

Risk-Based Newborn Drug Testing in a Setting With a Low Prevalence of Maternal Drug Use

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ABSTRACT

OBJECTIVES: Our objective in this study was to determine the predictive value of an institutional risk-based newborn drug-testing tool for detecting maternal drug use during pregnancy.

METHODS: For 5.5 months, the umbilical cords of all newborns born at the study institution were collected and analyzed at a national reference laboratory. In the context of usual clinical care, the decision to perform newborn drug testing is based on an institutional risk assessment tool. For the cohort without clinical indication for testing, cords were deidentified during the study period. Chart review was not performed. Study data were compared with a national data set during the same time period and to previous institutional data.

RESULTS: We tested 857 newborns, 257 of which had 1 or more identified risk factors. There were no drugs or drug metabolites that were significantly more common in the cohort without risk factors than in the clinical cohort. Alprazolam, methamphetamine, hydrocodone, and oxycodone were all significantly more commonly found in the risk-identified cohort. Amphetamine, methamphetamine, and cocaine were not detected in umbilical cords from any of the 600 newborns that would not have been identified for testing. Tetrahydrocannabinol (1.0%; $n = 6$) was the only illegal substance in the institution's state that would not have been detected.

CONCLUSIONS: Performing universal newborn drug testing in the study population would have identified an additional 6 newborns who were exposed prenatally to tetrahydrocannabinol out of 600 who were additionally tested. In areas with a low prevalence of maternal drug use, universal testing may not be cost-effective.

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The estimated prevalence of maternal drug use during pregnancy is based on maternal self-report but is likely an underestimate because of known underreporting by pregnant women.¹⁻⁴ According to a 2013 national survey of pregnant women in the United States, 5.4% self-reported using illicit drugs, and 9.4% self-reported drinking alcohol.³ Identifying substance-exposed newborns is mandated by federal law under the Child Abuse Prevention and Treatment Act and important to managing the health consequences resulting from the exposure and addressing social needs.⁵

The American College of Obstetricians and Gynecologists recommends all pregnant women be screened for substance abuse using a validated screening tool.⁶ The American Academy of Pediatrics recommends hospitals develop screening policies to detect maternal substance abuse.⁷ Neither organization currently endorses universal testing of biological samples.^{6,7} Without national or federal guidelines, institutions and clinicians must adopt their own policies in compliance with state laws for newborn drug testing.

In this study, we performed universal drug testing of all newborns during a 5.5-month period to determine overall prevalence and compare rates of maternal drug use detected by universal versus risk-based testing. Infants were categorized as “no identified risk” or “at risk” on the basis of an institutional risk assessment tool. The no-identified-risk cohort met none of the risk factors and thus would not have been tested for drugs for clinical purposes. Our hypothesis is that the prevalence of all drug use, including illegal drugs, would be lower in the group not identified for testing compared with the group with an identified risk factor. The institution in this study has historically had a relatively low prevalence of nonmedical drug use compared with published national data.⁸

METHODS

Institutional Description

The study institution is an 811-bed state academic medical center serving as a tertiary- and quaternary-care center with specialty services for high-risk obstetric

care and the largest NICU in the state. By institutional practice, the decision to perform newborn drug screening is based on a risk assessment tool containing 16 items related to maternal, delivery, and newborn risk factors (Table 1). If at least 1 risk factor is present, newborn drug testing is performed. The risk assessment tool was revised in 2014 and used throughout the entire study period. Beginning on August 27, 2013, umbilical cord tissue became the preferred specimen for newborn drug testing at the study institution (replacing meconium), with umbilical cords being collected and stored for all live births. The only exceptions to umbilical cord testing are for neonates transferred from other institutions, where meconium was the specimen instead, to the study institution. Umbilical cords are collected and stored for 2 weeks before being discarded, allowing time for the clinical team to assess risk factors.

