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Comparison of neonatal abstinence syndrome manifestations in preterm versus term opioid-exposed infants

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Abstract

Background—Twenty to 40% of infants exposed to in-utero opioids deliver preterm. There is currently no neonatal abstinence syndrome (NAS) scoring tool known to accurately assess preterm opioid-exposed infants. This can lead to difficulties in titrating pharmacotherapy in this population.

Purpose—To describe NAS symptoms in preterm opioid-exposed infants in comparison with matched full-term controls.

Methods—This was a retrospective cohort study from a single tertiary care center of methadone-exposed infants born between 2006 - 2010. Using modified Finnegan scores recorded every 3-4 hours beginning at 6 hours of life until 24-48 hours after medication discontinuation, NAS symptomatology was compared between 45 preterm infants and 49 full-term matched controls. Concurrent neonatal medical diagnoses were also compared.

Results—The median gestational age in the preterm group was 35 weeks (IQR 33-36) vs 39 weeks (IQR 38-40) in the term group. Preterm infants scored less frequently for many items including sleep disturbance (24.4 vs 46.2%), tremors (77.9 vs 89.7%), muscle tone (87.9 vs 97.4%), sweating (2.1 vs 9.4%), nasal stuffiness (11.9 vs 20.5%), and loose stools (7.0 vs 14.3%) when compared with full-term controls. Preterm infants scored more frequently for hyperactive moro reflex (26.4 vs 5.5%), tachypnea (19.3 vs 16.1%), and poor feeding (24.6 vs 11.8%).

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Implications for Practice—Provider awareness of differences in manifestations of preterm and term NAS infants, as well as concurrent prematurity diagnoses that can influence NAS scoring is needed. These findings mandate the development of a modified NAS scoring tool for the preterm NAS population.

Implications for Research—A preterm NAS scoring tool needs to be developed and validated to more accurately assess and treat preterm opioid-exposed infants.

Keywords

Neonatal Abstinence Syndrome; prematurity; preterm; NAS scoring; Finnegan scale; opioids; methadone

Background

There has been a widespread increase in opioid use disorder across the United States in recent years, with an estimated 5% of pregnant women diagnosed with an opioid use disorder annually.¹ Chronic opioid exposure during the pregnancy puts infants at risk for opioid withdrawal symptoms after birth, a condition known as neonatal abstinence syndrome (NAS). NAS is characterized by central nervous system (CNS) dysregulation and hyperirritability, gastrointestinal disturbances such as poor feeding and diarrhea, autonomic dysregulation, and respiratory abnormalities.² The national incidence of NAS has increased five-fold between 2000 and 2012, now accounting for 3% of all neonatal intensive care unit (NICU) admissions and contributing to significant health expenditures.³⁻⁵

Opioid use disorders in pregnancy are associated with an increased risk for premature delivery. Of all pregnant women on methadone maintenance therapy, 20-40% deliver prematurely, compared with 11% in the general population.⁶⁻⁸ The ideal way to assess and treat premature infants with NAS is unknown, with available symptom-based scoring systems designed for use in full-term infants.^{6,9-16} Few studies have examined NAS manifestations in preterm infants. Preterm infants are reported to have a lower risk developing NAS with lower peak NAS scores than term infants.¹³⁻¹⁴ Preterm infants have also been shown to require lower doses of opioid-replacement medications and have a shorter duration of opioid therapy than infants born at term.¹⁰ It is hypothesized that an underdeveloped CNS, decreased hepatic clearance of methadone, and a lower cumulative in-utero opioid exposure may decrease manifestations of NAS.^{10,14}

