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A Scoping Review of Neonatal Opioid Withdrawal and the Infant Gut Microbiome

Does Human Milk Optimize Infant Outcomes?

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ABSTRACT

Background: While a growing body of literature has established the role of human milk as a mechanism of protection in the formation of the infant gut microbiome, it remains unclear the extent to which this association exists for infants with neonatal opioid withdrawal syndrome.

Purpose: The purpose of this scoping review was to describe the current state of the literature regarding the influence of human milk on infant gut microbiota in infants with neonatal opioid withdrawal syndrome.

Data Sources: CINAHL, PubMed, and Scopus databases were searched for original studies published from January 2009 through February 2022. Additionally, unpublished studies across relevant trial registries, conference proceedings, websites, and organizations were reviewed for possible inclusion. A total of 1610 articles met selection criteria through database and register searches and 20 through manual reference searches.

Study Selection: Inclusion criteria were primary research studies, written in English, published between 2009 and 2022, including a sample of infants with neonatal opioid withdrawal syndrome/neonatal abstinence syndrome, and focusing on the relationship between the receipt of human milk and the infant gut microbiome.

Data Extraction: Two authors independently conducted title/abstract and full-text review until there was consensus of study selection.

Results: No studies satisfied the inclusion criteria, which resulted in an empty review.

Implications for Practice and Research: Findings from this study document the paucity of data exploring the associations between human milk, the infant gut microbiome, and subsequent neonatal opioid withdrawal syndrome. Further, these results highlight the timely importance of prioritizing this area of scientific inquiry.

Key Words: gastrointestinal microbiome, human milk, lactation, neonatal abstinence syndrome, neonatal withdrawal syndrome, opioid, review

In the United States, rates for opioid use among the general population increased from 44.8% in 2011 to 70.1% in 2018[1]; between 1999 and 2014, maternal opioid use disorder rates at delivery increased by 333%.[2] Nationally, one infant is born experiencing opioid withdrawal every 15 minutes[3]: representing over a 300% increase in the last decade.[4] As a result of prenatal opioid exposure (POE), many infants subsequently receive the clinical diagnosis of neonatal abstinence syndrome (NAS), a condition marked by an infant's withdrawal from polysubstance exposure, including opioids, and/or the more specific condition of neonatal opioid withdrawal syndrome (NOWS), which occurs when opioids are the predominant exposure and the appearance of opioid withdrawal symptoms is present following birth.[5] While these terms are often used interchangeably, we will defer to using NOWS since it more specifically encompasses the standardized clinical definition for opioid withdrawal in infants.[5]

Although any infant with POE is at risk for developing NOWS, the level of severity of withdrawal symptoms for each infant is unpredictable.[6] The symptomology of NOWS is expressed in several systems including the central nervous system (CNS), autonomic nervous system (ANS), and enteric nervous system (ENS).[7] Clinical presentation varies widely; however, gastrointestinal (GI) dysfunction is a consistent and persistent issue among infants with NOWS.[8,9] GI symptoms related to NOWS typically include poor feeding, regurgitation, vomiting, and

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diarrhea[8,9] and are hypothesized to be influenced by intestinal or gut dysbiosis.[10,11] Management approaches in the treatment of NOWS symptoms often differ across healthcare systems but generally include the use of nonpharmacologic (ie, environmental modifications, infant feeding methods, and parental contact) and pharmacologic (ie, morphine) treatments.[6,12] Despite the use of pharmacologic agents for the management of severe NOWS symptoms, nonpharmacologic approaches, including breastfeeding, are the recommended first line of defense.[6,13]

Findings from a recent meta-analysis suggest that lactation is associated with decreased severity of NOWS symptoms, shorter duration of hospital stay, and reduced need for pharmacologic treatment in infants with NOWS.[14] Although a growing body of literature highlights the effect of breastfeeding on NOWS-related outcomes, little is understood about the associated mechanistic effect. Suboptimal outcomes for infants with NOWS are principally attributed to GI dysfunction (ie, extended length of stay, need for pharmacologic treatment).[15] Moreover, human milk is integral to influencing the development of the infant gut microbiome and potentially alleviating GI dysfunction,[16-21] such as those associated with NOWS.[14]

