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Original Research

Necrotizing enterocolitis and its association with the neonatal abstinence syndrome

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Abstract.
OBJECTIVE: The purpose of this study was to describe an identified association between necrotizing enterocolitis (NEC) and prenatal opioid exposure with neonatal abstinence syndrome (NAS) in late preterm and full-term neonates.
STUDY DESIGN: In this single-center retrospective cohort study, we analyzed inborn neonates with the diagnosis of NEC discharged from 2012 through 2017. We compared infants with NEC > 35 weeks' gestation to those with NEC<35 weeks' gestation. We compared gestational age, birth weight, age of onset of symptoms, and incidence of prenatal drug exposure between groups. Significance was determined using Mann-Whitney and Fisher's exact tests.
RESULTS: Over the study period, 23 infants were identified with NEC, 9 (39%) were babies > 35 weeks at birth and 14 (61%) < 35 weeks. Those > 35 weeks had a higher birth weight, earlier onset of symptoms, and a higher percentage of prenatal exposure to opioids compared to those < 35 weeks' gestation. We further described seven infants with late gestational age onset NEC associated with prenatal opioid exposure.
CONCLUSIONS: In this cohort of infants with NEC discharged over a 6 year period we found a higher than expected percentage of infants born at a later gestational age. We speculate that prenatal opioid exposure might be a risk factor for NEC in neonates born at > 35 weeks.

Abbreviations

NEC	Necrotizing enterocolitis
NAS	Neonatal abstinence syndrome
WV	West Virginia
DOL	Day of life
GA	Gestational age
NICU	Neonatal intensive care unit
NPO	Nothing by mouth
TLRs	Toll-like receptors
TLR4	Toll-like receptor 4
ICD	International Classification of Diseases

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1. Introduction

Necrotizing enterocolitis (NEC) represents an important cause of morbidity and mortality in the preterm neonate. In infants of gestational ages of 22 0/7 to 28 6/7 weeks, mortality/1000 live births was 28 from NEC compared to 14 from congenital anomalies, 15 from bronchopulmonary dysplasia,

and 22 from infection [1]. The pathophysiology of NEC is incompletely understood but it is characterized by ischemic necrosis of the intestinal mucosa [2]. The incidence of NEC decreases with advancing gestational age [3]. Approximately 13% of reported cases of NEC, however, occur in term neonates [4]. Term infants with NEC frequently have predisposing co-morbidities including congenital heart disease, sepsis, polycythemia, umbilical vessel catheterization, and asphyxia [5–7].

Neonatal abstinence syndrome (NAS) is a withdrawal syndrome that typically occurs after *in utero* exposure to opioids [8]. Because of issues related to rurality, poverty, and incidence of licit and illicit opioid use, West Virginia (WV) has experienced sharp increases in the rates of NAS. We have reported a 9.4% incidence of NAS requiring medication treatment at our major teaching hospital [9]. NAS is characterized by symptoms affecting the central and autonomic nervous systems as well as the gastrointestinal system.

There is conflicting published evidence for the association of NAS and NEC. One study reports nine term infants developing NEC while being treated for withdrawal from maternal opioids [10]. Another study found no difference in the incidence of NEC in a large population comparing infants born to mothers with no opioid exposure to those infants with opioid exposure [11]. It is our goal in this study to further clarify the association between NEC and NAS in the late preterm and full-term neonates born at our institution.

2. Methods

A retrospective analysis was performed using the Marshall University School of Medicine clinical data warehouse to examine the association between NEC and NAS. Neonates with NEC were identified using the diagnosis codes 777.50–777.53 (ICD 9) and P77.1–P77.9 (ICD 10). Presence of NAS in these neonates was defined as the presence of diagnosis code 779.5 or P96.1. Data verification was done using chart review. Our study population included infants born between 1 January 2012 and 31 December 2017 with the diagnosis of NAS. The only exclusions were those infants with iatrogenic NAS resulting from postnatal opioid exposure used for medical management. We further identified all neonates with the discharge diagnosis of NEC Bell classification stage 2 or 3 [12]. Data were collected and reviewed after approval of the Marshall University Institutional Review Board.

