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Drug Positivity Findings from a Universal Umbilical Cord Tissue Drug Analysis Program in Appalachia

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Abstract

Background: West Virginia has high rates of opioid-related health crises and deaths that extend to pregnant women and newborns. Our institutional screening approach has included universal umbilical cord tissue drug analysis (UCTDA) since 2013. The objective of this study was to retrospectively report incidence of in utero drug exposure using UCTDA data.

Methods: Two sequential UCTDA data sets (October 2013 to September 2015, and October 2016 to September 2018) represent interrupted epochs given changes in interfaced data availability. UCTDA positivity (by drug class and parent drug) and numbers of drugs detected in each specimen were retrospectively analyzed. THC was removed from the analysis because of discontinuous testing, and 4 opioids were separated from the data set given the potential for both therapeutic and illicit use.

Results: UCTDA specimens that were positive for drugs (22% overall) decreased between Epochs 1 and 2, from 25% to 20%. Increased positivity was noted for hydrocodone (+407%), oxycodone (+240%), amphetamines (+506%), and cocaine (+417%). Fentanyl and morphine positivity decreased by 75% and 18%, respectively, whereas buprenorphine detection increased 195%. Most positive specimens (80% overall) had 1 drug present, but specimens positive for 2 to 6 discrete drugs were found.

Conclusion: Universal UCTDA allows for unbiased assessment of drug exposure in infants. With the additional knowledge of therapeutic indications for drug use, UCTDA may allow for analysis of trends in illicit drug use and the impact of interventions to curb neonatal abstinence syndrome.

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SUPPLEMENTAL MATERIAL

Supplemental material is available at *The Journal of Applied Laboratory Medicine* online.

INTRODUCTION

In the 2015–2016 National Survey on Drug Use and Health, 9% of pregnant women admitted to using illicit drugs in the first trimester, 4.8% in the second, and 2.4% through the third (1). Although maternal self-report of drug use is an inexpensive means of estimating likely in utero drug exposure, is easy to collect, and is widely accessible, it also has significant limitations (2–5). Potential psychological, social, and/or legal consequences may influence answers to such surveys and questionnaires, contributing to falsely low estimates of drug use in pregnancy. The American College of Obstetricians and Gynecologists (ACOG) has recommended that universal screening for substance use be performed at the first prenatal visit using validated screening questionnaires (6). However, the questionnaire is new, and there is a paucity of published incidence information derived from its use (7).

Neonatal Abstinence Syndrome

On a national level, reported cases of neonatal abstinence syndrome (NAS) have increased from 0.12% of hospital births in 2000 to 0.58% in 2012 (8). By 2016, data from 23 hospitals suggested estimated NAS incidence at 2% (9) but varied (10). The rate of admissions to the neonatal intensive care unit (NICU) for NAS has also increased, from 0.7% of NICU admissions in 2004 to 2.7% in 2013 (11–13). Given variations in NAS assessment, diagnosis, treatment, and NICU admission practices among healthcare facilities, every exposed infant might not exhibit signs and symptoms consistent with NAS diagnosis (10–13). For these reasons, correlation of NAS evaluations to test results reflecting recent drug exposure can aid the clinical workup (9–16).

As for other states in Appalachia, obstetric and neonatal populations in West Virginia have been disproportionately affected by the opioid epidemic. In 2013, West Virginia had the highest incidence of NAS (3.3% of hospital births) among 28 states studied (9). Meanwhile, the West Virginia University (WVU) Hospital NICU reported NAS incidence of 13.6% as early as 2011; at that time, the institution lacked a consistent drug testing program to pair with the clinical data (17).

Neonatal Drug Testing

Urine and meconium are the most commonly used matrices for detecting intrauterine drug exposures in newborns. Umbilical cord tissue drug analysis (UCTDA) is a recent alternative to testing for drug exposure in the newborn. Although all 3 specimen types involve noninvasive collection processes and have benefits, there are also limitations to each.

Urine-based drug screens can be performed rapidly. Because these screens are performed in most hospital laboratories and reflex to confirmation testing as necessary, presumptive screen results are known by the care team rapidly (i.e., within hours). In addition, a broad array of drug classes can be detected in the urine matrix, with minimal need for processing. However, urine-based screening in newborns is susceptible to poor collection practices (e.g., squeezing urine from diapers or bed pads) and challenged by low specimen volume that prohibits comprehensive testing and reflects short drug-detection windows (i.e., up to 3–5 days), with the potential for specimen adulteration. Moreover, because most urine-based

drug screens are based on immunoassays, the standard limitations associated with this approach apply (2, 3).

