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ORIGINAL ARTICLE

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Can umbilical cord testing add to maternal urine drug screen for evaluation of infants at risk of neonatal opioid withdrawal syndrome?

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ABSTRACT

Objective: This study evaluated maternal urine drug screen (UDS) at delivery and umbilical cord drug testing and its association with neonatal opioid withdrawal syndrome (NOWS) diagnosis and severity following opioid exposed pregnancy.

Methods: A retrospective chart review of 770 mother-infant dyads at five birthing hospitals in the United States Appalachian region for a five-year period was performed. Variables of interest included dyad demographics, results of maternal UDS at delivery and umbilical cord drug testing, and three neonatal outcomes: NOWS diagnosis, pharmacologic treatment administered for NOWS, and length of hospital stay (LOS) of the newborn.

Results: Opioid-positivity was between 8.5% and 66.3% based on maternal UDS at delivery or umbilical cord testing. Odds of NOWS diagnosis and increased infant LOS was best associated with opioid detection in maternal UDS alone (OR = 5.62, 95% CI [3.06, 10.33] and OR = 8.33, 95% CI [3.67, 18.89], respectively). However, odds of pharmacologic treatment for NOWS was best associated with opioid detection in both maternal UDS and umbilical cord testing on the same dyad (OR = 3.22, 95% CI [1.14, 9.09]).

Conclusion: Maternal UDS is a better option compared to umbilical cord testing for evaluation of opioid-exposed infants and risk of NOWS diagnosis and increased infant LOS.

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Neonatal opioid withdrawal syndrome (NOWS); neonatal abstinence syndrome (NAS); opioid use disorder (OUD); medication assisted treatment (MAT); opioid-exposed pregnancy; umbilical cord; urine drug screen; perinatology

Introduction

Use of opioids by pregnant women can cause adverse outcomes in the newborn including feeding difficulties, low birth weight, preterm delivery, and neonatal opioid withdrawal syndrome (NOWS) [1–3]. Clinically, symptoms of NOWS may not appear for more than 48 hours following birth, with onset sometimes delayed for up to 5–7 days depending on risk factors such as quantity, duration, timing of use and half-life of the drug [4–6]. Given the difficulty of determining exactly which infants had in-utero opioid exposure and are at risk of NOWS, some institutions have utilized testing of various biological specimens such as urine, meconium, or umbilical cord to establish better understanding of in-utero opioid exposure and risk of adverse maternal and neonatal outcomes [4,6,7]. The use of opioids during pregnancy is rising with one cross-sectional analysis revealing an increase in maternal opioid-related diagnoses by 131% to 8.2 per 1000 delivery hospitalizations between 2011 and 2017 [8]. Due to the rising prevalence of opioid use in pregnancy, some institutions have even adopted a universal drug testing protocol for women as they are admitted to the hospital for delivery [4,6]. Clinician awareness of opioid-exposure at time of delivery is important for determination of which infants should be monitored for NOWS symptoms or could be discharged in the usual time frame.

Currently, there are no formal recommendations from academic societies regarding drug testing of mother-infant dyads at delivery. The American College of Obstetricians and Gynecologists (ACOG) recommends universal screening of pregnant women for substance use at the first prenatal visit after counseling and consent, and the American Academy of Pediatrics (AAP) endorses informed consent for toxicology testing of pregnant women [9,10]. Both

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organizations discuss the need for collaboration between prenatal and pediatric care providers, sharing of drug testing and screening results, and minimizing unnecessary duplication of testing for optimal care of the mother-infant dyad [6]. In a recent paper, the AAP only recommended toxicology testing if results would be helpful in guiding clinical decision-making and if clinical details of the pregnancy are lacking [6].

The objective of this study was to determine correlation of maternal UDS at delivery and neonatal umbilical cord testing results with three neonatal outcomes related to NOWS: NOWS diagnosis, if morphine was required for NOWS treatment, and infant length of hospital stay. A secondary objective was to determine the level of agreement between maternal UDS at delivery and umbilical cord testing for opioid-detection. This study adds to the literature with the unique analysis of paired samples of maternal urine at delivery and umbilical cord.