As demonstrated in animal models,[22] researchers speculate that human milk likely mediates the effects of opioids on the infant gut microbiome.[10,22] As such, we postulate that investigating the mechanisms by which human milk optimizes outcomes in infants with NOWS is essential for the promotion of targeted intervention. Understanding of this specific mechanistic pathway in infants with NOWS is limited; accordingly, the purpose of this scoping review was to describe the current state of the literature regarding the effect of human milk on infant gut microbiota in infants with NOWS.

What This Study Adds

- Identification of the critical need to further our understanding of the mechanisms by which human milk influences the infant gut microbiome in high-risk neonatal populations.
- Exploration of novel opportunities for future research inquiry into the link between the role of human milk on gastrointestinal symptoms and the developing infant gut microbiome in infants with prenatal opioid exposure and subsequent neonatal opioid withdrawal syndrome (NOWS).

THE EARLY GUT MICROBIOME

The importance of establishing a balanced gut microbiome to optimize immune development among infants is well-documented.[11] Previous literature on the gut microbiome largely focused on animal models to characterize gut microbiota, or the microorganisms within the gut.[11] However, among humans, research characterizing the gut microbiome is limited to *healthy* full-term and preterm infants. Early gut microbiome development in the infant is influenced by multiple factors including birth type (ie, vaginal vs cesarean section), feeding type (ie, mother's own milk [MOM], donor human milk [DHM], or formula), environmental factors (ie, early and prolonged hospitalization), and use of antibiotics and/or probiotics.[11,23]

Current approaches to gut microbiota analyses apply culture-independent DNA methods to provide more granular data.[23] By these methods (16srRNA gene amplification and sequencing, as well as whole genome sequencing), facultative anaerobes are observed to seed the gut and establish early microbial colonization.[23] As the infant matures, the abundance of anaerobic genera, such as *Bifidobacterium*, *Bacteroides*, and *Clostridium*, increases.[16,23] This is due to lowering of the redox potential as oxygen is consumed and hypoxia results, favoring anaerobes such as bifidobacteria, especially in *healthy* full-term infants who are breastfed.[24] As such, bifidobacteria is considered the gold standard for health in newborn gut microbiomes.[16,24] Key terminology and definitions used in microbiota research are described in Table 1.

Studies examining the preterm infant's gut microbiome highlight the innate differences in microbiota diversity.[23] When compared with full-term infants, preterm infants showed a reduced microbiota diversity, reduced levels of strict anaerobes, and increased colonization by facultative anaerobes, which can be pathogenic.[25] Moreover, evidence suggests reduced colonization of bifidobacteria in preterm infants may lead to delayed immune maturation, predisposing these infants to an overabundance of Proteobacteria and Firmicutes—characteristics of gut dysbiosis.[26] These manifestations of the microbiota composition have been linked to higher rates of morbidity and mortality in premature infants, and subsequently associated with the development of GI-related conditions such as necrotizing enterocolitis (NEC).[17,27]

Although the literature is limited on the characteristics of the gut microbiome in infants with NOWS,[11] emerging clinical evidence suggests opioid exposure may affect perturbation of gut development and subsequent GI dysfunction.[11] The current evidence available exploring the influence of opioid exposure in preclinical animal and human models suggests substantial variability in the gut microbiota of affected samples; nonetheless, findings are consistent with gut dysbiosis.[28-30] For example, in animal models of addiction, increased colonization of Firmicutes was reported in samples of morphine-exposed mice[31]; however, in other studies, decreased colonization was observed in hydromorphone-exposed mice[32] and oxycodone-exposed rats.[33] Suggested mechanisms of gut dysbiosis in adult models include alterations in bacterial metabolites,

