HHS Public Access

Author manuscript

Hosp Pediatr. Author manuscript; available in PMC 2017 December 01.

Published in final edited form as:

Hosp Pediatr. 2017 June ; 7(6): 328–334. doi:10.1542/hpeds.2016-0218.

Male Sex Associated With Increased Risk of Neonatal Abstinence Syndrome

M. Katherine Charles, MD, MSPH[a], **William O. Cooper, MD, MPH**[a,b,c,d], **Lauren M. Jansson, MD**[e], **Judith Dudley, BA**[c], **James C. Slaughter, DrPH**[a,g], and **Stephen W. Patrick, MD, MPH, MS**[a,b,c,d,f]

[a]Vanderbilt University, School of Medicine, Nashville, Tennessee [b]Department of Pediatrics, Vanderbilt University, Nashville, Tennessee [c]Department of Health Policy, Vanderbilt University, Nashville, Tennessee [g]Department of Biostatistics, Vanderbilt University, Nashville, Tennessee [d]Vanderbilt Center for Health Services Research, Nashville, Tennessee [e]Department of Pediatrics, Johns Hopkins, University School of Medicine, Baltimore, Maryland [f]Mildred Stahlman Division of Neonatology, Vanderbilt University, Nashville, Tennessee

Abstract

BACKGROUND—Neonatal abstinence syndrome (NAS) is a postnatal opioid withdrawal syndrome. Factors associated with development of the syndrome are poorly understood; however, infant sex may influence the risk of NAS. Our objective was to determine if infant sex was associated with the development or severity of the syndrome in a large population-based cohort.

METHODS—This retrospective cohort study used vital statistics and prescription, outpatient, and inpatient administrative data for mothers and infants enrolled in the Tennessee Medicaid program between 2009 and 2011. Multivariable logistic regression models were used to evaluate the association between male sex and diagnosis of NAS, accounting for potential demographic and clinical confounders. NAS severity, as evidenced by hospital length of stay, was modeled by using negative binomial regression.

RESULTS—Of 102 695 infants, 927 infants were diagnosed with NAS (484 male subjects and 443 female subjects). Adjustments were made for the following: maternal age, race, and education; maternal hepatitis C infection, anxiety, or depression; in utero exposure to selective serotonin reuptake inhibitors and cigarettes; infant birth weight, small for gestational age, and year; and the interaction between opioid type and opioid amount. Male infants were more likely than female infants to be diagnosed with NAS (adjusted odds ratio, 1.18 [95% confidence interval,

Address correspondence to Stephen W. Patrick, MD, MPH, MS, Mildred Stahlman Division of Neonatology, Monroe Carell Jr Children's Hospital at Vanderbilt, 11111 Doctor's Office Tower, 2200 Children's Way, Nashville, TN 37232-9544. stephen.patrick@vanderbilt.edu.

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

Drs Patrick and Jansson conceptualized the study; Drs Charles, Slaughter, and Patrick and Ms Dudley conducted the initial analysis; and Dr Charles wrote the first draft of the article. All authors were involved in the analytic plan, interpretation of the results, and revision of the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

1.05–1.33]) and NAS requiring treatment (adjusted odds ratio, 1.24 [95% confidence interval, 1.04–1.47]). However, there was no sex-based difference in severity for those diagnosed with NAS.

CONCLUSIONS—Treatment of NAS should be tailored to an infant's individual risk for the syndrome. Clinicians should be mindful that male sex is an important risk factor in the diagnosis of NAS.

Neonatal abstinence syndrome (NAS) is a drug withdrawal syndrome that occurs after in utero exposure to opioids. The syndrome is characterized by an array of clinical signs, including central nervous system excitability (seizures, hypertonia, temperature instability, irritability, tremors, and excessive crying), respiratory difficulty, and gastrointestinal manifestations (poor feeding, vomiting, uncoordinated sucking, and loose stools).[1,2] From 2000 to 2012, the incidence of NAS throughout the United States increased nearly fivefold, concurrent with an increase in antenatal opioid use.[3–5] The increasing incidence of NAS resulted in a sharp rise in NAS-related costs and NICU utilization.[6–8]