Methods

Overview and methods of drug testing

This study is a retrospective chart review that utilized a database created and coded by manual extraction from the medical records of mother-infant dyads who delivered at five hospitals in the Southern Appalachian region of the United States during a five-year period. Institutional Review Board (IRB) approval was obtained for the creation of this database. During this time, there were 18,728 deliveries across the five hospitals, with 462 opioid exposed cases and 308 non-opioid exposed control cases identified for study inclusion. Due to high rates of opioid use within our patient population, during the study period, all hospitals switched to a policy of universal UDS for all mothers admitted for labor unless the mother delivered prior to the urine sample being obtained. The UDS was analyzed in-house and included detection of metabolites of the following substances: barbiturates, cocaine, cannabinoids, opioids, phencyclidine (PCP), amphetamines, and benzodiazepines. Additionally, all the affiliated hospitals within the study have a standard practice of testing umbilical cord tissue of infants of all mothers with either positive UDS at delivery, known current or history of drug use, or none or scant prenatal care. The umbilical cord tissue was tested for metabolites of opioids, amphetamines, cocaine, benzodiazepines, barbiturates, PCP, and gabapentin.

Selection of opioid-exposed cases and non-opioid exposed controls

Within the database, opioid exposure was determined by maternal history, CPT code, or documentation of medication assisted treatment (MAT) for opioid use disorder along with maternal UDS results. Non-opioid exposed control dyads were chosen and matched based on delivery year, delivery hospital, maternal age at delivery, maternal marital status, maternal medical insurance, maternal alcohol use (based on patient data from any source), and infant sex. Non-opioid exposed newborns had no known prenatal opioid exposure and no known additional illicit drug exposure based on all available information. The database included infants cared for in both the well-newborn nursery and neonatal intensive care unit. Dyads were excluded if there were multiple infants in the womb during gestation limiting the database to 761 dyads. Finally, an additional 38 cases were excluded that had neither maternal UDS at delivery nor umbilical cord testing performed resulting in a final sample size of 723.

Variables of interest, Finnegan scoring, and morphine administration

Demographic variables analyzed included maternal age, race, and marital status, prenatal care, tobacco use, infant sex, type of delivery, gestational age, birth weight, head circumference, APGAR score at 5 minutes, if the infant received breast milk, and newborn length of hospital stay (LOS). Neonatal outcomes analyzed were NOWS diagnosis, if morphine was required for NOWS treatment, and newborn LOS. NOWS diagnosis was determined based on criteria used at the clinical sites which are one or more of the following: (1) 2 consecutive Finnegan scores of 10, (2) 3 consecutive Finnegan scores of 8, or (3) received morphine for NOWS treatment. Throughout the study period, all nurses in the hospitals included were trained in Finnegan scoring every 2 years.

Morphine administration for NOWS treatment and newborn length of stay (considered both continuously as number of days and dichotomously with a median split at 4 days) were used as measures of NOWS severity. Morphine was the primary drug administered for treatment of NOWS throughout the study period. Morphine administration was performed only after transfer to a single tertiary care center which occurred for any infant with worsening Finnegan scores. Morphine treatment was based on criteria established by the center which included if the infant had greater

than 2 consecutive Finnegan scores of 10. Infants were weaned for Finnegan scores below 7 and based on clinician discretion depending on the clinical status of the infant and the score. All infants were monitored for at least 48 hours after discontinuation of morphine.

Data analysis

Analyses were conducted separately based on detection of opioids in the following groups: (1) dyads with maternal UDS at delivery, (2) dyads with umbilical cord testing, and (3) dyads with both types of testing. This final group of dyads with both types of testing had analyses run separately for a positive result in *either* maternal UDS or umbilical cord testing and for a positive result in *both* maternal UDS and umbilical cord testing. Thus, results are presented for four different testing categories. Analyses were also performed for drugs other than opioids and for buprenorphine and methadone specific metabolites; due to low sample size, this data is presented in the supplemental material.

Odds ratios (OR) were calculated for each of the three neonatal outcomes based on an opioid-positive result within each of the four testing categories. Correlation values using the phi, Φ, statistic (for NOWS diagnosis and if morphine was required) and point biserial correlation, r_{pb}, (for infant LOS as a continuous variable) were also calculated. Using dyads with both types of testing performed, positive and negative agreement between maternal UDS at delivery and umbilical cord was also determined. McNemar's exact significance test was performed to compare opioid-positivity rates between the two testing methods. All data analysis was conducted in IBM SPSS Statistics Application for PC.

Results

Population size and description

Out of 18,728 deliveries, 462 opioid exposed pregnancies and 308 non-opioid exposed controls were selected per inclusion criteria. Of the 723 cases in our study, 79% had a maternal UDS, 49% had umbilical cord testing, and 28% had both types of testing with positive opioid detection rates of 8.5%, 69.6% and 66.3%, respectively (for the latter, this percentage indicates positivity in paired samples of both maternal UDS and umbilical cord). A breakdown of the total number of opioid-exposed cases and non-opioid exposed controls, the number of dyads excluded and within each testing group, and frequency of opioid-positive and negative results can be viewed in Figure 1.