TABLE 1 Risk Factors Included in the Institutional Tool for Newborn Drug Testing

Maternal risk factors during pregnancy
Mother tested for drug use during pregnancy
Mother declined drug testing during pregnancy
Unexplained positive drug screen result for mother during pregnancy
Current or previous drug use, including maternal self-report
Altered mental status suggestive of influence and/or withdrawal from drug(s)
Physical signs suggestive of drug use
Previous infant exposure to prenatal drug use
Active alcohol use during current pregnancy
Active tobacco use during current pregnancy
Infection with hepatitis B and/or C, syphilis, or HIV
No, late, and/or poor prenatal care
Placental abruption
Social risk factors
History of domestic violence by current partner
History of child abuse, neglect, and/or previous child protective services involvement
Current incarceration
Neonate risk factors
Signs or symptoms consistent with neonatal withdrawal

Study Protocol Description

This study was institutional review board approved with a waiver of informed consent and deidentification of research subjects. From August 18, 2017 to February 2, 2018, umbilical cords of all newborns ($n = 857$) were analyzed. Umbilical cords undergoing testing for clinical indication (at-risk cohort) were collected and processed according to hospital protocol with no modifications on the basis of this research study. Umbilical cords from neonates who did not meet any risk factors for drug testing (no-identified-risk cohort) would not have been tested for clinical purposes) were retrieved at the point when they normally would have been discarded. The umbilical cords from the no-identified-risk cohort were deidentified completely (including maternal name, neonate name, date of birth, hospital admission dates, and sex) and given arbitrary specimen numbers. No subject identifiers were retained. Deidentification of the no-identified-risk cohort was important given that state law defines nonmedical maternal drug use as child abuse with a mandatory report to child protective services for evaluation.⁹

Umbilical cords were stored and sent in batches to the reference laboratory, with only the principal investigator name, study protocol descriptor, and deidentified specimen number accompanying each specimen. The reference laboratory had no access to any research subject identifiers. Data for the at-risk cohort were retrieved after specimen collection for the no-identified-risk cohort ended. Chart review was not performed for either cohort. An additional 29 at-risk newborns transferred to our institution were tested during the study period by meconium toxicology with identification of 5 instances of nonmedical drug use. Data from neonates who had meconium testing performed are not included in any of the subsequent analysis and discussion.

Routine Umbilical Cord Drug-Testing Analysis

All umbilical cords were sent for analysis at a national reference laboratory (ARUP Laboratories, Salt Lake City, UT). This reference laboratory performs umbilical

cord drug testing for 36 states across the United States, including the study institution's state, which comprised ~5% of the total specimens for umbilical cord drug testing. The umbilical cord toxicology panel used high-performance liquid chromatography–tandem mass spectrometry (LC/MS/MS) for all analytes except tetrahydrocannabinol (THC), for which enzyme-linked immunosorbent assay (ELISA) was used. The panel included qualitative identification by LC/MS/MS of drugs and metabolites for amphetamines and amphetamine-like drugs, barbiturates, benzodiazepines, cocaine, opioids, phencyclidine, and zolpidem (Table 2). All drugs in the testing panel except naloxone are currently controlled substances at the federal level in the United States as defined by the Drug Enforcement Administration. Study data were compared with the national reference laboratory aggregate data set during the same time period and the previously published retrospective data set (August 2013–August 2015) at the study institution.⁸

Additional Drug Analysis

After the prospective study period, the reference laboratory switched THC testing methodology from ELISA to an LC/MS/MS analysis specifically targeting the 9-carboxy metabolite of THC, the same analyte targeted in the meconium testing performed by the reference laboratory. This change also altered the positive cutoff for umbilical cord tissue from 1 ng/g (ELISA) to 0.2 ng/g (LC/MS/MS), although it should be pointed out that direct comparison of cutoffs between the 2 methods is complicated by the cross-reactivity of the ELISA method with the THC parent compound and multiple metabolites. The reference laboratory additionally offered testing for ethyl glucuronide (a marker of ethanol use during pregnancy) by LC/MS/MS subsequent to the study collection period. The LC/MS/MS testing for ethyl glucuronide and the THC metabolite was performed on specimens from both cohorts if sufficient specimen was available (see Table 2 for number of cords tested).

Statistical Analysis

Power calculations for the sample size for the study were based on the previous data

at our medical center showing nonmedical drug use in ~10% of umbilical cord specimens, with testing being performed in nearly 30% of live births.⁸ Using these estimates, the study was powered to detect a 10% difference in drug frequency between the no-identified-risk and at-risk cohorts with α .01 and a power of 0.9. Differences between drugs detected in the no-identified-risk versus at-risk cohorts were tested by Fisher's exact method.