Several symptom-based scoring tools have been developed to quantify the presence and severity of symptoms of opioid withdrawal in full-term neonates.^{11-12, 16-17} The Neonatal Abstinence Scoring System (NASS), more commonly referred to as the Finnegan Scale, requires frequent monitoring of the infant and recording of the presence and severity of 31 items.¹¹ NASS has become the most commonly used tool to guide pharmacologic treatment. Using this scale as part of a strict assessment and pharmacologic weaning protocol has been shown to result in a shorter duration of treatment and shorter length of hospital stay.¹⁸ The NASS was validated for use with infants delivered at term, but has not been evaluated in preterm infants.¹¹ An intra-observer reliability program exists for the NASS and is widely used as best practice for term NAS infants to ensure consistency in assessments. The other

available scoring tools such as the Lipsitz scale, Neonatal Narcotic Withdrawal Index, Neonatal Withdrawal Inventory, and the MOTHER study modified Finnegan were also designed for use in full-term infants but are less frequently used in clinical practice.^{11-12,16-17,19} It is unclear how prematurity and its own associated morbidities affect the ability of the available NAS scoring tools to accurately capture NAS symptoms in the preterm population.²⁰

As preterm delivery is increased in the presence of maternal opioid use disorders, it is important to accurately identify and appropriately treat NAS in these infants.^{6,13} The objective of this study was to compare the NAS symptom profile in preterm methadone-exposed infants versus matched term controls as a first step towards developing a custom NAS scoring tool for preterm infants that will help to guide optimal pharmacologic treatment of this high-risk population.

Methods

Study Design

This was a retrospective cohort study of pregnant women with opioid use disorders and their infants delivered at Boston Medical Center (BMC), a tertiary care center with a Level III NICU, from June 2006 through December 2010. BMC cares for the largest population of NAS infants in Massachusetts and one of the largest in the country with 150 opioid-exposed newborns annually. BMC has a specialty prenatal clinic Project RESPECT which is an established national leader in the care of pregnant women with substance use disorders.²¹

The entire database included 332 infants from 326 pregnancies that were born to 310 women on methadone or buprenorphine maintenance therapy. This study was approved by the Boston University Medical Center Institutional Review Board. There were 45 methadone-exposed preterm (<37 weeks gestational age) infants during the study period, and 6 preterm buprenorphine-exposed in the database. Given the small number of preterm buprenorphine-exposed infants, only the methadone-exposed were examined in this study. From the remaining 200 full-term methadone-exposed infants, 49 were randomly selected as matched controls. Controls were matched based on month and year of birth, and then compared for baseline characteristics.

Data were obtained from electronic medical records and included maternal age, prenatal drug exposures, details of methadone and buprenorphine treatment during the pregnancy, concomitant psychiatric medication use, gestational age at delivery, mode of delivery, infant birth weight, infant co-morbidities and diagnoses, as well as neonatal abstinence scores using a modified Finnegan scale (**Appendix A**), amount and duration of NAS pharmacologic treatment and length of infant hospital stay. The frequency of scoring for each Finnegan item was collected for all infants over the duration of their hospitalization. Infants were scored every 3-4 hours with routine newborn cares starting within 6 hours of birth and continuing either until 5-7 days of life (for infants who do not require pharmacotherapy) or 24-48 hours after discontinuation of medication. Pharmacologic treatment with first-line therapy was initiated if the infant had three consecutive modified Finnegan scores ≥ 8 or two consecutive scores ≥ 12 . First-line therapy for NAS varied during

the study period, with phenobarbital used until 2006, then diluted tincture of opium (DTO) of 0.4 mg morphine/mL from 2006-2009, and infants delivered mid-January 2009 through December 2010 had first-line treatment with neonatal morphine solution. In our statistical analyses, the amount of morphine in the total DTO dose administered was determined for DTO treated neonates. Morphine dosing was based on both severity of scores and neonatal birth weight. Adjunctive therapy with phenobarbital or clonidine was added for infants who continued to have scores ≥ 8 despite maximum dosing of DTO or morphine. Infants were weaned off DTO, morphine, and/or clonidine as inpatients and monitored for 24 – 48 hours prior to discharge. Phenobarbital was weaned in the outpatient setting.

