

ARTICLE



Characteristics and outcomes of neonatal opioid withdrawal syndrome in preterm infants: a retrospective cohort study in the current era

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OBJECTIVE: Compare Neonatal Opioid Withdrawal Syndrome (NOWS) in preterm and term infants.

STUDY DESIGN: Single center, retrospective chart review of all in-utero opioid exposed infants born between 2014 and 2019. Withdrawal symptoms were assessed using Modified Finnegan Assessment Tool.

RESULTS: Thirteen preterm (PT), 72 late preterm (LPT), and 178 term infants were included. Preterm and LPT compared to term infants had lower peak Finnegan scores (9/9 vs. 12) and received less pharmacologic treatment (23.1/44.4 vs. 66.3%). Similar onset, peak symptoms, and treatment duration was observed in LPT and term infants.

CONCLUSIONS: Preterm and LPT infants have lower Finnegan scores and require less pharmacologic therapy for NOWS. It is unclear if this is because our current assessment tool does not capture their symptoms or if they truly have less withdrawal. Onset of NOWS is similar in LPT and term infant, thus LPT infants do not require prolonged hospital monitoring for NOWS.

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INTRODUCTION

Opioid use in pregnancy has increased since the early 2000's, resulting in increased rates of Neonatal Opioid Withdrawal Syndrome (NOWS) and neonatal intensive care unit (NICU) admissions. Between 2004 and 2016, the incidence of neonatal abstinence syndrome (NAS) in the United States increased from 1.5 to 6.7 per 1000 hospital births, a more than six-fold increase [1].

NOWS is a condition describing the array of symptoms and neuro-behaviors experienced by a newborn withdrawing from in utero opioid exposure [2–4]. These symptoms affect multiple organ systems including: the central and autonomic nervous systems (CNS and ANS) as well as the gastrointestinal (GI) system. Specific symptoms include: hyperirritability, tremors, hypertonia, seizures, feeding and sleeping difficulties, tachypnea, temperature instability, and watery stools.

While much study has been devoted to improving the care of infants with prenatal opioid exposure, the majority of this research has focused on term infants. Our knowledge of how preterm infants are affected by NOWS is lacking. The few studies which have described NOWS in the preterm population have been small cohort studies of infants born prior to 2010 and often were limited to infants born to mothers who were in medication assisted treatment [5–8]. They described differing manifestations and severity of withdrawal between preterm and term infants. Doberczak et al. found preterm infants were less likely to require treatment, with later peak severity and less severe abstinence symptoms [5]. Similar findings were reported by Dysart et al.

describing shorter lengths of stay, shorter duration of treatment and lower maximum doses of pharmacotherapy [6], and Ruwanpathirana et al. describing lower maximum Finnegan scores, fewer preterm infants requiring treatment, and lower maximum doses of pharmacotherapy [8]. Allocco et al. were the first to describe differences in the presentation of symptoms based on the Finnegan scoring tool between preterm and term infants [7]. They reported preterm infants scored less frequently for sleep disturbances, tremors, hypertonicity, sweating, nasal stuffiness and loose stools, and more frequently for hyperactive moro, tachypnea and poor feeding [7]. One recent publication described pharmacologic outcomes for infants born between 2000 and 2014. They found no difference in initiation of pharmacologic treatment across gestational age groups, but did find that late preterm infants had a shorter treatment course than term infants [9]. It is important to note these cohorts are from the early phase of this current opioid epidemic, and likely do not reflect current prenatal exposures including increasing fentanyl and polysubstance or polydrug use.

The lack of evidence-based practice for the treatment of NOWS in preterm neonates, especially in the most recent phase of the opioid epidemic, necessitates further investigation to help guide best practices in this group. This study aims to compare the symptomatology and rate of pharmacologic treatment for NOWS in preterm and late preterm neonates to their term equivalents during the current opioid epidemic. We hypothesize preterm and late preterm infants will express a different spectrum of

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withdrawal symptoms, with decreased severity of symptoms, requiring less pharmacologic treatment compared to term infants. We also hypothesize the timing for onset of and peak NOWS symptoms in preterm and late preterm infants will differ from term infants.