RESULTS

Overall Rates for the Routine Umbilical Cord Drug Panel

During the study period, a total of 857 newborns had umbilical cord drug testing performed, with 257 in the at-risk cohort and 600 in the no-identified-risk cohort. Table 2 shows overall detection rates for all drugs and metabolites analyzed in umbilical cord tissue for this study and includes the positive cutoff values for the various drugs and metabolites. Comparative national data from the reference laboratory over the same time span are provided. A comparison with our previous study of umbilical cord testing using the same institutional protocol is also included (note that this previous study included only neonates who met risk criteria for drug testing).⁸ Table 2 also lists drugs and metabolites not detected in the study cohorts.

Overall, 22.6% of the at-risk cohort tested positive for 1 or more drugs compared with 8.7% of the no-identified-risk group ($P < .001$), with results being consistent with >1 parent drug in 5.8% of the at-risk cohort compared with 1.8% of the no-identified-risk cohort ($P < .005$). The following drugs or drug classes were significantly more prevalent in the at-risk than the no-identified-risk cohort: amphetamines (drug class), methamphetamine, alprazolam, hydrocodone, oxycodone and/or metabolites, and THC by ELISA. There were no drugs or metabolites that were significantly more common in the no-identified-risk cohort than the at-risk cohort. In general, the frequency of drugs and metabolites detected in the cohorts were less than or only slightly exceeded the overall national data at the reference

laboratory. The only exceptions were oxycodone and/or metabolites (5.4% in the at-risk cohort versus 4.7% nationally) and zolpidem (3.5% and 5.8% in the no-identified-risk and at-risk cohorts, respectively, versus 2.1% nationally). The following drugs that were identified as nonmedical use in our previous study of at-risk newborns using the same risk assessment tool and testing strategy ($n = 1035$ in that study) were not identified in any of the cords from the 600 no-identified-risk newborns: amphetamine, methamphetamine, cocaine and its metabolites, alprazolam, clonazepam, diazepam, and tramadol.⁸

Data for Testing for Ethyl Glucuronide and THC Metabolite by LC/MS/MS

After the specimen collection period ended, umbilical cord testing by LC/MS/MS for ethyl glucuronide (cutoff = 5 ng/g) and THC metabolite (cutoff = 0.2 ng/g) became available. Some of the umbilical cords in the current study had sufficient specimen for this additional testing.

In the no-identified-risk cohort, 566 (94.0%) of the 600 umbilical cords had testing for ethyl glucuronide, with 3 (0.6%) testing positive. These 3 specimens were negative for other drugs and metabolites. Testing for THC metabolite by LC/MS/MS was performed in 471 (79%) of the 600 cords, with 20 (4.2%) testing positive. This is higher than the 1.0% frequency that tested positive by ELISA in the entire cohort ($n = 600$).

In the at-risk cohort, 95 (37.0%) of the 257 umbilical cords had testing for ethyl glucuronide done, with 3 (3.5%) testing positive. These 3 specimens were negative for other drugs and metabolites. Testing for THC metabolite by LC/MS/MS was performed in 86 (33.5%) of the 257 cords, with 7 (7.4%) testing positive. This was higher than the 6.6% frequency that tested positive by ELISA in the entire cohort ($n = 257$).

Given that THC metabolite was the most common drug finding in both the study population cohort with 1 or more risk factors present (6.6%) and the reference laboratory national data (18.3%), state-by-state

TABLE 2 Summary of Drugs Detected in At-Risk (Clinical Testing Indicated) Versus No-Risk-Identified Cohort

