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Cleft Lip and/or Palate in Infants Prenatally Exposed to Opioids

Kerry Proctor-Williams
East Tennessee State University, williamk@etsu.edu

Brenda Louw
East Tennessee State University, louwb1@etsu.edu

Citation Information

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Kerry Proctor-Williams, PhD, CCC-SLP[1] [iD]
and Brenda Louw, DPhil, SLP[1]

Abstract

Objective: To determine the prevalence and odds ratios for cleft lip and/or palate (CL/P) among infants prenatally exposed to opioids with or without neonatal opioid withdrawal syndrome (NOWS).

Design: This study represents an exploratory, retrospective cohort study design of newborn medical health records from 2011 to 2016.

Setting: Records were drawn from a regional health system located in South Central Appalachia.

Population and Study Sample: The original population yielded 3 cohorts of infants: (1) infants with opioid exposure (OE) but not requiring pharmacological intervention (OE; N = 168); (2) infants with NOWS requiring pharmacological intervention (N = 294); and (3) infants with no opioid exposure (NOE; N = 16 090), the primary comparison group.

Main Outcome: Infants in the NOWS and OE groups showed significantly increased prevalence and odds ratios for CL/P when compared to those in the NOE group.

Results: Prevalence rates per 1000 live births for infants with OE (35.71) and infants with NOWS (6.80) were significantly higher than those for infants with NOE (1.37). Comparison of infants with OE to the NOE group revealed significantly increased odds for CL/P, isolated cleft palate (CP), cleft lip (CL), and cleft lip and palate (CLP) (27.05, 41.81, 19.26, 19.37, respectively; all *P*s < .008). The odds ratios for infants with NOWS compared to the NOE group were significantly higher for CL/P and CP (5.00 and 10.98, respectively; *P*s < .03) but not for CL and CLP.

Conclusion: The results provide additional evidence that prenatal OE should be considered among the critical environmental risk factors that can contribute to CL/P.

Keywords

epidemiology, hard palate, fetal development, palatal development, prenatal development, soft palate, etiology, drug use

Introduction

The United States is experiencing an opioid crisis which has important implications for cleft care. Among those caught in this epidemic are pregnant women, putting their unborn and newborn babies at immediate health risk and at later long-term risk for adverse neurodevelopmental and academic outcomes (Oei et al., 2017; Fill et al., 2018; Benninger et al., 2020). As a result, the serious public health problem of prescription drug use, misuse, and abuse in the United States is emerging as a possible new environmental risk factor for cleft lip and/or palate (CL/P).

Based on the 2015 National Survey on Drug Use and Health (NUSDUH), approximately 91.8 million Americans adults used opioids, 11.5 million illicitly used or misused opioid pain

relievers, 0.8 million used heroin, and 1.9 had an opioid use disorder (Wu et al., 2016; Han et al., 2017). Furthermore, there may be an additional 2.5 million or more individuals not included in the NUSDUH survey who receive legitimate opioid prescriptions but have an opioid use disorder nonetheless (Kolodny et al., 2015).

[1] Department Audiology and Speech-Language Pathology, East Tennessee State University, Johnson City, TN, USA

Corresponding Author:
Kerry Proctor-Williams, PhD, CCC-SLP, Department of Audiology and Speech-Language Pathology, East Tennessee State University, P.O. Box 70643, Johnson City, TN 37614, USA.
Email: williamk@etsu.edu

Over the last decade, prescribed use of opioids such as morphine, hydrocodone, and oxycodone for pain during pregnancy has increased substantially (Bateman et al., 2014; McQueen and Murphy-Oikenen, 2016). Several large-scale studies have found that more than 20% of women fill a prescription for a schedule C pain reliever during pregnancy, even following the addition of warning labels on boxes (Yang et al., 2008; Desai et al., 2014; Raval et al., 2014). Women's illicit use of opioids further adds to the risk of prenatal exposure to the fetus.

