that adipose or brain tissue might. In general, the half-lives of drugs of abuse are very short from as little as 1–2 hours for cocaine up to approximately 24 hrs for marijuana. This means that even in the case of marijuana, which has the longest systemic residence time, the terminal half-life (i.e. complete clearance of drug from the umbilical cord) would occur within 96 – 120 hrs (4 – 5 days). Meaning that unless the pregnant woman ingested the drug of abuse within a few days of birth, quantifying the drug would be difficult and variable. Montgomery et al (8) showed a good agreement with umbilical cord tissue and meconium, but meconium; being comprised of mostly of intestinal epithelia, lanugo, mucus, amniotic fluid, bile, and water, is also very hydrophilic and thus should also be considered a poor matrix for methamphetamines and other drugs of abuse for the same reasons as described above.

In our analysis, cotinine levels showed a better correlation with self-reported smoking than other drug use, which is similar to a report by Derauf et al (15), who showed a good correlation (kappa 0.56) with cigarette smoking and meconium cotinine levels. However, as

we have discussed, the umbilical cord and meconium are relatively hydrophilic so they could be expected to have the same or similar distribution and mean residence times for cotinine, making Derauf et al's conclusions empirically sensible. The real question, however, may not be related to fetal load of drugs at birth, but to quantify the amount of maternal drug use experienced by the fetus. While we did not have any other tissue or serum to run comparisons for these cords, which is a limitation of this paper, several important points in this respect are already known. For example, antipyrine (an amphetamine derivative) is used in placental perfusion experiments as a marker of pure diffusive transport with effectively no barrier (16). Most of the drugs of abuse studied herein (namely amphetamine, methamphetamine, THC and opioids) have similar pharmacokinetic characteristics to antipyrine and would be expected to equilibrate across the placenta and umbilical cord into the fetal system. In contrast, cocaine and cotinine show differing, slightly less fat-soluble profiles. For example, cocaine is transferred across the placenta at only 80% the rate of antipyrine (17) and some studies have suggested that the placenta acts as a depot for cocaine accumulation preventing transfer to the fetus (18). Additionally, previous studies have indicated that while nicotine (again highly fat soluble) is transferred into the fetal compartment up to 5 times the concentration in the maternal blood, cotinine concentrations in the fetal compartment were considerably lower than corresponding maternal serum levels (19). Again, it has been suggested that cotinine adducts the placenta, preventing equilibration of concentrations between maternal and fetal systems. These studies support our current findings regarding cocaine and cotinine levels in umbilical cords. Again, since both the umbilical cord and meconium are on the fetal side of the placenta, we would expect concordance in between both for drug detection, as was presented by Montgomery et al (8) and Derauf et al (15). Unfortunately, particularly for cotinine and cocaine, we conclude that the sensitivity of these tissues as a proxy markers is almost certainly less useful than maternal serum. This was also shown recently for meconium in a similar population (7).

In the current study, umbilical cord tissue seems a good matrix in which to measure marijuana use. This could be due to the fact that marijuana has a long terminal half-life in maternal tissues and a multiphasic elimination profile due to sequestration in fat. Thus, since the placenta presents no barrier to transport, as the THC leaches from maternal fat stores, it would be available for longer to fetal tissues as well.

A limitation of this study was a lack of uniform screening techniques for substance use. This was necessitated by the study design, which relied on de-identified clinical data and biologic specimens from a variety of prenatal care providers. While this may decrease the sensitivity of verbal screening in the study, and it seems that this is the case, as the rate of meth positivity is higher in the control groups than in the drug group, it may increase the generalizability of the study, as the subjects were from a wide array of backgrounds. This high rate of drug positivity in the control group again emphasizes the need for careful screening for substance abuse during pregnancy, using any of a variety of validated screening measures. Another limitation is the lack of information on environmental tobacco and drug exposure, again because of the study design.

A future direction of study will be using umbilical cord tissue as a means of confirming controls in a study of the placental effects of drugs, in which no other confirmatory measures are available. Indeed, based on the rates of detection reported herein, umbilical cord detection is a viable method for detecting the presence of illicit drugs, as the negative predictive values of the test were at least 89% for the main drugs we will be studying, methamphetamine and marijuana. In addition, given known differences in placental transport of cocaine and cotinine to the fetus, it is important to use a fetal tissue (such as umbilical cords, meconium or fetal hair) in order to obtain an accurate depiction of fetal drug exposure. In order to further define this relationship, future studies will center on determining maternal and fetal blood drug levels and comparing these to the levels observed in umbilical cords.