Drug or Metabolite	Cutoff Concentration, ng/g	Current Study (August 18, 2017–February 2, 2018)				Previous Study (August 27, 2013–August 2, 2015) ^b
		At-Risk Cohort (<i>n</i> = 257), ^a <i>n</i> (%)	No-Risk-Identified Cohort (<i>n</i> = 600), <i>n</i> (%)	Overall Prevalence (<i>n</i> = 857), %	Positive at National Reference Laboratory (All Clients), %	Umbilical Cord Positives (<i>n</i> = 1035), %
Amphetamines						
Methamphetamine	5	3 (1.2)*	0 (0.0)	0.1	3.5	1.0
Amphetamine	5	4 (1.6)*	0 (0.0)	0.5	4.2	1.4
Amphetamine only	5	1 (0.4)**	0 (0.0)	0.1	0.7	0.8
Barbiturates						
Butalbital	25	2 (0.8)	5 (0.8)	0.8	1.5	0.7
Benzodiazepines						
Alprazolam and/or metabolite		3 (1.2)*	0 (0.0)	0.4	1.1	0.2
Alprazolam (parent)	0.5	3 (1.2)*	0 (0.0)	0.4	1.1	—
α-hydroxyalprazolam	0.5	0 (0.0)	0 (0.0)	0.0	0.1	—
Clonazepam and/or metabolite		1 (0.4)	0 (0.0)	0.1	0.6	0.3
Clonazepam (parent)	1	1 (0.4)	0 (0.0)	0.1	0.6	—
7-aminoclonazepam	1	1 (0.4)	0 (0.0)	0.1	0.5	—
Diazepam	1	1 (0.4)	0 (0.0)	0.1	0.6	0.1
Lorazepam	5	0 (0.0)	1 (0.2)	0.1	0.1	0.3
Midazolam	1	0 (0.0)	2 (0.3)	0.2	0.7	0.0
Zolpidem (benzodiazepinelike)	0.5	15 (5.8)	21 (3.5)	4.2	2.1	6.5
Cocaine						
Cocaine and/or metabolites		1 (0.4)	0 (0.0)	0.1	3.5	0.1
Cocaine (parent)	0.5	0 (0.0)	0 (0.0)	0.0	2.7	—
Benzoylcegonine	0.5	1 (0.4)	0 (0.0)	0.1	3.5	—
<i>m</i> -hydroxybenzoylcegonine	1	0 (0.0)	0 (0.0)	0.0	1.8	—
Cocaethylene	1	0 (0.0)	0 (0.0)	0.0	0.2	—
Opioids						
Codeine	0.5	1 (0.4)	0 (0.0)	0.1	1.3	0.7
Fentanyl	0.5	1 (0.4)	4 (0.7)	0.5	2.0	6.4
Hydrocodone	0.5	4 (1.6)*	1 (0.2)	0.5	1.7	0.7
Norhydrocodone	0.5	4 (1.6)*	1 (0.2)	0.5	1.8	N/A ^b
Hydromorphone	0.5	0 (0.0)	2 (0.3)	0.2	0.8	1.1
Methadone and/or metabolite		1 (0.4)	0 (0.0)	0.1	3.1	0.4
Methadone (parent drug)	2	1 (0.4)	0 (0.0)	0.1	3.1	—
EDDP (metabolite)	1	1 (0.4)	0 (0.0)	0.1	3.1	—
Morphine	0.5	10 (3.9)	13 (2.2)	2.7	3.8	3.7
Oxycodone and/or metabolites		14 (5.4)*	12 (2.0)	3.0	4.7	4.1
Oxycodone (parent drug)	0.5	9 (3.5)	9 (2.0)	1.5	2.1	—
Oxymorphone	0.5	0 (0.0)	0 (0.0)	0.0	0.4	—
Noroxycodone	1	9 (3.5)	8 (1.3)	2.0	2.2	—
Noroxymorphone	0.5	5 (1.9)	5 (0.8)	1.2	1.9	—

TABLE 2 Continued

Drug or Metabolite	Cutoff Concentration, ng/g	Current Study (August 18, 2017–February 2, 2018)				Previous Study (August 27, 2013–August 2, 2015) ^b
		At-Risk Cohort (n = 257), ^a n (%)	No-Risk-Identified Cohort (n = 600), n (%)	Overall Prevalence (n = 857), %	Positive at National Reference Laboratory (All Clients), %	Umbilical Cord Positives (n = 1035), %
THC						—
ELISA	1	17 (6.6) ^{***}	6 (1.0)	2.7	18.3	9.0
LC/MS/MS	0.2	7 (7.4) ^c	20 (4.2) ^c	—	21.5	N/A
Ethyl glucuronide	5	3 (3.5) ^{c,*}	3 (0.6) ^c	—	4.6	N/A

EDDP, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; N/A, not available; —, not applicable.