Prenatal exposure to opioids and other drugs can have immediate and serious consequences for newborns. For about half of all prenatally drug exposed newborns, this includes a condition now called neonatal opioid withdrawal syndrome (NOWS) by federal agencies such as the US Food and Drug Administration (Jones et al., 2010; Patrick et al., 2020). It was previously called Neonatal Abstinence Syndrome, or NAS, which included withdrawal from drugs other than opioids as well (Patrick et al., 2020). Neonatal opioid withdrawal syndrome includes a constellation of physiological and behavioral characteristics that occur in a newborn infant because of the sudden systemic withdrawal at birth from the drugs, usually opioids, which the mother used during pregnancy (Finnegan et al., 1975; Kocherlakota, 2014; Barfield, 2016). It is important to note that not all prenatally drug exposed infants experience NOWS, but many do experience some withdrawal symptoms and are at-risk, nonetheless.

Accordingly, it does not come as much of a surprise that along with the increasing rates of opioid use during pregnancy, rates of NOWS have also dramatically increased (Davies et al., 2016). Between 2000 and 2009, the incidence of NOWS in the United States increased more than 300%. By 2012, the incidence of NOWS was 5.8 cases per 1000 births and prevalence was 30% to 50% of prenatally opioid exposed infants. Thus, about every 15 minutes in the United States a baby is born who experiences opioid withdrawal and every hour a baby is diagnosed with NOWS (Centers for Disease Control and Prevention, 2013; Patrick et al., 2015; Ko et al., 2016; National Institute on Drug Abuse, 2016; 2019).

Opioids as Teratogens for CL/P

According to Lind et al. (2017), the potential teratogenic effects of opioids during pregnancy are an area of great public health concern given that congenital disorders are serious, often costly, and can cause lifelong challenges. Broussard et al. (2011) and Yazdy et al. (2015) linked opioid use during pregnancy to congenital malformations.

The role of opioids as an environmental teratogen specifically in the development of CL/P has been studied for a number of years. Saxén (1975a) explored the link between maternal influenza, drug consumption and oral clefts in 599 children with oral clefts and matched controls. The conclusion was reached that the drugs, rather than the influenza, were teratogenic agents. In a second study (Saxén, 1975b), associations between drug consumption during pregnancy and children with oral clefts revealed an association between drug use and the birth of children with cleft lip with or without cleft palate. Bracken and Holford (1981) investigated the exposure to prescribed drugs in pregnancy and the association with congenital malformations in a case–control study involving 1427 identified infants and 3001 control cases, respectively. The authors posited that an association existed between prenatal fetal opioid exposure (OE) and CL/P. Bracken and Holford (1981) called for further research on the impact of simultaneous exposure to environmental factors and interactions of the many different substances to which the maternofetal unit could be exposed.

In another cohort study by Thomas (1995) on substance abusing mothers and CL/P in Australia over a 10-year period, it was determined that there was a ten-fold increase in CL/P in comparison to general incidence figures and a very high occurrence of Sudden Infant Death Syndrome. Thomas (1995) pointed out that although there was no evidence that narcotic drugs alone were teratogenic, other environmental factors such as low socio-economic status, low levels of maternal education, suboptimal nutritional status of the mothers, and polysubstance use could lead to an increased risk of structural anomalies. A retrospective cohort study was conducted by Meyer et al. (2015) on 609 opioid dependent pregnant women treated with methadone (n = 248) versus buprenorphine (n = 361) during pregnancy. Two infants had congenital malformations: 1 infant was born with an absent hand to a mother who conceived while being treated with methadone, and 1 infant was born with an isolated cleft palate to a mother who conceived while being treated with buprenorphine.

Recently Lind et al. (2017) conducted a systematic review to evaluate the association between prenatal opioid use and congenital malformations. Of the 68 studies included in the review, 17 studies (10 of 12 case control, and 7 of 18 cohort studies) documented statistically significant positive associations between prenatal opioid use and congenital malformations. Among the 10 case–control studies, clefts and ventricular/atrial septal defects were the most frequently reported specific malformations. However, Lind et al. (2017) concluded that uncertainty remains regarding the teratogenicity of opioids. Results were therefore inconclusive regarding the impact specifically of OE during pregnancy and the impact on the development of CL/P.

