

UC Davis

UC Davis Previously Published Works

Title

Severe Neonatal Opioid Withdrawal Requiring Pharmacotherapy: Impact of Region of Residence

Permalink

<https://escholarship.org/uc/item/1md4h832>

Authors

Sankaran, Deepika
Rawat, Shikha
Kachelmeyer, Jennifer L
[et al.](#)

Publication Date

2022-12-31

DOI

10.1055/a-1925-1659

Copyright Information

This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Peer reviewed

American Journal of Perinatology

Severe Neonatal Opioid Withdrawal Requiring Pharmacotherapy: Impact of Region of Residence

Deepika Sankaran, Shikha Rawat, Jennifer Kachelmeyer, Emily Li, Anne Marie Reynolds, Munmun Rawat, Praveen Chandrasekharan.

Affiliations below.

DOI: 10.1055/a-1925-1659

Please cite this article as: Sankaran D, Rawat S, Kachelmeyer J et al. Severe Neonatal Opioid Withdrawal Requiring Pharmacotherapy: Impact of Region of Residence. American Journal of Perinatology 2022. doi: 10.1055/a-1925-1659

Conflict of Interest: The authors declare that they have no conflict of interest.

This study was supported by National Heart, Lung, and Blood Institute (<http://dx.doi.org/10.13039/1000000050>), K12 HL138052, Eunice Kennedy Shriver National Institute of Child Health and Human Development (<http://dx.doi.org/10.13039/100009633>), R01HD104909, R03HD096510

Abstract:

Objectives: To evaluate the trend and to assess the impact of maternal region of residence in Western New York (WNY), on severe neonatal opioid withdrawal syndrome (NOWS).

Methods: Term infants' born at gestational age greater than or equal to 37 weeks with severe NOWS, defined as withdrawal resulting in receipt of pharmacologic therapy from WNY admitted to our Neonatal Intensive Care Unit (NICU) from 1/1/2008 to 12/31/2016 were included. Severe NOWS admission to our NICU from the 5 regions: Urban North, Erie Coastal, Niagara Frontier, Southern Tier, and Urban South were controlled with birth and insurance data

Results: Urban south residence was associated with increased risk of severe NOWS (adjusted odds ratio 1.8 (97.5% confidence interval: 1.1 – 2.9). The trend in admission for severe NOWS doubled between 2008-10 and 2014-16 ($p=0.01$). More infants born to maternal non-prescribed opioid users were placed in foster care at discharge (36.5% vs. 1.9%, $p<0.001$).

Conclusion: In WNY, neonates born to mothers from the urban south were twice at risk of being admitted for severe NOWS. A third of severe NOWS after non-prescribed opioid use were placed in foster care. Implementing targeted strategies at the community level may help improve outcomes in NOWS.

Corresponding Author:

MD Praveen Chandrasekharan, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, Pediatrics, Buffalo, United States, pkchandr@buffalo.edu, cpraveenkumar25@yahoo.com

Affiliations:

Deepika Sankaran, University of California Davis, Pediatrics, Sacramento, United States

Deepika Sankaran, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, Buffalo, United States

Shikha Rawat, Stony Brook University The State University of New York, Stony Brook University The State University of New York, Stony Brook, United States

[...]

Praveen Chandrasekharan, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, Pediatrics, Buffalo, United States

Severe Neonatal Opioid Withdrawal Requiring Pharmacotherapy: Impact of Region of Residence

Deepika Sankaran, MD^{1,2}, Shikha Rawat, PhD^{3,4}, Jennifer L. Kachelmeyer, BS¹, Emily S. Li, BA¹, Anne Marie Reynolds, MD MPH¹, Munmun Rawat, MD¹, Praveen Chandrasekharan, MD MS¹

¹Division of Neonatology, Department of Pediatrics, University at Buffalo, Buffalo, NY.

²Division of Neonatology, Department of Pediatrics, University of California at Davis, Sacramento, CA. ³Department of Economics, Stony Brook University, New York. ⁴Research Analyst, American Express.

Address for correspondence: Praveen Chandrasekharan, MD, MS, Division of Neonatology, Department of Pediatrics, University at Buffalo. 1001 Main street Buffalo NY 14203. Email: pkchandr@buffalo.edu, Phone - 716-323-0260, Fax – 716-323-0294

Abstract

Objectives To evaluate the trend and to assess the impact of maternal region of residence in Western New York (WNY), on severe neonatal opioid withdrawal syndrome (NOWS).

Methods Term infants' born at gestational age greater than or equal to 37 weeks with severe NOWS, defined as withdrawal resulting in receipt of pharmacologic therapy from WNY admitted to our Neonatal Intensive Care Unit (NICU) from 1/1/2008 to 12/31/2016 were included. Severe NOWS admission to our NICU from the 5 regions: Urban North, Erie Coastal, Niagara Frontier, Southern Tier, and Urban South were controlled with birth and insurance data

Results Urban south residence was associated with increased risk of severe NOWS (adjusted odds ratio 1.8 (97.5% confidence interval: 1.1 – 2.9). The trend in admission for severe NOWS

doubled between 2008-10 and 2014-16 ($p=0.01$). More infants born to maternal non-prescribed opioid users were placed in foster care at discharge (36.5% vs. 1.9%, $p<0.001$).

Conclusion In WNY, neonates born to mothers from urban south were twice at risk of being admitted for severe NOWS. A third of severe NOWS after non-prescribed opioid use were placed in foster care. Implementing targeted strategies at the community level may help improve outcomes in NOWS.

Key Points:

- Maternal region of residence is a risk factor for severe neonatal opioid withdrawal.
- Admissions for severe neonatal opioid withdrawal trended up from 2008-10 to 2014-16.
- A third of the infants born to mothers on non-prescribed opioids were discharged to foster care.

