Developmental Disorders and Medical Complications Among Infants with Subclinical Intrauterine Opioid Exposures

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Abstract

The objective was to compare diagnosis rates representing developmental outcomes and medical complications between infants with intrauterine opioid exposures who did not receive pharmacologic treatment for neonatal abstinence syndrome at the time of birth and infants for whom no exposure to substances of abuse were detected. This retrospective, descriptive study included approximately 95% of Hamilton County, Ohio resident births in 2014 and 2015. Universal maternal drug test results, performed at the time of birth, were documented and linked to electronic health records representing pediatric primary and subspecialty follow-up care as well as urgent care, emergency care, and inpatient services provided by Cincinnati Children's Hospital Medical Center through 2017, when all children were at least 24 months old. Diagnosis rates were compared between drug exposure groups using chi-square tests. Among infants born at >34 weeks gestation and without other complex clinical conditions, infants with subclinical opioid exposures (N=473) were more likely than infants with no drug exposures (N=14,933) to be diagnosed with behavioral or emotional disorders (3.0% vs 1.1%, $P=0.0008$), developmental delay (15.6% vs 7.6%, $P<0.0001$), speech disorder (10.1% vs 6.5%, $P=0.001$), or strabismus (3.4% vs 1.0%, $P<0.0001$), and more likely to be exposed to the hepatitis C virus (6.8% vs 0.1%, $P<0.0001$). Increased diagnosis rates among all opioid exposed infants, regardless of withdrawal severity, may warrant the additional allocation of resources for screening and follow-up. Awareness of the increased risk for certain developmental delays and medical conditions is critical to early intervention and treatment supporting improved outcomes.

Keywords: infant/newborn, neonatal abstinence syndrome, follow-up studies, opioids, developmental disabilities, strabismus

Introduction

SEVERE WITHDRAWAL AMONG infants following in utero opioid exposure, also referred to as neonatal opioid withdrawal syndrome or opioid neonatal abstinence syndrome (NAS), has emerged as a national epidemic.¹⁻⁴ However, infants demonstrating the most severe signs of withdrawal and who receive pharmacotherapy represent only a portion of infants who experience intrauterine opioid exposure – approximately 30%–80%.^{5,6} Previous studies have reported increased rates of long-term comorbidities and suboptimal outcomes among children treated for NAS including diagnoses of developmental delay, behavioral and cognitive problems,⁷⁻¹² motor problems,¹³⁻¹⁵ torticollis and plagioce-

phaly,¹⁶ ocular comorbidities,^{17, 18} otitis media,¹⁴ and exposure to the hepatitis C virus (HCV).¹⁹ Risk of poor long-term outcomes among opioid exposed infants who experience less severe withdrawal signs or who do not receive pharmacotherapy has not been well characterized. This may be in part because infants experiencing less severe withdrawal signs are difficult to identify, particularly using risk-based drug screening.

Using universal maternal drug testing, researchers in greater Cincinnati are uniquely poised to characterize outcomes among all opioid exposed infants, including those experiencing severe as well as subclinical withdrawal signs. Universal maternal drug testing at the time of delivery enables the identification of all late pregnancy, opioid exposed

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infants regardless of inpatient withdrawal course.²⁰ Electronic health record (EHR) data containing exposure information are integrated into a regional repository supporting neonatal surveillance of exposures to substances of abuse.^{21,22} The regional repository also integrates pediatric EHR data for regionally born infants who receive subsequent care through the Cincinnati Children's Hospital Medical Center (CCHMC) system.

The primary study objective was to compare diagnosis rates representing developmental outcomes and medical complications between infants with intrauterine opioid exposures who were managed exclusively with nonpharmacologic measures and infants for whom no exposure to substances of abuse was detected. It was hypothesized that despite having less severe withdrawal, these opioid exposed infants would experience higher rates of developmental delay and other complications compared to those with no detected exposures. The secondary objective was to compare diagnosis rates between opioid exposed infants who did receive pharmacologic treatment for opioid withdrawal (NAS) and those with less severe withdrawal.