Meconium-based drug screens generally have the longest detection windows for involved drugs, allowing for detection of remote and potentially chronic fetal drug exposures (i.e., accumulating since the 20th week of gestation), making them the most sensitive tests on the neonatal testing market. They remain the prominent tool for neonatal drug exposure detections. With the use of mass spectrometry for this testing at most laboratories, drug-specific detections are possible for a broad array of drugs and drug classes. However, turnaround times for testing are generally longer (i.e., days) for meconium-based drug analysis because testing is typically available at reference laboratories and/or rare hospital-based laboratories, and drug extraction steps are necessary for analysis. Among other limitations associated with meconium testing, collection of complete specimens can take days, requiring gradual and repeated collections. Furthermore, variable sample-storage approaches in the interim can compromise the stability of drug targets in the specimens. This factor can delay specimen deployment to the testing laboratory, prolonging turnaround time for analysis and reporting. Meconium can also be unavailable (i.e., passed before delivery or after discharge from the hospital, or not transferred with the newborn from one facility to another). In addition, adulteration, degradation, and/or contamination of recovered meconium specimens is possible (4, 5, 18–20).

UCTDA yields longer drug-detection windows than urine but does not reflect exposures as remote as meconium (i.e., UCTDA likely covers the last 6 weeks of gestation, through labor and delivery) (18–20). Similar to meconium, the testing approach allows for relatively sensitive and specific detection of a broad array of drugs and drug classes. In addition to the simple and noninvasive collection process, specimens are universally available at birth and can speed turnaround of testing and reporting compared with meconium. However, UCTDA is typically performed by reference laboratories and/or rare hospital-based laboratories, with turnaround times on the order of days. As for meconium, UCTDA requires drug-extraction steps before analysis that prolong turnaround. Although specimen rejections and possibilities for external contamination and tampering are relatively few when the umbilical cord is tested, inadequate cleaning and blotting of the specimen and improper storage can result in rejection. Some drugs do not partition well to the umbilical cord tissue compared with meconium in prior studies, but the opposite is also true. Although sensitivities for drug detections are considered lower in UCTDA compared with meconium analysis, some clinical groups have started to adopt UCTDA for newborn drug screening programs given the trade-offs in convenience, specimen availability, and method performance (18–20).

Currently, there are no specific federal guidelines for maternal and newborn drug testing in the United States, and ACOG did not specify direct drug testing among screening options in the 2017 guideline (6). Consequently, most institutions determine whether to test a newborn based on maternal risk assessment and/or clinical signs and symptoms of NAS (16). It is important to note that risk-based maternal testing approaches have been criticized for potential bias and discrimination in administering testing, resulting in an increased risk of missing in utero drug exposures when this approach is used (2–5, 16, 18).

Need for Improved NAS Assessment in West Virginia

In 2010, 19.2% of pregnant women tested positive for drugs and/or alcohol based on umbilical cord tissue samplings among 8 regionally diverse hospitals in West Virginia (21). This report and the rising incidence of NAS admissions in the WVU Children's Hospital (WVUCH) NICU (17) led to the establishment the WVUCH Standard Guideline for Diagnosis and Treatment of NAS, which was implemented in April 2013. One of several strategic approaches of this guideline was the implementation of a universal UCTDA screening program, which provides a unique opportunity to compare putative in utero drug exposures to previously reported figures. Universality was a condition of the program set forth by the WVUCH legal team to proactively prevent claims of disparity or bias in testing practice (22).

Origin of the Study

Shortly after establishing universal UCTDA at WVUCH, 163 specimens (of approximately 1500) submitted for testing in 2014–2015 had positive fentanyl (FEN) results, and 31 specimens from the same group had positive morphine (MOR) results (data not shown). This finding prompted a quality assessment by the NICU, with assistance by the laboratory. In all FEN-positive UCTDA samples, the mother had been administered FEN by epidural, by an intravenous route, or both: 18 cases (11%) received only intravenous FEN, 29 cases (18%) received only epidural FEN, and 116 cases (71%) received FEN via both routes. In 30 of the 31 MOR-positive UCTDA specimens, the mothers received MOR by intravenous, epidural, subcutaneous, or intramuscular routes; for the single exception, MOR was given to the mother 5 months before delivery. These findings prompted design of a summary study of overall UCTDA positivity in the program. The aims of this study were (*a*) to retrospectively report the incidence of in utero drug exposure at WVUCH using the universal UCTDA as the marker of exposure, (*b*) to detail exposure patterns by drug compounds and numbers of discrete drugs found in positive specimens, and (*c*) to compare findings with other reports originating in the region.