METHODS

Study design

This was a retrospective chart review of all prenatal opioid exposed infants who were admitted to Rainbow Babies and Children's Hospital, a tertiary care center with Level IV NICU, between January 1, 2014 and December 31, 2019. This study was approved by the University Hospitals Institutional Review Board. Infants exposed to in utero opioids were identified from either our unit database or by medical record search using International Classification of Diseases, Ninth Revision (ICD-9) (760.72, 779.5, 292.0) and International Classification of Diseases, Tenth Revision (ICD-10) codes (P96.1, P04.14, P04.49).

Infants were categorized based on gestational age into preterm (<34 weeks gestational age), late preterm (34 0/7 to 36 6/7 weeks gestational age) and term infants (≥ 37 weeks gestational age). The inclusion criteria were: admission within the first 7 days of life, neonate with a positive urine or meconium toxicology screen, and/or a neonate whose mother had a history of opioid use during pregnancy by report or toxicology screen. Infants were excluded if they: were treated with opioids for reasons other than NOWS, were treated with an opioid prior to transfer, had no modified Finnegan scores recorded or were diagnosed with intraventricular hemorrhage greater than grade 2, necrotizing enterocolitis, congenital anomalies affecting the central nervous system, and neonatal encephalopathy, inclusive of infants treated with therapeutic hypothermia.

Medical records of identified infants and their mothers were reviewed by members of the research team and de-identified information was entered in a REDCap database. REDCap (Research Electronic Data Capture), is a secure web-based software platform designed to support data capture for research studies [10, 11]. Data obtained from maternal electronic medical records (EMR) included: demographics, obstetric care and complications, opioid treatment program during pregnancy and history of prenatal drug use including opiates (heroin and morphine), opioids (fentanyl, buprenorphine, methadone and unspecified opioids), stimulants (amphetamines, cocaine, and nicotine), hallucinogens (phencyclidine), depressants (benzodiazepines, barbiturates, cannabinoids, alcohol), and SSRIs. Collection of infant data included: demographics, additional neonatal co-morbidities (respiratory complications, PPHN, sepsis and feeding intolerance), urine and/or meconium drug screens, modified Finnegan scores and details regarding NOWS treatment and clinical course.

NOWS assessment and treatment

Inborn infants were monitored for signs of withdrawal in the newborn nursery, neonatal step down unit, or neonatal intensive care unit (NICU) with withdrawal assessment scores obtained every 3 hours for a minimum of the first 3–7 days of life per unit guidelines. In the newborn nursery, the Lipsitz scoring tool was used to assess withdrawal symptoms and the Modified Finnegan Neonatal Abstinence Scoring Tool (FNAST) was used in the NICU and NICU stepdown unit. The above scoring tools were used in all infants regardless of gestational age. The nursing staff in the NICU and stepdown units received inter-rater reliability training to improve consistency with the Modified Finnegan scoring tool. In the nursery, a Lipsitz score of ≥ 4 would necessitate transfer to the NICU or step down unit and would then be scored with FNAST and pharmacologic therapy initiated per protocol. A large number of infants were out-born; they were admitted directly to the NICU or the stepdown unit and FNAST scores were obtained. In order to keep the data on the modified Finnegan scores as reliable as possible, infants in this cohort who received morphine at an outside referral center were excluded, as we could not guarantee that these infants were scored by a clinician who was trained and achieved inter-rater reliability in use of the modified Finnegan tool. In our experience, many of the infants who were treated prior to admission to our hospital, did not require a continued therapy once scored by a trained nurse. Only scores obtained in our hospital were used in our data collection. Pharmacologic treatment was initiated per protocol, with morphine as first line treatment. If adjunctive medications were required phenobarbital was used.

Definitions

In this study, polysubstance use was defined as the use of two or more substances (opioids/opiates, stimulants, hallucinogens and depressants), and excluded SSRI, nicotine and alcohol. Polysubstance use and polydrug use are sometimes used interchangeably, and although it is not clearly defined in the literature some sources have defined polysubstance use as the use of multiple illicit drugs or prescription drugs used in non-medical circumstances, and polydrug use as the use of more than one drug at the same time, involving illicit and legal substances i.e., alcohol, medications [12, 13].