Most recently 2 very large retrospective cohort studies were conducted by Mullens et al. (2019) and Danis et al. (2020) to better understand the association between NOWS and CL/P. Mullens et al. (2019) analyzed 11 599 live hospital births in West Virginia University's tertiary care center between 2013 and 2017. Findings indicated a higher prevalence of CL/P in infants with NOWS (6.79 per 1000 live births) as compared to 1.63 per 1000 live births in the general population. Isolated cleft palate (CP) and isolated cleft lip (CL) were significantly more prevalent in NOWS patients compared to the general population and were associated with in-utero OE (Mullens et al., 2019). Danis et al. (2020) used the 2016 nationwide Kid's Inpatient Database to evaluate the associations between NOWS and CL/P in the United States. The data set consisted of 3 769 272 weighted in-hospital births. Danis et al. also determined an

association between NOWS and CL/P, specifically for isolated CP, suggesting that prenatal exposure to opioids may be an environmental risk factor in the development of CL/P. Both these studies call for further research to better characterize this relationship, which is not yet well understood despite the growing body of research.

Rationale and Hypotheses

Motivating the current study, an early research project on Speech-Language Pathology services for infants with NOWS in a Neonatal Intensive Care Unit of the local health system revealed a surprising number of infants with NOWS and CL/P (Bowman et al., 2018). At about the same time, clinical faculty anecdotally reported an increase in infants with prenatal OE or NOWS and submucous clefts at the ETSU Speech-Language Hearing Clinic. Then, the eye-opening publication of Mullens et al. (2019) appeared. Shortly after its publication, we gained access to a large local database that included infants with NOWS, prompting consideration of a population-based replication study. While engaged in data analysis in our study, Danis et al. (2020) published their research and we realized we could extend the findings of the Mullens et al. (2019) and Danis et al. (2020) studies by more specifically describing the sample in 3 ways. First, we defined a novel experimental group: infants prenatally opioid exposed but without NOWS. Second, we confirmed that infants coded as NOWS actually met diagnostic criteria for NOWS. Finally, we focused on infants whose primary prenatal drug exposure was to opioids.

We hypothesized that across CL/P categories, infants with NOWS would have prevalence rates and odds ratios higher than those not exposed to opioids (Mullens et al., 2019; Danis et al., 2020). We had no predictions about infants prenatally opioid exposed but without NOWS.

Methods

Research Ethics

The East Tennessee State University Medical Institutional Review Board reviewed the study protocol, granted ethics approval, and ensured that Health Insurance Portability and Accountability Act regulations were followed. The researchers received only deidentified information.

Research Design

This study represents an exploratory, retrospective, cohort design to examine the prevalence, odds-ratios, demographic, and potentially contributing factors of CL/P in infants with OE or with NOWS.

Population

The Ballad Health System chart review database, which houses electronic health records from the system's delivery hospitals provided the information used in this study. Ballad Health System is an Appalachian regional health care organization that serves communities in Northeast Tennessee, Southwest Virginia, and Southeast Kentucky. For this retrospective study, the extracted database included all newborn records ($N = 18$ 728) from 5-year period (July 1, 2011-June 30, 2016). Of these, 16 597 charts were sufficiently complete for the purposes of the study. Of these, 16 090 infants who were not exposed to drugs, including opioids, comprised the reference group for the study sample.

Study Sample

Infants with NOWS. From this initial database, the medical records of all infants (n = 507) who received an *International Classification of Disease, Ninth Revision* (*ICD-9*) (779.5) or *International Classification of Disease, Tenth Revision* (*ICD-10*) code (P96.1) for NOWS, received a detailed review to confirm prenatal OE and a criterion-based diagnosis of NOWS. Prenatal OE was determined by either a positive maternal urine drug screen and/or report at delivery. The NOWS criteria for pharmacological treatment used in the Ballad Health System was 2 consecutive Modified Finnegan (Jansson et al., 2009) scores of 10. Of the original 507 infants receiving a NOWS *ICD* code, 45 were excluded because their drug exposure did not include opioids or their exposure to opioids was postnatal, rather than prenatal. Thus, the detailed review resulted in identification of 462 infants who were opioid exposed. Of these infants, 294 were identified with NOWS and 168 were not. All infants opioid exposed received an additional code to indicate their status. This resulted in 2 mutually exclusive opioid exposed groups: infants without NOWS and infants with NOWS.