Despite the known increase in socioeconomic burden related to NAS, little is known about the pathophysiologic mechanism of opioid withdrawal in neonates. Previous studies suggest that the type of opioid used, cumulative exposure to short-acting opioids during pregnancy, tobacco use, benzodiazepine use, selective serotonin reuptake inhibitor (SSRI) use, and variants in the *OPRM1* and *COMT* genes may increase the severity of NAS.[9–12] Although some of the published literature suggests that male infants are more likely to be diagnosed with or have more severe NAS,[10,13,14] other studies failed to replicate this finding.[15,16] Furthermore, male infants have been described as having higher rates of jaundice, fetal distress, lower Apgar scores, and higher perinatal mortality.[17–19] Male vulnerability has also been shown in other developmental outcomes, including diminished capacity for self-regulation and increased susceptibility to developmental deficits in infancy.[20,21]

The primary objective of the present study was to determine if male sex was associated with a higher likelihood of being diagnosed with NAS among a large population-based cohort. Our secondary aim was to determine whether male infants with NAS were more likely than female infants with NAS to have a severe, complicated course, as measured by infant length of stay (LOS) during birth hospitalization.

METHODS

Study Design

In this retrospective, longitudinal cohort study of mothers and infants enrolled in Tennessee's Medicaid program (TennCare), inpatient, outpatient, and vital records from 108 different facilities were linked with outpatient prescription claims from 2009 to 2011. All maternal opioid prescriptions reimbursed by TennCare were available in the pharmacy claims data. These data have been used extensively in assessing the safety of medications during pregnancy.[22–24]

Mother–infant dyads were included if they met the following criteria: (1) the mother was 15 to 44 years old at the time of delivery; (2) the mother was enrolled in TennCare at least 30

days before delivery; and (3) the infant was enrolled in TennCare within 30 days of birth. Infants were excluded if they had congenital anomalies reported on either the birth certificate or the inpatient file (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM], codes for congenital anomaly, 740x–759x, excluding codes 747.0 [patent ductus arteriosus] and 747.8 [other anomalies of the circulatory system]) or presumed iatrogenic NAS reported in the inpatient records with the following ICD-9-CM codes: chronic lung disease (770.7), any intraventricular hemorrhage (772.1x), periventricular leukomalacia (779.7), necrotizing enterocolitis (777.5x), or spontaneous bowel perforation (777.6) as previously described.[8,11] A total of 112 852 mother–infant dyads were identified; with 10 145 excluded and 12 infant records missing sex specification, the final sample size comprised 102 695 infants. The study was approved with a waiver by the Vanderbilt University institutional review board, the State of Tennessee Department of Health, and the Bureau of TennCare.

Descriptive Characteristics

Maternal demographic characteristics were collected from the infant's birth certificate, including age in years, maternal race (white, African American, or other), and education in years. Education was categorized into some high school (<12 years), completed high school (12 years), and any college (>12 years). Using the mother's outpatients and inpatient records, we collected the following comorbid conditions (ICD-9-CM code): hepatitis C infection (070.41, 070.44, 070.51, 070.54, and 070.7x), depression (296.2x, 296.3x, and 311), and anxiety disorder (300x).

Infant birth weight and gestational age were collected from the birth certificate. Low birth weight was classified as <2500 g, and preterm birth was classified as <37 weeks. Infants less than the 10th percentile for gestational age according to 2011 US birth weight references were classified as small for gestational age.[25]

Exposures

To account for potential confounding exposures, we obtained antenatal exposure to prescription opioids, SSRIs, and cigarettes. Maternal opioid use was recorded if the mother filled any prescription opioid during pregnancy, obtained from TennCare pharmacy files. Opioid exposure was classified according to drug type: short-acting (eg, oxycodone hydrochloride), long-acting (eg, oxymorphone hydrochloride extended release), or maintenance (eg, methadone, buprenorphine).[11] Opioid doses were converted to oral morphine milligram equivalents for comparison.[8,11] Antenatal SSRI exposure was counted if a maternal prescription was filled within 30 days of delivery. Cigarette use was obtained from birth certificates and then categorized according to 1 to 10, 11 to 20, 21 to 40, and >40 cigarettes per day.