Statistical analysis

Statistical analysis of modified Finnegan scores was performed on the single highest score in infants not requiring treatment and in the single highest score prior to administration of morphine in infants requiring treatment of NOWS. We were unable to analyze cumulative scores due to the large number of outborn infants, as analysis was limited to scores obtained at our institution to improve reliability.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA) [14]. Maternal and Infant Demographics, as well as outcomes and Finnegan scores were described in terms of medians and interquartile range (25th and 75th percentiles) for continuous measures and frequency and percentages for categorical variables. To compare group differences in continuous measures, Kruskal–Wallis tests were performed and, when significant, followed up by Dunn post-hoc tests, when not significant, followed by Mann–Whitney *U* tests (between pairs of groups). Logistic regression was used to determine group differences in the presence/absence of dichotomous measures. Maternal Age alone was analyzed using analysis of variance (ANOVA) followed by Tukey's HSD post-hoc test. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 340 mother-infant dyad charts were reviewed, 77 infants were excluded based on the defined criteria. 263 infants met our criteria: 13 preterm (PT), 72 late preterm (LPT) and 178 term infants. (Fig. 1)

Maternal characteristics

Maternal characteristics are shown in Table 1. The majority of mothers in all gestational categories were Caucasian. A lower percentage of mothers of preterm and late preterm infants received prenatal care and were receiving medication for opioid use disorder at the time of delivery when compared to term infants, however, we were not powered to find significance. A high incidence of polysubstance use was noted across all groups (70.2–76.9%), with heroin, buprenorphine, opioids, cocaine, cannabinoids and amphetamines being the most common. A similar percentage of mothers endorsed SSRI and nicotine use, across all gestational age groups. Overall, obstetric complications were similar across all groups with the exception of antepartum hemorrhage which was higher in mothers of preterm and late preterm infants (15.4 and 8.3 vs 1.1%) when compared to mothers of term infants.

Infant characteristics

Infant characteristics are displayed in Table 2. A large number of infants observed for NOWS were out-born and transferred to our hospital for concerns of needing pharmacological treatment of withdrawal. Higher percentages of neonatal complications including respiratory distress, hyperbilirubinemia and feeding intolerance were seen in preterm and late preterm infants compared to term infants.

NOWS outcomes and modified finnegan scores (Tables 3 and 4)

There was a similar time of onset of (46.0 vs 51.2 h, median, *p* = 0.20) and peak symptoms (52.4 vs 67.1 h, median, *p* = 0.11) for NOWS in LPT infants compared to term. Lower rates of

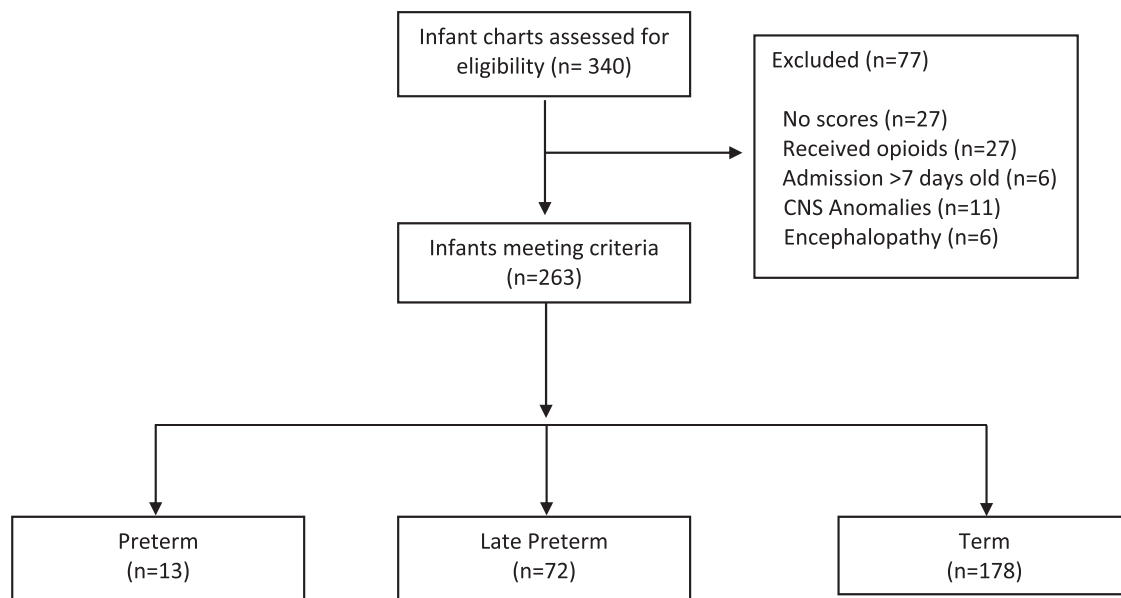


Fig. 1 Flow diagram of study participants.