Methods

Study population

CCHMC is an urban academic medical center and the only children's hospital serving greater Cincinnati. The 629-bed medical center provides pediatric primary and subspecialty care as well as urgent care, emergency care, and inpatient services. Additionally, CCHMC physicians direct newborn care in 13 of the region's delivery hospitals, thereby encountering an overwhelming majority of the county's newborns in the delivery hospital setting.²¹ This retrospective descriptive study includes Hamilton County, Ohio (the county in which CCHMC and the city of Cincinnati are located) resident births from January 2014 through December 2015 who encountered a CCHMC physician during their initial hospitalization at any of the region's delivery hospitals. The Institutional Review Board at CCHMC approved this study and granted a waiver of informed consent.

Universal drug testing and exposure categorization

Late pregnancy exposures to substances of abuse were captured at the time of delivery. Universal maternal urine testing for drug use was implemented prior to the study period in late 2013 and performed for approximately 98% of mothers delivering in regional delivery hospitals.²⁰ Consent for drug testing of urine is obtained during the routine hospital admission process at the time of delivery. Urine samples testing positive with an on-site immunoassay are sent for mass spectrometry confirmation. Final test results are documented in physician billing records using regionally standardized exposure- and withdrawal-related diagnosis codes. In the Cincinnati region, the diagnosis of NAS is used consistently to represent infants who received pharmacologic treatment with a first-line opioid weaning medication, typically methadone, morphine, or buprenorphine.²³ Opioid exposed newborns are assessed using the modified Finnegan Neonatal Abstinence Scoring Tool.²⁴ This widely used tool enables standardized assessment of central nervous system, metabolic, vasomotor, respiratory, and gastrointestinal dis-

turbances to generate a score indicating withdrawal severity. Pharmacologic treatment is initiated when infants receive 3 consecutive Finnegan scores ≥ 8 , or 2 consecutive scores ≥ 12 within a 24-hour period.

For this analysis, exposures were grouped into 4 mutually exclusive categories: (1) No substances detected; (2) Non-opioid substance exposure – intrauterine exposures to substances of abuse (including amphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, and phencyclidine) but no detected opioids; (3) Opioid exposure without NAS – intrauterine exposures to opioids (including short-acting opioids such as heroin or prescription pain medications and long-acting opioids including buprenorphine or methadone) with or without detected exposures to other substances of abuse and for which the infant was exclusively managed with nonpharmacologic measures; (4) Opioid exposure with NAS – severe withdrawal from in utero opioid exposure (with or without detected exposures to other substances of abuse) for which the infant was treated pharmacologically and weaned with opioids. No distinction was made between legal or illicit use in this analysis. Because of the lack of granularity of documentation of the specific type of non-opioid substance exposures detected and the varying effects of the drugs in that category, infants in the non-opioid substance exposures category were excluded from comparative analysis.

Data sets

Data elements captured by physician billing records during the initial neonatal encounter at each delivery hospital were extracted, transformed, and loaded into a regional perinatal repository – the Maternal and Infant Data Hub (MIDH).²¹ Likewise, CCHMC EHR data representing all encounters at each regional inpatient or outpatient facility were loaded into the MIDH and linked to neonatal records using a previously detailed and validated probabilistic and deterministic approach utilizing patient identifier fields.^{21, 25} Once linked, a de-identified data set was produced from the MIDH including substance exposures, demographics, birth characteristics, and diagnoses representing developmental measures and other complications.

Demographic measures included infant race and ethnicity (recoded as: black, non-Hispanic; white, non-Hispanic; other, non-Hispanic; or Hispanic) and insurance provider (recoded as: public or self-pay; or private). Additional birth characteristics including birth weight, gestational age, and sex of each patient were obtained from the delivery hospital encounter records. Length of stay in days for the initial birth hospitalization also was captured, including any transfers between hospitals prior to initial homebound discharge. As times of admission and discharge were unavailable, inpatient days represent distinct calendar dates of hospitalization.