Statistical Methods

Maternal and infant demographics factors, and infant NAS outcomes were compared using independent sample t-tests and chi-square as appropriate in the preterm versus term groups. Then, the frequency of scoring for each Finnegan item was compared using chi-square in the preterm versus term infants. Median, interquartile range (IQR), risk difference, risk ratio, and corresponding 95% confidence intervals were calculated. A multivariable model was then created adjusting for covariates associated with both preterm birth and NAS outcomes including prenatal use of psychiatric medications. Assuming an average of 20 days of 6 Finnegan scores per day per infant, we will have over 90% power to detect a 5% difference in scoring frequency between the preterm and term groups. Among infants with diagnoses of respiratory disorders (meconium aspiration, respiratory distress syndrome, transient tachypnea of the newborn), feeding difficulties (immature feeding requiring feeding tube), necrotizing enterocolitis, neurologic disorders (intraventricular hemorrhage, hypoxic ischemic encephalopathy), sepsis, and temperature instability requiring isolette we compared the proportion of scoring for related items on the Finnegan scale. All analyses were performed using SAS (Version 9.4).

Results

The demographics of our mother-infant pairs are shown in **Tables 1** and **2**. The median GA was 39 weeks (IQR 38-40) in the term group (n=49) and 35 weeks (IQR 33-36) in the preterm group (n=45). More mothers in the preterm group were taking prescribed psychiatric medications (**Table 1**). The median birth weight was lower, and incidence of respiratory diagnoses, feeding immaturity, and temperature instability were higher in the preterm group. NAS outcomes including need for pharmacologic treatment (98% in the term versus 91% in the preterm), need for adjunctive medication therapy, and length of hospitalization did not differ significantly between the two groups (**Table 2**).

A total of 6544 scores for the preterm and 7422 scores from the term infants were documented, with a mean of 149 scores per infant during the hospitalization (**Table 3**). Preterm infants differed significantly in frequency of scoring for 14 out of the 19 items on the Finnegan scoring tool. (**Figure 1**) Specifically, preterm infants scored less frequently for sleep disturbance, tremors, restlessness, increased muscle tone, excoriations, sweating, fever, nasal stuffiness, sneezing, excessive sucking, and loose stools in comparison with full-term controls ($p<0.05$). Preterm infants scored more frequently for hyperactive moro reflex,

tachypnea, and poor feeding ($p<0.05$). The preterm group scored for items sweating, yawning, nasal flaring, and regurgitation / vomiting less than 5% of the time ($p<0.05$) (**Figure 1, Table 3**). When adjusted for exposure to any psychiatric medication (benzodiazepines, SSRIs, and/or other psychiatric medications), the mean differences in scoring frequency between preterm and term groups for restlessness, fever, tachypnea, excessive sucking, regurgitation, loose stools, and excoriations were no longer statistically significant. Adjustment for psychiatric medications increased the mean differences in scoring frequency between preterm and term infants for crying, sleep, moro reflex, tremors, tone, sweating, nasal stuffiness, sneezing, and poor feeding ($p<0.05$).

For infants with a respiratory diagnosis, frequency of scoring for the Finnegan item of respiratory distress was higher when compared with infants without a respiratory diagnosis [25.7% versus 17.5%, mean difference of 8.3% (95% CI 5.6-10.3%), $p<0.05$]. Similarly, for infants with a diagnosis of feeding immaturity requiring nasogastric feedings, frequency of scoring for the Finnegan item of feeding immaturity was higher [31.7% versus 19.1%, MD 19.3% (95% CI 17.0-21.7%), $p<0.05$]. No preterm infants with a diagnosis of temperature instability requiring an isolette were scored for fever.

Discussion

We compared preterm and term methadone-exposed infants for NAS symptomatology using a modified Finnegan scale, finding significant differences in frequency of scoring for a majority of items on the scale. Specifically, we found that premature infants scored less frequently for autonomic, respiratory, and gastrointestinal symptoms. Symptomatology was influenced by co-exposure to maternal psychiatric medications. The differences in NAS symptomatology in preterm infants and frequency of concurrent diagnoses that cloud assessments necessitate the development of a modified scoring tool for the preterm NAS population.