pharmacologic treatment were observed in PT and LPT infants compared to term and were statistically significant. No infants in this cohort that met criteria for our study received IV morphine. There was no difference observed in the maximum dose of morphine (mg/kg/day), duration of treatment and the use of additional adjunctive medications when comparing LPT and term infants. Highest total Modified Finnegan scores were lower for LPT infants compared to term (9 vs 12), with LPT infants scoring less frequently for increased muscle tone (85.5 vs 96.6%), excoriations (18.8 vs 34.5%), and elevated temperature (63.8 vs 91.2%), all of these differences are statistically significant.

DISCUSSION

We compared a modern cohort of preterm, late preterm and term infants with prenatal opioid exposure and their withdrawal symptoms and NOWS outcomes. Our cohort of late preterm and term infants presented with symptoms of NOWS at similar hours of life and also had similar timing for their peak symptoms. This assures us that late preterm infants can be monitored for the same duration in the hospital as term infants following the AAP recommendations to observe infants with in utero opioid exposure for the first 3–7 days of life [15].

When comparing preterm and late preterm infants to term infants, we observed that both preterm and late preterm infants received less pharmacologic treatment for NOWS. We noted decreased length of treatment in preterm infants, but a similar duration of treatment when comparing late preterm and term infants. It was previously described that preterm infants have shorter treatment courses and lower doses of pharmacologic treatment when compared to term infants [6, 8]. The similar length of treatment seen with the late preterm and term infants in our cohort is likely reflective of the adherence to our institutions' treatment protocol and the decreased length of treatment seen in preterm infants was likely the result of deviation from protocol, as preterm infants were sometimes started on lower initial morphine doses and weaned quicker than our protocol dictates.

Preterm and late preterm infants exhibited lower total overall Finnegan scores compared to term infants, which is similar to what was observed by previous investigators [5, 8]. Additionally, late preterm infants scored less for increased tone, excoriations

and elevated temperature. We hypothesize this is related to preterm infants' physiologic and neurologic immaturity as well as decreased cumulative drug exposure which has been suggested by previous investigators [1, 3, 16–18]. We had expected to see more differences in specific signs of withdrawal, but this may be due to the fact we analyzed a single modified Finnegan score in addition to the small sample size of infants. Understanding that preterm infants are physiologically and neurologically immature brings to question whether the signs scored in the Finnegan Neonatal Abstinence Scoring system are an adequate assessment of withdrawal in this population of infants. Studies have demonstrated preterm infants have an immature pattern of organization and synaptogenesis in the brain which likely explains this neurologic immaturity [19]. It is unknown whether the application of the Finnegan scoring tool leads to an over or under estimation of withdrawal symptoms. Preterm infants have higher rates of respiratory distress syndrome, which was demonstrated in our cohort, and commonly present with tachypnea and nasal flaring which could also be related to withdrawal. Similarly, preterm infants commonly have feeding intolerance related to premature motor organization, rhythmic sucking and the ability to coordinate a suck-swallow-breath pattern [20]. Many of the signs scored for in NOWS with the Finnegan scoring tool can be associated with prematurity alone and the inability to delineate the etiology of these symptoms complicates the interpretation of withdrawal scores and decisions regarding treatment.

The pathophysiology of NOWS in term infants is largely explained by the presence of μ opioid receptors in the brain and gastrointestinal tract. This results in the CNS, ANS and GI symptoms observed [16]. The original Finnegan scoring tool is the only validated withdrawal assessment tool in existence for NOWS, and is only validated for term infants [21, 22]. Modified versions of the Finnegan scoring tool are used by many hospitals across the United States to assess for NOWS in both preterm and term infants, despite not being validated [23, 24]. Thus, it is unknown if the elements of the modified Finnegan tool are valid to assess a preterm infant for opioid withdrawal.