Opioid use in the United States of America (USA) has been declared an epidemic and a national crisis.¹ This crisis is attributed to the widespread use of both non-prescribed/illicit and prescribed opioids that has been catapulting over the past two decades.² Among the 2 million Americans currently dependent on opioids, many are women of childbearing age.³ The rate of maternal opioid use has increased from 1.5 to 6.5 per 1000 deliveries from 1999-2014 along with an increase in health care expenditures related to neonatal opioid withdrawal syndrome (NOWS).⁴⁻⁶ State and federal policies to combat this epidemic have slowed the increase in prescription drug abuse although there has been an increase in non-prescribed opioid use and subsequent mortality.^{7,8}

Previously known as neonatal abstinence syndrome, NOWS is defined by an array of signs and symptoms of withdrawal in infants after in-utero exposure to opioids.⁹ The incidence of NOWS has been reported to be as high as 20 cases per 1000 live births.¹⁰ Neonates requiring pharmacotherapy are often considered to have *severe NOWS* and monitored in the neonatal intensive care unit (NICU) with prolonged length of stay adding to the economic burden. The average cost per infant with NOWS has been reported as \$ 22,552 with highest total costs for births covered by Medicaid (\$ 477 million).¹¹ The impact of maternal epidemiological and environmental factors (maternal race, socioeconomic and education status, that are variable with maternal zone of residence) could potentially help in identifying women of childbearing age who are at risk of opioid dependence, which in-turn could aid in targeting preventive interventions at the community level to decrease the incidence and economic burden of NOWS. In infants with severe NOWS, pharmacotherapy is recommended in addition to non-pharmacological measures.⁶ To date, there are no studies exploring the influence of maternal geographical zone of residence on and its association with severe NOWS admission. Our primary objective was to determine if the maternal region of residence is associated with increased risk of admission for severe NOWS. Our secondary objective was to evaluate the trends in severe NOWS over a nine-year period and to describe the maternal and infant characteristics amongst infants with severe NOWS born to mothers on non-prescribed and prescribed opioids, respectively.

Methods:

The Institutional Review Board at The State University of New York at Buffalo approved the study with waiver of informed consent (STUDY00002861). Data for this retrospective cohort study were obtained from the electronic medical records in the Regional Perinatal Center (RPC:

Women and Children's Hospital of Buffalo/ John R. Oishei Children's Hospital), Buffalo, NY. The RPC is located in the Urban North region of Erie County, NY, USA. Our level IV NICU, is a tertiary care center and a regional referral center, which caters to 11 hospitals in the Western New York region. There is one other level III NICU in Urban North region of Erie County that admit infants with severe NOWS. We do not have data from this center.

Data on severe NOWS: Newborn infants born at ≥ 37 weeks gestational age (GA) in Erie County and admitted with the diagnosis of NOWS requiring pharmacotherapy ("severe NOWS") to our NICU at Buffalo from 1/1/2008 to 12/31/2016 were included.¹¹ Preterm and late preterm neonates were excluded due to inherent differences in their characteristics including birth weights, length of stay and prematurity related morbidities. Infants with iatrogenic withdrawal from opioids administered as medical treatment (e.g., sedation) and infants with the diagnosis of neonatal abstinence syndrome due to maternal use of substances of abuse that were exclusively non-opioids (such as tetrahydrocannabinol or cocaine) were excluded. During the study period, the modified Finnegan scoring system was consistently utilized to assess the severity of NOWS and to direct therapy.

Maternal characteristics: The following maternal demographic data were collected: age, marital status, self-disclosed race/ethnicity, health insurance and zone of residence. "Non-prescribed opioid use" was defined as exposure to illicit opioids such as heroin, fentanyl, or prescription opioids (such as methadone, buprenorphine etc.) that were being used without a prescription during pregnancy. "Prescribed opioid use" was defined as exposure to opioid medications prescribed by a clinician to the mother during the current pregnancy. Obstetric and past medical history, including information on type of opioid use from maternal history (non-prescribed vs.

prescribed), history of chronic painful conditions, physical/sexual/domestic abuse and psychiatric history obtained from medical records, and urine toxicology results at the time of delivery (which has a limitation of reliably detecting substance abuse only for 24-48 hours). In addition, information on maternal tobacco use, season of delivery and custody of previous children were also collected. We evaluated the effect of season of birth on admission for severe NOWS due to reported higher adverse effects including opioid use-related deaths in winter months.¹² Based on the zone improvement plans (ZIP) in Erie County (location of the RPC), maternal zones of residence were identified and coded with random alphabets to protect patient information.

Infant characteristics: Information on infant characteristics including GA at birth, birth weight, sex, diet at discharge, discharge weight, type of health insurance, length of stay (LOS) and custody of infant at the time of discharge were collected. All patient identifiers were coded and the code key was stored separately.

Erie County data (<https://www.health.ny.gov/statistics/chac/perinatal/>): To study the effect of the maternal region of residence on the rate of admission with severe NOWS , we identified the maternal zone of residence for all live term infants ≥ 37 weeks born in Erie County during the same period.¹³ Data on birth, maternal characteristics including race and education levels are available from 2008 to 2016 in the public database, for each of these 3-year periods (2008-2010, 2011-2013, and 2014-2016) and were used with permission. The number of term births from 2008 to 2016 in 39 zones of residence (that contributed to severe NOWS) in Erie County was 78,961.¹³ Vermette et al. divided WNY to four regions based on climate zones.¹⁴ We further

divided Urban into Urban North (UN) and Urban South (US) (as designated by Buffalo City Council) geographically based on location. Percentages of severe Nows admissions to our NICU were compared based on maternal region of residence from these 5 regions: UN, US, Erie Coastal (EC), Niagara Frontier (NF) and Southern Tier (ST) (Figure 1).

Data presentation and statistical analysis: Categorical data are presented as numbers and percentages and continuous data are presented as mean and standard deviation or median and interquartile ranges. Categorical variables were analyzed by chi-square test, parametric continuous variables by t-test and non-parametric continuous variable by Wilcoxon-rank-sum test. A logistic regression analysis was performed to assess the associated risk factors for severe Nows admissions, such as total live term births, total admissions to the NICU during the study period, maternal race, educational status, and source of health insurance. Since the hospital is located in Urban North region, we chose this region as a reference to compare the regional differences in severe Nows admission to our unit. To understand the change in number of severe Nows admission we controlled the birth data for insurance information (whether they were Medicaid beneficiaries) in the years 2008-2010, 2011-2013, and 2014-2016, using 2008-2010 as reference. The statistical analysis was conducted using SAS version 9.4 software and R studio, and all tests were performed with a nominal significance level of 0.05.

Results:

During the study period there were 3683 admissions of term infants born at GA ≥ 37 weeks. Among them, 291 neonates were admitted from Erie County and had the diagnosis of neonatal abstinence syndrome or neonatal opioid withdrawal syndrome (8% of all NICU admissions); 160

were excluded (17 had iatrogenic withdrawal, 125 neonates whose mother was not on any opioid but were on tetrahydrocannabinol or cocaine, and 18 were repetitions- duplication of the same patient being transferred from a Level II affiliated facility-Millard Fillmore Suburban Hospital sharing electronic records with the RPC, Figure 1).

Out of 126 neonates who met inclusion criteria, 74 (58.7%) were born to mothers on non-prescribed opioids and 52 (41.3%) to mothers on prescribed opioids.

