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Bowel habits in preterm infants: Observations from the first 2 weeks of life

Ulrikke Lyng Beauchamp[1] | **Susanne Soendergaard Kappel**[1] | **Ilan Jasper Nader Koppen**[2] | **Marc Alexander Benninga**[2] | **Lise Aunsholt**[1,3]

[1]Department of Neonatology, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark

[2]Department of Pediatric Gastroenterology and Nutrition, Emma Children's Hospital, Amsterdam UMC Location AMC, University of Amsterdam, Amsterdam, the Netherlands

[3]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Correspondence

Lise Aunsholt, Department of Neonatology, JMC, Copenhagen University Hospital Rigshospitalet, Juliane Maries Vej 6, 2100 Copenhagen Ø, Denmark.
Email: lise.aunsholt@regionh.dk

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Abstract

Objectives: Uniform descriptions of normal preterm infant bowel habits are lacking, causing ambiguity in identifying abnormal bowel habits in this population. This study examines preterm infants' bowel habits and their association with maternal and infant factors in the first 2 weeks of life.

Methods: An observational study included infants with a gestational age (GA) < 31 weeks from January to September 2021. From infant and maternal medical records, information on prenatal events, 2 weeks of bowel habit observations, enteral feeding, and laxative treatment was obtained. Extremely preterm infants (EPI) and very preterm infants (VPIs) were defined as GA < 28 weeks and GA ≥ 28 weeks, respectively.

Results: Of the 93 infants, 53 (57%) were included, and 37 (70%) were EPI. EPI received first enteral feeds at a median of 5 h after birth versus 2 h after birth in VPI ($p < 0.01$). EPI passed their first meconium at a median of 30 h (interquartile range [IQR] 12–49 h) after birth versus 26 h in VPI (IQR: 10–40, $p = 0.2$). In 21% of all infants, saline enemas were used to induce the passage of meconium. In 41% of EPIs ($n = 15$) laxatives were initiated before 2 weeks of age. Stool frequency varied from 0 to 9 stools daily, and prenatal events did not affect bowel habits.

Conclusion: This study provides a day-by-day description of bowel habits, enteral feeds, and laxative treatment but shows no associations with prenatal events in preterm infants. For future research, we recommend implementing homogeneous observation tools to enable comparison between studies.

KEYWORDS

extremely preterm, laxatives, maternal antibiotics, meconium, stool characteristics

1 | INTRODUCTION

Preterm birth (before 37 weeks of gestation) is associated with both immediate and prolonged challenges that impact survival rates and overall health outcomes.[1] Infants born before 28 weeks of gestational age (GA) are referred to as extremely preterm infants (EPIs) and infants born after 28 weeks of GA are referred to as very preterm infants (VPIs), complications related increase with decreasing GA.[2–4] The gastrointestinal tract (GIT), when immature, relies on maturation for proper digestion and nutrient absorption. Factors such as enteral nutrition, release of growth factors and hormones play key roles in this process.[5] The consequence of GIT immaturity implies feeding intolerance and affects bowel habits.[5–7] Infant bowel habits can be characterized by stool frequency, volume, consistency, and color, along with abdominal presentation, for example, distention, discoloration, and visual peristalsis.

Ulrikke Lyng Beauchamp and Susanne Soendergaard Kappel are co-first authors.

Prenatal administration of maternal drugs (e.g., antibiotics, indomethacin, and magnesium sulfate), maternal age, tobacco use, and mode of delivery all impact the abundance and diversity of the intestinal microbiome in the offspring.[8–13] Further, changes in the microbiome have been observed in infants following postnatal infection and antibiotic treatments,[14] highlighting the critical role of both prenatal and postnatal factors in shaping the infant gut microbiome and its implications for intestinal health. These factors also affect susceptibility to intestinal injury (e.g., spontaneous intestinal perforation [SIP]) and impact motility.[8–13,15,16]

The immaturity of the GIT, along with exposure to pre- and postnatal events, may delay meconium passage in preterm compared with term infants.[17–22] In healthy term infants, the first meconium normally passes within the first 48 h of life, while in preterm infants, meconium passage is often delayed.[23] This may lead to a perception of feeding intolerance that impacts clinical practices in neonatal intensive care units (NICUs), often resulting in the use of enemas to stimulate the passage of meconium.[24] After complete meconium passage, oral laxatives are frequently used to facilitate and ease defecation based on symptoms interpreted as signs of constipation.[7,25,26] However, an universal definition of constipation in preterm infants is lacking, which complicates the interpretation of symptoms and the following treatment.[27–29]

This study aimed to present a detailed description of bowel habits in EPI and VPI within the first 2 weeks of life. We hypothesized that prenatal and perinatal factors influence the early bowel habits of preterm infants.