This study sample is unique in the vigilance taken to define the sample. First, it included only infants whose prenatal drug exposure involved opioids. Second, it included only infants *prenatally* opioid exposed. It did not include infants who experienced withdrawal in response to *postnatal* opioid exposure as a result of surgeries (eg, for heart defects, necrotizing enterocolitis, etc). Finally, infants were categorized based on objective criteria recorded in the medical record and not on *ICD* codes alone.

Infants with CL/P. Because the time of record collection spanned the transition from use of *ICD-9* to *ICD-10*, both sets of codes were used to identify the presence of CP, CL, or CLP (see Table 1). In total, the database included 30 infants with CL/P: 22 who were not opioid exposed (NOE); 6 who were opioid exposed but not NOWS; and 2 who were opioid exposed with NOWS.

Potential Confounding Variables

To examine whether it was possible that opioids served as a potential teratogenic agent, other potentially confounding variables available in the database that have known links to CL/P were examined. These fell into 4 categories: demographic

Table 1. *ICD-9* and *ICD-10* Codes Used to Identify Presence of CP, CL, and CLP.

Diagnoses	ICD-9	ICD-10
CP	749.00, 749.01, 749.02, 749.03, 749.04	Q35.1, Q35.3, Q35.5, Q35.9
CL	749.10, 749.11, 749.12, 749.13, 749.14	Q36.0, Q36.1, Q36.9,
CLP	749.20, 749.21, 749.22, 749.23, 749.24, 749.25	Q37.0, Q37.1 Q37.2, Q37.3, Q37.4, Q37.5, Q37.8, Q37.9

Abbreviations: CL, cleft lip; CLP, cleft lip and palate; CP, cleft palate only; *ICD, International Classification of Disease.*

Table 2. Odds Ratios for All Types of CL/P for the OE and NOWS Groups Compared to NOE Group.

Cleft type	n	Odds ratio	95% CI	z	P
Infants with OE					
CL/P	6	27.05	10.82-67.60	7.057	<.0001[a]
CL	3	41.81	10.72-163.10	5.375	<.0001[a]
CP	1	19.26	2.24-165.78	2.694	.0071[a]
CLP	2	19.37	4.21-89.10	3.807	.0001[a]
Infants with NOWS					
CL/P	2	5.00	1.17-21.37	2.173	.03[a]
CL	0	3.64	0.21-63.89	0.884	.38
CP	1	10.98	1.28-94.27	2.184	.029[a]
CLP	1	5.49	0.70-43.01	1.621	.105

Abbreviations: CL, cleft lip only; CLP, cleft lip and palate; CL/P, cleft lip and/or cleft palate; CI, confidence interval; CP, cleft palate only; n, population size; NOWS, neonatal opioid withdrawal syndrome; OE, opioid exposed; p, statistical probability; z, standard deviation.
[a]Significant at *P* < .05.

variables, birth-related variables, maternal health variables, and other drug exposures. The variables related to these categories and available in the database can be seen in Table 2.

Data Analysis

Data analysis was conducted to test the hypotheses. Associations between NOWS and CL/P were quantified by calculating prevalence rates and odds ratios for the reference and study groups: (1) infants not prenatally opioid exposed (NOE); (2) infants opioid exposed, not NOWS (OE); and (3) infants with NOWS requiring pharmacological care (NOWS). Odds ratios were determined using the MEDCALC© online statistical program, version 19.4, Odds Ratio Calculator (Altman, 1991; Sheskin, 2004, as cited in MEDCALC©). As no infants with NOWS had CL, 0.5 was added to all cells (Deeks and Higgins, 2010; Pagano and Gauvreau, 2000, as cited in MEDCALC©).