MATERIALS AND METHODS

The study was approved by the WVU Internal Review Board.

Institution/Program

The WVUCH Perinatal Center in Morgantown, West Virginia, is the largest in the state, with approximately 1500 deliveries per year. It is a tertiary perinatal center that receives maternal and neonatal transfers from the upper half of the state, including the north and east panhandles. The WVUCH NICU Committee on NAS oversees universal programs for (*a*) maternal urine drug analysis during the first obstetric visit, on admission for delivery, and as additional testing as needed; (*b*) newborn UCTDA; (*c*) standardized NAS scoring (Finnegan system); (*d*) optimized nonpharmacological treatment; and (*e*) score-based pharmacological treatment. The universal UCTDA comprises the sole focus of this study.

Specimens

Segments (15 cm) of umbilical cords were collected and routed to the reference laboratory (ARUP Laboratories) for testing. For newborns transferred to WVUCH and/or outreach clients, available umbilical cord tissue samples were either transferred to WVUCH with the patient or routed to the specimen-processing area by the physician's office and similarly prepared and shipped.

Testing Methods and Results

Drug screening at ARUP was performed using a combination of LC-TOF MS, LC-MS/MS, and ELISA. Results were qualitative. Supplemental Table 1 lists drugs, metabolites, and detection cutoffs included in the original UCTDA, as well as subsequent updates made by the reference laboratory. Metabolites detected with a parent drug in Table 1 and Table 2 were counted as a single positive drug for the purposes of summarization. For example, a report with positive results for buprenorphine (BUP) glucuronide and BUP would only count as a single drug.

For result transmission back to WVU Hospital (WVUH) between 2013 and July 2016, the ARUP interface connected to WVUH's SunQuest laboratory information system (version 6.2) and, in turn, interfaced with the Epic (2014 version) electronic medical record. For results transmitted in July 2016 and beyond, the ARUP interface sent results through Epic Beaker to Epic (2016–2019 versions, with annual updates).

Data Periods or Epochs

Collection of sequential UCTDA results started October 17, 2013; consecutive reports from this date to October 31, 2015, represent Epoch 1. Data from October 1, 2015, to September 30, 2016, are absent, in association with a laboratory information system changeover; sequential reports were not obtainable in a comparative format for an equivalent number of days. Data collected from October 1, 2016, to September 30, 2018, represent Epoch 2. An unavoidable change to the testing profile at the reference laboratory occurred in the 2017–2018 data capture, when the reference laboratory excluded THC from the main UCTDA by the end of February 2018; consequently, THC data are not shown this report.

Statistical Analysis

FEN, MOR, BUP, and methadone (MTD) were separated from remaining drug-positivity data owing to their roles in pain control during labor and delivery (FEN and MOR) and in maintenance therapy for opioid-related substance use disorder (SUD; BUP and MTD). Table 1 includes illicit drugs and prescription drugs with high abuse potential, and Table 2 includes drugs commonly used in labor and SUD.

Excel 2016 (Microsoft Corp) spreadsheets were used for data review, analysis, and graph generation. Incidences of drug exposures were presented as counts and percentages in terms of specimens. Homoscedastic versus heteroscedastic comparisons were used based on F-test results, and *t*-tests (2-tailed) were used to compare grouped summary data ($P < 0.05$ was deemed significant). Percentage changes between Epochs were calculated when >10 positive

findings were found in either Epoch, using the following calculation: [(count, Epoch 2) – (count, Epoch 1)] / (count, Epoch 1) × 100%.

RESULTS

UCTDA Overview and Positivity over Time

Of 6100 total live births at WVUH across both Epochs, 99.2% had UCTDA completed, including 98.6% of 3063 births in Epoch 1 and 99.8% of 3037 births in Epoch 2 (Table 1). Gaps in UCTDA results were typically due to cancellations for specimens that had exceeded stability or were not properly prepared before delivery to the laboratory (data not shown).