What is Known

- Preterm birth is associated with gastrointestinal immaturity, which affects feeding intolerance and bowel habits, leading to variations in stool frequency, consistency, and the need for defecation aids.
- A definition of constipation in preterm infants is lacking, complicating clinical management and treatment decisions.

What is New

- A day-by-day description of early bowel habits in extremely and very preterm infants.
- Laxative treatment was frequently initiated within the first 2 weeks of life, despite the absence of diagnostic criteria for constipation in preterm infants, highlighting the need for a definition.

2 | METHODS

This observational study included infants with GA < 31 weeks admitted to a Level IV NICU in Copenhagen, Denmark, between January and September 2021. Infants with congenital abnormalities, outborn or admitted to the NICU later than 24 h after birth were not included in the study.

2.1 | Ethics statement

The study was approved by the Department of Regional Development, Health Research and Innovation in the Capital Region of Denmark (R-21063391) and did not require parental consent by Danish law.[30] Data were stored according to the Danish Data Protection Law (journal no. P-2021-765). The authors declare that this study was carried out in compliance with international standards for research practice and reporting. Written informed consent from parents was not required for this study in accordance with Danish law.

2.2 | Data collection

Data from the first 2 weeks of life was extracted from the electronic medical records (Epic Systems®) and entered into REDCap®.[31] Data collection took place from December 2021 to May 2022. Maternal data included prenatal and perinatal events (e.g., prescription of antibiotics and indomethacin for further information, see Supporting Information S1), while infant data included demographics, feeding regimes, bowel habits, and use of defecation aids (bowel massage by hand or by mobilizing the legs, rectal stimulation with cotton swab or thermometer, saline enema or gas relief by inserting a small feeding tube in the rectum). With the exception of baseline data, all other data were registered per feed and, as such, up to 12 times per day (Supporting Information S1). Further, the number of hours from birth till the first and last meconium passage (defined by a change in color) was registered. The analysis did not include infants with less than 6 days of admission.

Data collection ceased in cases of need for surgery or fasting for more than three consecutive days (total parental nutrition). All data up to 24 h before these events were included in the analysis.

2.3 | Data categories

According to GA, infants were grouped into EPIs (GA < 28) and VPIs (GA ≥ 28). Bowel habits included observations of meconium passage, stools (frequency, amount, color, and consistency), as well as abdominal appearance. Existing categories in Epic comprised multiple possibilities for similar observations, and many of these were not applicable to preterm infants.

Therefore, the original categories from Epic were converted to new categories when included in the analysis (Figure 1A). Amongst causes for initiating defecation aids, the original categories were chosen; however, "pain" was removed due to lack of use. For stool color, abdominal appearance, and defecation aid, the research group defined the most abnormal observation according to categories (Figure 1A) or the most risky procedure defined by possible risks of intestinal perforation. If more observations or procedures had been performed simultaneously, the most abnormal or riskiest ones were registered.

2.4 | Statistics

All baseline characteristics and clinical categorical variables were summarized and compared using a chi-square test. Normally distributed variables were reported as mean with standard deviation (SD) and compared using Student's *t* test. Whereas the non-normally distributed variables were reported as medians with corresponding first and third quartiles (Q1–Q3), or counts (*n*) and percentage (%), and compared using the Wilcoxon rank-sum test. A Cox proportional hazards model was applied for comparison of time-to-event data (e.g., time to first feed). Numeric outcomes were analyzed using a mixed-effects linear regression model. Reasons for shorter periods of fasting (<72 h) were noted, and data were included in the analysis.

Statistical significance was defined as p values < 0.05. All statistical analyses were performed using the statistical software R (version 4.0.0).