Altered neurobehavior, including an inability to appropriately manage stimulation and stress, including during routine newborn care such as diapering and vital signs is normal for preterm infants, but determining whether yawning, sneezing and mottling are due to NAS or prematurity is left to the caregivers' interpretation.²² Preterm infants demonstrate poor self-regulation and higher stress than term infants. Tone and reflexes are decreased among even healthy preterm infants, therefore scoring items such as hypertonia are difficult to assess in the setting of concurrent NAS.²² Due to lack of brown fat and inability to regulate temperature, heated isolettes are frequently utilized. Depending on the probe position, temperature setting and other ambient factors, hyperthermia can result from iatrogenic causes and can complicate NAS scoring. Nasal flaring, tachypnea and retractions are often due to respiratory distress syndrome, a known complication of prematurity related to lack of surfactant, and its relationship to NAS is difficult to discern. Poor feeding is a frequent finding of premature infants until after 32-34 weeks, thus poor feeding is not a precise scoring component of NAS among preterm infants. Further, regurgitation is often the result of poor lower gastro-esophageal tone, presence of a nasogastric tube and potentially not related to NAS.²⁰

Of particular importance in this discussion is the immaturity of the preterm brain. Preterm infants are born during a critical period of rapid brain growth and development; this can be altered by the environment and postnatal treatments, putting infants at much higher risk for neurodevelopmental impairment than their term counterparts.²³ Infants with in-utero opioid exposure are also at risk for adverse neurodevelopmental outcomes, with higher reported rates of developmental delays compared with the general population.²⁴⁻²⁶ The combination of preterm birth and in-utero opioid exposure puts the infant at particularly high risk for poor neurodevelopmental outcomes.

The majority of preterm infants in our study were treated with replacement opioids for NAS. There are currently no standardized treatment guidelines for preterm opioid-exposed infants, with institutional practice varying greatly and lack of any randomized trials. Opioid withdrawal, if inadequately treated, can be painful for the preterm infant, increasing stress which could negatively affect short-term and long-term outcomes.²⁷⁻²⁸ On the other hand, treatment with medications such as morphine during this critical period of brain growth comes with potential risk of impaired neurodevelopment.²⁹⁻³⁰ There is conflicting evidence on the treatment of pain in the preterm infant, with providers needing to balance the risk of pain and stress with the risk of the medication exposure. A recent study by Zwicker et al found that very preterm infants exposed to neonatal morphine had decreased cerebellar growth and worse cognitive outcomes at 18 months of age.³¹ However, other studies have found that these initial differences did not persist once children were school-aged.^{29-30,32} More definitive studies are needed before recommendations can be made.

We found an increased prevalence of psychiatric medication exposure in our preterm group. Concurrent use of psychiatric medications such as benzodiazepines and selective serotonin reuptake inhibitors (SSRIs) have been associated with more severe NAS, with higher rates of medication treatment and longer hospitalizations.³³⁻³⁴ The likely influenced the distribution of Finnegan scores particularly neurologic symptoms which are typically associated with these medications.³⁵ We therefore adjusted our results for psychiatric medication exposure; results remained significant for many of the scoring items. Maternal psychiatric illness and psychiatric medication use has been reported as associated with preterm birth, presumably related to higher maternal stress.³⁶⁻³⁷ We also hypothesize that those women who delivered preterm were more unstable in their addiction with higher rates of illicit opioid use and perhaps higher rates of psychiatric co-morbidities.

The next step in this research is to develop and validate a preterm infant scoring tool, keeping in mind which symptoms are more common and specific for opioid withdrawal in the preterm population, and addressing the issue of co-morbid preterm medical diagnoses. The validation process should include intra-observer reliability between providers, and should be tested in a blinded fashion between opioid exposed and control preterm infants to establish validity. In addition, the cut-off score for initiation of pharmacologic treatment should be determined using receiver operating characteristic (ROC) curves before used in clinical practice. Determination of the best pharmacologic treatment regimens for preterm infants who do require therapy also requires further research.

Strengths of this study include a detailed description of preterm infant symptomatology for NAS in comparison to full-term infants from a center that specializes in the care of substance exposed newborns. This study however has a number of limitations. First, results are based on retrospective data collection of infant's scores, without real-time assessment of the infants and face-to-face nursing feedback on the scoring. No standardized scoring was used to ensure intra-rater reliability during the study period, however, since 2013, all nurses at our hospital have undergone a reliability training program for Finnegan scoring with re-certification every 2 years. This was a retrospective study that aimed to identify general differences in symptomatology of preterm versus term infants as a first step in development of a new scoring tool for preterm infants. The BMC NAS treatment algorithm also changed over the study period, and nonpharmacologic care for the NAS population was not as strongly emphasized as it is in current practice.