Outcomes

The primary outcome of the present study was NAS, recorded as drug withdrawal syndrome in the newborn (ICD-9-CM code 779.5) anywhere in the infant's birth hospitalization record. This code was previously validated by comparing the accuracy of administrative coding for 779.5[26] versus manual chart review, yielding 88.1% sensitivity and 97%

specificity.[11] As a proxy for severity of NAS expression, we also collected data on infant LOS during birth hospitalization as well as clinical diagnoses previously described in the literature. Clinical conditions (ICD-9-CM code) included transient tachypnea of the newborn (770.6), meconium aspiration syndrome (770.11 and 770.12), respiratory distress syndrome (769x), other respiratory diagnosis (770x excluding 770.7 and codes higher), jaundice (774x), feeding difficulty (779.3x), seizures (779.00 and 780.3), and hemolytic disease (773x). Infants were presumed to be pharmacologically treated if the hospitalization was >6 days, as previous literature has shown that infants with NAS are unlikely to have an LOS <6 days.[1,27]

Statistical Analysis

All covariates in regression models were established a priori from the literature. Bivariate comparisons were analyzed by using the χ^2 and Wilcoxon rank-sum tests. Data were missing or unreliable for <1% of birth weight, gestational age, maternal education, and maternal race. Birth weights <500 g and gestational ages <24 weeks were regarded as unreliable and considered missing. There were missing data for 2.8% of number of cigarettes smoked in the study population. Missing data were handled by multiple imputation with predictive mean matching using 10 imputations.[28] To allow for flexible associations of continuous variables (birth weight, oral morphine equivalents, maternal age, gestational age, number of pregnancies, and number of births) with each outcome, restricted cubic splines were used. Interaction terms were tested between male sex and each of the following: opioid of exposure type (short-acting, long-acting, and maintenance opioids), opioid dose (oral morphine equivalents), birth weight, and SSRI exposure. We also tested the interaction between opioid type and dose. Only the interaction between opioid type and dose was statistically significant for short-acting opioids ($P < .001$) and maintenance opioids ($P < .001$).

Two multivariable logistic regression models were fit, with exposure of interest being male sex and outcomes of NAS and NAS requiring pharmacologic treatment, controlling for cumulative opioid dose, opioid type, opioid dose × opioid type, maternal age, maternal race (white, African American, or other), maternal education, maternal depression or anxiety, maternal SSRI use, cigarette use during pregnancy, maternal hepatitis C infection, birth weight, small for gestational age, and year. The Huber-White sandwich estimator[28] was used to account for correlation arising from taking repeated observations from the same hospital.

For infants diagnosed with NAS, a multivariable negative binomial model was fitted to test the association between male sex and LOS (days), controlling for cumulative opioid dose, opioid type, opioid dose × opioid type, maternal SSRI use, cigarette use during pregnancy, birth weight, small for gestational age, and year. Statistical analyses were completed by using Stata version 14.0 (StataCorp, College Station, TX).

RESULTS

Of the 102 695 infants in the present study, 50.7% were male, and 49.3% were female. There were no significant differences between male and female infants in terms of maternal characteristics, comorbidities, opioid use, and other substances used. Male infants had a

heavier mean birth weight (3235 vs 3119 g; $P < .001$) and were less likely to be low birth weight (8.9% vs 10.7%; $P < .001$), but they were slightly more likely to be preterm (10.9% vs 10.2%; $P < .001$). There was no sex difference in those who were small for gestational age (Table 1).

Among the 927 infants with NAS included in the study, there were similar numbers of male and female subjects (484 vs 443). Sex differences between infants with NAS were similar to the overall birth cohort; however, male infants were more likely to be African American than female infants with NAS (5.4% vs 2.3%; $P = .02$). Male infants with NAS had heavier birth weights (2996 vs 2848 g; $P < .001$) and were less likely to be low birth weight (17.4% vs 23.7%; $P < .02$) than female infants with NAS (Table 2).

In unadjusted analyses, there were no significant differences in health care utilization patterns between male and female infants with NAS. Male infants with NAS were more likely to be diagnosed with transient tachypnea of the newborn (15.7% vs 10.4%; $P = .02$) or other respiratory diagnoses (16.1% vs 11.5%; $P = .04$) with the exception of meconium aspiration syndrome and respiratory distress syndrome. There were no sex-related differences between diagnoses of jaundice, feeding difficulty, seizures, or hemolytic disease in infants with NAS (Table 3).