3 | RESULTS

3.1 | Study population

By screening medical records, 93 infants were identified. After eligibility assessment, a total of 53 infants with GA between 23 + 4 and 30 + 6 weeks were included together with their 43 mothers (8 twins and 1 triplet). Data collection in seven infants was incomplete, for six due to surgery, while one infant had more than three consecutive days of total parenteral nutrition. The final study population is shown in the CONSORT diagram (Supporting Information S2). In total, 7372 observations were collected during the study period. Of the 53 infants, 37 (70%) were born at 23 + 3 to 27 + 6 weeks of gestation (EPI) with a mean birth weight of 900 g (±178 g), and 16 (30%) were born at 28 + 0 to 30 + 6 weeks of gestation (VPI) with a mean birthweight of 1171 g (±323 g). Demographics of infants and mothers are described in Tables 1 and 2.

For all infants, there was a great variation in time to first enteral feeding (1–19 h) independent of GA, although median duration was longest in the EPI compared to the VPI (5 vs. 2 h, $p < 0.05$, Table 3). The volume of initial enteral feeds varied from 1 to 2 mL for EPI and 1 to 4 mL for VPI infants and consisted of either the mother's own milk (MOM), human donor milk (HDM), or a combination of the two. Across the study period, the proportion of HDM feeds was highest during the first 2 days of life, switching to MOM, hence, comprising the highest proportions of feeds from Day 3 of life and onwards. By Day 14 of life, 85% of all feeds consisted of exclusively MOM. Fortification (with Pre-NAN FM85®, Nestlé) was initiated in 40 infants at a mean day of 8 postnatal days (±2).

3.2 | Bowel habits in EPI and VPI

Time to first meconium passage varied from 38 min to 81 h and was in 21% of all infants stimulated by a saline enema. There was no difference in time of first meconium passage between GA groups (median: 30 h for EPI, and 26 h for VPI infants, $p = 0.2$, Table 3). Infants with the highest birthweight had the shortest time to last meconium passage ($p < 0.01$). This variable did not differ between the two GA groups ($p = 0.09$, Table 3). Time to first and last meconium passage was not associated with the timing of the first enteral feed (both, $p = 0.1$).

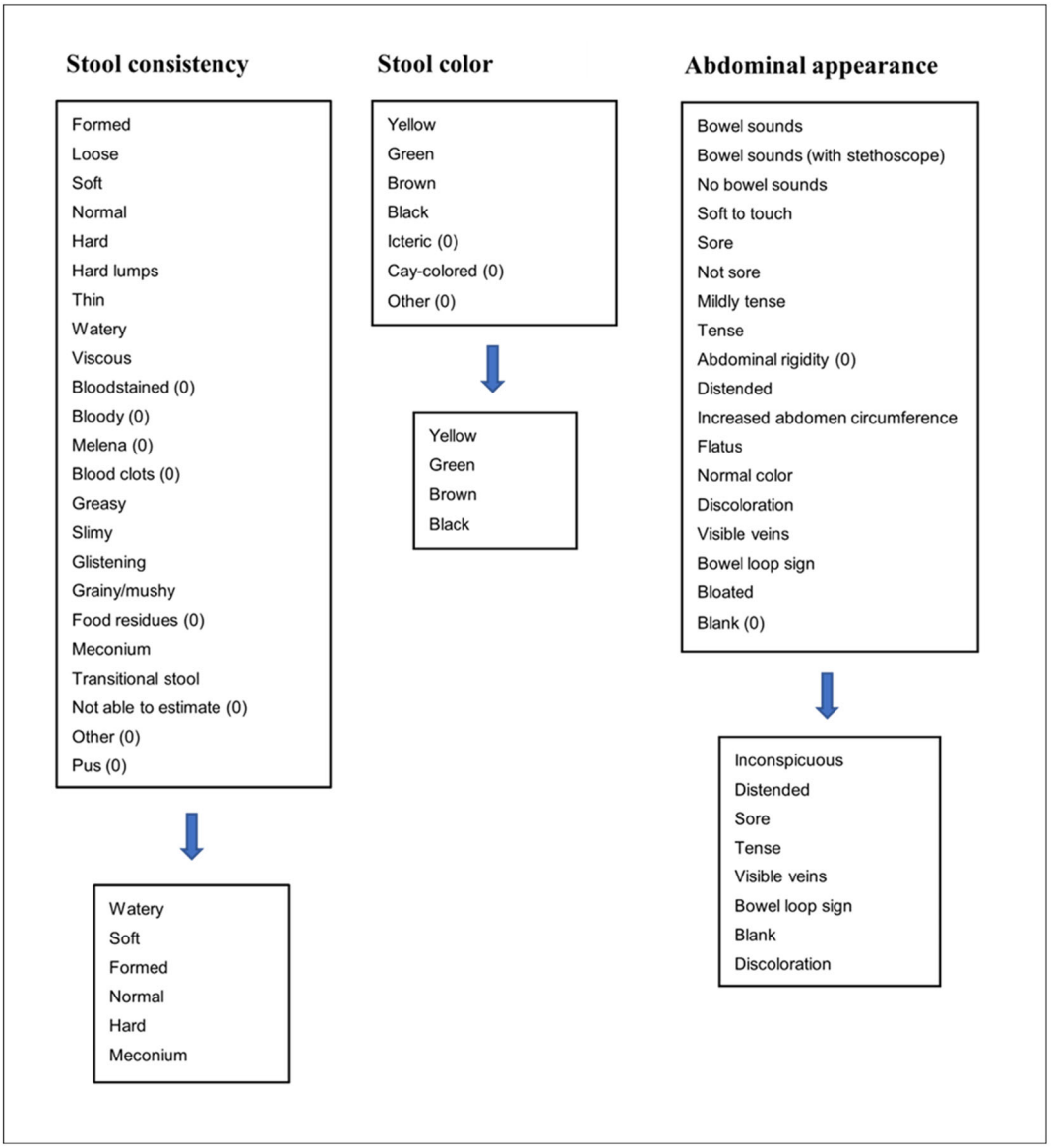
Included infants had a defecation frequency of 0–9 stools per day during the first 14 days of life. The amount, color, and characteristics of stools changed from Day 1 onwards, as presented in Figure 1B. Further, there was a change in the description of abdominal appearance in the same time period.