Diagnoses were identified from delivery hospital encounter records and CCHMC EHRs with *International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification* codes. Medical diagnoses having previously reported associations with NAS selected by the study team included: behavioral and emotional disorders (including attention-deficit hyperactivity disorder), developmental delay, sensory processing disorder, speech disorder, motor function developmental disorder, otitis media, torticollis, plagiocephaly, strabismus, and exposure to HCV. As the American Academy

of Pediatrics emphasizes the importance of screening for developmental delays at 24 months of age,²⁶ the study team identified diagnoses assigned at any encounter between January 2014 and December 2017, during which time all cohort members were at least 24 months old.

The MIDH contained records representing 20,868 Hamilton County, Ohio resident newborns during the study period – approximately 95% of the 21,940 county births reported by vital statistics.²⁷ Because of presumable non-generalizable differences in development associated with more severe prematurity, as well as congenital anomalies or complex chronic conditions (eg, sickle cell anemia, cystic fibrosis, diaphragmatic hernia),²⁸ infants born at ≤ 34 weeks gestation ($N=957$), those diagnosed with a complex clinical condition or congenital anomaly ($N=3306$), and those with only non-opioid exposures ($N=1061$) were excluded from analysis.

Analysis

Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC). The study team analyzed patient characteristics according to exposure category using chi-square tests for the categorical diagnosis variables. To confirm previously described associations, the team compared diagnosis rates among those with NAS subsequent to opioid exposure and those with no detected substances. Next, infants in the category of opioid exposure without NAS were compared separately to those without detected substances and those with NAS. Probability values for each test are reported. For each set of tests, significance was determined using the Bonferroni-Holm correction for multiple comparisons using a baseline significance threshold of 0.05.²⁹ Finally, CCHMC provides the largest system of primary care for Medicaid insured children in the region. To limit the effects of loss to follow-up in assigning developmental diagnoses, a sensitivity analysis was conducted using only infants identified as insured by Medicaid or self-pay at the time of birth, who were more likely than privately in-

sured infants to receive primary care through the CCHMC system.

Results

A total of 15,544 infants were included in the study cohort representing 14,933 infants with no detected exposures to substances of abuse, 473 infants with opioid exposures but without NAS, and 138 infants experiencing NAS after intrauterine opioid exposure (Fig. 1). Population demographics and birth characteristics are shown in Table 1.

The first comparison of the NAS group to those with no detected substances confirmed previously reported findings, identifying significant associations in the cohort with NAS group membership and the diagnoses of behavioral or emotional disorders, developmental delay, HCV exposure, motor function developmental disorder, plagiocephaly, sensory disorder, speech disorder, strabismus, and torticollis (Table 2). Diagnosis of otitis media was not found to be associated with NAS in the study population.

In comparison to infants with no detected exposures, those with opioid exposures but no NAS were significantly more likely to be diagnosed with behavioral or emotional disorders, developmental delay, exposure to HCV, speech disorder, and strabismus (Table 3). Opioid exposed infants without NAS were significantly less likely to be diagnosed with developmental delay, exposure to HCV, plagiocephaly, sensory disorder, strabismus, or torticollis than opioid exposed infants who experienced NAS. Compared to infants with no detected exposures the diagnosis of developmental delay was highest among infants with NAS (7.6% versus 28.3%). However, the diagnosis was still twice as likely among opioid exposed infants without NAS (7.6% versus 15.6%). After correction for multiple comparisons, within the sensitivity analysis of 8049 Medicaid insured or self-paying patients, rates were no longer significantly different comparing opioid exposed infants without NAS to infants with no detected exposures for the diagnoses of behavioral or emotional disorders ($P=0.04$) and speech disorder ($P=0.03$).