Associations between the reference group (NOE) and the opioid exposed groups (OE and NOWS) with other potential confounding variables were compared using Fisher exact test, 1-tailed, for categorical data, and *t*-tests for independent samples with continuous data (Hays, 1994; Kim, 2017) using STATISTICA© data analysis software system (2009).

Results

Examination of the database revealed that CL/P was present in all groups: NOE, OE, and NOWS.

Population, Sample, and Prevalence

The prevalence of CL/P was 1.37, 35.71, and 6.80 per 1000 live births in the NOE, OE, and NOWS groups, respectively as shown in Figure 1.

Odds Ratios

Comparison of infants with OE to the NOE reference group revealed significantly increased odds for CL/P, CP, CL, and CLP (see Table 2). For infants with OE, odds ratios ranged from 19.26 to 41.8 (all *P*s < .008). Furthermore, the odds of infants with OE were higher for each type of CL/P than were those of infants with NOWS in comparison to the infants with NOE. The odds ratio for infants with NOWS in comparison with infants with NOE were significant for CL/P and CP (both *P*s < .03) but not for or CL and CLP (both *P*s > .11).

Infant Demographic and Birth Variables

The infants with OE and those with NOWS did not differ significantly from the infants in the NOE group on any of the demographic or birth variables examined, with the exception of length of stay in the hospital. See Table 3 for descriptive information. The OE and NOWS groups did not differ from the NOE group in sex, race, insurance type (all Fisher exact *P*s > .60). Compared to the infants with NOE, the infants with OE (all *t*s(1, 26) > 0.19; all *P*s > .19) and infants with NOWS (all *t*s(1, 22) > 0.20; all *P*s > .05) did not differ in gestation (wks), birth weight (g), birth length (in), Apgar scores at 1 and 5 minutes. The infants with NOWS, however, had significantly longer hospital stays, than the infants with NOE (*t*(1,22) = 5.86; *P* < .0001). The infants with OE showed a similar trend, but the difference in length of stay did not quite reach significance (*t*(1,26) = 2.03; *P* = .053).

Maternal Demographics and Health

The mothers of infants with OE and those with NOWS did not differ significantly from the mothers of infants in the NOE group on any of the demographic or birth variables examined, with the exception of maternal weight at delivery and mental health disorders. See Table 3 for descriptive information. Compared to the mothers of the NOE group, those of the OE group (all *t*s(1, 26) > 0.19; all *P*s > .60) and NOWS group (all *t*s(1, 22) > 1.0; all *P*s > .16) did not differ in age at delivery or parity (ie, number of births of greater than 24 weeks gestational age). While greater proportions of the mothers of infants with OE or
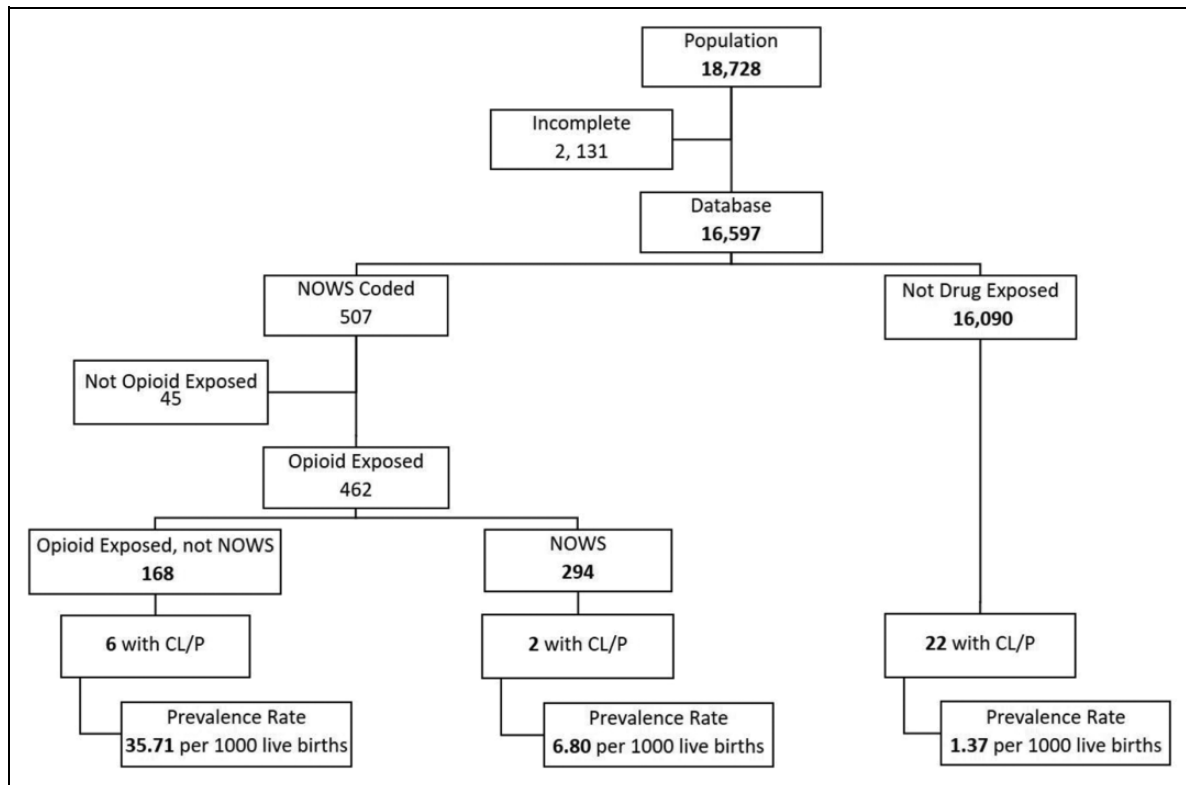
Figure 1. Population and sample sizes, and prevalence rates of CL/P.