3.3 | Defecation aid and laxative treatment

In 34 infants, defecation was stimulated with saline enemas from 1 to 11 times (median: 1) during Week 1. During Week 2, 13 infants were stimulated with saline enemas from 1 to 7 times (median: 2). Further, gas relief and rectal stimulation were documented in 9 and 12 infants during Week 1, respectively (gas relief: median: 1, min–max: 1–4 times, rectal stimulation: median: 1, min–max: 1–3 times) and in 12 and 17 infants during Week 2, respectively (gas relief: median: 1, min–max: 1–13 times, rectal stimulation: median: 1, min–max: 1–4 times).

During the observation period, 27 infants were treated with laxatives. The median postnatal age at the prescription of laxatives was 11 days for VPI and 12 days for EPI infants ($p = 0.02$, Table 3). Prescription of laxatives was lactulose in 85% and macrogol in

(A)



(B)

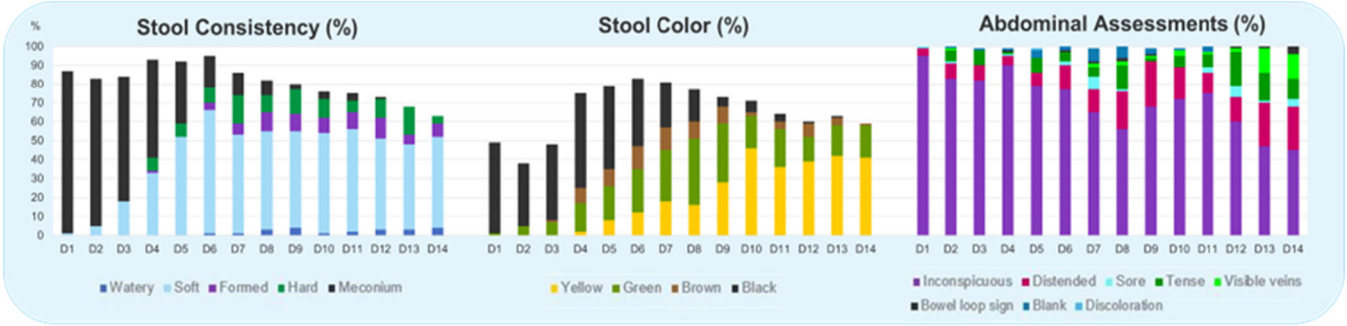


FIGURE 1 (A) Categories available for documentation in medical records and final categories used for analysis (after blue arrows). (0) shows categories not documented during the study period. (B) Visual presentation of stool consistency, color, and abdominal assessments.