Overall, 22% of 6051 specimens submitted to the WVUH laboratory were positive for ≥1 drug. Among positive specimens excluding THC (removed) and FEN, MOR, BUP, and MTD (separated), 665 discrete instances of drug detection were documented. Of drug groups tested, the remaining opioids were most commonly detected (5%), followed by sedatives and hypnotics (3%) and stimulants (3%). The most commonly detected drugs were oxycodone or oxymorphone, amphetamines, hydrocodone, zolpidem, and cocaine.

In Epoch 1, 25% of 3021 specimens had drugs present, with 239 discrete detection events. Sedatives and hypnotics were most commonly detected (4% of specimens), followed by opioids (3%) and stimulants (1%). Zolpidem was the most common drug detected (1.8% of specimens). All other drugs were found in <1% of specimens.

In Epoch 2, 20% of 3030 specimens had drugs present, with 426 discrete detection events. Opioids were most commonly detected (6% of specimens), followed by stimulants (5%) and sedatives or hypnotics (3%). Amphetamines were most commonly detected (3.2% of specimens), followed by oxycodone or oxymorphone (2.8%), hydrocodone (2.5%), and cocaine (2%). All other drugs were found in <1% of specimens.

The detection of stimulants between Epochs increased 430% (F-test, $P = 0.017$; heteroscedastic 2-tailed t-test, $P = 0.098$). Although not statistically significant, these data reflect 506% and 417% increases in the detection of amphetamines (0.6% vs 3.2% of specimens) and cocaine (0.4% vs 2%), respectively. Although rates of opioid positivity were not statistically different between Epochs (F-test, $P = 0.003$; heteroscedastic 2-tailed t-test, $P = 0.184$), hydrocodone positivity increased 407%, oxycodone/oxymorphone positivity increased by 240%, and tramadol positivity decreased by 63%. Zolpidem positivity decreased by 55% between Epochs.

Opioids Used in Labor and Delivery and Sud Maintenance

Opioids commonly used for pain control in labor and delivery – FEN and MOR – were positive in 7.9% of specimens overall (Table 2). FEN positivity decreased by 75% from Epoch 1 (8.8% overall) to Epoch 2 (2.2%), whereas MOR showed a small change (18% decrease). Opioids used for SUD recovery maintenance—BUP and MTD—were positive in 7.1% of specimens overall. BUP positivity increased by 195% from Epoch 1 (3.1% overall) to Epoch 2 (9.2%), whereas MTD showed no change.

Numbers of Drugs Detected in Positive Specimens

Most positive specimens contained only 1 drug (80% in Epoch 1 vs 79% in Epoch 2) or 2 drugs (17% in Epoch 1 vs 15% in Epoch 2; Table 3). Although specimens were present in each data set that had >2 drugs present, they were relatively few. In Epoch 1, the maximum number of drugs present in a given specimen was 4, and 2.9% of positive specimens had >2 drugs present. In Epoch 2, the maximum number of drugs present in a given specimen was 6, and 5.5% of positive specimens had >2 drugs present. These differences were not statistically significant ($P = 0.500$).

DISCUSSION

Among the strengths of this study, the most prominent are the universal approach to UCTDA in the WVUCH program, the large resulting data set, and the analysis of sequential UCTDA results across 2 Epochs. These factors allowed an analysis of trends for prominent illicit and prescribed medications in West Virginia newborns. Limitations of the study included the single institutional cohort, the lack of a comparative study against another matrix (i.e., meconium), and an interruption to data gathering that yielded the 2 sequential Epochs rather than a single sequential cohort. We also did not parse which drugs were found in single vs polydrug exposures owing to the deidentified and retrospective data set analyzed. Despite these limitations, this study still provides an initial retrospective report regarding the impact of the opioid crisis in Appalachia through the lens of possibly the most vulnerable population—new-borns—and points to further opportunities for more detailed analysis.

Overall Drug-Positivity Rates

This report represents the largest cohort of universal UCTDA reported to date, with 6051 specimens tested over 2 Epochs spanning a 5-year period. MOR, FEN, BUP, and MTD were separated from other results given their respective roles in labor analgesia and treatment of SUD (18, 22). Despite this separation, the incidence of positive drug findings in UCTDA demonstrates a near doubling of drugs detected over time. When summed collectively (5% for opioids, 3% for stimulants, and 3% for sedatives/hypnotics), the positivity rate in this cohort was approximately 11%. This rate is similar to the reported rate of NAS in the WVUCH NICU (13.6%) (17), lower than the rate reported in UCTDA for West Virginia in a prior study (19.2%) (21), and comparable to maternal self-report rates (1, 23). In addition, the separated opioids (MOR, FEN, BUP, MTD) were present in 15% of specimens and represent a large number of potentially significant drug exposures among newborns. Given the high rate of opioid use in our geographic region, the medical vs illicit use of these substances begs further investigation.