TABLE 1. Key Terminology and Definitions in Microbiome Research

Terminology	Definition
Microbiota	The collection of genomes from all the microorganisms in the environment
Microbiome	Specific microorganisms that are found within a certain environment
Dysbiosis	An imbalance between the types of organisms in a person's natural microflora, especially that of the gut, thought to contribute to a range of conditions of illness
Brain–gut axis	The bidirectional communication pathway between the central nervous system and the gastrointestinal system
Culture-independent DNA methods	A methodological approach to identify large proportions of illness-causing bacteria
16srRNA gene sequencing	The process of defining populations of bacteria by sequencing variable regions within the bacterial 16S rRNA gene
Whole genome sequencing	The process of defining the DNA sequence of whole genomes at one time
Facultative anaerobes	Organisms that can adapt to survive in environments where molecular oxygen is present or absent
Anaerobic genera	*Bifidobacterium* *Bacteroides* *Clostridium*
Proteobacteria Firmicutes	A major group (phylum) of illness-causing bacteria often found in the gut; consistent with gut dysbiosis
Lactobacillus	Belonging to a genus of bacteria that promote health
Redox potential	A process characterized by oxidation–reduction potential and indicative of more anaerobic conditions
Alpha diversity	Represents the variance within a particular sample; characterized by richness and evenness of species
Beta diversity	Represents how samples vary against each other

including short-chain fatty acids, bile acids, and bacterial diversity.[28,29]

In utero opioid exposure and the progression to NOWS may be associated with gut microbiome dysbiosis and GI dysfunction,[10,11] similar to that seen in the preterm infant and among infants with NEC,[16,17] even when affected infants with NOWS are born at full term. Furthermore, emerging evidence suggests that an association may exist between NOWS and NEC, as seen in infants born after 35 weeks' gestation.[27,34] While it is not clear whether NOWS causes NEC, authors suggest that increased expression of GI symptomology and issues with infant feeding may induce these perturbations.[27,34] Associated alterations may have both short- and long-term implications on the health of infants with NOWS.[10,27]

WHY STUDY HUMAN MILK AND THE INFANT GUT MICROBIOME IN INFANTS WITH NOWS?

NOWS is a condition that is marked by stress.[35] Infants experiencing NOWS not only experience the physiological state of withdrawal, but due to the need for sometimes extensive medical and nursing care, many infants undergo separation from their mothers as they receive treatment in the neonatal intensive care unit.[12] Previous literature examining the effects of stress on the gut microbiome in various populations, including adult and preterm infant samples, suggests the presence of a feedback loop between stress and gut dysbiosis.[23,28,36]

This bidirectional loop is known as the brain–gut axis when signals are sent from the CNS to the ENS, and conversely, the gut–brain axis when signals are sent from the ENS to the CNS[36] (see Figure 1). For example, it is hypothesized that when an infant experiences NOWS-related GI disturbance, this is communicated and interpreted by the brain as pain, which elicits stress. As this stress increases, the CNS may signal the onset of increased GI secretion and motility.[11] These GI alterations may manifest as diarrhea, a symptom consistent with NOWS.[37] When considering the benefits of human milk for infants with NOWS, previous evidence suggests that rates of diarrhea are significantly lower in breastfed infants when compared with those fed formula.[38]

Human milk contains complex and dynamic biologic components that are influenced by numerous factors including the mother's diet and biophysical and psychosocial status and the maternal and infant environment.[23,28,36] Human milk differs from the nutrient concentration and composition of formula and offers an optimal source of nutrition, as it hosts growth factors, cytokines, immunoglobulins, and digestive enzymes important for the infant's development and maturation.[18] Moreover, human milk has been shown to directly promote both immune health and gut maturation.[18]