15% of cases, and in addition, 11% of lactulose prescriptions were later substituted by macrogol. Prescribed laxatives were not ceased within the observation period. In 24 infants, the justification for initiation of laxative treatment was documented as formed or hard stools ($n = 16$), defecation difficulties including pushing and grunting ($n = 6$), fortification of human milk ($n = 3$), and delayed meconium passage

TABLE 1 Demographics and characteristics of infants and mothers in the cohort.

	GA 23 + 0 to 27 + 6	28 + 0 to 30 + 6	*p* value
Infants, *n* = 53	37	16	
Gender (males), *n* (%)	20 (54)	10 (63)	ns
Birth weight (g), mean (SD)	900 (±178)	1171 (±323)	<0.05*
ELBW (<1000 g), *n* (%)	22 (60)	5 (31)	ns
VLBW (≥1000 g to <1500 g), *n* (%)	15 (41)	9 (56)	ns
LBW (≥1500 g to <2500 g), *n* (%)	-	2 (13)	
Twins, *n* (%)	7 (19)	1 (6)	ns
Triplets, *n* (%)	-	1 (6)	ns
Cesarean section, *n* (%)	25 (68)	14 (88)	ns
APGAR score 5 min, median (Q1–Q3), *n* = 50	10 (8–10)	10 (7–10)	ns
PDA, *n* (%)	22 (60)	4 (25)	<0.05*
IVH I, *n* (%)	2 (5)	3 (19)	ns
IVH II, *n* (%)	5 (14)	1 (6)	ns
IVH III, *n* (%)	1 (3)	-	
IVH IV, *n* (%)	1 (3)	-	
NEC, *n* (%)	1 (3)	-	
SIP, *n* (%)	5 (14)	-	ns
Mothers, *n* = 43	30	13	
Age at delivery (years), median (Q1–Q3)	30.5 (27–33)	30 (26–32)	ns
Fertility treatment, *n* (%)	9 (30)	3 (23)	ns
Smoker, *n* (%)	3 (10)	2 (15)	ns
GDM, *n* (%)	2 (7)	2 (15)	ns
Pre-eclampsia/eclampsia, *n* (%)	2 (7)	2 (15)	ns
PPROM > 24 h, *n* (%)	13 (43)	6 (46)	ns
Abruptio placentae, *n* (%)	4 (13)	-	ns
Chorioamnionitis, *n* (%)	3 (10)	2 (15)	ns
Indomethacin, *n* (%)	10 (33)	1 (8)	ns
Atosiban (Tractocile), *n*	22 (73)	3 (23)	ns
Tranexamic acid, *n*	8 (27)	-	
Magnesium sulfate, *n* (%)	28 (93)	12 (92)	ns
Antenatal corticosteroids before birth, *n* (%)	30 (100)	12 (92)	ns
One dose only, *n* (%)	12 (40)	1 (8)	<0.05*
Full treatment, *n* (%)	18 (60)	11 (85)	ns

Abbreviations: ELBW, extremely low birth weight; GA, gestational age; GDM, gestational diabetes mellitus; IVH, intraventricular hemorrhage; LBW, low birth weight; NEC, necrotizing enterocolitis; ns, non-significant; PDA, persistent ductus arteriosus; PPROM, preterm prelabour rupture of membranes; SD, standard deviation; SIP, spontaneous intestinal perforation; VLBW, very low birth weight.

*significance.

($n = 1$). In two cases, there was more than one cause for laxative treatment.

3.4 | SIP and NEC

During the study period, five EPI were diagnosed with SIP and one with NEC; no VPI were diagnosed with either. All six infants had GI surgery during the first 14 days of life. For one infant, surgery was performed before the first meconium passage. Five infants received intrapartum indomethacin within 2 days before birth; one of these was diagnosed with SIP within 2 weeks of age.

3.5 | Pre- and perinatal events

Within 4 weeks before/or at delivery, 38 (88%) mothers received antibiotics (Type and accumulated days are listed in Table 2). For 98% of all mothers, antenatal corticosteroid therapy (one or two doses) was administered before preterm delivery. Prenatal intravenous infusion with magnesium sulfate was administered to 93% of mothers, of whom eight received an additional bolus close to birth. The time from the last infusion or bolus with magnesium sulfate to birth was a median of 3.6 h (0.1–55) (Table 2).

Of all 43 mothers, 11 received treatment with indomethacin during pregnancy for tocolysis (26%, Table 1). No differences were found between infants diagnosed with SIP and those who received intrapartum indomethacin (2 vs. 3, ±indomethacin, respectively, $p = 0.9$).