In conclusion, preterm and term infant have different NAS symptomatology and the currently available scoring tools are difficult to use in the preterm population. A scoring tool tailored to the unique characteristics of preterm infants can more accurately, and objectively, capturing the experience of preterm infants with prenatal substance exposure and allow for better tailoring of pharmacologic management. This could lead to improved outcomes for this group of high-risk infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. U.S. Department of Health and Human Services, Substance Abuse and Mental Health Administration. Results from the 2011 National Survey on Drug Use and Health: National Findings. SAMHSA; <http://www.samhsa.gov/>. Published 2011. [May 21, 2016]
2. Kocherlakota P. Neonatal abstinence syndrome. *Pediatrics*. 2014; 134(2):e547–e561. doi: 10.1542/peds.2013-3524. [PubMed: 25070299]
3. 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. doi: 10.1001/jama.2012.3951. [PubMed: 22546608]
4. 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):667. doi: 10.1038/jp.2015.63.
5. Tolia VN, Patrick SW, Bennett MM, et al. Increasing incidence of the neonatal abstinence syndrome in U.S. neonates. *N Engl J Med*. 2015; 372(22):2118–2126. doi: 10.1056/NEJMs1500439. [PubMed: 25913111]
6. Almario CV, Seligman NS, Dysart KC, Berghella V, Baxter JK. Risk factors for preterm birth among opiate-addicted gravid women in a methadone treatment program. *Am J Obstet Gynecol*. 2009; 201(326):e1–6. doi: 10.1016/j.ajog.2009.05.052. [PubMed: 19631928]
7. Berghella V, Lim PJ, Hill MK, Cherpes J, Chennat J, Kaltenbach K. Maternal methadone dose and neonatal withdrawal. *Am J Obstet Gynecol*. 2003; 189(2):312–317. [PubMed: 14520184]
8. Martin, JA.; Hamilton, BE.; Ventura, SJ., et al. National Vital Statistics Reports: From the Centers for Disease Control and Prevention. Vol. 60. National Center for Health Statistics, National Vital Statistics System; 2011. Births: Final data for 2009.; p. 1-70.
9. Doberczak TM, Kandall SR, Wilets I. Neonatal opiate abstinence syndrome in term and preterm infants. *J Pediatr*. 1991; 118(6):933–937. [PubMed: 2040931]