Maternal opioid use (Table 1): Self-reported Caucasian mothers constituted 73% and 78.9% of the mothers on non-prescribed and prescribed opioids, while self-reported African American mothers constituted 14.9% and 11.6% respectively. Distribution of maternal age, parity and marital status was similar between the two groups. Non-prescribed opioid-dependent mothers trended to be Medicaid beneficiaries compared to those on prescribed opioids, although not statistically significant ($p=0.08$). Fifty-three percent and sixty percent of mothers in non-prescribed and prescribed groups respectively had mental health concerns that were not associated with pregnancy (Table 1). About 18% of the mothers on non-prescribed opioids did not have custody of their previous children compared to about 2% of mothers on prescribed opioids ($p < 0.01$).

Region of residence and severe NOWS: Using UN as controls, infants with severe NOWS born to mothers from US had higher chances of admission to our NICU (Figure 3). Figure 3 shows the percentage of term infants diagnosed with severe NOWS out of all term infants born in our hospital during the study period from each zip code in Erie County. While the eastern part of the county tends to have a lower proportionate incidence of severe NOWS, the southern and certain western areas have higher incidence. Logistic regression analysis using the incidence of severe

NOWS as the dependent variable and region dummies as explanatory variables showed that Urban South had a higher (at 1% level of significance) incidence of severe NOWS relative to UN.

The trend in admissions for severe NOWS: The overall trend in severe NOWS has doubled from 0.11% of total term births in 2008-10 to 0.22% of total term births in 2014-16 ($p=0.01$) (Figure 4).

Infant outcomes: Birth weights, GA, sex distribution and LOS were not different between infants born to mothers on non-prescribed vs. prescribed opioids (table 2). The racial distribution (self-reported by mothers) are also show in table 2. A third of the infants with severe NOWS were Medicaid beneficiaries. One-third of all infants born to mothers who were on non-prescribed opioids were placed in foster care (36.5% vs. 1.9%, $p<0.001$) while 98.1% of the infants born to mothers on prescribed opioids were discharged with custody to the mother without need for supervision ($p< 0.01$).

Discussion:

In our single-center study, we present data over the 9-year study period from 39 zones in Erie County, Buffalo, NY. Between 2008 and 2016 there has been a significant increase in the number of admissions for neonates with severe NOWS to our NICU in spite of a stable reported population (figure 4).¹⁵ The increasing trend is similar to that of opioid use and NOWS in USA.^{16,17} Use of both non-prescribed and prescribed opioids has increased in women of childbearing age, despite the restrictions that have recently been introduced.^{18,19} Honein et al. have highlighted the opioid crisis as a “public health emergency of our time.”²⁰ Our data support the dire need for focused strategies at the community level to address this crisis during

pregnancy. Disrupting opioid use in a long-term user during pregnancy could lead to untoward effects. However, a reduction in opioid overprescribing is feasible with effective interventions as previously described by Mesenberger et al.^{21,22}

To our knowledge, we report the first association between the maternal zone of residence and its influence on opioid use during pregnancy leading to severe Nows. Patrick S.W et al. observed geographic variation in Nows from a nation-wide sample of hospital discharges.²³ Previous studies have found that the incidence of Nows varies significantly among the states. The geographic variations in Nows are consistent with the variations in opioid pain prescribing practices and use of synthetic opioids; the incidence of Nows and maternal opioid use was disproportionately higher in rural relative to urban counties.²⁴⁻²⁷ We identified high-risk zones of maternal residence where the use of non-prescribed and prescribed opioids leading to severe Nows was higher compared to the other zones. Patrick S.W et al., have reported an association of Nows with the 10-year unemployment rate and mental health clinician shortage at a county level.²⁸ Guy et al. have described the factors implicated in the mechanism of increased risk in certain areas, which included racial differences (non-Hispanic White), metropolitan status, lack of high school education, higher unemployment, lower proportion of population younger than 25 years, higher Medicaid enrollment, lower concentrations of primary care physicians and mental health care clinicians per 100,000 persons, and higher rate of opioid prescriptions per 100 persons.²⁹ As the next step, we intend to investigate specific factors playing a role in the urban south region contributing to higher severe Nows admissions to our institution

Racial differences have been reported in the incidence of Nows.⁶ Based on the 2010 census, self-reported Caucasians constituted 46% and self-reported African Americans represented 37% of the population in Buffalo.³⁰ The racial distribution of opioid-dependent

mothers in the current study are consistent with the racial/ethnic differences reported in opioid prescribing for pain management in adults in the emergency department.³¹ Previously a large database study reported differences in hospital admission for NOWS based on race¹¹. Significant racial and ethnic disparities in prenatal receipt of medication for opioid use disorder has been reported from a state-wide database in Massachusetts³². We did not find any racial predilection with opioid use during pregnancy leading to severe NOWS, however NOWS infants managed with non-pharmacological measures were not included in our study and our sample size was small. While acknowledging that our numbers are small, 6/11 (55%) of AA infants and 2/4 (50%) of Hispanic infants went into foster care, while only 19/49 (20%) of Caucasian infants were placed in foster care (table 2). Future studies are warranted that evaluate racial distributions and indications for foster care placements.

Approximately half of our maternal population, regardless of the type of (non-prescribed vs. prescribed) opioid use, were Medicaid beneficiaries. Presence of maternal mental health comorbidities in our study is a significant association that needs to be addressed during health promotion in women of childbearing age. Psychosocial and economic factors influence maternal opioid use and can negatively impact the living conditions for the neonates³³. Additionally, we attempted to evaluate if the season of birth (winter vs summer months) could affect severe NOWS due to severe winters in Buffalo, but we did not find an association.

Infants born to mothers on non-prescribed opioids had higher rates of being cared for by foster parents. Based on data from 580 USA counties and 8 states between 2009 and 2017, Loch et al recently reported that every diagnosis of NOWS among 10 births was associated with 41% higher rate of foster care placement, while rural county of residence was associated with 19% higher rate of foster care placement³⁴. These reinforce the findings of the child welfare system

that reported an increase of >10,000 infants in foster care over 7 years in the past decade, most of which was secondary to parental substance abuse³⁵. Mother-infant bonding during the neonatal period promotes wellbeing in both the mother and the infant. Children who are raised in foster care have increased vulnerability to psychopathology, and expressive and receptive language delays, demonstrating the importance of social enrichment, although early placement reduces the risk significantly.³⁶⁻³⁸ In addition, children placed in foster care are 2-3 times as likely to have adverse social issues as adults.³⁹ Recent studies have also shown that infants with NOWS can have educational disabilities affecting their school performance.^{40,41} In the future, more research is needed to study the effect of maternal non-prescribed and prescribed opioid use and developmental outcomes in the offspring. Additionally, similar studies performed at population-level in different geographical areas may provide more pertinent data to develop targeted strategies at the community level. Moreover, larger multi-center observational studies may provide valuable input on risk factors including racial, socioeconomic and geographical predisposition to severe NOWS.