FIG. 1. Study cohort including exposure categories and exclusions, Hamilton County, Ohio resident births, 2014–2015. NAS, neonatal abstinence syndrome

TABLE 1. DEMOGRAPHICS AND BIRTH CHARACTERISTICS OF THE STUDY COHORT

	<i>No detected exposure</i>		<i>Opioid exposure without NAS</i>		<i>Opioid exposure with NAS</i>	
	<i>N = 14,933</i>		<i>N = 473</i>		<i>N = 138</i>	
Insurance at Birth						
Private; N,%	7397	49.5	73	15.4	2	1.4
Public or self-pay; N,%	7517	50.3	400	84.6	132	95.7
Unknown; N,%	19	0.1	0	0.0	4	2.9
Race and Ethnicity						
Hispanic; N,%	869	5.8	13	2.7	3	2.2
Non-Hispanic black; N,%	3479	23.3	132	27.9	15	10.9
Non-Hispanic white; N,%	5363	35.9	169	35.7	81	58.7
Non-Hispanic other; N,%	3145	21.1	93	19.7	27	19.6
Unknown; N,%	2077	13.9	66	14.0	12	8.7
Birth Characteristics						
Female sex; N,%	7394	49.5	235	49.7	62	44.9
Gestational age weeks; mean, SD	38.8	1.3	38.5	1.4	38.3	1.6
Birth weight grams; mean, SD	3347.7	489.2	3156.3	498.2	3037.7	513.2
Birth hospital length of stay; days, SD	2.6	1.3	3.9	2.5	16.6	7.8

NAS, neonatal abstinence syndrome; SD, standard deviation

Significance of all other associations remained unchanged (data not shown).

Discussion

The study team is unaware of previous studies focusing specifically on diagnoses among opioid exposed infants who did not express severe signs of withdrawal – most likely because of difficulty in identifying these infants without a universal mechanism for maternal drug testing. Many of the diagnoses were less common among infants with less severe withdrawal than among infants with NAS. However, increased detection compared to those with no drug exposures may warrant the additional allocation of resources for screening and follow-up of behavioral or emotional disorders, developmental delay, HCV exposure, speech disorders, and strabismus among all opioid exposed infants regardless of withdrawal severity.

Awareness of the increased risk for complications or delays among all opioid exposed infants is critical as early intervention and treatment support improved outcomes. For example, the American Academy of Pediatrics recommends that all children undergo visual acuity screening by the age of 4, and if available, instrument-based screening may be performed as early as 1–3 years of age. The study data suggest that all opioid exposed children may potentially benefit from earlier visual screening, including screening for eye muscle alignment, leading to earlier initiation of treatment. Standardized screening and developmental testing also may facilitate timely referral to early intervention programs. Finally, HCV is transmitted in approximately 5% of infants exposed to the virus perinatally. However, because antibodies cross the placenta, testing of exposed infants is not immediately informative and is recommended at 18 months of age.³⁰ If not followed closely, many of these children may not receive recommended testing for the virus

TABLE 2. COMPARISON OF DIAGNOSIS RATES BETWEEN OPIOID EXPOSED INFANTS WITH NEONATAL ABSTINENCE SYNDROME AND THOSE WITH NO DETECTED EXPOSURES

	<i>No detected exposure</i>		<i>Opioid exposure with NAS</i>		<i>P value</i>
	<i>N= 14,933</i>		<i>N= 138</i>		
Behavioral or emotional disorder; N,%	171	1.1	8	5.8	<0.0001*
Developmental delay; N,%	1138	7.6	39	28.3	<0.0001*
Hepatitis C exposure; N,%	21	0.1	48	34.8	<0.0001*
Motor function developmental disorder; N,%	215	1.4	7	5.1	0.0004*
Otitis media; N,%	4221	28.3	43	31.2	0.45
Plagiocephaly; N,%	270	1.8	14	10.1	<0.0001*
Sensory disorder; N,%	1095	7.3	29	21.0	<0.0001*
Speech disorder; N,%	964	6.5	19	13.8	0.0005*
Strabismus; N,%	149	1.0	15	10.9	<0.0001*
Torticollis; N,%	322	2.2	12	8.7	<0.0001*

NAS, neonatal abstinence syndrome.

*Statistical significance after Bonferroni-Holm correction for multiple comparisons.