Table 3. Occurrence of Demographic and Contributing Factors in NOE, OE, and NOWS Groups With CL/P.

	NOE		OE		NOWS	
Categories	n	%, M (SD)	n	%, M (SD)	n	%, M (SD)
Demographic						
Infant sex (male)	14	63.6%	4	66.7%	1	50%
Infant race (white)	21	95.5%	6	100%	2	100%
Public insurance	10	45.5%	3	50%	1	50%
Maternal age (yrs)	22	25.6 (5.0)	6	25.2 (3.3)	2	29.5 (5.0)
Single	9	40.1%	5	83.3%	2	100%
Birth						
Gestation (wks.)	22	39.0 (1.1)	6	39.7 (1.1)	2	39.9 (0.8)
Birth weight (g)	22	3370.7 (497.1)	6	3416.5 (541.5)	2	3654.5 (1075.5)
Birth length (in)	22	20.1 (1.0)	6	20.5 (1.2)	2	21 (1.4)
Apgar 1 min	21	7.9 (0.8)	6	7.8 (0.8)	1	8.0 (0.0)
Apgar 5 min	21	8.9 (0.3)	6	9.0 (0.0)	1	9.0 (0.0)
Length of stay (d)	22	2.6 (1.2)	6	1.5 (1.2)	2	12.0 (8.5)
Maternal health						
Parity	22	0.8 (0.7)	6	1.0 (1.1)	2	1.5 (0.7)
Delivery Wt. (lbs.)	19	190.3 (36.0)	6	171.8 (36.1)	2	251.0 (72.1)
Prenatal care (yes)	22	100%	6	100%	2	100%
Malnutrition (yes)	5	22.7%	1	16.7%	1	50%
Obesity (yes)	5	22.7%	0	0%	1	50%
Mental health (yes)	2	9.09%	4	66.7%	0	0%
Drug exposures						
Alcohol	1	4.5%	0	0%	0	0%
Nicotine	8	36.4%	2	33.3%	1	50%
Marijuana	1	4.5%	2	33.3%	0	0%

Abbreviations: d, days; g, grams; in, inches; lbs, pounds; M, mean; min, minutes; *n*, sample size; NOE, no opioid exposure; NOWS, neonatal opioid withdrawal syndrome; OE, opioid exposure; SD, standard deviation; wks., weeks.