Interventions designed to minimize the negative effects of peri- and postpartum risk factors may reduce gut dysbiosis. While literature is steadily growing regarding the role of infant feeding methods on the establishment of gut microbiota in various populations of high-risk infants, evidence suggests that *Bifidobacterium* and *Lactobacillus* predominate the gut microbiome of *healthy* full-term infants fed human milk.[24,39,40] Further, data from a secondary analysis conducted by Cong and colleagues[16] on preterm infants suggest that when compared with infants fed DHM or formula, infants fed MOM had greater α-diversity. Similarly, greater α-diversity was seen in a population of preterm very-low-birth-weight infants who received MOM.[41] These findings suggest that MOM contributes to a more favorable microbial community.[16]

While there is evidence to support the benefits of human milk on NOWS-related outcomes, the biologic mechanism remains unknown.[14] Given the protective role of human milk and the importance of establishing a healthy gut microbiota among the preterm infant, it is plausible that this mechanism extends to infants with NOWS through modified pathways. As such, the purpose of this scoping review was to describe the current state of the literature regarding the effect of human milk on infant gut microbiota in infants with NOWS.

METHODS

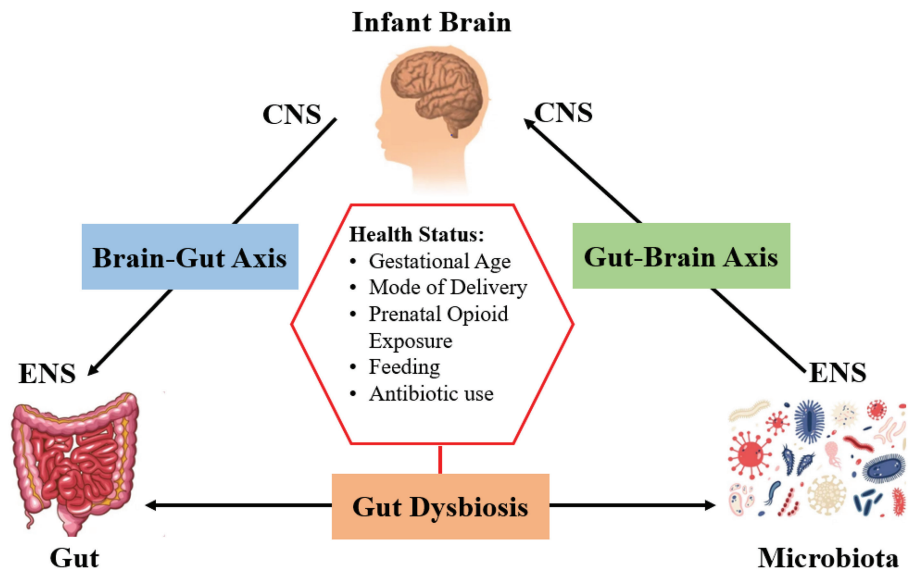
Design

For this scoping review, we utilized the Version 2 of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram, which includes the searches of databases, clinical trial registers, preprint registers, and gray literature searches (ie, websites and citation lists).[42] Scoping reviews are an appropriate methodology for reviewing emerging topics in literature, as there are no methodological restrictions for study inclusion.[43] A scoping review allows for the mapping of evidence on a specific topic of scientific interest, particularly when little is known about that topic.[43,44] As such, a scoping review was used to describe the current state of the literature regarding the effect of human milk on infant gut microbiota in infants with NOWS (see Supplemental Digital Content 1 for the PRISMA-SCR Checklist, available at: http://links.lww.com/ANC/A191).

Sample

To map the existing literature and determine gaps, a comprehensive database search for published literature was conducted in tandem with a gray literature search for unpublished study information and data. A search for unpublished studies was performed across relevant trial registries, websites, and organizations per Cochrane guidelines.[45] Additionally, conference proceedings were reviewed for possible inclusion. Due to the reviewers' limited reading fluency in any secondary languages, results were limited to English. There were no exclusions placed on infant characteristics (ie, gestational age, birth weight, etc.). Studies were excluded if they did not include a sample of infants with the condition of NOWS/NAS, as defined by withdrawal from in utero exposure to opioids with or without the

FIGURE 1



Brain–gut–brain axis in infants with prenatal opioid exposure. CNS indicates central nervous system; ENS, enteric nervous system.

presence of other psychotropic substances.[5] Additionally, studies that did not evaluate the relationship between human milk receipt or infant feeding method and the infant gut microbiome in this population were excluded. In 2009, guidelines for the use of human milk were changed to encourage lactation for infants with NOWS[46]; thus, studies were included if published between 2009 and the date of the search in 2021.