^a Statistically significant compared with no-risk-identified cohort by Fisher's exact test. Compounds that were not detected in the low cohorts but were detected at the national reference laboratory included buprenorphine (frequency 1.4%), buprenorphine glucuronide (frequency 1.8%), norbuprenorphine (frequency 5.3%), dihydrocodeine (frequency 0.4%), meperidine (frequency 0.4%), 6-acetylmorphine (heroin metabolite; frequency 0.5%), naloxone (frequency 0.1%), propoxyphene (frequency <0.1%), tapentadol (frequency <0.1%), tramadol (frequency 0.8%), *N*-desmethyltramadol (frequency 0.7%), *O*-desmethyltramadol (frequency 0.7%), 3-4 methylenedioxyamphetamine or ecstasy (frequency 0.0%), phentermine (frequency <0.1%), midazolam α -hydroxy metabolite (frequency <0.1%), nordiazepam (frequency 0.8%), oxazepam (frequency <0.1%), phencyclidine (frequency <0.1%), phenobarbital (frequency <0.1%), and temazepam (frequency 0.2%).

^b Testing unavailable in the previous published study time period.

^c THC metabolite analysis by LC/MS/MS and ethyl glucuronide could not be performed on all specimens.

* $P < .05$; ** $P < .01$; *** $P < .0001$.

data from the reference laboratory were also analyzed. Table 3 shows data for 33 US states whose umbilical cord drug testing contributed at least 0.1% of the total specimens analyzed by the reference laboratory during the study period. Of the 6 states shown with legalized recreational marijuana use, 4 (Colorado, Nevada, Oregon, and Washington) had the highest percent positivity for umbilical cord testing. Our state had the lowest percent positivity (2.8%) of all states. It is important to keep in mind that these data come from a variety of institutions within the state using varying protocols for selecting newborns for drug testing. Nevertheless, the data do show state-to-state variability in percent positivity.

DISCUSSION

Newborn drug testing is commonly performed by using either meconium or umbilical cord tissue, 2 specimens that are capable of detecting maternal drug use during the third trimester of a term birth. Protocols for determining which newborns to test vary across institutions, with 2 broad strategies being either risk-based or universal testing.^{10–15} Universal newborn drug testing avoids systematic bias (eg, discrimination against racial minorities or lower social economic groups) and can

identify newborns with drug exposure who would be missed by more limited testing protocols. However, universal testing may not be feasible and/or cost-effective for all institutions, especially those with a low prevalence of maternal drug use. In the current study, a risk-based institutional assessment tool was effective in identifying the vast majority of intrauterine exposure to illegal substances at an academic medical center with a historically low prevalence of maternal nonmedical drug use relative to reported national data. This study adds to the existing studies in high-prevalence areas by providing perspective from a low-prevalence setting.^{16,17}

Multiple maternal risk factors associated with nonmedical drug use during pregnancy have been identified in previous studies.^{4,7,18} Known maternal characteristics associated with nonmedical drug use during pregnancy include inadequate prenatal care, known or admitted history of drug use a previous unexplained fetal demise, precipitous labor, placental abruption, hypertensive episodes, severe mood swings, cerebrovascular unintentional injuries, myocardial infarction, and repeated spontaneous abortions.⁷ Per the American Academy of Pediatrics, the presence of 1 of these risk factors is a potential indication for newborn drug testing.⁷ In a previous study at this

institution, 96.9% of cases of maternal nonmedical drug use involved a history of prenatal maternal drug and/or tobacco use, inadequate prenatal care, and/or the presence of certain social risk factors, such as incarceration.¹⁹ Even well-designed risk-based protocols can be limited by factors such as interuser variability and application.