Demographic characteristics of opioid-exposed and non-opioid exposed groups can be viewed in Table 1. Maternal and infant characteristics between opioid-exposed and non-opioid exposed groups were similar; there was no significant difference between maternal race, marital status, prenatal care, or tobacco use during pregnancy. In both groups, most mothers were white, single, received at least some prenatal care, and used tobacco during pregnancy. Infant characteristics were similar for sex, type of delivery, mean gestational age, APGAR at 5 minutes, and if the newborn received breastmilk.

Neonatal outcomes

As shown in Table 2, an opioid-positive test result in maternal UDS or umbilical cord testing significantly increases odds of NOWS diagnosis and increased length of stay beyond 4 days. Compared to opioid-positivity in umbilical cord, opioid positivity in maternal UDS alone yielded stronger correlation with these two outcomes (OR 5.62, 95% CI [3.06–10.33] and OR 8.33, 95% CI [3.67–18.89] for NOWS diagnosis and infant LOS, respectively). Morphine administered for NOWS treatment showed the strongest correlation with opioid-positivity in both maternal UDS and umbilical cord testing on the same dyad (OR 3.22, 95% CI [1.14–9.09]) rather than either test independently.

Measures of agreement

Positive and negative agreement and frequency of opioid-positivity between maternal UDS at delivery and umbilical cord can be viewed in Table 1 of the supplemental material. There was reasonably good negative agreement between the two testing methods and poor positive agreement (97.1% and 12.9%, respectively). Additionally, there was a significant difference in opioid-positivity rates for the two testing methods among paired samples based on McNemar's test ($p < .001$).

Discussion

Few studies have attempted to understand the predictive nature of biological drug testing for NOWS. Wexelblatt et al. published a retrospective cohort study of almost 3000 patients with a maternal UDS at

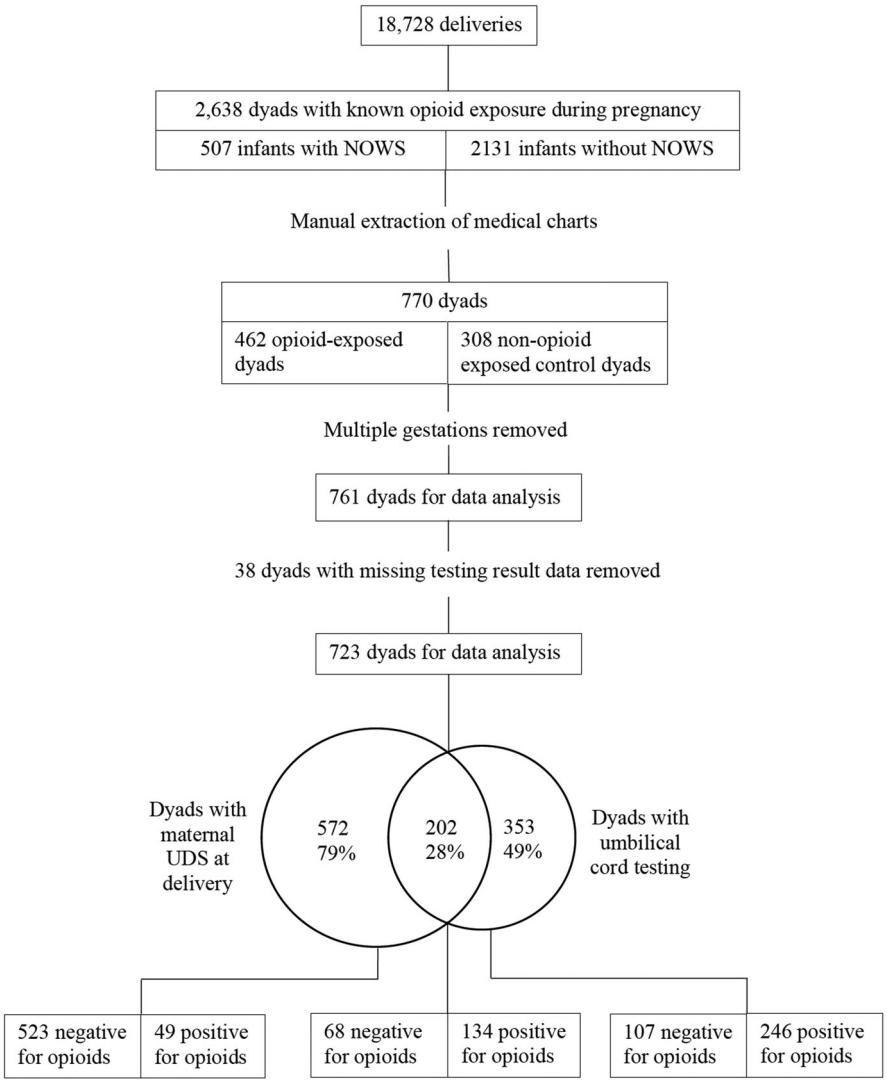

Figure 1. Outline depicting creation of data analysis groups. Number of dyads that had a maternal UDS at delivery, umbilical cord testing, or both were 572, 353, and 202, respectively. Among dyads with both testing types, 134 were positive in at least one testing matrix and 68 were negative in both matrices. UDS: Urine drug screen.