Criteria for inclusion were studies that:

- were published between 2009 and 2021,
- papers written in English,
- primary research,
- included a sample of infants with NOWS/NAS, and
- focused on the relationship between the receipt of human milk and the infant gut microbiome.

Criteria for exclusion were studies that:

- did not include a sample of infants with the condition of NOWS/NAS (ie, wrong population),
- did not evaluate the relationship between human milk receipt or infant feeding method and the infant gut microbiome in infants with NOWS/NAS (ie, wrong outcome),
- published outside the date range of 2009 to 2021,
- were nonhuman subjects (ie, animal models), and
- were nonprimary research studies (ie, wrong design).

Search Strategy and Information Sources

The search plan and syntax were developed in coordination with a health sciences librarian (E.L.) and performed in February 2022. An initial search string was written for PubMed and then translated across all included databases (see Supplemental Digital Content 1, available at: http://links.lww.com/ANC/A191). The search string combined keywords and subject headings related to the review question and was subjected to peer review prior to completion according to PRESS guidelines.[47] PubMed (1946—February 1, 2022) and Scopus (1823—February 1, 2022) were searched directly (see Supplemental Digital Content 2, available at: http://links.lww.com/ANC/A192). The Cumulative Index of Nursing and Allied Health Literature (1937—February 1, 2022) was searched using the EBSCO platform. The following search terms were used: prenatal opioid exposure or neonatal opioid withdrawal syndrome or neonatal abstinence syndrome; lactation or breastfeeding or breastfed or human milk; microbiome or gut microbiome. In this review, POE (prenatal opioid exposure) is defined as in utero exposure to prescription opioids, heroin, and prescribed or illicitly obtained methadone or buprenorphine. Subsequently, NOWS/NAS is defined as the condition resulting from POE. For the included studies, human milk included the receipt of expressed human milk or MOM, DHM, or direct lactation.

A gray literature search for unpublished studies and data was also performed in February 2022. Citations for conference proceedings were included in the database search results detailed earlier. A comprehensive search for unpublished studies and data was also completed. All searches consisted of abridged versions of the database search string primarily using the keywords: neonatal abstinence syndrome; neonatal opioid withdrawal syndrome; milk; feeding; biome; microbiome; and microbiota. Refer to Figure 2 PRISMA diagram for numerical results listed by website, registry, and organization name.