Cabell Huntington Hospital served as a tertiary care perinatal referral center for Southern West Virginia, Eastern Kentucky and Southeastern Ohio, and thus this report included drug exposed maternal patients referred for delivery from throughout the tristate area. Neonates born > 35 weeks' gestation at our institution were initially admitted to the newborn nursery unless medical issues such as respiratory distress, infection or metabolic problems necessitated NICU care. All mothers on admission for delivery at this hospital had a urine drug screen. The policy of mandatory maternal drug testing was enacted in 2012, so that all mothers delivering at our institution received a urine drug screen during the study period. Any mother with a positive drug screen at delivery, a history of positive screen during pregnancy, past history of drug abuse or admission of drug use during pregnancy was followed up with an umbilical cord tissue toxicology at delivery (United States Drug Testing Laboratories, Des Plaines, IL, USA). All newborns were observed for signs of NAS using the Finnegan Scoring Tool [13]. If symptoms of NAS developed, the neonate was managed using a protocol for methadone treatment of NAS previously described [14].

All statistical analyses were done using GraphPad Prism version 7.03, by GraphPad Software Inc., La Jolla, CA. Intergroup comparisons of gestational age, birth weight, and days of onset of NEC were completed using the Mann-Whitney test. Fisher's exact test was used for comparing prenatal drug exposure. The statistical analyses did not take any of the potential confounding factors (small for gestational age, hypoglycemia, polycythemia, partial exchange transfusion, and umbilical catheter use) into account as only one of the seven neonates who had NAS associated NEC was in the cohort. All other infants had no reported confounding factors.

3. Results

Over the study period of 6 years, we identified 16,212 live births delivered at our institution with 508 neonates<1500 grams including 242 babies <1000 grams. Eighteen percent of the live births delivered were verified as prenatally exposed to one or more nonprescribed drugs or prescribed methadone or buprenorphine by maternal urine screen and umbilical cord tissue sample (#2902). Fifty percent of the

Table 1
Neonates with NEC (#23)

	NEC ≥ 35 weeks	NEC < 35 weeks	
Number	9	14	
Gestational Age	37.2 (±1.4)	27.5 (±3.2)	$p < 0.001$
Birth Weight (grams)	2730 (±616)	1113 (±632)	$p < 0.001$
Onset of NEC (days)	3.3 (±1.6)	14.9 (±13.8)	$p < 0.01$
Prenatal drug exposure	7	0	$p < 0.01$

exposed neonates required pharmacologic treatment for NAS (#1440). We identified 23 neonates with the diagnosis of NEC over the same study period. Nine of these infants (39%) were > 35 weeks' gestational age (group A) and fourteen (61%) were<35 weeks' gestation (Group B). A comparison of the two groups is illustrated in Table 1.

Seven babies were born > 35 weeks' gestation to drug exposed mothers and developed NEC. Their course and history are illustrated in Table 2. Only patient #3 demonstrated co-morbidities previously described as associated with NEC including small for gestational age, hypoglycemia, polycythemia, partial exchange transfusion, and umbilical venous catheter use. This infant was initially admitted to the NICU for management of low birth weight and transient hypoglycemia. The remaining six infants with NEC were initially cared for in the well-born nursery and transferred to the NAS treatment ward when begun on methadone therapy. These babies were then transferred to the NICU when symptoms of NEC developed. All seven infants had one minute Apgar scores > 7 and five minute scores > 8. Only infant 3 had hypoglycemia. All seven of these neonates required pharmacologic treatment for NAS.

4. Discussion

In this single-center retrospective cohort study, we have found 23 neonates over a six-year study period with NEC. Nine infants (39%) were greater than or equal to 35 weeks' gestation and seven of these were associated with maternal drug exposure. Although the association between prenatal drug exposure and NEC could be coincidental, we suggest that the absence of other risk factors in all but one of these babies and the high number of cases at a later gestational age compared to all cases of NEC in this series might suggest a causal relationship of prenatal drug exposure and NEC.

A previous study has documented an association with NEC and prenatal exposure to cocaine or methamphetamine [7]. Another study, however, showed no significant association with cocaine exposure in full-term or near-term infants with NEC and controls [17].