In general, no pre- or perinatal events were associated with effects on bowel habits in preterm infants when investigating the mode of delivery and medication during pregnancy (Table 1).

TABLE 2 Maternal prenatal and perinatal drugs.

N	43
Magnesium sulfate, *n* (%)	40 (93)
Time from last infusion or bolus to birth (hours), median (min–max)	3.6 (0.1–55)
Antenatal corticosteroids, one dose (%)	13 (30)
Time from one dose to birth (hours) median (min–max)	5 (0.3–21)
Antenatal corticosteroids, full treatment (%)	29 (67)
Time from full treatment to birth (days) median (min–max)	5.4 (0.5–45)
Rescue dose after full treatment, *n* (%)	7 (17)
Indometacin, $n = 11$	
Indomethacin treatment duration (days), median (min–max)	2 (1–24)
Time from discontinuation to birth (days), median (min–max)	4 (0–29)
Blood pressure medication	
Nifedipine (Adalat or Cordaflex), *n*	13
Labetalol (Trandate), *n*	4
Methyldopa (Aldomet), *n*	2
Maternal antibiotics administered maximum of 4 weeks before birth	
Cefuroxime (preoperative),[a] *n*	38
Metronidazole, *n*	23
Cefuroxime (not preoperative), *n*	18
Penicillin, *n*	18
Pivmecillinam, *n*	13
Ampicillin, *n*	5
Gentamycin, *n*	3
Meropenem, *n*	2
Nitrofurantoin, *n*	2
Erythromycin, *n*	1
Amoxicillin, *n*	1

[a]Cefuroxime before cesarean section.

4 | DISCUSSION

In this retrospective study, including 53 VPIs and EPIs, we investigated early bowel habits and the subsequent needs for defecation treatments during the first 2 weeks of life. Further, the association of pre-, peri-, and postnatal factors' impact on bowel habits was studied. Our results highlight a wide variability in time to first meconium passage and defecation patterns, even within specific GA groups, and a high frequency of interventions. Interestingly, none of the pre-, peri, or postnatal factors showed a significant association with early bowel habits. However, the considerable variability in bowel habits observed in this study may have limited the ability to detect statistically significant associations with perinatal factors. Thus, the absence of such associations should be interpreted with caution.

Early initiation of enteral feeding stimulates the maturation of the intestine with a potential effect on the timing of meconium passage in VPI and EPI.[32] In contrast to previous studies,[33–35] we found that enteral feeding was initiated within the first 24 h after birth in all included infants, even the most preterm. Furthermore, we found no relation between the timing of the first feed and the last meconium passage, similar to other studies,[7,19,21,36] indicating that other factors besides enteral feeding influence motility.

Stool characteristics in weeks 1 and 2 were previously described by Bekkali et al.[7] In the present study, the day-by-day description in the medical records

TABLE 3 Bowel habits and feeds, Days 0–14 postnatal.

	GA 23 + 0 to 27 + 6	GA 28 + 0 to 30 + 6	Total *n*	*p* value
N	37	16	53	
Time to first feed (hours), median (Q1–Q3)	5 (3.5–8.5)	2 (2–6)		<0.05*
Type of feeds				
MOM, proportion of total feeds, %	72	71		ns
HDM, proportion of total feeds, %	20	21		ns
Combination of both, proportion of total feeds, %	5	4		ns
Missing, %	3	4		
Time to first meconium (hours), median (Q1–Q3)	30 (12–49)	26 (10–40)	52	ns
Time to last meconium (hours), median (Q1–Q3)	125 (100–153)	90 (60–111)	47	ns
Treatment with laxatives (lactulose), *n* (%)	15 (41)	12 (75)	27	<0.05*
Time to first laxatives (days), median (Q1–Q3)	12 (9–13)	11 (11–13)		<0.05*
First meconium by enema, *n* (%)	9 (24)	2 (13)		ns

Abbreviations: GA, gestational age; HDM, human donor milk; MOM, mother's own milk; ns, non-significant.
*significance.

comprised comprehensive, heterogeneous, and unspecific categories, hence modified as described in the method section, to simplify and enable comparison. Even though applied scoring scales were different in the two studies, results were comparable, supporting that the use of a validated scoring scale provides detailed information regarding stool characteristics, improving daily clinical assessments and practice.