Universal testing may increase because rates of opioid use during pregnancy and neonatal abstinence syndrome (NAS) have dramatically increased.²⁰ Between 2000 and 2009, antepartum maternal opiate use increased nearly fivefold.^{16,20} Between 2000 and 2012, the incidence of NAS increased from 1.2 to 5.8 per 1000 hospital births per year, with Eastern, Southern, Central, and New England states being disproportionately affected.^{16,20} Compared nationally, the incidence of NAS in the study state is notably lower with a rate of 2.2 per 1000 hospital births in 2013.²¹ In response to the opioid epidemic, the Comprehensive Addiction and Recovery Act was signed into law in 2016, removing the term “illegal” to define a substance-exposed newborn and requiring states to develop a Plan of Safe Care for these newborns and families.²² In 2013, Cincinnati-area hospitals adopted universal urine drug testing of pregnant women in response to a significant increase

TABLE 3 Percent Positivity for THC in Umbilical Cord Specimens Analyzed by National Reference Laboratory by State

State	Positivity for Tetrahydrocannabinol in Umbilical Cord Specimens, %	Marijuana Legalization Status During Study Period in This Report (August 2017–February 2018) ^a
Nevada	39.1	Recreational use allowed
Washington	36.4	Recreational use allowed
Oregon	36.3	Recreational use allowed
Montana	35.3	Medical use allowed, recreational use illegal
Colorado	31.8	Recreational use allowed
Wisconsin	31.7	CBD and/or cannabis oil with low THC allowed, recreational use illegal
New Hampshire	29.6	Medical use allowed, recreational use decriminalized
Virginia	25.0	CBD and/or cannabis oil with low THC allowed, recreational use illegal
Texas	25.0	CBD and/or cannabis oil with low THC allowed, recreational use illegal
Georgia	23.2	CBD and/or cannabis oil with low THC allowed, recreational use illegal in most counties, decriminalized in some counties
Minnesota	22.7	Medical use allowed, recreational use decriminalized
Michigan	22.7	Medical use allowed, recreational use legalized in 2018
North Carolina	22.3	CBD and/or cannabis oil with low THC allowed, recreational use decriminalized
Ohio	20.6	Medical use allowed, recreational use decriminalized
Arkansas	20.4	Medical use allowed, recreational use illegal
Idaho	20.0	Illegal
Tennessee	19.7	CBD and/or cannabis oil with low THC allowed
Louisiana	19.1	Medical use allowed, recreational use illegal
Florida	18.6	Medical use allowed, recreational use illegal
Illinois	18.2	Medical use allowed, recreational use decriminalized
Missouri	17.4	Medical use allowed, recreational use decriminalized
Oklahoma	16.9	CBD and/or cannabis oil with low THC allowed, recreational use allowed starting June 2018
Indiana	16.6	CBD and/or cannabis oil with low THC allowed, recreational use illegal
Utah	15.6	CBD and/or cannabis oil with low THC allowed, medical use allowed starting March 2018
South Dakota	14.8	Illegal
Kentucky	14.5	CBD and/or cannabis oil with low THC allowed, recreational use illegal
Wyoming	14.3	CBD and/or cannabis oil with low THC allowed, recreational use illegal
Massachusetts	13.3	Recreational use allowed
California	12.8	Recreational use allowed
New York	11.6	Medical use allowed, recreational use illegal
Alabama	10.4	CBD and/or cannabis oil with low THC allowed, recreational use illegal
West Virginia	5.4	Medical use allowed, recreational use illegal
Iowa	2.8	CBD and/or cannabis oil with low THC allowed, recreational use illegal
All specimens in United States	18.3	Drug Enforcement Administration schedule I (no accepted medical use) at the federal level

^a Adapted from Wikipedia. Legality of cannabis by U.S. jurisdiction. Available at: https://en.wikipedia.org/wiki/Legality_of_cannabis_by_U.S._jurisdiction. Accessed November 15, 2018. CBD, cannabidiol.

in newborns with NAS and a study showing that risk-based testing by using an 8-item maternal screening tool missed 20% of mothers with a positive opioid urine drug screen result.^{13,17} In a recent study of newborns with NAS in Detroit, 26% of mothers in the control group tested positive for drug use.²⁵ In our study, opioids were detected in 13.6% and 5.5% of umbilical

cords in the at-risk and no-identified-risk cohorts, respectively. In the absence of chart review, it is not possible to determine if the opioid had been prescribed and/or the clinical outcome of the newborn. Had clinical signs of withdrawal developed in either the mother or newborn, testing would have been indicated per the risk assessment tool.