delivery and concluded that this testing method is helpful in the identification of infants at risk of developing NOWS [4]. Their study had an opioid-positive maternal UDS rate of 3.2% compared to 8.5% in our study. Notably, of the pregnant women in the study with an opioid-positive urine drug screen, 20% had a negative risk-based screen making a case for universal testing using maternal UDS [4]. Another recent report showed that 54% of women who either tested positive themselves or their newborn tested positive for an illicit drug did not disclose drug-use before delivery [11].

Although there are many benefits to using maternal urine for biological drug testing such as ease of sample collection and cost, a major limitation is that the window of detection for opioids is only 2–5 days, approximately [12,13]. In contrast, umbilical cord's window of detection is likely several weeks prior to delivery, with some studies suggesting up to 6 weeks of coverage [14]. Umbilical cord drug testing has also been shown to perform as well as meconium testing for evaluation of in-utero drug exposure which historically has been accepted as the gold standard testing method [6,15–25]. In addition, the umbilical cord is present and easily obtained at every delivery, is often un-needed and discarded, and would not produce results complicated by drugs administered to the newborn after birth [26,27].

Our study included 572 maternal UDS and 353 umbilical cord specimens and found greater odds of

Table 1. Maternal and neonatal demographics based on opioid exposure status.

		Non-opioid exposed $N = 296$	Opioid exposed $N = 427$	t or X^2 statistic[d]	p-Value
Mean maternal age (years)[a]		26.0 (3.1)	26.79 (5.0)	−2.077	.02
Maternal race[b]	White	95.9% (282)	97.4% (409)	2.432	.49
	Black	3.1% (9)	1.7% (7)		
	Hispanic	0.0% (0)	0.2% (1)		
	Other[c]	1.0% (3)	0.7% (3)		
Maternal marital status	Married	26.5% (78)	25.8% (108)	1.775	.78
	Single	63.6% (187)	64.2% (269)		
	Divorced	4.8% (14)	5.3% (22)		
	Separated	5.1% (15)	4.3% (18)		
	Widowed	0.0% (0)	0.5% (2)		
Received prenatal care	Yes	97.9% (274)	97.3% (395)	0.220	.64
Tobacco use during pregnancy	Yes	86.5% (256)	84.5% (361)	0.528	.47
Infant sex	Male	55.4% (164)	55.3% (236)	0.001	.97
	Female	44.6% (132)	44.7% (191)		
Type of delivery	Vaginal	72.3% (214)	65.6% (280)	3.652	.06
	Cesarean section	27.7% (82)	34.4% (147)		
Mean gestational age (weeks)		38.8 (1.4)	38.8 (1.3)	−0.026	.50
Mean birth weight (g)		3201.2 (546.2)	3011.1 (452.3)	5.101	<.001
Mean head circumference (cm)		34.0 (1.8)	33.5 (1.5)	2.864	.002
Mean APGAR 5 min		9.0 (0.5)	9.0 (0.5)	0.461	.32
Infant received breastmilk	Yes	59.1% (175)	54.1% (231)	1.792	.18
Mean length of stay (days)		2.1 (1.2)	10.9 (10.4)	−14.601	<.001

[a]Mean (standard deviation) are reported for continuous variables. [b]Percentage of dyads (N value) are reported for categorical variables. [c]Other includes Asian or Pacific Islander or "Other" as listed in electronic medical record. [d]*t*-Statistic is reported for continuous variables and chi-square statistic (X^2) is reported for categorical variables.

NOWS diagnosis and increased infant length of stay for opioid-detection in maternal UDS alone compared to the umbilical cord, although both testing methods did yield significant odds ratios. Our results are in line with a proposed and validated model for NOWS prediction where maternal opioid use within the last 30 days prior to delivery was found to be associated with the development of neonatal abstinence syndrome which is also more likely to yield a positive maternal UDS [28]. Our results are also similar to those of a study by Isemann et al. who showed that need for pharmacotherapy following opioid exposed pregnancy could be predicted by the identification of opioids in maternal UDS and umbilical cord along with symptoms at 36 hours post-birth [29].