Laxative treatment for preterm infants is often prescribed, although there are no diagnostic criteria for constipation in this patient group. Pediatric functional gastrointestinal disorders are diagnosed according to the ROME IV criteria, but these do not apply to the NICU population.[37] More than half of the included infants in our study were treated with laxatives, similar to other studies.[7,38,39] Surprisingly, laxative treatment was already initiated within the first 2 weeks of life, mainly because of hard and formed stools, defecation difficulties, and human milk fortification. In this study, most infants had lactulose prescribed as the first choice of osmotic laxative, with a possible change to macrogol later. Randomized controlled trials investigating the efficacy of laxatives in preterm infants are difficult to perform due to a lack of definitions for constipation and treatment success in this patient group. Although macrogol is the drug of choice when treating functional constipation in toddlers and children,[40] this has never been tested in preterm infants and further requires a large volume of fluids, making it less easily applicable for preterm infants within the first 14 days of life.

Previously, it has been shown that pre- and perinatal factors may affect the gut microbiota[41–45]; however, to our knowledge, none have investigated the relationship between these factors and early bowel habits in preterm infants. Specifically, prenatal antibiotics negatively influence the infant gut microbiome.[7,33] One could anticipate this may cause loose stools and perhaps a distended abdomen, explained by the dysbiosis, but 84% of the included mothers received pre- or perinatal antibiotics, thus lowering the number of nonexposed infants; hence, the anticipation could not be confirmed in this study.

Preterm infants, particularly EPIs, are at risk of acute onset of gastrointestinal diseases (e.g., SIP and NEC), also within the first 2 weeks of life.[46] In our study, five infants were diagnosed with SIP and one with NEC. Others have shown associations between prenatal maternal administration of drugs (e.g., indomethacin and magnesium sulfate) and increased risk of SIP. When investigating the association between SIP and indomethacin or SIP and magnesium sulfate administrations, we found no associations. However, there are indications that these associations are related to the timing of administration before birth or at specific GA of the fetus.[47–49] In our study, the infants were older (overall mean GA of 27 weeks) and indomethacin was administered at a mean of 7 days before delivery compared to within 2 days before birth in other studies,[47–49] potentially explaining the differences between our results.

We acknowledge that this study has some limitations. At first, we decided to stratify the group of infants according to GA as we expected that bowel habits in EPI and VPI differentiate; hence, accepting this reduced the sample size, particularly in the EPI group. The uneven distribution of EPI and VPI infants reflects the admission pattern to our NICU during the inclusion period. While no infants were systematically excluded, the limited study period may introduce a risk of sampling bias, which

could affect the generalizability of comparisons between the two groups. Further, it is important to note that modifying the categories used to describe bowel habits could lead to inconsistencies with the original observations, potentially compromising the validity of the analysis. However, our results were comparable to the results of Bekkali, reducing the risk of this limitation.[50] The strengths of this study are the day-to-day assessment and documentation of bowel habits, enteral intake, prescription of medication, and other defecation treatments, providing a unique detailed data set. Further, results from included patients were comparable with results from a recent Danish cohort of VPIs and international results, indicating reliable results.[50]

5 | CONCLUSION

In conclusion, this study provides a detailed description of early-life bowel habits and the use of laxatives in EPI and VPI, with no associations between pre-, peri-, and postnatal factors. Despite a lack of consensus regarding diagnostic criteria for laxative prescription, surprisingly, this was already frequent within the first 2 weeks of life. This emphasizes the need to establish consensus-based diagnostic criteria and treatment guidelines for functional constipation in preterm infants. In particular, our findings call attention to the frequent use of laxatives without standardized clinical indications, suggesting a potential risk of overtreatment. Increased clinical awareness and clearer criteria for assessing bowel dysfunction are warranted to support evidence-based decision-making in this population. Further, future studies should include the use of validated scales, for example, the Amsterdam Stool Scale, to enable comparison between studies in the meta-analysis, thereby paving the way for consensus without the need for large randomized controlled trials with the risk of low feasibility.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data supporting this study's findings are not publicly available because they contain information that could compromise the privacy of the participants. However, data from the study are available to editors and reviewers from the corresponding author, LA, upon reasonable request.

ORCID

Susanne Soendergaard Kappel https://orcid.org/0000-0002-2023-298X
Lise Aunsholt https://orcid.org/0000-0003-0965-429X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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