The results of our study show that the newborns with no risk factors from the risk-based tool present at our institution comprise a group with consistently lower drug rates in umbilical cord tissue than the cohort with an identified risk factor (or factors). There were no drugs and metabolites that were significantly more common in the no-identified-risk cohort

compared with the at-risk cohort. The 600 no-identified-risk-factor cords contained no positive results for the following drugs identified in our previous study as associated with cases of maternal nonmedical drug use prompting report to child protective services: amphetamine, methamphetamine, codeine, cocaine and its metabolites, alprazolam, clonazepam, diazepam, and tramadol.⁸ Only 1 in 600 was positive for hydrocodone.⁸

One challenge with newborn drug testing is that testing results will not distinguish between legitimate administration and/or use of prescribed medications and nonmedical drug use. It is possible that some of the prescription-controlled substances detected in umbilical cord tissue in the no-identified-risk cohort (butalbital, fentanyl, hydrocodone, hydromorphone, midazolam, morphine, oxycodone, and zolpidem) were from nonmedical use. However, on the basis of our previous study that involved a detailed chart review of neonates with positive umbilical cord drug findings (equivalent to the at-risk cohort in the current study), these particular drugs were explainable in a high percentage of cases by documented prescriptions during pregnancy, with nonmedical use of oxycodone, hydrocodone, and hydromorphone being clearly demonstrated in only 0.1% to 0.2% of the total population.⁸ This low prevalence most likely explains the relatively low prevalence of opioid replacement therapy (eg, methadone and buprenorphine) in the cohorts studied here. Because treatment of an opioid abuse disorder is an indication for testing, it is not surprising that neither methadone nor buprenorphine were detected in the no-identified-risk cohort.

Regardless of maternal intent, identifying newborns exposed prenatally to opioids is important because of the potential for withdrawal. Because results for umbilical cord testing are not immediately available and may not be available until after discharge, this testing may best be used to confirm intrauterine opioid exposure. Confirmation may be especially useful for states such as ours that define child abuse as the detection of a substance in the newborn's body by a medical test.²⁴

Ultimately, the major difference in the study population between risk-based and universal testing was the identification of THC cases in the no-identified-risk cohort. When using ELISA testing for THC with a positive cutoff of 1 ng/g, 1.0% of the no-risk-identified cohort (6 of 600) tested positive. Identification of these missed case patients has clinical relevance because national organizations recommend women be counseled to abstain from THC use while breastfeeding, although data are lacking on the effect of THC use while breastfeeding.²⁵ The decision to test for THC may be influenced by the legal status of marijuana because individual states have enacted varying laws legalizing recreational and/or medicinal use.²⁶

Limitations of our study include conductance at a single academic site with a low prevalence of maternal drug use during pregnancy. Because chart review was not performed, it is not possible to determine if the detection of a prescription medication (or medications) was due to misuse or medical use under the guidance of a licensed health care provider. Additionally, in the absence of chart review, it is not possible to determine the outcome of opioid-exposed newborns.

CONCLUSIONS

In our population with a low prevalence of maternal drug use during pregnancy, the major difference between universal and risk-based testing was the identification of missed cases of THC exposure. Institutions should consider their prevalence of maternal drug use when developing newborn drug-testing practices.