Compared to maternal UDS, umbilical cord drug testing has several limitations which limit its clinical utility. These limitations are partly due to our hospitals' use of an outside laboratory for initial testing which incurs greater healthcare costs and increased time for results to be received by the provider. During the period from which data was collected for this study, umbilical cord results were usually received by the provider within 5–7 days. Currently, umbilical cord results are received within 2–5 days compared to 45 minutes for initial UDS results which can be obtained "in-house". Given the limitations of umbilical cord testing, the practical advantages of maternal UDS, and our study results which showed significant correlation between opioid-positive maternal UDS and neonatal outcomes, we suggest that maternal UDS can and should be used to evaluate infants for opioid-exposure and risk of NOWS. Umbilical cord testing, when used in conjunction with maternal UDS results, remains a viable option for confirmatory testing if such testing is needed for other purposes.

Major limitations to this study include its retrospective nature and lack of control for maternal and neonatal comorbid conditions and perinatally administered drugs. Additionally, maternal drug use throughout pregnancy and type of opioid used (i.e. long versus short acting) was neither quantified nor included in the database; thus, there is a lack of understanding of opioid use frequency, duration, and dosage during pregnancy which could contribute to understanding the drug testing results. However, a population-based study has proved that even short-term opioid use can increase risk of NOWS [30]. Thus, our study's wider definition of opioid exposure including all opioids and any mention of opioid use in the maternal history helps to identify all infants at risk of NOWS. Lastly, the authors wish to acknowledge the potential psycho-social implications of drug testing of the mother-infant dyad and agree with the AAP's recommendation to ensure informed consent of the mother prior to drug testing. As our region experienced elevated rates of opioid use, our hospitals instituted universal UDS at delivery to identify infants at risk of NOWS [31]. Across the United States, legislation regarding opioid use during pregnancy is variable, and

Table 2. Association between opioid-positive samples and neonatal outcomes based on maternal UDS and/or umbilical cord testing[d].

	Testing group											
	Dyads with positive maternal UDS at delivery			Dyads with positive umbilical cord testing			Dyads with a positive result in either testing method			Dyads with a positive result in both testing methods		
Neonatal outcomes	*N*	Phi, ϕ or r_{pb}[a]	Odds ratio (CI)[c]	*N*	Phi, ϕ or r_{pb}[a]	Odds ratio (CI)[c]	*N*	Phi, ϕ or r_{pb}[a]	Odds ratio (CI)[c]	*N*	Phi, ϕ or r_{pb}[a]	Odds ratio (CI)[c]
NOWS diagnosis	572	0.33*	5.62* (3.06, 10.33)	353	0.35*	2.58* (1.60, 4.15)	202	0.54*	1.91* (1.03, 3.56)	202	0.17*	3.60* (1.22, 10.66)
Morphine required for NOWS treatment	572	0.11*	2.57* (1.24, 5.32)	353	0.20*	2.56* (1.56, 4.20)	202	0.11	1.97* (0.88, 4.43)	202	0.16*	3.22* (1.14, 9.09)
Infant length of stay[b]	572	0.15*	8.33* (3.67, 18.89)	353	0.20*	6.70* (3.59, 12.49)	202	0.17*	5.12* (2.54, 10.30)	202	0.08	2.34 (0.52, 10.63)

[a]Phi ϕ is used for the dichotomous variables of NOWS diagnosis and morphine required for NOWS treatment; point biserial correlation; r_{pb} is used for the continuous variable of infant length of stay. [b]For r_{pb}, infant length of stay is used as a continuous variable (number of days); for odds ratio calculation, infant length of stay is dichotomous with a median split at 4 days. [c]Indicates the 95% confidence interval. [d]Results of similar data analysis for specific metabolites and for meconium and infant urine are available in the supplemental material. $*p < .05$.

possible punitive action for a mother who tests positive for opioid or non-opioid substances makes toxicology testing a controversial issue [32].

Conclusion

This study adds to the literature on drug testing of the mother-infant dyad for determination of NOWS diagnosis and severity with the unique analysis of paired samples of maternal urine at delivery and umbilical cord. Our findings suggest that maternal UDS is more beneficial for predicting neonatal outcomes related to NOWS compared to umbilical cord testing. Umbilical cord testing may add value when used in conjunction with maternal UDS at delivery, but it is not required for evaluation of opioid-exposed infants unless confirmatory testing is needed for other purposes.

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Disclosure statement

The authors report there are no competing interests to declare.

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