Some of the barriers faced at the community level in the care for opioid-dependent women are inadequate access to contraception and treatment for opioid dependence, fewer options for medication-assisted therapy during pregnancy, lack of expertise among providers caring for them and limited resources for their care.^{42,43} Strategies that could have a significant impact include emphasis on health education in women of childbearing age (preconception) and pregnant women belonging to high-risk areas, providing nonjudgmental, enduring support by removing the stigma associated with opioid dependence, and improving social perceptions, and education of clinicians to enhance their knowledge on the specialized and comprehensive care of opioid-dependent pregnant women, with a focus on mental health.⁴⁴ Establishing provider-patient

partnerships with regards to risk factors, setting goals and expectations, optimizing the access to medication-assisted treatment, and increasing the involvement of the mothers at the bedside in management of NOWS in the form of kangaroo care and breastfeeding, with alternate ways of NOWS scoring (such as “Eat, Sleep, Console”), could play a role in improving the overall care and cost-effectiveness in management of NOWS.⁴⁵⁻⁴⁷ Organizations such as The Center for Substance Abuse Prevention of the Substance Abuse and Mental Health Services Administration (SAMHSA) support the implementation of such effective preventive interventions.

There are several limitations to our study. Although a large data set was included over a 9-year period, we did not study the effect of maternal non-prescribed vs. prescribed opioid use on NOWS admissions managed with non-pharmacological interventions alone, since these infants were not admitted in our NICU. We also did not have access to data for all the women belonging to childbearing age group who were on opioids in WNY to study the overall effect and were limited to the data of maternal information obtained from infants admitted to the NICU. This is a single center study and infants with severe NOWS admitted to another level III NICU in Buffalo were not included. We did not collect data on toxicology screening of the infant’s urine or meconium due to inconsistencies in the documentation. Furthermore, we did not identify specific risk factors in the Urban South region that contributed to higher severe NOWS admissions, and this requires adequately powered and focused studies.

Conclusion:

There has been a significant increase in severe NOWS admissions to our NICU located in Erie County reflecting an increase in opioid use in women of childbearing age. We report a

geographical predilection for maternal use of opioids (both non-prescribed and prescribed), which has had a significant impact on their infants being admitted to NICU for severe Nows. Though Federal and State policies and restrictions have been brought about to restrict prescription opioid use, they need to be complemented by implementing preventive strategies targeting the high-risk communities to potentially decrease non-prescribed and prescribed opioid use in pregnant women, and improve care for mother-infant dyad.

Conflict of interest Disclosures (included financial disclosures): The authors have no financial relationships relevant to this article to disclose.

Funding source: Dr. Chandrasekharan is supported by Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) R01HD104909/R03HD096510 and National Institutes of Health (NIH)/National Heart Lung and Blood Institute (NHLBI) K12 HL138052 and Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award number UL1TR001412 to the University at Buffalo. Dr. Sankaran was supported by Children's Miracle Network at UC Davis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The funding agencies had no role in the design of this manuscript.

Disclosure: The data was previously presented as a poster in Pediatric Academic Societies meeting and in Eastern Society of Pediatrics Research meeting in 2019.

Contributions: Deepika Sankaran, Shikha Rawat, Jennifer L. Kachelmeyer, Emily S. Li, Anne Marie Reynolds, Munmun Rawat, and Praveen Chandrasekharan made substantial contributions to conception, design and drafting of the manuscript. All the authors have critically revised and

approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work.

References:

1. Wen LS, Warren KE. Combatting the opioid epidemic: Baltimore's experience and lessons learned. *Journal of public health (Oxford, England)* 2018;40(2):e107-e111
2. Gomes T, Khuu W, Martins D, et al. Contributions of prescribed and non-prescribed opioids to opioid related deaths: population based cohort study in Ontario, Canada. *BMJ (Clinical research ed)* 2018;362:k3207
3. Villapiano NLG, Winkelman TNA, Kozhimannil KB, Davis MM, Patrick SW. Rural and Urban Differences in Neonatal Abstinence Syndrome and Maternal Opioid Use, 2004 to 2013. *JAMA Pediatrics* 2017;171(2):194-196
4. Patrick SW, Schumacher RE, Benneyworth BD, et al. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. *Jama* 2012;307(18):1934-1940
5. Haight SC, Ko JY, Tong VT, Bohm MK, Callaghan WM. Opioid Use Disorder Documented at Delivery Hospitalization - United States, 1999-2014. *MMWR Morb Mortal Wkly Rep* 2018;67(31):845-849
6. Patrick S.W BWD, Poindexter B.B and COMMITTEE ON FETUS AND NEWBORN, COMMITTEE ON SUBSTANCE USE AND PREVENTION, *Pediatrics* October 2020 eDhdop-. Neonatal Opioid Withdrawal Syndrome.

7. Dart RC, Severtson SG, Bucher-Bartelson B. Trends in opioid analgesic abuse and mortality in the United States. *The New England journal of medicine* 2015;372(16):1573-1574
8. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in Drug and Opioid Overdose Deaths--United States, 2000-2014. *MMWR Morb Mortal Wkly Rep* 2016;64(50-51):1378-1382
9. Hudak ML, Tan RC. Neonatal drug withdrawal. *Pediatrics* 2012;129(2):e540-560
10. Milliren CE, Gupta M, Graham DA, et al. Hospital Variation in Neonatal Abstinence Syndrome Incidence, Treatment Modalities, Resource Use, and Costs Across Pediatric Hospitals in the United States, 2013 to 2016. *Hospital pediatrics* 2018;8(1):15-20
11. Strahan AE, Guy GP, Jr, Bohm M, Frey M, Ko JY. Neonatal Abstinence Syndrome Incidence and Health Care Costs in the United States, 2016. *JAMA Pediatrics* 2020;174(2):200-202
12. Goedel WC, Marshall BDL, Spangler KR, et al. Increased Risk of Opioid Overdose Death Following Cold Weather: A Case-Crossover Study. *Epidemiology* 2019;30(5):637-641
13. <https://www.health.ny.gov/statistics/chac/perinatal/>.
14. Vermette SJ. Proceedings of the Rochester Academy of Science, vol. 21, 27-41. <https://cdm16694contentdmoclcorg/digital/collection/p16694coll84/id/6829> 2020
15. <https://www.census.gov/quickfacts/fact/table/buffalocitynewyork> NP.
16. Gomes T, Tadrous M, Mamdani MM, Paterson JM, Juurlink DN. The Burden of Opioid-Related Mortality in the United StatesThe Burden of Opioid-Related Mortality in the