10. Dysart K, Hsieh H, Kaltenbach K, Greenspan JS. Sequela of preterm versus term infants born to mothers on a methadone maintenance program: differential course of neonatal abstinence syndrome. *J Perinat Med.* 2007; 35(4):344–346. [PubMed: 17511598]
11. Finnegan, LP.; Kron, RE.; Connaughton, JF.; Emich, JP. Basic and Therapeutic Aspects of Perinatal Pharmacology. Raven Press; New York, NY: 1975. A scoring system for evaluation and treatment of the neonatal abstinence syndrome: A new clinical and research tool.; p. 139-153.
12. Lipsitz PJ. A proposed narcotic withdrawal score for use with newborn infants. *Clin Pediatr (Phila).* 1975; 14(6):592–594. [PubMed: 1126108]
13. Liu WF, Singh K, Faisal M, Li S. Maternal methadone treatment and neonatal abstinence syndrome. *Am J Perinatol.* 2015; 32(11):1078–86. doi: 10.1055/s-0035-1549218.
14. Ruwanpathirana R, Abdel-Latif ME, Burns L, et al. Prematurity reduces the severity and need for treatment of neonatal abstinence syndrome. *Acta Paediatr.* 2015; 104(5):e188–194. doi: 10.1111/apa.12910. [PubMed: 25620086]
15. Casper T, Arbour M. Evidence-based nurse-driven interventions for the care of newborns with neonatal abstinence syndrome. *Adv Neonatal Care.* 2014; 14(6):376–80. doi: 10.1111/jmwh.12087. [PubMed: 25068529]
16. Maguire D, Cline GJ, Parnell L, Tai CY. Validation of the Finnegan neonatal abstinence syndrome tool-short form. *Adv Neonatal Care.* 2014; 14(6):376–80. doi: 10.1097/ANC.0000000000000033. [PubMed: 25068529]
17. 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]
18. Hall ES, Wexelblatt SL, Crowley M, et al. A multicenter cohort study of treatments and hospital outcomes in neonatal abstinence syndrome. *Pediatrics.* 2014; 134(2):e527–e534. doi: 10.1542/peds.2013-4036. [PubMed: 25070317]
19. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med.* 2010; 363:2320–2331. doi: 10.1056/NEJMoa1005359. [PubMed: 21142534]
20. McIntire DD, Leveno KJ. Neonatal mortality and morbidity rates in late preterm births compared with births at term. *Obstet Gynecol.* 2008; 111(1):35–41. doi: 10.1097/01.AOG.0000297311.33046.73. [PubMed: 18165390]
21. Boston Medical Center. [January 15, 2016] Project RESPECT. <http://www.bmc.org/obgyn/services/specialprograms-project-respect.htm>.
22. Pineda RG, Tjoeng TH, Vavasseur C, et al. Patterns of altered neurobehavior in preterm infants within the neonatal intensive care unit. *J Pediatr.* 2013; 162(3):470–476. e1. doi: 10.1016/j.jpeds.2012.08.011. [PubMed: 23036482]
23. Pickler RH, McGrath JM, Reyna BA, et al. A Model of Neurodevelopmental Risk and Protection for Preterm Infants. *J Perinat Neonatal Nurs.* 2010; 24(4):356–65. doi: 10.1097/JPN.0b013e3181fb1e70. [PubMed: 21045616]
24. D'Apolito K. Substance abuse: infant and childhood outcomes. *J Pediatr Nurs.* 1998; 13(5):307–316. [PubMed: 9798367]
25. Ornoy A, Segal J, Bar-Hamburger R, et al. Developmental outcome of school-age children born to mothers with heroin dependency: Importance of environmental factors. *Dev Med Child Neurol.* 2001; 43:668–675. [PubMed: 11665823]
26. Sundelin Wahlsten V, Sarman I. Neurobehavioural development of preschool-age children born to addicted mothers given opiate maintenance treatment with buprenorphine during pregnancy. *Acta Paediatr.* 2013; 102:544–549. doi: 10.1111/apa.12210.
27. Whitfield MF, Grunau RE. Behavior, pain perception, and the extremely low-birth weight survivor. *Clin Perinatol.* 2000; 27(2):363–79. [PubMed: 10863655]
28. Ranger M, Grunau RE. Early repetitive pain in preterm infants in relation to the developing brain. *Pain Manag.* 2014; 4(10):57–67. doi: 10.2217/pmt.13.61. [PubMed: 24641344]
29. McPherson C, Grunau RE. Neonatal pain control and neurologic effects of anesthetics and sedatives in preterm infants. *Clin Perinatol.* 2014; 41(1):209–27. doi: 10.1016/j.clp.2013.10.002. [PubMed: 24524456]