In the adjusted analyses (accounting for maternal age, race, and education; maternal hepatitis C infection, anxiety, and depression; SSRI and cigarette use; infant birth weight, small for gestational age, and year; and the interaction between opioid type and oral morphine equivalents), male infants were more likely to be diagnosed with NAS (adjusted odds ratio, 1.18 [95% confidence interval (CI), 1.05–1.33]) and more likely to be diagnosed with NAS requiring pharmacologic treatment (adjusted odds ratio, 1.24 [95% CI, 1.04–1.47]) than female infants (Table 4). Among infants with NAS, there was no difference in overall LOS (adjusted incidence rate ratio, 1.07 [95% CI, 0.92–1.24]) or in LOS if pharmacologically treated (adjusted incidence rate ratio, 1.03 [95% CI, 0.91–1.17]) between male and female infants (Table 5).

DISCUSSION

In this large retrospective cohort study of mothers and infants, male infants were more likely to be diagnosed with NAS and NAS requiring pharmacotherapy than female infants, even after accounting for potential confounding factors previously described in the literature. With a total cohort of >100 000 infants, including nearly 1000 infants with NAS, this study represents, to the best of our knowledge, the largest reported cohort to date investigating sex-related differences in incidence and severity of NAS.

These findings contribute to an increasing body of evidence regarding male vulnerability to NAS. Using a large, representative statewide cohort and controlling for multiple previously established confounders, we found that male infants had increased vulnerability to being diagnosed with NAS and NAS requiring pharmacotherapy, although we found no differences in length of hospitalization. Male infants with NAS were diagnosed with associated respiratory difficulties more frequently but were not more likely than female infants to be

diagnosed with other associated clinical complications of NAS. Our results differ from Unger et al,[16] who reported no sex-related differences in the diagnosis of NAS in a secondary analysis of a randomized controlled, multicenter trial that included 131 infants. In a study from Holbrook and Kaltenbach,[15] there was also no difference in male initiation, duration, or dose of treatment among a cohort of 308 infants with NAS. Our findings of no difference in NAS LOS differ from those of Jansson et al.[14] These investigators found that among 64 methadone-exposed infants, male infants had significantly higher NAS scores within the first 4 days of life ($P < .05$), significantly longer treatment duration (13.4 vs 9.0 days; $P < .05$), and significantly longer hospital stays (15.9 vs 12.0 days; $P < .05$), although male infants were not significantly more likely to require treatment. Our study enhances the existing literature by including a large cohort from >100 hospitals, enhancing our power to detect sex differences in NAS and differences in LOS.

There is a growing body of evidence suggesting that male infants and children are more highly impaired than female infants and children after exposure to prenatal and perinatal adversities, although the mechanism by which sex influences early development is still incompletely understood.[29] There is no unifying theory to explain male susceptibility to NAS; however, many hypotheses converge on sex-based differences in neurologic development, with male infants requiring a longer maturation period, thus allowing a prolonged period of vulnerability. A prenatal rodent model has further suggested that mesolimbic opioid receptors in male subjects are more sensitive to methadone exposure than female subjects.[30] Clinical correlates of impaired neurologic function are the hallmarks of NAS, and previous studies have shown that male infants are more susceptible to developing autonomic dysregulation with low vagal tone in response to maternal methadone exposure.[14] Male infants were also more susceptible to maternal vagal lability after methadone administration, which correlated with more severe NAS expression.[13]

Across the United States, opioid use, both licit and illicit, is rapidly increasing, leading to a considerable increase in the annual incidence of NAS.[3,5,7,8,31] There is an urgent need for a more complete understanding of the risk factors that predict the development and severity of NAS to guide clinical care. Biological sex is an important immutable variable, but it is often underappreciated and underinvestigated as a risk factor in early childhood development.[29] Recently, the National Institutes of Health renewed its call for investigators to consider the influence of sex in clinical and preclinical research.[32] Our findings lend additional support for further investigation into sex-related differences in the diagnosis and expression of NAS. A better understanding of sex-based vulnerability can guide the development of health care delivery, tailoring prenatal counseling and postnatal care based on the infant's risk of being diagnosed with NAS.