United States, 2001-2016The Burden of Opioid-Related Mortality in the United States, 2001-2016. JAMA Network Open 2018;1(2):e180217-e180217

17. Hirai AH, Ko JY, Owens PL, Stocks C, Patrick SW. Neonatal Abstinence Syndrome and Maternal Opioid-Related Diagnoses in the US, 2010-2017. *Jama* 2021;325(2):146-155
18. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016CDC Guideline for Prescribing Opioids for Chronic Pain, 2016CDC Guideline for Prescribing Opioids for Chronic Pain, 2016. *Jama* 2016;315(15):1624-1645
19. HHS GOV- opioid epidemic. E-pub 2019:<https://www.hhs.gov/opioids/about-the-epidemic/index.html>
20. Honein MA, Boyle C, Redfield RR. Public Health Surveillance of Prenatal Opioid Exposure in Mothers and Infants. *Pediatrics* 2019
21. Meisenberg BR, Grover J, Campbell C, Korpon D. Assessment of Opioid Prescribing Practices Before and After Implementation of a Health System Intervention to Reduce Opioid OverprescribingAssessment of a Health System Intervention to Reduce Opioid OverprescribingAssessment of a Health System Intervention to Reduce Opioid Overprescribing. *JAMA Network Open* 2018;1(5):e182908-e182908
22. Mark J, Argentieri DM, Gutierrez CA, et al. Ultrarestrictive Opioid Prescription Protocol for Pain Management After Gynecologic and Abdominal SurgeryOpioid Protocol for Pain Management After Gynecologic and Abdominal SurgeryOpioid Protocol for Pain Management After Gynecologic and Abdominal Surgery. *JAMA Network Open* 2018;1(8):e185452-e185452

23. Patrick SW, Davis MM, Lehmann CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. *J Perinatol* 2015;35(8):650-655
24. Ko JY, Patrick SW, Tong VT, et al. Incidence of Neonatal Abstinence Syndrome - 28 States, 1999-2013. *MMWR Morb Mortal Wkly Rep* 2016;65(31):799-802
25. Villapiano NL, Winkelman TN, Kozhimannil KB, Davis MM, Patrick SW. Rural and Urban Differences in Neonatal Abstinence Syndrome and Maternal Opioid Use, 2004 to 2013. *JAMA Pediatr* 2017;171(2):194-196
26. Haffajee RL, Lin LA, Bohnert ASB, Goldstick JE. Characteristics of US Counties With High Opioid Overdose Mortality and Low Capacity to Deliver Medications for Opioid Use Disorder. *JAMA Network Open* 2019;2(6):e196373-e196373
27. Kiang MV, Basu S, Chen J, Alexander MJ. Assessment of Changes in the Geographical Distribution of Opioid-Related Mortality Across the United States by Opioid Type, 1999-2016. *JAMA Network Open* 2019;2(2):e190040-e190040
28. Patrick SW, Faherty LJ, Dick AW, et al. Association Among County-Level Economic Factors, Clinician Supply, Metropolitan or Rural Location, and Neonatal Abstinence Syndrome. *Jama* 2019;321(4):385-393
29. Guy GP, Jr., Zhang K, Bohm MK, et al. Vital Signs: Changes in Opioid Prescribing in the United States, 2006-2015. *MMWR Morb Mortal Wkly Rep* 2017;66(26):697-704
30. Buffalo demographics- census. E-pub 2014:<https://web.archive.org/web/20140504172555/http://quickfacts.census.gov/qfd/states/20140504172536/20140503611000.html>

31. Pletcher MJ, Kertesz SG, Kohn MA, Gonzales R. Trends in Opioid Prescribing by Race/Ethnicity for Patients Seeking Care in US Emergency Departments. *Jama* 2008;299(1):70-78
32. Peeler M, Gupta M, Melvin P, et al. Racial and Ethnic Disparities in Maternal and Infant Outcomes Among Opioid-Exposed Mother–Infant Dyads in Massachusetts (2017–2019). *American Journal of Public Health* 2020;110(12):1828-1836
33. SAMHSA. 2016:<https://www.samhsa.gov/capt/practicing-effective-prevention/prevention-behavioral-health>
34. Loch SF, Stein BD, Ghertner R, et al. Neonatal Opioid Withdrawal Syndrome Is Associated With Infant Foster Care Entry At The County Level. *Health Aff (Millwood)* 2021;40(11):1776-1783
35. American Academy of Pediatrics Council on Foster Care A, and Kinship Care; Waite, Douglas; Greiner, Mary V.; and Laris, Zach (2018) "Putting Families First: How the Opioid Epidemic is Affecting Children and Families, and the Child Welfare Policy Options to Address It," *Journal of Applied Research on Children: Informing Policy for Children at Risk: Vol. 9 : Iss. 1 , Article 4.*, <https://digitalcommons.library.tmc.edu/childrenatrisk/vol9/iss1/4> Aa.
36. Wade M, Fox NA, Zeanah CH, Nelson CA. Effect of Foster Care Intervention on Trajectories of General and Specific Psychopathology Among Children With Histories of Institutional Rearing: A Randomized Clinical TrialEffect of Foster Care Intervention on Psychopathology Among Children With Histories of Institutional RearingEffect of Foster

Care Intervention on Psychopathology Among Children With Histories of Institutional Rearing. *JAMA Psychiatry* 2018;75(11):1137-1145

37. Windsor J, Benigno JP, Wing CA, et al. Effect of foster care on young children's language learning. *Child development* 2011;82(4):1040-1046
38. McGowan EC, Lupton AR, Lowe J, et al. Developmental Outcomes of Extremely Preterm Infants with a Need for Child Protective Services Supervision. *The Journal of pediatrics* 2019
39. Jr. JJD. Child Protection and Adult Crime. *Journal of Political Economy* 2008;Volume 116(4):https://www.jstor.org/stable/10.1086/590216?seq=590211#page_scan_tab_contents
40. Fill MA, Miller AM, Wilkinson RH, et al. Educational Disabilities Among Children Born With Neonatal Abstinence Syndrome. *Pediatrics* 2018;142(3)
41. Oei JL, Melhuish E, Uebel H, et al. Neonatal Abstinence Syndrome and High School Performance. *Pediatrics* 2017;139(2)
42. Meyer M, Phillips J. Caring for pregnant opioid abusers in Vermont: A potential model for non-urban areas. *Preventive medicine* 2015;80:18-22
43. Ko JY WS, Barfield WD, et al. . CDC Grand Rounds: Public Health Strategies to Prevent Neonatal Abstinence Syndrome. *MMWR Morb Mortal Wkly Rep* 2017 2017;66:242–245. :<https://www.cdc.gov/mmwr/volumes/66/wr/mm6609a6602.htm#suggestedcitation>
44. Madras BK. The Surge of Opioid Use, Addiction, and Overdoses: Responsibility and Response of the US Health Care SystemThe Surge of Opioid Use, Addiction, and OverdosesEditorial. *JAMA Psychiatry* 2017;74(5):441-442