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REFERENCES

1. Forray A. Substance use during pregnancy. *F1000Res*. 2016;5:887

2. Gartner K, Elliott K, Smith M, Pearson H, Hunt G, Martin RE. "People in regular society don't think you can be a good mother and have a substance use problem": participatory action research with women with substance use in pregnancy. *Can Fam Physician*. 2018; 64(7):e309–e316
3. US Department of Health and Human Services; Substance Abuse and Mental Health Services Administration; Center for Behavioral Health Statistics and Quality. *National Survey on Drug Use and Health, 2013*. Ann Arbor, MI: Inter-university Consortium for Political and Social Research; 2015
4. Lester BM, ElSohly M, Wright LL, et al. The Maternal Lifestyle Study: drug use by meconium toxicology and maternal self-report. *Pediatrics*. 2001;107(2): 309–317
5. Child Welfare Information Gateway. Parental drug use as child abuse. 2015. Available at: <https://www.childwelfare.gov/topics/systemwide/laws-policies/statutes/drugexposed/>. Accessed November 1, 2018
6. Committee on Obstetric Practice. Committee Opinion No. 711: opioid use and opioid use disorder in pregnancy. *Obstet Gynecol*. 2017;130(2):e81–e94
7. Hudak ML, Tan RC; Committee on Drugs; Committee on Fetus and Newborn; American Academy of Pediatrics. Neonatal drug withdrawal [published correction appears in *Pediatrics*. 2014; 133(5):937]. *Pediatrics*. 2012;129(2). Available at: www.pediatrics.org/cgi/content/full/129/2/e540
8. Palmer KL, Wood KE, Krasowski MD. Evaluating a switch from meconium to umbilical cord tissue for newborn drug testing: a retrospective study at an academic medical center. *Clin Biochem*. 2017;50(6):255–261
9. IA Stat. §232.77. Juvenile Justice. 2016
10. Concheiro M, Huestis MA. Drug exposure during pregnancy: analytical methods and toxicological findings. *Bioanalysis*. 2018;10(8):587–606

11. Cotten SW. Drug testing in the neonate. *Clin Lab Med.* 2012;32(3):449–466
12. Patrick SW, Schiff DM; Committee on Substance Use and Prevention. A public health response to opioid use in pregnancy. *Pediatrics.* 2017;139(3):e20164070
13. Price HR, Collier AC, Wright TE. Screening pregnant women and their neonates for illicit drug use: consideration of the integrated technical, medical, ethical, legal, and social issues. *Front Pharmacol.* 2018;9:961
14. Wabuye SL, Colby JM, McMillin GA. Detection of drug-exposed newborns. *Ther Drug Monit.* 2018;40(2):166–185
15. Wright TE, Terplan M, Ondersma SJ, et al. The role of screening, brief intervention, and referral to treatment in the perinatal period. *Am J Obstet Gynecol.* 2016;215(5):539–547
16. Patrick SW, Davis MM, Lehman CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009-2012. *J Perinatol.* 2015;35(8):650–655
17. Wexelblatt SL, Ward LP, Torok K, Tisdale E, Meinen-Derr JK, Greenberg JM. Universal maternal drug testing in a high-prevalence region of prescription opiate abuse. *J Pediatr.* 2015;166(3):582–586
18. De Santis M, De Luca C, Mappa I, Quattrocchi T, Angelo L, Cesari E. Smoke, alcohol consumption and illicit drug use in an Italian population of pregnant women. *Eur J Obstet Gynecol Reprod Biol.* 2011;159(1):106–110
19. Wood KE, Sinclair LL, Rysgaard CD, Strathmann FG, McMillin GA, Krasowski MD. Retrospective analysis of the diagnostic yield of newborn drug testing. *BMC Pregnancy Childbirth.* 2014;14:250
20. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. *JAMA.* 2012;307(18):1934–1940
21. Ko JY, Patrick SW, Tong VT, Patel R, Lind JN, Barfield WD. Incidence of neonatal abstinence syndrome - 28 states, 1999-2013. *MMWR Morb Mortal Wkly Rep.* 2016;65(31):799–802
22. Comprehensive Addiction and Recovery Act of 2016, Pub. L. No. 114–198. 130 Stat. 695 (2016)
23. Karunakaran P, February M, Cepeda E. Infants with neonatal abstinence syndrome and their drug dependent mothers compared to matched controls: we have a drug problem. *Pediatrics.* 2018;142(1):179
24. Iowa-Legislature. Juvenile Justice Definitions In. Vol 232.682019
25. Ryan SA, Ammerman SD, O'Connor ME; Committee on Substance Use and Prevention; Section on Breastfeeding. Marijuana use during pregnancy and breastfeeding: implications for neonatal and childhood outcomes. *Pediatrics.* 2018;142(3):e20181889
26. National Conference of State Legislatures. State medical marijuana laws. 2019. Available at: www.ncsl.org/research/health/state-medical-marijuana-laws.aspx#5. Accessed February 25, 2019