Without an appropriate withdrawal assessment tool for preterm infants, it is unclear if we are potentially over- or under-treating their symptoms. The long-term sequelae of both in utero and/or postnatal opioid exposure to the developing brain are not fully

Table 1. Maternal demographics.

	Preterm (<i>n</i> = 13) <i>N</i> (%)	Late preterm (<i>n</i> = 72) <i>N</i> (%)	Term (<i>n</i> = 178) <i>N</i> (%)	PT vs T <i>p</i> -value	LPT vs T <i>p</i> -value
Maternal demographics					
Age (mean, std dev)	26.69 (3.75)	29.97 (4.90)	28.16 (4.39)	0.50	0.01
Race Caucasian	9/10 (90%)	47/60 (78.3%)	145/161 (90.1%)	0.99	0.02
No Antenatal Care	3/8 (37.5%)	19/54 (35.2%)	13/122 (10.7%)	0.04	<0.001
Obstetric complications					
Preeclampsia	1/13 (7.7%)	11/72 (15.3%)	15/178 (8.4%)	0.93	0.11
Gestational Diabetes	0/13 (0.0%)	5/72 (6.9%)	6/178 (3.4%)	–	0.22
Multiple Gestation	0/13 (0.0%)	2/72 (2.8%)	1/178 (0.6%)	–	0.19
Antepartum Hemorrhage	2/13 (15.4%)	6/72 (8.3%)	2/178 (1.1%)	0.008	0.01
Chorioamnionitis	2/13 (15.4%)	1/72 (1.4%)	8/178 (4.5%)	0.11	0.26
STI	1/13 (7.7%)	11/72 (15.3%)	16/178 (9.0%)	0.87	0.15
HIV	1/13 (7.7%)	1/72 (1.4%)	0/178 (0.0%)	–	–
Hepatitis B	0/13 (0.0%)	1/72 (1.4%)	4/178 (2.2%)	–	0.66
Hepatitis C	5/13 (38.5%)	21/72 (29.2%)	59/178 (33.1%)	0.70	0.54
Drug exposure					
Polysubstance use ^a	10/13 (76.9%)	52/72 (72.2%)	125/178 (70.2%)	0.61	0.75
Heroin	8/13 (61.5%)	36/72 (50.0%)	69/178 (38.8%)	0.12	0.10
Fentanyl	0/13 (0.0%)	0/72 (0.0%)	2/178 (1.1%)	–	–
Opioids	7/13 (53.8%)	36/72 (50.0%)	63/178 (35.4%)	0.19	0.03
Buprenorphine	4/13 (30.8%)	22/72 (30.6%)	102/178 (57.3)	0.07	<0.001
Methadone	1/13 (7.7%)	14/72 (19.4%)	20/178 (11.2%)	0.70	0.09
Amphetamines	3/13 (23.1%)	11/72 (15.3%)	25/178 (14.0%)	0.38	0.80
Gabapentin	0/13 (0.0%)	1/72 (1.4%)	8/178 (4.5%)	–	0.26
Barbiturates	0/13 (0.0%)	1/72 (1.4%)	6/178 (3.4%)	–	0.41
Benzodiazepines	1/13 (7.7%)	6/72 (8.3%)	21/178 (11.8%)	0.66	0.43
Cannabinoids	5/13 (38.5%)	15/72 (20.8%)	47/178 (26.4%)	0.35	0.36
Cocaine	5/13 (38.5%)	28/72 (38.9%)	41/178 (23.0%)	0.22	0.01
Phencyclidine	0/13 (0.0%)	2/72 (2.8%)	1/178 (0.6%)	–	0.19
SSRI	2/7 (28.6%)	17/53 (32.1%)	31/113 (27.4%)	0.95	0.54
Nicotine	10/10 (100.0%)	38/51 (74.5%)	101/125 (80.8%)	–	0.35
Alcohol	1/5 (20.0%)	7/39 (17.9%)	6/77 (7.8%)	0.36	0.11
Drug treatment					
Treatment Program at time of delivery	4/11 (36.4%)	26/69 (37.7%)	102/176 (58.0%)	0.17	0.005
Buprenorphine	3/4 (75.0%)	18/26 (69.2%)	89/102 (87.3%)	0.49	0.03
Buprenorphine dose at delivery (mg/kg/d) (median, IQR)	8 (8–8)	8 (8–16)	12 (8–16)	0.48	0.53
Methadone	1/4 (25%)	8/26 (30.8%)	13/102 (12.7%)	0.49	0.03
Methadone dose at delivery (mg/kg/d) (median, IQR)	160 (160–160)	105 (80–148)	90 (50–110)	0.17	0.38