There are some important limitations to the present study. Our data were obtained from hospital administrative data and vital statistics, and misclassification or omission of important information is possible; however, our previous validation studies using this cohort suggest that this risk is small. Next, we attempted to control for opioid type and amount, and the interaction between these 2 factors; however, this approach may be an imperfect comparison of a diverse class of medications. We accounted for in utero exposures based on previous literature, but it was not possible to capture all possible exposures or to precisely

quantify the amount of each exposure. We make the assumption that infants with an LOS >6 days required pharmacotherapy; however, it is possible that some infants with an LOS >6 days were not treated with a medication for NAS. In addition, there is likely clinician and hospital variability in diagnoses of NAS; to the extent this variation exists, we attempted to account for such differences by accounting for center in our analysis and adjusting the precision of our estimates accordingly. Last, we used LOS as a representation of NAS severity without access to widely accepted scoring tools (the Lipsitz tool, the Finnegan Neonatal Abstinence Scoring System, or the Neonatal Withdrawal Inventory)[33–35] or explicit documentation of pharmacologic treatment; however, LOS may not accurately reflect illness severity.

CONCLUSIONS

Male infants were more likely to be diagnosed with NAS than female infants after controlling for potential confounders. Clinicians should be mindful of an infant's risk for NAS, allowing for individualized health care. Faced with increasing rates of opioid use during pregnancy, continued efforts should be made to understand the factors that predict NAS diagnoses and severity, with careful attention to sex-related differences.

Acknowledgments

We thank the Tennessee Bureau of TennCare of the Department of Finance and Administration for providing the data. We also thank the Office of Health Statistics at the Tennessee Department of Health for providing access to vital records data.

FUNDING: Supported by the National Institute on Drug Abuse of the National Institutes of Health under award number K23DA038720. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Funded by the National Institutes of Health (NIH).

References

1. Hudak ML, Tan RC, Committee on Drugs; Committee on Fetus and Newborn; American Academy of Pediatrics. Neonatal drug withdrawal. Pediatrics. 2012; 129(2) Available at: www.pediatrics.org/cgi/content/full/129/2/e540.
2. Kocherlakota P. Neonatal abstinence syndrome. Pediatrics. 2014; 134(2) Available at: www.pediatrics.org/cgi/content/full/134/2/e547.
3. Creanga AA, Sabel JC, Ko JY, et al. Maternal drug use and its effect on neonates: a population-based study in Washington state. Obstet Gynecol. 2012; 119(5):924–933. [PubMed: 22525903]
4. Desai RJ, Hernandez-Diaz S, Bateman BT, Huybrechts KF. Increase in prescription opioid use during pregnancy among Medicaid-enrolled women. Obstet Gynecol. 2014; 123(5):997–1002. [PubMed: 24785852]
5. Epstein RA, Bobo WV, Martin PR, et al. Increasing pregnancy-related use of prescribed opioid analgesics. Ann Epidemiol. 2013; 23(8):498–503. [PubMed: 23889859]
6. Tolia VN, Patrick SW, Bennett MM, et al. Increasing incidence of the neonatal abstinence syndrome in US neonatal ICUs. N Engl J Med. 2015; 372(22):2118–2126. [PubMed: 25913111]
7. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000–2009. JAMA. 2012; 307(18):1934–1940. [PubMed: 22546608]
8. Patrick SW, Davis MM, Lehman CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. J perinatol. 2015; 35(8):650–655. [PubMed: 25927272]