45. Koh HK. Community-Based Prevention and Strategies for the Opioid Crisis. *The JAMA Forum*. *Jama* 2017;318(11):993-994
46. Patrick SW, Schiff DM. A Public Health Response to Opioid Use in Pregnancy. *Pediatrics* 2017;139(3)
47. Grossman MR, Lipshaw MJ, Osborn RR, Berkwitt AK. A Novel Approach to Assessing Infants With Neonatal Abstinence Syndrome. *Hospital pediatrics* 2018;8(1):1-6

Figure 1: Modified Division of Western New York into five regions of maternal residence:

Modified division of Western New York (to include division of Urban into Urban North and Urban South), adapted with permission from Vermette et al., *Proceedings of the Rochester Academy of Science*, vol. 21, 27-41.

<https://cdm16694contentdmoclcorg/digital/collection/p16694coll84/id/6829>. 2020.

Figure 2: Consort flow diagram: Consort diagram representing the process of data collection.

Figure 3: Percentage of term infants admitted with severe Nows out of all term infants born during the study period from each zip code in Erie County. While the eastern part of the county tends to have a lower proportionate incidence of severe Nows, the southern and certain western areas have higher incidence. Logistic regression analysis using the incidence of severe Nows as the dependent variable and region dummies as explanatory variables showed that Urban South had a higher ($p < 0.001$) incidence of severe Nows relative to UN. Compared to UN (control), there was a higher chance of NICU admission for severe Nows from US, ST, NF and EC. UN, Urban North. US, Urban South. ST, Southern Tier. NF, Niagara Frontier. EC, Erie Coastal.

Figure 4: The trend in severe NOWS admission: The overall trend in severe NOWS admissions has doubled between 2008-10 and 2014-16 (0.11% to 0.22%) (p=0.01), with 2008-10 as the reference period.

Table 1: Description and comparison of maternal characteristics between those on non-prescribed and prescribed opioids respectively.

Variable	Mother on non-prescribed opioids (n=74)	Mother on prescribed opioids (n=52)	p-value
Age distribution in years n (%)			
<20	7 (9.5)	3 (5.8)	0.95
21-25	25 (33.8)	18 (34.6)	
26-30	23 (31.1)	13 (25.0)	
31-35	14 (18.9)	10 (19.2)	
36-40	3 (4.1)	2 (3.8)	
>41	1 (1.3)	2 (3.8)	
Not reported	1 (1.3)	4 (7.7)	
Self-disclosed Race/ ethnicity n (%)			
Caucasian	54 (73.0)	41 (78.9)	0.94
African American	11 (14.9)	6 (11.6)	
American Indian/ Alaskan	1 (1.3)	1 (1.9)	
Hispanic	4 (5.4)	2 (3.8)	
Not reported	4 (5.4)	2 (3.8)	
Marital status n (%)			
Unmarried	61 (82.4)	42 (80.8)	0.83

Married	7 (9.4)	7 (13.5)	
Divorced/ separated	3 (4.1)	1 (1.9)	
Not reported	3 (4.1)	2 (3.8)	
Parity n (%)			
Primiparous	15 (20.3)	8 (15.4)	0.91
Multipara (2-4)	43 (58.1)	32 (61.5)	
Grand multipara (≥5)	15 (20.3)	11 (21.2)	
Not reported	1 (1.3)	1 (1.9)	
Place of delivery n (%)			
Inborn¹	36 (48.6)	34 (65.4)	0.06
Outborn	38 (51.4)	18 (34.6)	
Season of delivery n (%)			
Winter	33 (44.6)	30 (57.7)	0.15
Summer	41 (55.4)	22 (42.3)	
Maternal urine toxicology result at delivery n (%)			
Opioids only	25 (33.8)	23 (44.3)	0.03*
More than one in addition to opioid²	19 (25.7)	5 (9.6)	
Negative	14 (18.9)	9 (17.3)	
Cocaine	12 (16.2)	0 (0)	
THC	6 (8.1)	2 (3.8)	
Not Available	8 (10.8)	13 (25.0)	
History of Polysubstance abuse/ recreational drug use n (%)	9 (12.2)	7 (13.5)	0.83

History of alcohol use during pregnancy n (%)	6 (8.1)	0 (0)	0.24
History of tobacco smoking n (%)	41 (55.4)	25 (48.0)	0.42
Medicaid beneficiaries/ public source of prenatal care payment n (%)	50 (67.6)	27 (51.9)	0.08
Maternal psychiatric disorder n (%)			
Depression	16 (21.6)	17 (32.7)	0.71
Bipolar disorder	6 (8.1)	4 (7.7)	
Anxiety	11 (14.9)	10 (19.2)	
Post-partum depression	4 (5.4)	0 (0)	
Post-traumatic stress disorder	2 (2.7)	0 (0)	
Maternal history of chronic painful condition n (%)			
Chronic back pain/ kidney stones	8 (10.8)	15 (28.8)	0.66
Injury/ surgery	7 (9.5)	5 (9.6)	
Migraine	2 (2.7)	2 (3.8)	
Fibromyalgia	1 (1.3)	3 (5.8)	
Crohn's disease	1 (1.3)	0 (0)	
Maternal history of abuse- (physical, domestic, or sexual) n (%)	2 (2.7)	1 (1.9)	1
History of ≥ 1 abortions n (%)	36 (48.7)	33 (63.5)	0.10
Mother does not have custody of other children n (%)	13 (17.6)	1 (1.9)	<0.01*
*p-value significantly different (p<0.05)			
¹ Inborn: born in the RPC. Outborn: born in a different hospital and transferred to RPC.			
² Screens that were positive for more than one were counted in their individual category in addition to			

the “More than one in addition to opioid” category

THC: Tetrahydrocannabinol

Table 2: Comparison of infant characteristics between those with severe NOWS born to mothers on non-prescribed vs. prescribed opioids.