Analysis of variance (ANOVA), followed up by Tukey's HSD post-hoc test, was used to compare group differences in maternal age. To compare group differences in other continuous measures, Kruskal–Wallis tests were performed and, when significant, followed up by Dunn post-hoc tests, when not significant, followed by Mann–Whitney *U* tests (between pairs of groups). Logistic regression was used to determine group differences in the presence/absence of dichotomous measures.

PT Preterm, LPT Late Preterm, T Term, STI Sexually Transmitted Infection, SSRI Serotonin Reuptake Inhibitor, IQR Interquartile Range 25–75

^aPolysubstance use was defined as two or more substances (opioids/opiates, stimulants, hallucinogens and depressants), excluding SSRI, nicotine and alcohol use.

elucidated, but animal models have suggested there are sustained long-term impacts affecting both social and cognitive behaviors [25]. Effects of illicit drugs have been shown to impact fetal development resulting in abnormal growth parameters at birth, as well as alterations in neurotransmitter pathways, disruptions in

synaptic connections and maturation of signaling circuitry, and overall brain development [16, 17, 25, 26]. Clinical research has shown harmful long-term effects on cognitive function, behavioral, motor and childhood development, some of which have been shown to last through adulthood [25, 27]. However, these

Table 2. Infant demographics.

	Preterm (<i>n</i> = 13) <i>N</i> (%)	Late preterm (<i>n</i> = 72) <i>N</i> (%)	Term (<i>n</i> = 178) <i>N</i> (%)	PT vs T <i>p</i> -value	LPT vs T <i>p</i> -value
Gestational Age (weeks) (median, range)	33.00 (25.14–33.86)	35.64 (34.00–36.86)	39.00 (37.00–42.00)	–	–
Sex					
Male	9 (69.2)	40 (55.6)	88 (49.4)	0.18	0.38
Female	4 (30.8)	32 (44.4)	90 (50.6)		
Birthweight (g) (median, IQR)	1790 (1675–2038)	2443 (2180–2735)	3080 (2730–3360)	<0.001	<0.001
Length (cm) (median, IQR)	42.0 (39.0–45.0)	46.0 (44.0–48.0)	49.0 (47.5–51.0)	<0.001	<0.001
Head Circumference (cm) (median, IQR)	29.5 (27.3–30.5)	32.0 (30.5–33.4)	33.5 (32.5–35.0)	<0.001	<0.001
Transfer of Care	5 (38.5)	39 (54.2)	142 (79.8)	0.002	<0.001
Infant Diagnoses					
RDS, TTN, Pneumonia	11 (84.6)	35 (48.6)	32 (18.0)	<0.001	<0.001
PPHN	0 (0.0)	1 (1.4)	3 (1.7)	—	0.87
Sepsis	3 (23.1)	5 (6.9)	7 (3.9)	0.009	0.32
Hyperbilirubinemia	10 (76.9)	33 (45.8)	31 (17.4)	<0.001	<0.001
Feeding Intolerance	12 (92.3)	39 (54.2)	31 (17.4)	<0.001	<0.001

To compare group differences in continuous measures, Kruskal–Wallis tests were performed and, when significant, followed up by Dunn post-hoc tests, when not significant, followed by Mann–Whitney *U* tests (between pairs of groups). Logistic regression was used to determine group differences in the presence/absence of dichotomous measures.

PT Preterm, LPT Late Preterm, T Term, IQR Interquartile Range 25–75, RDS Respiratory Distress Syndrome, TTN Transient Tachypnea of Newborn, PPHN Persistent Pulmonary Hypertension, Rx Treatment.

Table 3. NOWS treatment and outcomes.