Notably, over time, some of the detection cutoffs used by the reference laboratory were decreased (Supplemental Table 1 contains all cutoffs, with changes over time). Two examples that coincide with significant shifts in positivity for stimulants in Epoch 2 are amphetamines (from 8 ng/g in 2013 to 5 ng/g in 2016) and cocaine (from 8 ng/g in 2013 to 0.5 ng/g in 2016). These changes could conceivably be the sole reason for the increase in positivity or perhaps a contributor. However, given that the data were deidentified and there is no ability to correlate on a case-by-case basis, the extent to which changes in cutoffs

affected rates is currently unknown. More study of the data set and linkages to maternal data are indicated in future analyses.

Although the current study lacked correlation to meconium, the WVUCH universal testing program deliberately selected UCTDA for clear advantages regarding specimen availability and collection. The costs of parallel testing for so many patients, and for so long, would have prevented implementation, which is likely a greater disservice to patients and caregivers than selecting one testing modality and moving forward. In addition, the idea of randomly selected paired specimen studies was outside of the scope of practice and resource availability for the study. However, despite lacking correlation data from within the current study, UCTDA and meconium testing from the same reference laboratory and in a similar time frame have already been compared and published. Colby reported result agreements of 85% for opioids, 96% for cocaine, and 97% for amphetamines in a paired-specimen analysis of 217 specimen sets from the same reference laboratory. Cohen's j scores varied widely, as did projected sensitivity for UCTDA, which was generally lower in UCTDA than meconium (19). Montgomery et al. reported concordance of 96.6% for amphetamines, 94.9% for opiates, 99.2% for cocaine, and overall agreement ranging from 90.7% to 100% among 118 paired samples of umbilical cord and meconium from the same reference laboratory. Sensitivity in the UCTDA was generally lower than meconium (20). Taken together, the data generated in the current study likely demonstrate adequate capture of the majority of positive specimens in the cord matrix.

A study conducted among 8 West Virginia facilities reported a 19.2% incidence of drug positivity among 759 randomly selected, nonsequential, deidentified, umbilical cord tissue specimens (21); the UCTDA-based exposure rate was 2–3 fold higher than the exposure rates determined by maternal self-report in the same study. However, that study included ethanol biomarkers (5.1% positivity), relied largely on immunoassay-based screening tests, and reported an absence of cocaine and BUP in the findings (21). Removing alcohol biomarkers in that study yields an overall rate (14.1%) that is slightly higher than the overall drug positivity rate noted in the current study, despite differences in the drugs found in each. However, methodological differences and drug-use trends over time and regionally could potentially confound this and other comparisons to some degree.

In 2015 and 2016 Substance Abuse and Mental Health Services Administration (SAMHSA) data, 0.2% and 0.5%, respectively, of pregnant women self-reported cocaine use in the previous month. Amphetamine data were not reported (24). Data herein demonstrated relatively low positivity for amphetamines and cocaine positivity in Epoch 1 that compared relatively well with the survey results but higher rates in Epoch 2. This result is somewhat surprising considering that cocaine was not detected, and methamphetamine was detected only once in a prior 2010 study of 8 facilities across West Virginia (21). In a University of Iowa study, cocaine was found in only 0.1% of umbilical cord tissue and methamphetamine in 1% (16). Clearly, positivity data vary by region, by method of analysis (18–20), and likely by program testing philosop (i.e., risk-based or universal testing policy) (22).

Deaths involving heroin increased significantly in West Virginia between 2014 and 2017, from 163 to 244 (25). However, the incidence of positive UCTDA for heroin metabolite 6-

acetylmorphine (6-MAM) was extremely low (Table 1). Furthermore, the presence of MOR as a heroin metabolite is confounded by medical use in labor and delivery (18). Whether these data truly demonstrate lower incidence of heroin use in the WVUCH pregnant population, discontinued use of heroin during pregnancy given success of medication-assisted therapy in SUD maintenance, or poor sensitivity of the UCTDA specifically for heroin/6-MAM, needs further exploration. A study of UCTDA from the University of Iowa also demonstrated no 6-MAM positivity (16), and although meconium testing could be considered as an adjunct to UCTDA in selected cases in which heroin use is suspected, it too suffers from confounding opioid use in labor and delivery (4, 5, 22).