Table 2: Infant characteristics			
Variable	Mother on non-prescribed opioids (n=74)	Mother on prescribed opioids (n=52)	p-value
Gestational age (weeks) mean (standard deviation)	38.5 (1.2)	38.4 (1.2)	0.67
Gender n (%)			0.80
Male	41 (55.4)	30 (57.7)	
Female	33 (44.6)	22 (42.3)	
5 min Apgar score n (%)			1
≥ 5	72 (97.3)	52 (100)	
< 5	2 (2.7)	0 (0)	
Birth weight (kg) mean (standard deviation)	3.0 (0.5)	3.1 (0.5)	0.24
Discharge weight (kg) mean (standard deviation)	3.3 (0.7)	3.3 (0.8)	0.83
Infant diet at discharge ¹ n (%)			0.04*
Formula	70 (94.6)	43 (82.7)	
Breastmilk	3 (4.0)	9 (17.3)	
Mixed	1 (1.4)	0 (0)	
Infant Calorie (Kcal/oz) intake at discharge n (%)			

20 Kcal/oz	55 (74.3)	30 (57.7)	0.12
22-24 Kcal/oz	16 (21.6)	20 (38.5)	
>27 Kcal/oz	3 (4.1)	2 (3.8)	
Medicaid beneficiaries n (%)	24 (32.4)	15 (28.8)	0.67
Length of stay/LOS (days) ² median (interquartile range)	15.5 (8-35)	18.5 (8-27)	0.83
Infant's custody at discharge n (%)			
Foster care	27 (36.5)	1 (1.9)	<0.001*
Adoption	4 (5.4)	0 (0)	
Custody to mother, without supervision	37 (50.0)	51 (98.1)	
Custody to mother with supervision	4 (5.4)	0 (0)	
Racial distribution of infants placed in foster care n (%)			
Caucasian	19/ 27 (70.3)	0 (0)	0.19
African American	5/ 27 (18.5)	1 (100)	
Hispanic	2/ 27 (7.4)	0 (0)	
Not reported	1/ 27 (3.7)	0 (0)	
Infants placed in foster care from each Race n (%) (number of severe NOWS infants belonging to that Race as denominator)			
Caucasian	19/54 (35.2)	0	N/A
African American	5/11 (45.5)	1/6	
Hispanic	2/4 (50)	0	
Not reported	1/4 (25)	0	
*p-value significantly different (p<0.05)			

Continuous data presented as mean (standard deviation)

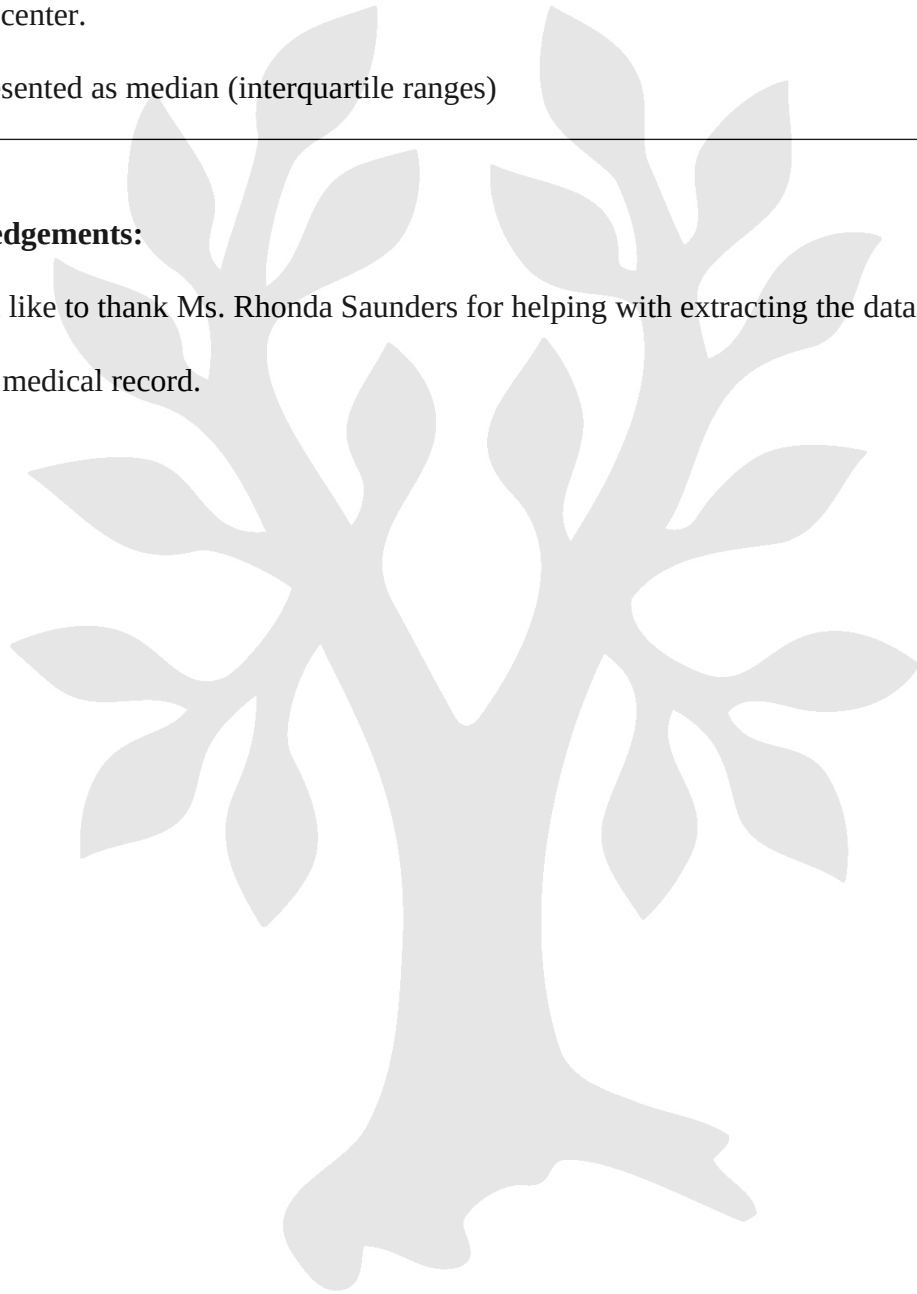
Categorical data presented as number (percentage), compared by Chi-square test or Fisher exact as appropriate.

¹Data on feeding were missing for 1 infant in non-prescribed group whose care was transferred to a different center.