	Preterm (<i>n</i> = 13) <i>N</i> (median, IQR)	Late preterm (<i>n</i> = 72) <i>N</i> (median, IQR)	Term (<i>n</i> = 178) <i>N</i> (median, IQR)	PT vs T <i>p</i> -value	LPT vs T <i>p</i> -value
Required Pharmacologic Rx					
Morphine (%)	3/13 (23.1)	32/72 (44.4)	118/178 (66.3)	0.005	0.002
Morphine + Phenobarbital (%)	0/3 (0.0)	6/32 (18.8)	19/118 (16.1)	–	0.72
Highest morphine dose (mg/kg/d)	0.40 (0.40–0.40)	0.48 (0.40–0.86)	0.40 (0.40–0.72)	0.21	0.41
Onset of NOWS (h)	77.7 (62.3–86.1)	46.0 (24.7–67.6)	51.2 (31.1–78.2)	0.24	0.20
Peak Symptoms (h)	77.7 (62.3–127.4)	52.4 (35.3–86.3)	67.1 (43.5–100.6)	0.42	0.11
Length of Morphine Rx (days)	6.4 (6.0–10.8)	13.1 (9.6–22.2)	12.1 (8.8–18.4)	0.046	0.17
Length of Phenobarbital Rx (days)	–	14.7 (7.1–31.1)	13.3 (5.4–29.6)	–	0.64
Length of Stay (days)	22.7 (15.0–50.4)	13.5 (7.1–19.1)	15.0 (7.5–20.3)	0.002	0.60

To compare group differences in continuous measures, Kruskal–Wallis tests were performed and, when significant, followed up by Dunn post-hoc tests, when not significant, followed by Mann–Whitney *U* tests (between pairs of groups). Logistic regression was used to determine group differences in the presence/absence of dichotomous measures.

PT Preterm, LPT Late Preterm, T Term, IQR Interquartile Range 25–75, Rx Treatment, H h.

studies are limited by confounding factors include poor follow-up, polysubstance exposures, and socioeconomic sequelae of maternal drug use [2]. When looking at preterm infants specifically, exposure to opioids during critical periods of brain development may be associated with poor motor development and neurocognitive function during early childhood years [27]. It appears there is a delicate interplay between necessary treatment of NOWS and avoidance of unnecessary opioid exposure, with little research to support recommendations in preterm infants.

Our study observed that mothers who delivered preterm and late preterm infants had a higher percentage of no antenatal care and lower percentage in treatment for opioid use disorder. Although no evidence supports a causal relationship for the above, there is a relationship between illicit drug use and poor pregnancy outcomes including intrauterine growth restriction, preterm delivery and placental abruption [28–31]. We believe this demonstrates the

importance of mothers receiving appropriate prenatal care and receiving treatment for their opioid use disorder.

Strengths of this study include the use of a standardized protocol for identifying affected patients, non-pharmacologic care, withdrawal scoring, and initiation and weaning of pharmacologic treatment for NOWS which had been well-established throughout the time period reviewed. Next, our hospital guidelines for infants with opioid exposure included our nursing staff achieving inter-rater reliability training to improve the standardization and consistency of scoring and reduce person-to-person variability in administering the FNAST. Both of these have been shown to improve care as well as length of stay [32]. Lastly, this is the only study describing NOWS in preterm infants during the current wave of the opioid epidemic and, when compared to previous studies, is the largest cohort of preterm infants described to date. While there were many strengths, there are also several limitations

Table 4. Characteristics of modified finnegan score.