9. Choo RE, Huestis MA, Schroeder JR, Shin AS, Jones HE. Neonatal abstinence syndrome in methadone-exposed infants is altered by level of prenatal tobacco exposure. Drug Alcohol Depend. 2004; 75(3):253–260. [PubMed: 15283946]
10. O'Connor AB, O'Brien L, Alto WA. Are there gender related differences in neonatal abstinence syndrome following exposure to buprenorphine during pregnancy? J Perinat Med. 2013; 41(5): 621–623. [PubMed: 23612625]
11. Patrick SW, Dudley J, Martin PR, et al. Prescription opioid epidemic and infant outcomes. Pediatrics. 2015; 135(5):842–850. [PubMed: 25869370]
12. Pritham UA, Paul JA, Hayes MJ. Opioid dependency in pregnancy and length of stay for neonatal abstinence syndrome. J Obstet Gynecol Neonatal Nurs. 2012; 41(2):180–190.
13. Jansson LM, Dipietro JA, Elko A, Velez M. Maternal vagal tone change in response to methadone is associated with neonatal abstinence syndrome severity in exposed neonates. J Matern Fetal Neonatal Med. 2007; 20(9):677–685. [PubMed: 17701668]
14. Jansson LM, Dipietro JA, Elko A, Velez M. Infant autonomic functioning and neonatal abstinence syndrome. Drug Alcohol Depend. 2010; 109(1–3):198–204. [PubMed: 20189732]
15. Holbrook A, Kaltenbach K. Gender and NAS: does sex matter? Drug Alcohol Depend. 2010; 112(1–2):156–159. [PubMed: 20576365]
16. Unger A, Jagsch R, Bäwert A, et al. Are male neonates more vulnerable to neonatal abstinence syndrome than female neonates? Gend Med. 2011; 8(6):355–364. [PubMed: 22088886]
17. Bekedam DJ, Engelsbel S, Mol BW, Buitendijk SE, van der Pal-de Bruin KM. Male predominance in fetal distress during labor. Am J Obstet Gynecol. 2002; 187(6):1605–1607. [PubMed: 12501071]
18. Sheiner E, Hadar A, Hallak M, Katz M, Mazor M, Shoham-Vardi I. Clinical significance of fetal heart rate tracings during the second stage of labor. Obstet Gynecol. 2001; 97(5 pt 1):747–752. [PubMed: 11339928]
19. Scrafford CG, Mullany LC, Katz J, et al. Incidence of and risk factors for neonatal jaundice among newborns in southern Nepal. Trop Med Int Health. 2013; 18(11):1317–1328. [PubMed: 24112359]
20. Nagy E, Loveland KA, Orvos H, Molnar P. Gender-related physiologic differences in human neonates and the greater vulnerability of males to developmental brain disorders. J Gend Specif Med. 2001; 4(1):41–49. [PubMed: 11324239]
21. Weinberg MK, Tronick EZ, Cohn JF, Olson KL. Gender differences in emotional expressivity and self-regulation during early infancy. Dev Psychol. 1999; 35(1):175–188. [PubMed: 9923473]
22. Cooper WO, Habel LA, Sox CM, et al. ADHD drugs and serious cardiovascular events in children and young adults. N Engl J Med. 2011; 365(20):1896–1904. [PubMed: 22043968]
23. Cooper WO, Ray WA, Griffin MR. Prenatal prescription of macrolide antibiotics and infantile hypertrophic pyloric stenosis. Obstet Gynecol. 2002; 100(1):101–106. [PubMed: 12100810]
24. Griffin MR, Ray WA, Livengood JR, Schaffner W. Risk of sudden infant death syndrome after immunization with the diphtheria-tetanus-pertussis vaccine. N Engl J Med. 1988; 319(10):618–623. [PubMed: 3261837]
25. Duryea EL, Hawkins JS, McIntire DD, Casey BM, Leveno KJ. A revised birth weight reference for the United States. Obstet Gynecol. 2014; 124(1):16–22. [PubMed: 24901276]
26. Centers for Disease Control and Prevention, Centers for Medicare & Medicaid Services. ICD-9-CM International Classification of Diseases, Ninth Revision, Clinical Modification. Washington, DC: US Department of Health and Human Services, Centers for Disease Control and Prevention; Available at: http://purl.access.gpo.gov/GPO/LPS8749. Accessed February 15, 2016
27. Lainwala S, Brown ER, Weinschenk NP, Blackwell MT, Hagadorn JI. A retrospective study of length of hospital stay in infants treated for neonatal abstinence syndrome with methadone versus oral morphine preparations. Adv Neonatal Care. 2005; 5(5):265–272. [PubMed: 16202968]
28. Harrell, FE. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis. New York, NY: Springer; 2001.
29. DiPietro JA, Voegtline KM. The gestational foundation of sex differences in development and vulnerability. Neuroscience. 2017; 342:4–20. [PubMed: 26232714]