Study Selection

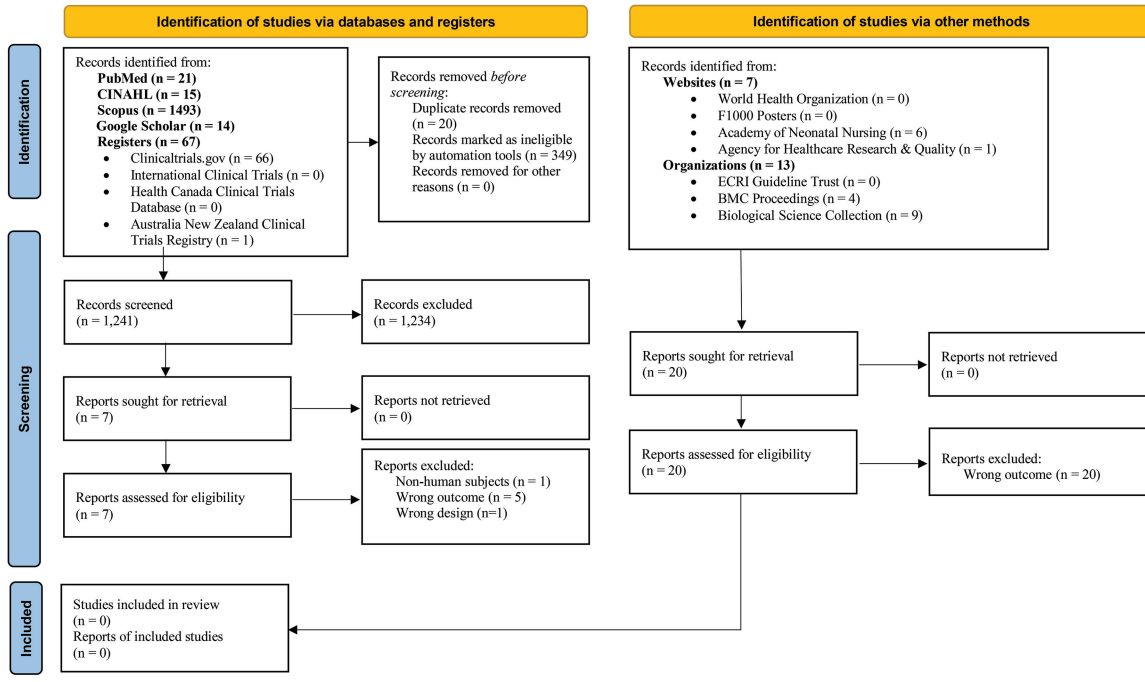
We retrieved 1610 articles through database and register searches and 20 through manual reference searches including review of websites, organizations, and citation searches. Citations were imported into EndNote X9 (Clarivate Analytics) and reviewed for duplication. Once duplicate articles (n = 20) and those removed by automation (ie, using an externally derived machine learning classifier remove articles based on the exclusion criteria) (n = 349), a total of 1241 database and register citations were imported into Rayyan (Qatar Computing Research Institute) to facilitate blinded review. During the title and abstract review process, a total of 1234 articles were reviewed by 2 people and excluded (A.C. and graduate research assistant). There were no discrepancies regarding study inclusion and exclusion at this level. A total of 7 articles obtained from the database and register search and 20 articles obtained by manual reference searchers underwent full-text review (K.M.B. and A.C.). Again, there were no discrepancies regarding the inclusion and exclusion of articles. Ultimately, all studies were excluded based on criterion of exclusion (see Figure 2 PRISMA diagram). Since no studies satisfied the inclusion criteria, citation chaining was not performed, and no contacts were made for additional studies and data.

RESULTS

No studies met the full criterion for inclusion in this scoping review. Since a synthesis of the data could not be conducted, we were unable to map or characterize evidence to support the review topic. As such, we report an empty review.

Of the 7 items that underwent full-text review, 3 articles[7,11,28] and 2 clinical trials[48,49] were excluded as they did not include all 3 variables of interest: human milk, infant gut microbiome, and the condition of neonatal opioid withdrawal syndrome. Similarly, none of the items obtained by manual reference searches (N = 20) included all 3 variables of interest.

FIGURE 2



Adapted from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram for updated systematic reviews, which included searches of databases, registers, and other sources.

Although 2 articles did include all 3 variables of interest, 1 article was nonhuman subjects research,[22] and 1 article was the wrong study design based on the inclusion criteria (ie, not a primary study).[10]

Excluded Articles

While no articles met full criteria for inclusion, important information can be gained regarding potential relationships between a human milk diet and the development of the infant gut microbiome in infants with NOWS. In a review article on the benefits of human milk for infants with NOWS, Bogen and Whalen[10] suggested that human milk could be used as a measure for diversifying the gut microbiome of infants with NOWS, leading to better short- and long-term health outcomes.