30. Kaneyasu M. Pain management, morphine administration, and outcomes in preterm infants: a review of the literature. *Neonatal Netw.* 2012; 31(1):21–30. doi: 10.1891/0730-0832.31.1.21. [PubMed: 22232038]
31. Zwicker JG, Miller SP, Grunau RE, et al. Smaller Cerebellar Growth and Poorer Neurodevelopmental Outcomes in Very Preterm Infants Exposed to Neonatal Morphine. *J Pediatr.* 2016; 172:81–87. e2. doi: 10.1016/j.jpeds.2015.12.024. [PubMed: 26763312]
32. Steinhorn R, McPherson C, Anderson PJ, et al. Neonatal morphine exposure in very preterm infants – cerebral development and outcomes. *J Pediatr.* 2015; 166(5):1200–1207. e4. doi: 10.1016/j.jpeds.2015.02.012. [PubMed: 25919729]
33. Wachman EM, Newby PK, Vreeland J, et al. The relationship between maternal opioid agonists and psychiatric medications on length of hospitalization for neonatal abstinence syndrome. *J Addict Med.* 2011; 5(4):293–9. doi: 10.1097/ADM.0b013e3182266a3a. [PubMed: 21857233]
34. Patrick SW, Dudley J, Martin PR, et al. Prescription opioid epidemic and infant outcomes. *Pediatrics.* 2015; 135(5):842–50. doi: 10.1542/peds.2014-3299. [PubMed: 25869370]
35. Kieviet N, van Ravenhorst M, Dolman KM, et al. Adapted Finnegan scoring list for observation of anti-depressant exposed infants. *J Matern Fetal Neonatal Med.* 2015; 28(17):2010–4. doi: 10.3109/14767058.2014.977247. [PubMed: 25316560]
36. Yonkers KA, Norwitz ER, Smith MC, et al. Depression and serotonin reuptake inhibitor treatment as risk factors for preterm birth. *Epidemiology.* 2012; 23(5):677–85. [PubMed: 22627901]
37. Yonkers JA, Smith MV, Forray A, et al. Pregnant women with posttraumatic stress disorder and risk of preterm birth. *JAMA Psychiatry.* 2014; 71(8):897–904. doi: 10.1001/jamapsychiatry.2014.558. [PubMed: 24920287]

What this Study Adds: This study highlights the differences in symptom profile between preterm and term opioid-exposed infants, necessitating development of a preterm NAS scoring tool.

Figure 1. Frequency of scoring for Finnegan scale items in preterm (n=45) versus term (n=49) infants. Scoring items with frequency <5% for both preterm and term infants (seizures, yawning, nasal flaring, regurgitation) are not included. * indicates p-value <0.05.

Table 1**Maternal Demographics**

Variable	Preterm (N=45) N(%)	Full-term (N=49) N(%)	Relative Risk / Mean difference* (95% CI)
Maternal age (years) (Median, IQR)	27 (24-34)	27 (25-30)	0.46 (−1.94, 2.86)
Dose of methadone at delivery (mg/day) (Median, IQR)	60 (50-83)	65 (40-85)	−1.98 (−16.28, 12.32)
C-section delivery	27 (60.0)	21 (42.9)	1.40 (0.94, 2.09)
Nicotine smoking in third trimester	32 (71.1)	34 (69.4)	1.02 (0.79, 1.33)
Breastfed to any extent	4 (8.9)	7 (14.3)	0.62 (0.19, 1.98)
Psychiatric medications			
Benzodiazepines	9 (20.0)	6 (12.2)	1.63 (0.63, 4.23)
SSRIs	12 (26.7)	6 (12.2)	2.61 (1.00, 6.84)
Other	10 (22.2)	3 (6.1)	3.63 (1.07, 12.36)
Illicit / un-prescribed drug use			
Opioids	22 (48.9)	17 (34.7)	1.41 (0.87, 2.29)
Cocaine	12 (26.7)	14 (28.6)	0.93 (0.48, 1.80)

Key: SSRIs = Selective serotonin reuptake inhibitors; Other psychiatric medications = antipsychotics, clonidine, tricyclic antidepressants, or wellbutrin; Opioids = heroin or un-prescribed oxycodone; IQR = inter-quartile range

* Relative risk / mean differences calculated with term infants as the reference group, and preterm infants as the comparison group.

Table 2

Infant Demographics and NAS Outcomes

Variable	Preterm (N=45) N(%)	Full-term (N=49) N(%)	Relative Risk / Mean difference (95% CI) *
Gestational age (weeks) (Median, IQR)	35 (33-36)	39 (38-40)	-5.04 (-5.78, -4.31)
Birth weight (grams) (Median, IQR)	2215 (1880 - 2535)	2995 (2695 - 3280)	-849.66 (-1052.11, -647.21)
Infant diagnoses			
Neurologic	0	0	-
Sepsis	0	0	-
Necrotizing Enterocolitis	0	0	-
Respiratory	9 (20.0)	1 (2.0)	7.08 (1.69, 29.65)
Feeding immaturity	19 (42.2)	7 (14.3)	2.96 (1.37, 6.36)
Temperature	16 (35.6)	0	
NAS Outcomes			
Need for Treatment	41 (91.1)	48 (98.0)	0.93 (0.84, 1.03)
Need for 2 Meds	12 (26.7)	12 (24.5)	1.09 (0.55, 2.17)
Length of Rx (days)	18 (12-26)	17 (14-22)	1.27 (-2.64, 5.17)
Length of hospitalization (days) (Median, IQR)	24 (18-33)	20 (19-27)	3.55 (-1.01, 8.12)