30. Hou Y, Tan Y, Belcheva MM, Clark AL, Zahm DS, Coscia CJ. Differential effects of gestational buprenorphine, naloxone, and methadone on mesolimbic mu opioid and ORL1 receptor G protein coupling. Brain Res Dev Brain Res. 2004; 151(1–2):149–157. [PubMed: 15246701]
31. Lind JN, Petersen EE, Lederer PA, et al. Centers for Disease Control and Prevention (CDC). Infant and maternal characteristics in neonatal abstinence syndrome—selected hospitals in Florida, 2010–2011. MMWR Morb Mortal Wkly Rep. 2015; 64(8):213–216. [PubMed: 25742381]
32. Clayton JA, Collins FS. Policy: NIH to balance sex in cell and animal studies. Nature. 2014; 509(7500):282–283. [PubMed: 24834516]
33. Finnegan LP, Connaughton JF Jr, Kron RE, Emich JP. Neonatal abstinence syndrome: assessment and management. Addict Dis. 1975; 2(1–2):141–158. [PubMed: 1163358]
34. Lipsitz PJ. A proposed narcotic withdrawal score for use with newborn infants. A pragmatic evaluation of its efficacy. Clin Pediatr (Phila). 1975; 14(6):592–594. [PubMed: 1126108]
35. Zahorodny W, Rom C, Whitney W, et al. The neonatal withdrawal inventory: a simplified score of newborn withdrawal. J Dev Behav Pediatr. 1998; 19(2):89–93. [PubMed: 9584937]

TABLE 1

Characteristics of Infants and Mothers According to Infant Sex, TennCare, 2009 to 2011

Characteristic	Male Infants (*n* = 52 146)	Female Infants (*n* = 50 549)	*P*
Maternal characteristics			
Age, mean ± SD, y	24.1 ± 5.2	24.0 ± 5.2	.04
Education			.77
Some high school	12 739 (24.4)	12 340 (24.4)	
Completed high school	21 834 (41.9)	21 269 (42.1)	
Any college	17 573 (33.7)	16 940 (33.5)	
Race			.28
White	35 875 (69.1)	34 916 (69.4)	
African American	15 369 (29.6)	14 787 (29.4)	
Other	706 (1.4)	635 (1.3)	
Maternal comorbidities			
Hepatitis C infection	313 (0.6)	314 (0.6)	.67
Depression	1774 (3.4)	1718 (3.4)	.98
Anxiety disorder	1188 (2.3)	1215 (2.4)	.18
Opioid use characteristics			
Any opioid use	14 481 (27.8)	14 166 (28.0)	.36
Short-acting opioid	14 028 (26.9)	13 680 (27.1)	.19
Long-acting opioid	88 (0.2)	78 (0.2)	
Maintenance opioid	365 (0.7)	408 (0.8)	
Oral morphine equivalents, mean ± SD	1164 ± 5106	1247 ± 5526	.18
Other substance use			
SSRI use in past 30 d	1336 (2.6)	1323 (2.6)	.58
Tobacco use	15 828 (30.4)	15 514 (30.7)	.24
No. of cigarettes/d			
1–10	9713 (64.5)	9390 (63.2)	.09
11–20	3528 (23.4)	3541 (23.8)	
21–40	377 (2.5)	399 (2.7)	
>40	1447 (9.6)	1524 (10.3)	
Infant characteristics			
Gestational age, mean ± SD, mo	38.6 ± 2.1	38.7 ± 2.1	<.001
Preterm (<37 wk)	5678 (10.9)	5141 (10.2)	<.001
Birth weight, mean ± SD, g	3235 ± 575	3119 ± 543	<.001
Low birth weight (<2500 g)	4629 (8.9)	5402 (10.7)	<.001
Small for gestational age	9274 (17.8)	9069 (17.9)	.51

Data are presented as *n* (%) unless otherwise indicated.

TABLE 2

Infant and Maternal Characteristics Associated With NAS Diagnoses According to Infant Sex, TennCare, 2009 to 2011