Opioids Used for Medication-Assisted Therapy or Sud Maintenance

In Table 2, WVUCH data reflect an increase in BUP positivity but no change in MTD positivity. This change was not unexpected. First, there has been a general shift in preference from MTD to BUP for medication-assisted therapy in patients with SUD. In 2013, West Virginia had 4299 patients treated with MTD and 387 with BUP in outpatient treatment facilities (26). By 2017, data reflect that 3109 were treated with MTD and 3539 were treated with BUP in outpatient facilities, and another 1488 were treated with BUP at other facilities (27). Neither study detailed the numbers of pregnant patients among those receiving medication-assisted therapy, but WVUCH data in this article echo the shift toward the use of BUP as a therapy of choice among pregnant patients with SUD in West Virginia. A reason for this is likely linked to data previously reported from WVUCH (17) that demonstrated NAS in 81% of newborns exposed to MTD but only 26% in those exposed to BUP; early SUD management decisions in pregnant patients likely take this finding into consideration in an effort to decrease the risk of NAS in the newborns of patients requiring maintenance therapy.

Opioids Used for Pain Control in Labor and Delivery

FEN positivity decreased from 8.8% to 2.2% overall in the WVUCH cohort in Table 2. Possible reasons include (*a*) decreased use among pregnant women before presentation for delivery, (*b*) better provider awareness of known SUD among pregnant patients in their care, or (*c*) change in general practice with regard to pain control in labor. Although the answer likely relies on a combination of these, the magnitude of the decrease observed in Table 2 is likely weighted toward more controlled clinical use of FEN in the labor and delivery setting, particularly for pregnant patients with SUD.

FEN-related deaths have consistently risen in West Virginia for the duration of the study Epochs (122 in 2014 vs 618 in 2017) (24). Therefore, it is unlikely that the population of pregnant patients with SUD in West Virginia have avoided FEN misuse. However, WVU has had success with implementing an obstetrics-specific arm of its Comprehensive Opioid Addiction Therapy (COAT) program since 2015 (end of Epoch 1). This effort to achieve early clinical capture of pregnant patients with SUD and to establish medication-assisted therapy with BUP or MTD throughout the pregnancy has an as yet unquantified influence over the use of these potentially addicting drugs in the labor suite. Data from SAMHSA show that nearly half of pregnant women using heroin and more than one-third

using nonheroin opioids were receiving medication-assisted therapy. Most were treated in outpatient clinic settings like COAT (23).

Linking these concepts back to matrix and method in terms of determining the “true source” of these drugs in a specimen, the challenge in separating how MOR, FEN, and other opioids were used by or administered to a patient is not limited to one or another facet of testing (i.e., matrix alone, method alone, or a combination of these). No test in current clinical use would clarify the source of these drugs when they are present in clinical specimens. Only review within the clinical context can aid that assessment.

Concern about Polypharmacy

Polypharmacy is the practice of taking multiple drugs—specifically, defined as taking >5 drugs— concurrently. This definition is the same for pregnant and nonpregnant patients, although the consequences of polypharmacy in pregnant women and their newborns remains poorly characterized. In a 2018 study of >9000 women in their first trimester, approximately one-third met the definition of polypharmacy from reported or recorded prescribed drugs, supplements, and/or over-the-counter medications (25). Arguably, any use of illicit drug in addition to prescribed or other known medications will further increase an already appreciable risk of increased morbidity. Consequently, if polypharmacy is redefined for neonatal illicit drug testing as screening returns with >2 drugs present, the data in this article reflect a near doubling in specimens with polypharmacy (Table 3) from Epoch 1 to Epoch 2. This difference did not reach statistical significance, owing to low numbers of cases with >2 drugs present in each Epoch. However, the increase in maximal number of drugs found in a specimen (from 4 to 6) and an increase in the numbers of specimens with multiple drugs present demonstrate new areas of concern and future study. For example, better characterization of health outcomes and/or resource needs for interventional and care services related to these patients should be determined compared with patients with fewer drugs found by UCTDA.