	Preterm (<i>n</i> = 13)	Late preterm (<i>n</i> = 69)	Term (<i>n</i> = 148)	PT vs T <i>p</i> -value	LPT vs T <i>p</i> -value
Highest Total Finnegan Score (median, IQR)	9.0 (6.5–10.5)	9.0 (7.0–12.0)	12.0 (10.0–15.0)	0.001	<0.001
Highest Total CNS Score (median, IQR)	7.0 (3.5–8.5)	6.0 (4.0–8.0)	7.0 (6.0–10.0)	0.19	0.003
Highest Total ANS Score (median, IQR)	2.0 (2.0–3.0)	3.0 (2.0–4.0)	3.0 (3.0–4.0)	0.02	0.002
Highest Total GI Score (median, IQR)	2.0 (1.0–2.5)	2.0 (1.0–4.0)	3.0 (2.0–3.0)	0.03	0.20
CNS Disturbances					
Crying	30.8%	36.2%	47.3%	0.26	0.13
Sleeping	84.6%	85.5%	85.1%	0.96	0.94
Moro Reflex	61.5%	46.4%	40.5%	0.15	0.42
Disturbed Tremors	92.3%	91.3%	93.2%	0.90	0.61
Undisturbed Tremors	69.2%	56.5%	48.6%	0.17	0.28
Muscle Tone	84.6%	85.5%	96.6%	0.06	0.006
Excoriation	23.1%	18.8%	34.5%	0.41	0.02
Myoclonic Jerk	15.4%	4.3%	4.7%	0.13	0.90
Sweating	0.0%	8.7%	14.2%	—	0.26
ANS Disturbances					
Elevated Temperature	84.6%	63.8%	91.2%	0.44	<0.001
Yawning	15.4%	20.3%	17.6%	0.84	0.63
Mottling	53.8%	60.9%	59.5%	0.69	0.84
Nasal Stuffiness	30.8%	44.9%	37.8%	0.61	0.32
Sneezing	76.9%	73.9%	65.5%	0.41	0.22
Nasal Flaring	7.7%	8.7%	13.5%	0.56	0.31
Respiratory rate	92.3%	84.1%	87.8%	0.64	0.45
GI Disturbances					
Sucking	69.2%	65.2%	77.7%	0.49	0.05
Poor Feeding	23.1%	44.9%	36.5%	0.34	0.24
Regurgitation/Vomiting	38.5%	33.3%	25.7%	0.32	0.24
Stools	30.8%	52.2%	55.4%	0.10	0.66

To compare group differences in continuous measures, Kruskal–Wallis tests were performed and, when significant, followed up by Dunn post-hoc tests, when not significant, followed by Mann–Whitney *U* tests (between pairs of groups). Logistic regression was used to determine group differences in the presence/absence of dichotomous measures.

PT Preterm, T Term, LPT Late Preterm, CNS Central Nervous System, ANS Autonomic Nervous System, GI Gastrointestinal.

to our study. This is a retrospective chart review and relied on a unit data base of infants exposed to opioids in utero in addition to identification of patients based on ICD 9 and 10 codes related to opioid exposure and NOWS and thus if an infant was not identified as being opioid exposed or not billed as such, they would have been missed. While our unit uses the same NOWS protocol for all opioid exposed newborns no matter the gestational age, the use of the protocol is dependent on the medical team to order its use on preterm infants. Since there is no universal treatment protocol/recommendations for preterm infants with NOWS, some infants with opioid exposure may not have been scored for withdrawal, thus we could be missing their data. Our sample size of those preterm infants <34 weeks is small, precluding us from making conclusions for those smallest infants. We did feel it was important to characterize late preterm infants separately from preterm infants as they are different compared to infants <34 weeks gestation. Late preterm infants do not always require a NICU admission and can be discharged from the nursery in the first few days of life, so separating this group allowed us to examine the characteristics of their withdrawal and assess if current lengths of observation are applicable. Lastly, some Modified Finnegan scores were not able to be used for analysis, specifically looking at the breakdown of signs, as early versions of

the EMR did not allow these details to be entered and some infants scoring sheets were not scanned into the EMR.

In conclusion, our study provides more current information on NOWS in preterm infants, a population that has not been well described in the literature. We concluded late preterm infants require less pharmacologic treatment for NOWS which is possibly due to their neurologic immaturity and currently withdrawal assessment tools do not account for this difference from term infants. The timing and duration to peak symptoms were not significantly different between the late preterm and term infants in our cohort. Thus, monitoring for the same duration as term infants would be appropriate, following the AAP Guidelines of 3–7 days depending on exposure, while recognizing the limitations with the current scoring tools ability to appropriately assess withdrawal in this population. As described before, further studies are required to evaluate the appropriate and accurate assessment of opioid withdrawal symptoms and treatment for preterm infants with NOWS.

DATA AVAILABILITY

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

AH, MC and LZ contributed to the conception and design of this study. AH and ACH completed the data collection. NM completed data analysis. AH, MC and AMH contributed to data analysis interpretation. AH wrote the first draft of the manuscript, with all authors revising it critically for important intellectual content. All authors approved the final version to be published.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

All components of this research project adhered to the institution's research guidelines and ethical standards. This study was approved by the University Hospitals Institutional Review Board.

ADDITIONAL INFORMATION

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