Abu and colleagues[22] examined the impact of brief prenatal hydromorphone, a type of opioid, exposure on the maternal and neonatal microbiome using a murine model. Fecal samples were collected from a group of hydromorphone-exposed dams and their offspring, as well as a nonexposed control group. Using 16sRNA sequencing, gut microbiome analysis was performed across various time points to investigate gut microbiota establishment.[22] As a secondary outcome, stomach contents were examined as a surrogate for human milk.[22]

While the analysis of the stomach contents revealed no significant change in the α-diversity between hydromorphone exposed and nonexposed offspring, the β-diversity of the stomach samples was significantly different.[22] These findings suggest that regarding α-diversity, the species richness and evenness within the microbiota of individual dams' stomach contents were not changed based on exposure type (ie, hydromorphone exposure vs nonexposed); however, based on β-diversity, the species of microbiota found within the stomach content was consistent based on group differences (ie, dams exposed to hydromorphone vs nonexposed dams).[22] Further, the authors found that the stomach contents (ie, human milk) contributed to approximately 50% of the offspring's stomach and gut microbiota taxa, with an abundance of *Staphylococcus* and *Lactobacillus* present in the microbiota samples.[22] Findings suggest that not only does the makeup of the gut microbiome differ in offspring with prenatal hydromorphone exposure when compared with nonexposed controls, but stomach contents also contribute to the establishment of the gut microbiota.[22] These findings underscore the importance of studying this phenomenon in human subjects to understand whether similar mechanisms exist.

DISCUSSION

NOWS remains a persistent issue for infants born with POE.[4,5] Evidence suggests that human milk improves several NOWS-related outcomes[14]; however, a paucity of literature exists examining how human milk mitigates NOWS during the early neonatal period. Furthermore, little is known about the development and establishment of the gut microbiome within this population.[11] This scoping review aimed to describe the current state of the literature regarding the effect of human milk on infant gut microbiota in infants with NOWS. To our knowledge, no studies have been published focusing on this research topic. Consequently, we report an empty review.

Opinions vary widely regarding the degree to which empty reviews are relevant to science. Despite this fact, several noted databases have published empty reviews.[50] For example, authors of a review of the Cochrane Library determined that of reviews completed prior to 2010, approximately 10% of published reviews were empty reviews.[50,51]

Several critiques of empty reviews have been presented in the literature previously, including that empty reviews may occur when the scope of the review is too limited.[50,51] However, when there is limited data to address a particular subject matter, empty reviews provide the opportunity for authors to assert their interest in a specific area of research.[51] More importantly, while empty reviews often leave more questions than answers, they can be particularly useful in helping to identify gaps in knowledge regarding a particular subject.[51] Lastly, empty reviews help minimize publication bias.

Findings from several studies suggest a relationship between human milk, the gut dysbiosis, and several conditions including prematurity[16] and NEC.[17] Nonetheless, to our knowledge, no studies have examined the linkages between the 3 study variables: human milk, the infant gut microbiome, and NOWS. Given the outcome of our review and increasing incidence of POE and infants born with NOWS,[4] this appears to be an area in urgent need of study.

Implications for Practice and Future Study

Several reviews have been published examining the links between human milk and breastfeeding (ie, lactation) in infants with POE and subsequent NOWS-related outcomes.[14] A recent meta-analysis evaluated the protective association between breastfeeding and optimized outcomes for infants with NOWS.[14] Outcome variables included in the review were symptom severity; need for and duration of pharmacologic treatment; and length of stay.[14] Findings from the meta-analysis suggest that breastfeeding is associated with decreased initiation and duration of pharmacologic treatment and length of stay.[14] While statistical significance was not observed for the association between symptom severity of NOWS and breastfeeding, the meta-analysis[14] emphasized the importance of clinical significance, which is characterized as meaningful findings for patient outcomes.[14]