Another interesting finding is the high rate of marijuana positivity, despite low-levels of self-reported marijuana use. Other studies in Hawaii have shown a self-reported marijuana use during the third trimester of pregnancy rate of 0.4 to 4.9% (12, 20). Possible explanations include vast underreporting of direct marijuana use, which is a distinct possibility, and/or unwitting under-reporting of marijuana contact through proximity. During pregnancy, cardiac output is increased by 30% which directly increases pulmonary flow and favors uptake of substances across the alveolar membranes of the lung (21). Hyperventilation, caused by increased progesterone levels and an increase in tidal volume during pregnancy, may also promote the alveolar passage of substances. These physiological changes, in the context of exposure to marijuana smoke; likely mean that during pregnancy women experience much higher uptake of cannabinoids from environmental exposure than non-pregnant women. Additionally, our high positive rate for marijuana exposure in fetuses, if correct, indicates an extremely high level of marijuana use in the Hawaiian population. Indeed, this statement would seem to be confirmed by a multi-center study performed in military personnel, which reported an unusually high rate of methamphetamine and marijuana use in the Hawaiian population (22). This clearly requires further study, as there are few definitive works in the literature on the effects of marijuana in pregnancy including developmental effects of this exposure on fetal and infant brain development.

Conclusion

This is the first study to measure cotinine levels in umbilical cord tissue, and is also the first study to compare findings from umbilical cord tissue with self-reported drug use. Our finding is that umbilical cords are very predictive for drug use (at least 89% for all drugs tested). Further study is needed to compare umbilical cord cotinine levels with maternal and cord serum levels to confirm if this is a viable method to corroborate maternal smoking habits and fetal exposure to second hand smoke. Perhaps the most surprising and troubling finding presented herein was the extremely high rate of marijuana use/exposure in pregnant women in Hawaii. The study was not specifically designed to investigate population trends in drug use, rather to assess the use of umbilical cords as proxy markers of drug use. However, we have presented compelling evidence for a silent epidemic of marijuana use/exposure during pregnancy in Hawaii, which requires urgent and careful further study.

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Table 1

Characteristics of the cohort and test results

	Control n=38		Smoker n=37		p-value vs. control	Drugs n=28		p-value vs. control
Age (SD)	29.3	5.5	30.1	6.5	NS	28.6	5.7	NS
Gravidity (SD)	2.6	1.9	4.6	2.3	p=0.12	5.5	3.4	p=0.0018
Parity (SD)	0.9	1.2	2.7	2	p=0.002	3	2.3	p=0.0002
Smokers (percentage)	0	0%	37	100%		20	71%	
Smoking at delivery	0	0%	35	95%		14	50%	
Cord Positive-cotinine	1	3%	10	27%		3	11%	
Cord Positive-meth	4	11%	0	0%		2	7%	
Potentially Positive-meth	2	5%	1	3%		0	0%	
Cord Positive MJ	7	18%	5	14%		6	21%	
Potentially Positive-MJ	5	13%	1	3%		0	0%	
Cord Positive-Cocaine	0	0%	2	5%		1	4%	
Potentially Positive-Cocaine	1	3%	2	5%		0	0%	

Meth=methamphetamines, MJ=marijuana.

Table 2

Correlation of maternal self-report and cord cotinine levels

Maternal Self Report	Cord Cotinine positive	Number
+	+	13
+	−	36
−	+	1
−	−	54

Kappa =0.26 (0.07–0.5) fair agreement

Sensitivity 27%

Specificity 98%

Positive Predictive Value 93%

Negative Predictive Value 60%

Table 3

Correlation with maternal self-report of any history of drug usage and cord drug positivity

Maternal Self Report	Cord Drug positive	Number
+	+	9
+	−	19
−	+	11
−	−	64

Kappa = 0.19 (−0.05–0.4) slight agreement

Sensitivity 32%

Specificity 85%

Positive Predictive Value 45%

Negative Predictive Value 77%

Table 4

Correlation of maternal self-report and cord drug methamphetamine

Maternal Self Report	Cord Drug positive	Number
+	+	2
+	−	10
−	+	4
−	−	87

K=0.16 (−0.3–0.6) slight agreement

Sensitivity 17%

Specificity 96%

Positive Predictive Value 33%

Negative Predictive Value 89%

Table 5

Correlation of maternal self-report and cord drug marijuana

Maternal Self Report	Cord Drug positive	Number
+	+	3
+	−	3
−	+	15
−	−	82

K= 0.18 (−0.2–0.5) slight agreement

Sensitivity 50%

Specificity 85%

Positive Predictive Value 17%

Negative Predictive Value 96%