Costs and Consequences of the Universal Testing Program

The ultimate cost efficacy of the WVUCH universal NAS program, of which the UCTDA program is one component, remains to be determined. The universal approach at WVUCH was intended to capture more accurate exposure rates among newborns, to guide the plan of care and management for exposed infants, and to identify mothers with SUD who could gain appropriate access to treatment programs as needed. In this practice, hospital social services personnel are involved in cases of newborns who have positive UCTDA findings and/or NAS, and they report to Child Protective Services (CPS) as deemed necessary for the welfare of the newborn. In many of these cases, maternal SUD is identified before delivery and is 1 of 5 factors that are predictive of reports to CPS (28). Consequently, CPS is often involved in prenatal SUD cases before delivery. Test results collected from both the mother (i.e., urine drug screens with definitive reflex testing) and the newborn (i.e., UCTDA) provide additional information for documenting newborn discharge disposition from the hospital. This information can also aid care planning for the mother herself, when results are received in a timely way. However, because the tests are screens and not confirmations

collected under chain of custody, test results alone are not adequate to prompt a call to CPS. Clinical and social factors are always taken into account (28).

In a 2014 national report, 31% of documented reasons for placing children in foster care related to parental SUD. There are 61% of infants and 41% of older children in foster care for this reason (28). WVUCH data from 2016 to 2018 reported a 93% CPS referral rate for 215 newborn infants with prenatal opioid exposures based on International Classification of Diseases, 10th Revision coding. Of note, the overlap in time and numbers with Epoch 2 of the current study and 188 positive “nontherapeutic” opioid findings therein (Table 1) is corroborative (29). In the CPS referral study cohort, 30% of newborn infants with exposure were placed in foster care, and 36% required pharmacological treatment. Of newborns receiving pharmacological treatment in the cohort, 42% were placed in foster care.

In general, newborn infants who exhibit signs and symptoms of opioid withdrawal and who require pharmacological treatment also require longer lengths of stay in the hospital (10, 16). These factors typically (but not always) allow social services personnel to gather adequate data to inform a report to CPS (28, 29). Among infants with NAS, UCTDA results do usually return in time to enable care team review, given that the length of stay for infants with NAS approaches 2 weeks. However, not all exposed newborns immediately exhibit signs and symptoms of NAS (8, 10–13), and with days needed to turn around results of UCTDA, some newborn infants are unavoidably discharged before data gathering is complete. Whether the results of UCTDA are adequately transferred to CPS after discharge for any given newborn infant being investigated is another question that requires further exploration.

CONCLUSIONS

UCTDA confirmed relatively high positivity rates at WVUCH previously reported in other studies, but it highlighted regional differences in drugs detected; these differences could be a consequence of universal vs risk-based testing approaches. Newborn screening (regardless of matrix) yields positive results for opioids used during delivery and in medication-assisted therapy, which limits differentiation of medical and illicit use in those cases. Increasing in utero exposure of stimulants in the WVUCH cohort warrants further investigation and, potentially, strategic intervention plans. The total costs of universal testing (financial and human) remain to be determined, but increased positivity rates increase clinical interventions that ultimately place a burden on foster and social services in addition to healthcare delivery. There is less understanding about how UCTDA data are or can be used by case workers once a newborn is discharged.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Nonstandard Abbreviations:

ACOG	American College of Obstetricians and Gynecologists
NAS	neonatal abstinence syndrome
NICU	neonatal intensive care unit
WVU	West Virginia University
UCTDA	umbilical cord tissue drug analysis
WVUCH	West Virginia University Children's Hospital
FEN	fentanyl
MOR	morphine
BUP	buprenorphine
WVUH	West Virginia University Hospital
MTD	methadone
SUD	substance use disorder
SAMHSA	Substance Abuse and Mental Health Services Administration
6-MAM	metabolite 6-acetylmorphine
COAT	Comprehensive Opioid Addiction Therapy
CPS	Child Protective Services

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IMPACT STATEMENT

The opioid epidemic continues to evolve in response to the availability of illicit substances and the public health policy designed to treat and diminish substance use. The clinical impact (neonatal abstinence syndrome) and social outcomes (foster care) of maternal substance use have physical, psychological, and financial consequences for society. Unbiased, accurate assessment of trends in substance use are critical to inform effective intervention. This study characterizes a universal assessment of neonatal drug exposure using umbilical cord tissue analysis over a discontinuous 5-year period in a cohort of children in Appalachia. These data illustrate the severity of the problem and the impact of interventional strategies in a population in which drug use is prevalent.

Table 1.