NOWS were single compared to mothers of infants with NOE, the differences were not significant (all Fisher exact *P*s > .07).

The mothers of infants with NOWS weighed significantly more than those of infants with NOE ($t(1,22) = 2.11$; $P = .048$). The weights of the mothers of the OE group did not significantly differ from those of the NOE group ($t(1,26) = 1.10$; $P = .28$). A significantly greater proportion of mothers of infants with OE experienced mental health disorders than those of infants with NOE ($P = .01$). The proportions in the NOWS and OE groups did not differ ($P = .84$). The proportion of mothers in the OE and NOWS groups did not differ significantly in malnutrition or obesity (all Fisher exact *P*s > .25) when compared to the mothers of the NOE group.

Exposure to Other Substances

There were no positive urine drug screen results or maternal self-report of benzodiazepines, cocaine, barbiturates, amphetamines, and codeine. The proportions of mothers of infants with OE or NOWS did not differ from those of infants with NOE in use of alcohol, nicotine, or marijuana (all Fisher exact *P*s > .10).

Trimester of Opioid Use

Of the 2 mothers of infants with NOWS, one reported she used opioids throughout the pregnancy, while the other reported she used only during the third trimester. Of the 6 mothers of infants with OE, 4 reported opioid use during the first trimester at least. More specifically, 2 mothers reported opioid use throughout the pregnancy, 1 reported use only during the first trimester, 1 reported use only during the first and second trimesters, and 2 reported use only during the third trimester.

Discussion

Prevalence of CL/P

The prevalence of CL/P in this study's comparison sample was generally representative of those reported more broadly and in Mullens et al. (2019) and Danis et al. (2020). The prevalence per 1000 live births of CL/P in the NOE comparison group at 1.37 was almost identical to that of Danis et al. (2020) at 1.35. It was somewhat higher than the US national figure of 1.06 (National Institute on Dental and Craniofacial Research, nd) and the rates in Tennessee and Virginia at 1.10 and 1.05, respectively (National Birth Effects Prevention Network, 2010). This study's prevalence rate was lower than that reported by Mullens et al. (2019) at 1.63 and the international rate range at 1.42 to 2.00 (World Health Organization, 2001).

In the NOWS groups, the prevalence of CL/P per 1000 in this study at 6.80 was virtually identical to that of Mullins et al. (2019) at 6.79. Both of these prevalence numbers were much higher than that reported by Danis et al. (2020) at 3.13, most likely due to the national nature of their study and large population.

The similarities of our data for infants in the NOE and NOWS groups to that of other reports and studies gives initial credence to the surprisingly high prevalence of CL/P in the newly introduced sample of infants with OE. They showed a prevalence rate of 35.71 per 1000 live births. However, this remarkable result needs verification through replication.

Odds Ratios of CL/P

Infants with NOWS. In comparison the infants with NOE, those with NOWS had a significantly higher odds for CL/P and CP (5.00 and 10.98, respectively) but did not differ in their likelihood of CL and CLP. These findings of significance mirror those of Danis et al. (2020) though they report lower odds for CL/P and CP (2.33 and 4.97, respectively). Mullens et al. (2019) also found significantly higher odds ratios for CL/P (4.18), but not for CP or CLP. However, they uniquely found an increased likelihood of CL, with an odds ratio of 5.92.

The differences in the odds ratios and patterns of significant differences for infants with NOWS may be related to a number of factors. Danis et al. (2020) ascribed the differences to sample demographics (ie, race and sex), sample size, and incidence of NOWS in different states across the US. This view is supported by WHO (2001), which attributes the range of prevalence to the considerable variance across geographical regions and ethnic groupings.