Characteristic	Male Infants (*n* = 484)	Female Infants (*n* = 443)	*P*
Maternal characteristics			
Age, mean ± SD, y	26.0 ± 4.7	26.2 ± 4.7	.51
Education			.95
Some high school	142 (29.3)	132 (29.8)	
Completed high school	212 (43.8)	196 (44.2)	
Any college	130 (26.9)	115 (26.0)	
Race			.02
White	456 (94.6)	428 (97.3)	
African American	26 (5.4)	10 (2.3)	
Other	—[a]	—[a]	
Maternal comorbidities			
Hepatitis C infection	54 (11.2)	50 (11.3)	.95
Depression	51 (10.5)	48 (10.8)	.88
Anxiety disorder	50 (10.3)	44 (9.9)	.84
Opioid use characteristics			
Any opioid use	298 (61.6)	297 (67.0)	.08
Short-acting opioid	184 (38.0)	175 (39.5)	.32
Long-acting opioid	10 (2.0)	11 (2.5)	
Maintenance opioid	104 (21.5)	111 (25.1)	
Oral morphine equivalents, mean ± SD	10 453 ± 16 080	10 719 ± 16 302	.84
Other substance use			
SSRI use in past 30 d	45 (9.3)	50 (11.3)	.32
Tobacco use	380 (78.9)	361 (81.5)	.26
No. of cigarettes/d			
1–10	103 (21.3)	81 (18.3)	.42
11–20	190 (39.3)	166 (37.5)	
21–40	124 (25.6)	128 (28.9)	
>40	13 (2.7)	19 (4.3)	
Infant characteristics			
Gestational age, mean ± SD, mo	38.2 ± 2.2	38.5 ± 2.0	.07
Preterm (<37 wk)	81 (16.7)	69 (15.6)	.63
Birth weight, mean ± SD, g	2996 ± 541	2848 ± 497	<.001
Low birth weight (<2500 g)	84 (17.4)	105 (23.7)	.02
Small for gestational age	165 (33.1)	155 (35.0)	.77

Data are presented as *n* (%) unless otherwise indicated.

[a] Value <10 and suppressed.

TABLE 3

Outcomes of Infants With NAS According to Sex, TennCare, 2009 to 2011

Variable	Male Infants (*n* = 484)	Female Infants (*n* = 443)	*P*
Newborn health care utilization patterns			
NAS requiring pharmacologic treatment[a]	309 (63.8)	274 (61.9)	.53
LOS, median (IQR)	10 (5–21)	9 (5–19)	.62
LOS if pharmacologically treated, median (IQR)	17 (10–28)	16 (10–29)	.84
Newborn comorbidities			
Transient tachypnea	76 (15.7)	46 (10.4)	.02
Meconium aspiration syndrome	14 (2.9)	13 (2.9)	.97
Respiratory distress syndrome	35 (7.3)	22 (5.0)	.15
Other respiratory diagnosis	78 (16.1)	51 (11.5)	.04
Jaundice	184 (38.0)	155 (35.0)	.34
Feeding difficulty	58 (12.0)	61 (13.8)	.42
Seizures	13 (2.7)	15 (3.4)	.53
Hemolytic disease	11 (2.3)	14 (3.2)	.41

Data are presented as *n* (%) unless otherwise indicated. IQR, interquartile range.

[a]Hospitalization >6 days.

TABLE 4

Adjusted Odds of Male Infants Being Diagnosed With NAS or NAS Requiring Pharmacologic Treatment Compared With Female Infants

Variable	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)
NAS	1.05 (0.93–1.20)	1.18 (1.05–1.33)
NAS requiring pharmacologic treatment	1.09 (0.93–1.29)	1.24 (1.04–1.47)

Total sample = 102 446 infants (249 infants not included due to missing data unable to be imputed). Odds can be interpreted as the likelihood an infant will be diagnosed with NAS. For example, in adjusted analyses, we found that male infants have a higher odds (odds ratio [OR], 1.18) of being diagnosed with NAS, which can be interpreted that male infants are 18% more likely to be diagnosed with NAS. The CI for this finding (1.05–1.33) does not cross 1, meaning that it is a statistically significant outcome.

[a]Adjusted for maternal age, race, and education; maternal hepatitis C infection or psychiatric diagnosis (anxiety or depression); in utero exposure to SSRIs and cigarettes; infant birth weight, small for gestational age, and year; and the interaction between opioid type and opioid amount.

TABLE 5

Adjusted Length of Hospital Stay for Male Infants Diagnosed With NAS and NAS Requiring Pharmacologic Treatment Compared With Female Infants

Variable	Unadjusted IRR (95% CI)	Adjusted IRR[a] (95% CI)
LOS, d	1.04 (0.92–1.17)	1.07 (0.92–1.24)
LOS, pharmacologically treated, d	1.01 (0.90–1.13)	1.03 (0.91–1.17)

Total sample = 927 infants. Incidence rate ratios (IRRs) can be interpreted as percent change. For example, the adjusted LOS for male infants with NAS was 1.07. This finding can be interpreted that male infants have a 7% longer hospitalization than female infants. However, the CI (0.92–1.24) crosses 1, making this finding not statistically significant.

[a]Adjusted for the interaction between opioid type and opioid amount, SSRI or tobacco exposure, small for gestational age, birth weight, and year.