TABLE 3. COMPARISON OF DIAGNOSIS RATES AMONG OPIOID EXPOSED INFANTS WITHOUT NEONATAL ABSTINENCE SYNDROME, OPIOID EXPOSED INFANTS WITH NEONATAL ABSTINENCE SYNDROME, AND INFANTS WITH NO DETECTED EXPOSURES

	<i>No detected exposure</i>		<i>Opioid exposure without NAS</i>		<i>Opioid exposure with NAS</i>		<i>P value^a</i>	<i>P value^b</i>
	<i>N=14,933</i>		<i>N=473</i>		<i>N=138</i>			
Behavioral or emotional disorder; N,%	171	1.1	14	3.0	8	5.8	0.0008*	0.12
Developmental delay; N,%	1138	7.6	74	15.6	39	28.3	<0.0001*	0.0008*
Hepatitis C exposure; N,%	21	0.1	32	6.8	48	34.8	<0.0001*	<0.0001*
Motor function developmental disorder; N,%	215	1.4	13	2.7	7	5.1	0.03	0.18
Otitis media; N,%	4221	28.3	155	32.8	43	31.2	0.03	0.72
Plagiocephaly; N,%	270	1.8	5	1.1	14	10.1	0.23	<0.0001*
Sensory disorder; N,%	1095	7.3	49	10.4	29	21.0	0.01	0.001*
Speech disorder; N,%	964	6.5	48	10.1	19	13.8	0.001*	0.23
Strabismus; N,%	149	1.0	16	3.4	15	10.9	<0.0001*	0.0004*
Torticollis; N,%	322	2.2	6	1.3	12	8.7	0.19	<0.0001*

^aComparison of opioid exposure without NAS and no detected exposure.

^bComparison of opioid exposure without NAS and opioid exposure with NAS.

*Statistical significance after Bonferroni-Holm correction for multiple comparisons. NAS, neonatal abstinence syndrome.

because the time between identification and testing is significant. Although torticollis was identified among infants with severe withdrawal, it may not be present in other opioid exposed infants – possibly because of increased muscle tone among infants who experience severe withdrawal.

There were some notable limitations to this analysis, including limitations inherent to the retrospective study design. Although opioid exposure was identified using universal testing, details of exposure extent and duration were unavailable. Neither did the study team have access to a detailed profile of any polysubstance exposures. Variability in exposure characteristics may contribute to variation in rates of developmental diagnoses and medical complications. It is possible that diagnosis rates underrepresent true incidence of the conditions studied as children lost to follow-up would not have been assigned diagnoses within the CCHMC EHR. To minimize the effects of any potential differential in children lost to follow-up, sensitivity analysis was conducted of Medicaid insured and self-paying patients who were most likely to seek care within the CCHMC system. Although diagnoses of behavioral or emotional disorders and speech disorder were no longer statistically different after correction for multiple comparisons, based upon the small *P* values (<0.05) it is possible those differences would be significant given a larger cohort of opioid exposed infants. Study diagnoses were identified using administrative data without validated clinical chart review. Although the limitations of administrative data derived from EHRs have been well documented, proponents also have described the important role that these data can play in advancing clinical research within that context of known limitations, including supporting epidemiologic surveillance.^{31–33}

The study team plans to validate these initial findings to further characterize risk factors for developmental delays and complications, and to develop a standardized screening schedule for earlier detection and referral of these high-risk infants through enrollment and analysis of a prospective cohort. These efforts are aimed at identifying the best tools and time points for evaluation of opioid exposed infants, which

may extend into school age or beyond. Because of the magnitude of intrauterine exposures on infants, it is critical that these best practices be spread to general pediatricians and integrated into standard well-child care. To facilitate improved care among this population, future research efforts should focus on the analysis of early intervention and school readiness measures and should continue to evaluate pediatric developmental trajectory beyond the first few years of life.

Conclusions

Understanding that all opioid exposed infants, regardless of withdrawal severity, may be at increased risk for long-term medical problems is critical for pediatric providers and policy makers. Improved outcomes for this population may be achieved through targeted screenings and more timely identification of developmental delays and medical complications.

Author Disclosure Statement

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