We are aware of only one previous study that documented nine term infants with NEC that developed while being treated for withdrawal from maternal

Table 2
Infants > 35 weeks with NEC (#7)

Patients	Maternal drug exposure by umbilical cord toxicology and urine drug screen	GA (birth weight in grams)	Onset of NEC (days)	Feeding	Symptoms	Outcome
1	Buprenorphine	37.3 (1970)	1	NPO	Hematochezia, Pneumatosis, Perforation	Surgery-survived
2	Methadone	38 (3005)	5	Formula	Hematochezia, Pneumatosis	Medical management-survived
3	Buprenorphine, benzodiazepine	37.3 (1865)	7	Formula	Hematochezia, Pneumatosis, Perforation	surgery, E.coli sepsis, died
4	Buprenorphine	38 (3290)	5	Formula	Hematochezia, Pneumatosis	Medical management-survived
5	Methadone	37 (2892)	3	Formula	Hematochezia, Pneumatosis	Surgery stricture-survived
6	Heroin, gabapentin, methadone	39 (3800)	4	Formula	Hematochezia, Pneumatosis	Medical management-survived
7	Benzodiazepine, methadone, cocaine	39 (2785)	1	Formula	Hematochezia, Pneumatosis, Perforation	Peritoneal drain-survived

opioids [10]. These nine infants were cared for in five different hospitals over a six year period and five neonates in this study were small for gestational age. The authors speculate that NEC might have resulted from an overexpression of the gastrointestinal symptoms seen in opioid withdrawal coupled with overfeeding with milk-based formula. In our population of neonates with late gestational age onset of NEC and prenatal drug exposure, one baby was NPO (#1) and two babies (#1 and #7) showed no other symptoms of NAS including diarrhea and feeding intolerance when NEC developed. In one large study, infants born to more than 80,000 Tennessee women with no opioid exposure during pregnancy had the same incidence of NEC as 30,000 infants born to mothers exposed to opioids. The incidence of NEC was not broken down by gestational age, opening the possibility of term infants with NEC being more prevalent in the prenatally opioid exposed population [11].

The pathophysiology of NEC remains incompletely understood. NEC in the preterm neonate is felt to have a multifactorial cause. Factors implicated have included genetic predisposition, intestinal immaturity, abnormal microbial intestinal colonization and an immunoreactive intestinal mucosa [15, 16]. NEC in the term infant has differences from that seen in the preterm infant. The disease usually appears in the first week of life and is associated with predisposing problems including prolonged rupture of membranes, low Apgar scores, congenital heart disease, hypoglycemia, polycythemia, intrauterine growth retardation, exchange transfusion, and umbilical vessel catheterization [4, 17].

Toll-like receptors (TLRs) are a group of proteins that belong to the pattern recognition receptor family, a key component of the innate immune system. Activation of TLRs leads to the synthesis of pro-inflammatory cytokines and chemokines [18]. It is hypothesized that upregulation of TLRs, specifically TLR4, in preterm, stressed intestinal epithelium allows for initiation of the pro-inflammatory cascade that results in the final common pathway of NEC [19]. Emerging evidence indicates that select opioids can activate TLR4 leading to elevated cytokine levels [20, 21]. Our unproven hypothesis is that the upregulation of the immune system and release of cytokines by some opioids could be a factor in causation of NEC in these mature neonates after *in utero* exposure to opioids.

This study is retrospective and represents a small number of infants with NEC from a single center. While all the radiographs and medical records were reviewed, other diagnoses can have the same clinical features of NEC including milk protein allergy, spontaneous intestinal perforation and bacterial enteritis. Another limitation is that three of the seven opioid exposed neonates had other nonprescribed substances present in their cord tissue sample that may have contributed to the development of NEC. The major limitation of this study is that we cannot be sure of the causal relationship of maternal drug use and NEC.

The association of NEC and prenatal opioid exposure with NAS in the late preterm and full-term neonate could be more prevalent than previously recognized. Our recommendation is that physicians be alert to this possibility. While the number of cases of NEC (7) is less than 1% of total infants with NAS requiring treatment at our institution, we now aggressively manage infants with prenatal opioid exposure who show signs of early NEC including bilious aspirates or vomiting, abdominal distention and tenderness, or hematochezia with bowel rest, assess the need for antibiotics, and consider the use of an elemental formula on refeeding.

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