Another source of difference may be attributed to the use of different criteria across hospital systems in identification of NOWS. There is no commonly accepted protocol or standard endorsed by the American Medical Association for nonpharmacological or pharmacological intervention and monitoring of symptoms to aid diagnosis of NOWS (Kocherlakota, 2014). Also, this study made significant efforts to accurately identify infants with NOWS who received pharmacological intervention and those prenatally opioid exposed who did not receive pharmacological intervention and may or may not have had NOWS. This resulted in 45 infants initially coded as having NOWS being excluded. Furthermore, we divided the original NOWS sample into 2 distinct groups, NOWS and OE, based on a deep review of the infants' medical records. Thus, the infants with NOWS in our study may not have included some of the infants identified as NOWS in the studies of Mullens et al. (2019) and Danis et al. (2020). Furthermore, it may be that some of the infants identified as OE in our study appeared in their studies as NOWS. This may have contributed to differences in odds ratios across studies. Irrespective of classification, all 3 studies confirmed an association between NOWS and CL/P.

Infants with OE. The inclusion of infants with OE in this study provides new data about the likely teratogenicity of opioids for CL/P. This group showed significantly higher and concerning odds ratios for CL/P (27.05), CL (41.81), CP (19.26), and CLP (19.37) in comparison to infants with NOE. It appears that the current study corroborates previous studies (eg, Saxén, 1975a; Saxén, 1975b; Bracken and Holfrod, 1981; Thomas, 1995;

Meyer et al., 2015) that pointed to the association of fetal OE and CL/P. Our data further specifies that in utero exposure to opioids is a contributory environmental risk factor in CL/P whether or not the infants show withdrawal signs or require pharmacological intervention.

Other Potentially Confounding Variables

There were few differences in the demographic, maternal health, birth, or drug exposures variables that we explored. Among the few differences, the significantly longer length of stay in the hospital for infants with NOWS than those with NOE reflects the complexity of their care and recovery from withdrawal symptoms (Kocherlakota, 2014; Patrick et al., 2015). The mothers of infants with NOWS weighed significantly more and a significantly greater proportion of mothers of infants with OE experienced mental health disorders than those of infants with NOE.

The demographic and health conditions of mothers and infants in this study reflect the health disparities endemic in this rural Appalachia region (Erwin et al., 2017). Thus, with respect to confounding variables, the mothers and infants in the NOE group may not be as different from those in the OE and NOWS groups as they might be in other areas of the nation. The presentation of confounding variables in the NOE, OE, and NOWS groups did not differ. Thus, the potential unique contribution of prenatal exposure to opioids as the primary environmental difference between the groups is revealed.

Limitations

Like Mullens et al. (2019), our sample was limited to a specific geographical region in Appalachia, in contrast to the national database utilized by Danis et al. (2020). Also, given the relatively small numbers of infants in the NOE, OE, and NOWS groups, the current study lacked the power for confidently detecting differences in demographic and contributing factors between the NOWS group and the NOE and OE groups. Furthermore, the retrospective nature of the data prevented capture of a full spectrum of other potential confounding variables necessary for investigation of the multifactorial nature of CL/P.

Future Directions

Now that there are similar findings from 3 large scale studies of the association between prenatal OE and CL/P, consideration of a theoretical view is warranted. Both Mullens et al. (2019) and Danis et al. (2020) emphasized the need for better understanding of the environmental risk factors for CL/P in the NOWS population. However, the likelihood of isolating risk factors individually is challenging, given the complexity of the population (Kocherlakota, 2014; Bailey et al., 2017). In the future, researchers may want to consider approaching this problem holistically. The Multifactorial Threshold (MF/T) model as applied to CL/P offers this opportunity (Zajac and Vallino,

2017). The MF/T model postulates that when an individual has a predisposition toward a given disorder, and is exposed to certain environmental conditions, the disorder will present itself (Zajac and Vallino, 2017). For example, prenatal exposure to opioids along with other adverse environmental factors, combined with a genetic susceptibility of the fetus, may push the fetus over the threshold and lead to a CL/P.

Conclusions

This study clearly indicated that for infants prenatally exposed to opioids there is increased prevalence and likelihood of having CL/P. Together with the findings of the recent large-scale studies of Mullens et al. (2019) and Danis et al. (2020), it is clear that opioids are a substantial environmental risk factor for CL/P, particularly considering the opioid crisis in the US.

ORCID iD

Kerry Proctor-Williams https://orcid.org/0000-0003-0841-6468

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