²LOS presented as median (interquartile ranges)

Acknowledgements:

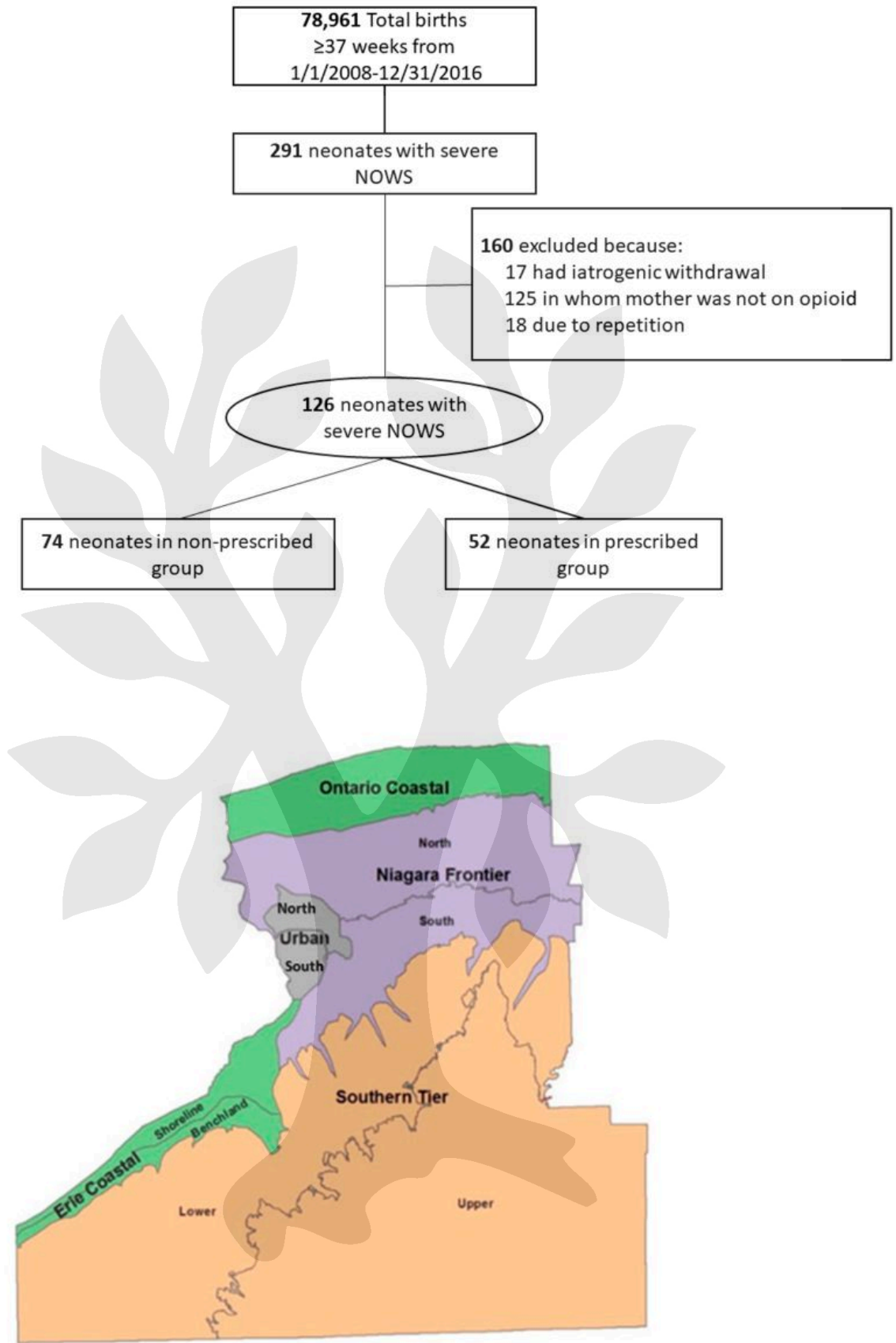
We would like to thank Ms. Rhonda Saunders for helping with extracting the data from the electronic medical record.



Supplement table 1			
	Non-prescribed	Prescribed	
Type of opioid exposure based on history n (%)	Polysubstance abuse/ recreational drug use: 9 (12.2%)	Polysubstance abuse/ recreational drug use: 7 (13.5%)	<0.01*
	Non-prescribed ^a : 4 (5.4%)	Non-prescribed ^a : 0 (0.0%)	
	Prescribed/natural ^b : 40 (54%)	Prescribed/natural ^b : 41 (78.8%)	
	Non-prescribed +prescribed: 19 (25.7%)	Non-prescribed + prescribed: 0 (0.0%)	
	Unclassified: 6 (8.1%)	Unclassified: 4 (7.7%)	
^a Non-prescribed opioids based on history: heroin and fentanyl ^b Prescribed/ natural opioids: buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, kratom, methadone, morphine, norbuprenorphine, nubain, opium, oxycodone, oxymorphone, Percocet, suboxone, subutex, tramadol			

Supplement table 2	
Region	N TOTAL 126
UN	41
US	65
EC	12
NF	5
ST	3

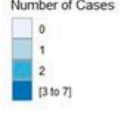
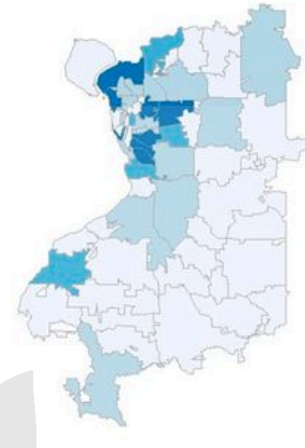
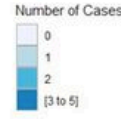
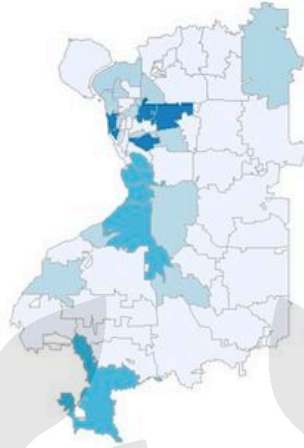
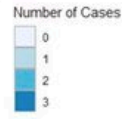
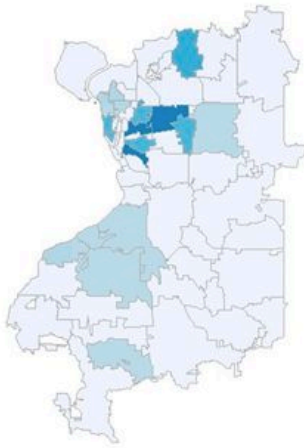




Incidence of severe NOWS 2008 - 10

Incidence of severe NOWS 2011 - 13

Incidence of severe NOWS 2014 - 16



	CI	OR	2.5 %	97.5 %
Year_2008-2010		Ref		
medicaid		0.75	0.51	1.09
Year_2011-2013		1.42	0.89	2.31
Year_2014-2016		2.03	1.31	3.21

CI – confidence interval, OR – odds ratio

Percentage of term infants admitted with severe NOWS out of all term infants born during the study period from each zip code in Erie County

	CI	OR	2.5%	97.5%
region_UN		Ref		
medicaid		0.73	0.49	1.07
region_EC		1.02	0.62	1.72
region_NF		1.01	0.30	2.62
region_ST		1.32	0.21	4.46
region_US		1.76	1.11	2.89

CI – confidence interval, OR – odds ratio