One observed limitation of this body of literature is that the majority of studies included in the meta-analysis used retrospective cohorts.[14] Typical of retrospective studies, causation between variables cannot be inferred, only association.[52] Although human milk improves the outcomes of infants with NOWS, the mechanism and the potential contribution of gut alteration remains unknown; thus, prospective study of this phenomenon is warranted. The next generation of work should lead to interventions aimed at mitigating some of the issues related to GI dysfunction in infants with NOWS, including nutritional interventions. However, due to the limited availability of relevant literature providing an association between human milk, the infant gut microbiome, and NOWS, delineation of these relationships will likely be initially dependent on studies using both descriptive and observational methodologies.[28]

It is important to note that several challenges may exist when conducting research to address these phenomena. While human milk has been shown to be beneficial for both mothers and infants impacted by NOWS, several systemic barriers exist regarding the provision of human milk within this population.[53,54] To adequately study the proposed relationship between human milk, the infant gut microbiome, and NOWS-related outcomes, policies within healthcare systems must be in place to support both the receipt of human milk and direct breastfeeding for infants with NOWS.[54] Nurses can be instrumental in advocating for the breastfeeding dyad, working collaboratively to ensure the comprehensive health and social needs of the family are met and that the infant feeding plan of care is tailored to the individual needs of the mother and the infant.[53,54]

Further, engagement in research for this population is a multifaceted issue. Pregnant and postpartum women with opioid use disorder and their infants often face a myriad of challenges regarding engaging in healthcare-related activities, including research, which may stem from stigma-related treatment.[55] In return, researchers may struggle to gain access to, engage, recruit, and retain systematically underrepresented populations, which further marginalizes these patients.[56] Given the longstanding concerns of patients regarding participating in research, more specifically genomic studies, targeted approaches, such as the utilization of community-based participatory research methodologies, may prove to be a valuable tool for engagement.[57]

The importance of the gut microbiome and GI dysfunction for infants with POE and NOWS has largely been speculated.[11] Although the condition of

Summary of Recommendations for Practice and Research	
What we know:	• Evidence suggests associations between the use of human milk and lactation and optimized neonatal opioid withdrawal syndrome (NOWS)–related outcomes for infants with prenatal opioid exposure.
What needs to be studied:	• There is an identified gap in the available evidence regarding the effects of prenatal opioid exposure on the infant gut microbiome. • Prospective studies investigating mechanistic associations between human milk, the infant gut microbiome, and NOWS are warranted.
What can we do today:	• Current evidence supports the use of human milk as an optimal nutritional source for infants with prenatal opioid exposure and NOWS. Nurses should encourage the provision of human milk and lactation for infants in this population.

NOWS is hypothesized to contribute to the presentation of gut alterations, little is known about the characterization of gut microbiota in this infant population.[11] As knowledge of the association between human milk and mitigation of GI-specific symptoms among infants with NOWS increases, understanding the mechanisms underpinning these associations will be critical to identifying potential therapeutic targets. Investigating the use of targeted nutritional immunological interventions (ie, provision of human milk and pre- and probiotic supplementation) may be a fundamental contribution to improve NOWS-related outcomes, specifically those related to GI dysfunction, via the gut microbiome.[20] Given current evidence, nurses can promote the use of human milk as the optimal source of nutrition for infants with POE and NOWS.[14]

Limitations

The search strategy utilized in this study produced 0 publication, as no study was identified addressing the association between human milk, infant gut microbiome, and the condition of NOWS. As such, we are unable to draw definite conclusions regarding the relationships between these variables. Further, given the potentially restrictive nature of the inclusion criteria, the risk of omission of relevant studies is present. However, a gray literature search mitigated this risk.

CONCLUSION

It is becoming increasingly apparent that human milk and lactation are important to optimize outcomes in infants with NOWS.[14] Furthermore, growing evidence supports the link between the role of human milk on the developing infant gut microbiome and several neonatal conditions.[17,36,40] To date, there is a dearth of available literature examining this association for infants with NOWS. The reporting of an empty scoping review emphasizes the critical need to further our understanding of the mechanisms by which human milk influences the infant gut microbiome and the possible role this plays in infants affected by NOWS. Investigations addressing this void in knowledge represent novel opportunities for future research.

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