Drugs Detected in Umbilical Cord Tissue Specimens.

	Total *n*	Overall, %	Of drugs, %	Epoch 1 *n*	Overall, %	Epoch 2 *n*	Overall, %	Epoch 1 vs 2 % Change, %
Total UCTDA orders	6051			3021		3030		
Live births	6100			3063		3037		
% Births with UCTDA	99.2			98.6		99.8		
Positive specimens[a]	1357	22		753	25	604	20	−20
Opioids[b]	279	5	42	91	3	188	6	+107
Codeine	23	0.4	3.5	12	0.4	11	0.4	−8
Dihydrocodeine	4	0.1	0.6	2	0.1	2	0.1	NC
Hydrocodone	91	1.5	13.7	15	0.5	76	2.5	+407
Meperidine	12	0.2	1.8	9	0.3	3	0.1	NC
Heroin	6	0.1	0.9	4	0.1	2	0.1	NC
Oxycodone and/or oxymorphone	110	1.8	16.5	25	0.8	85	2.8	+240
Tramadol	33	0.5	5.0	24	0.8	9	0.3	−63
Stimulants	189	3	28	30	1	159	5	+430
Amphetamines	113	1.8	17	16	0.6	97	3.2	+506
Cocaine	74	1.2	11.1	12	0.4	62	2.0	+417
Phentermine	2	<0.1	0.3	2	0.1	0	0.0	NC
Sedatives/Hypnotics	197	3	30	118	4	79	3	−33
Alprazolam	27	0.4	4.1	11	0.4	16	0.5	+45
Butalbital	14	0.2	2.1	11	0.4	3	0.1	−73
Clonazepam	29	0.5	4.4	12	0.4	17	0.6	+42
Diazepam	19	0.3	2.9	11	0.4	8	0.3	−27
Lorazepam	3	<0.1	0.5	3	0.1	0	0.0	NC
Midazolam	16	0.3	2.4	8	0.3	8	0.3	NC
Phenobarbital	8	0.1	1.2	8	0.3	0	0.0	NC
Temazepam	4	0.1	0.6	1	<0.1	3	0.1	NC
Zolpidem	77	1.3	11.6	53	1.8	24	0.8	−55
Total drugs detected[a]	665			239		426		+78

NC, no change.

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[a] Given the retrospective nature of data capture and categorization and the exclusion of THC from the report, the number of positive specimens and the total number of drugs detected are not equal.

[b] Four opioids (FEN, MOR, BUP, and MTD) have been separated and summarized separately in Table 2 given common use for pain control in labor and delivery and SUD maintenance programs.

Table 2.

Breakout of Drugs Commonly Used in Labor and Substance Use Disorder (SUD) Management.

	Total *n*	Overall, %	Epoch 1 *n*	Overall, %	Epoch 2 *n*	Overall, %	Epoch 1 vs 2 Change, %
UCTDA performed	**6051**		**3021**		**3030**		
Opioids commonly used for pain control in labor/delivery							
FEN	333	5.5	267	8.8	66	2.2	−75
MOR	146	2.4	80	2.6	66	2.2	−18
Sum	479	7.9	347	11.5	132	4.4	−62
Opioids commonly used for SUD maintenance							
BUP	375	6.2	95	3.1	280	9.2	+195
MTD	56	0.9	28	0.9	28	0.9	0
Sum	431	7.1	123	4.1	308	10.2	+150

UCTDA, umbilical cord tissue drug analysis; FEN, fentanyl; MOR, morphine; BUP, buprenorphine; MTD, methadone; Overall %, UCTDA positive for the drug in question as a percent of all UCTDA performed for the time period.

Table 3.

Counts and percentages of negative and positive UCTDA and breakouts according to number of discrete drugs identified.

Finding	Total	Overall, %	Epoch 1	Overall, %	Epoch 2	Overall, %
UCTDA performed	6051		3021		3030	
Positive UCTDA	1357	22	753	25	604	20
Of Positive UCTDA						
Number of drugs found	*n*	%	*n*	%	*n*	%
1	1081	80	605	80	476	79
2	221	16	126	17	95	15
3	34	2.5	16	2.1	18	3
4	15	1.1	6	0.8	9	1.5
5	3	0.2	0	0	3	0.5
6	3	0.2	0	0	3	0.5

UCTDA, umbilical cord tissue drug analysis; Overall %, count of the number of drugs in question in umbilical cord tissue samples in positive UCTDA performed.

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