Key: NAS = Neonatal abstinence syndrome; Rx = treatment; IQR = inter-quartile range; Neurologic = diagnosis of intraventricular hemorrhage or hypoxic ischemic encephalopathy; respiratory = diagnosis of respiratory distress syndrome, transient tachypnea of the newborn, meconium aspiration syndrome; feeding immaturity = required nasogastric tube for feeding; temperature = required isolette for temperature instability

* Relative risk / mean differences calculated with term infants as the reference group, and preterm infants as the comparison group.

Table 3

Preterm infant scoring item frequency

Scoring Item	Scoring Frequency and % of all scores Preterm (N=45)	Scoring Frequency and % of all scores Term (N=49)	% difference between Preterm and Term (95% CI)	% difference adjusted for psychiatric medications (95% CI) *
Crying	414 (6.3)	545 (7.3)	-1.0 (-1.8, -0.1)	-2.4 (-7.2, 2.4)
Sleep	1599 (24.4)	3442 (46.2)	-21.8 (-23.3, -20.3)	-36.0 (-51.2, -20.9)
Hyperactive Moro	1728 (26.4)	410 (5.5)	20.9 (19.7, 22.1)	28.0 (14.1, 41.8)
Tremors	5095 (77.9)	6674 (89.7)	-11.8 (-13.0, -10.6)	-30.5 (-54.3, -6.6)
Restlessness	802 (12.3)	1112 (14.9)	-2.7 (-3.6, -1.7)	-6.4 (-13.7, 0.8)
Muscle tone	5755 (87.9)	7247 (97.4)	-9.4 (-10.3, -8.6)	-25.6 (-50.5, -0.8)
Excoriations	472 (7.2)	718 (9.6)	-2.4 (-3.2, -1.7)	-4.5 (-10.9, 1.9)
Seizures	1 (0.01)	3 (0.04)	-0.03 (-0.08, 0.03)	-0.04 (-0.14, 0.07)
Sweating	141 (2.1)	702 (9.4)	-7.3 (-7.9, -6.7)	-12.9 (-14.6, -2.7)
Fever	1284 (19.6)	1659 (22.3)	-2.7 (-4.0, -1.3)	-6.8 (-13.8, 0.2)
Yawning	27 (0.4)	43 (0.6)	-0.2 (-0.4, 0.07)	-0.4 (-0.8, 0.05)
Nasal stuffiness	779 (11.9)	1525 (20.5)	-8.6 (-9.8, -7.4)	-16.7 (-31.6, -1.9)
Sneezing	457 (7.0)	842 (11.3)	-4.3 (-5.3, -3.4)	-7.0 (-10.8, -3.1)
Nasal flaring	7 (0.1)	18 (0.2)	-0.1 (-0.3, 0.0)	-0.2 (-0.5, 0.2)
Tachypnea	1266 (19.3)	1197 (16.1)	3.3 (2.0, 4.5)	2.2 (-8.0, 12.3)
Excessive sucking	767 (11.7)	1044 (14.0)	-2.3 (-3.4, -1.2)	-4.4 (-11.3, 2.6)
Poor feeding	1610 (24.6)	879 (11.8)	12.8 (11.5, 14.0)	15.0 (1.2, 29.0)
Regurgitation or vomiting	268 (4.1)	249 (3.3)	0.8 (0.1, 1.4)	0.7 (-1.8, 3.3)
Loose stools	457 (7.0)	1066 (14.3)	-7.3 (-8.4, -6.3)	-12.4 (-18.1, 6.7)
Total number of scores	6544	7442		

* Results adjusted for variable of any psychiatric medication exposure, including benzodiazepines, SSRIs, and other psychiatric medications.