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Original Article

The First Stool Passage Time in Extremely Low Birth Weight Infants

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Abstract ***Objective:*** Timely passage of meconium represents the maturation of the gastrointestinal tract in newborns. Few studies have evaluated the time to first meconium passage in extremely low birth weight infants (ELBWIs). We investigated the time to first stool passage in ELBWIs and risk factors for delayed passage. ***Methods:*** The medical records of all ELBWIs (birth weight <1000 g) hospitalised in the neonatal intensive care unit of Asan Medical Center between January 2000 and December 2015 were retrospectively reviewed. Time to first stool passage after birth and associated factors were analysed. ***Results:*** This study included 546 ELBWIs with a mean gestational age of 26.9±2.4 weeks and a mean birth weight of 800.0±156.1 g. Their mean age at the time of first stool passage was 2.64±4.2 days, with 90% of the infants passing stool by nine days after birth. Multiple logistic regression analysis indicated that delayed stool passage was associated with lower gestational age, male gender, severe sepsis, and intracranial haemorrhage (ICH) ($p<0.05$). ***Conclusion:*** Time to first stool passage was longer in ELBWIs than in normal birth weight infants. Lower gestational age, male, severe sepsis, and ICH could delay the time of the first stool passage.

Key words *Extremely low birth weight infant; Gestational age; Meconium*

Introduction

Passage of the first stool in neonates within the first 24 hours of life is considered a sign of well-being and maturation of the gastrointestinal tract.[1-3] About 90% of healthy full-term neonates pass their first stool by 24 hours and about 100% by 48 hours. Delayed passage of the first stool in term neonates may be associated with lower intestinal obstruction caused by, for example, meconium plug syndrome, Hirschsprung disease, or an imperforate anus. Other causes can include more generalised problems, such as sepsis or hypothyroidism, and unanticipated maternal complications, such as magnesium sulfate administration or narcotic use.[1]

In contrast to healthy full-term neonates, a delay in the passage of the first stool is a common occurrence in very low birth weight infants (VLBWIs). This delay is probably due to physiologic immaturity of the motor mechanisms of the gut, lack of a triggering effect of enteral feeding on gut hormones, and/or the occurrence of severe respiratory distress syndrome, which may singly or in concert adversely affect gastrointestinal motility.[2]

A study reported that passage of the first stool was delayed in one-fifth of all VLBWIs, with birth weights ranging from 500 to 1,500 g and gestational ages between 25 and 35 weeks.[2] Few studies, however, have assessed

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passage of the first stool in extremely low birth weight infants (ELBWIs), defined as those of birth weight <1,000 g. Recent developments in neonatal intensive care have greatly improved survival rates of ELBWIs.[4] This study assessed the times of the first stool passage in ELBWIs and evaluated the factors contributing to a delayed first stool passage.

Methods

Patient Population

The medical records of neonates of birth weight <1000 g hospitalised in the neonatal intensive care unit (NICU) of Seoul Asan Medical Center between January 2000 and December 2015 were reviewed retrospectively. The study protocol was approved by the Institutional Review Board of Asan Medical Center (protocol number S2019-1015-0001), and all study procedures complied with articles in the Declaration of Helsinki. ELBWIs who did not survive more than 72 hours and those transferred into or out of the NICU after two postnatal days were excluded.

Medical Data

We collected data of meconium passage time and compared them between early and late groups. Factors associated with meconium passage including gestation age, birth weight, gender, multiparty, Apgar score, maternal $MgSO_4$ or opioid use, perinatal and postnatal events (congenital infection, sepsis, fetal hydrops, intracranial haemorrhage (ICH), Twin-to-Twin Transfusion syndrome, haemodynamically significant patent ductus arteriosus (PDA), or severe Respiratory distress syndrome, etc.), congenital anomalies and genetic disorder were studied. In addition, time to feeding advance, rates of parenteral nutrition-associated liver disease, meconium plug syndrome, and an increase in hospital stay were included in the analysis.

We also analysed ELBWIs patients' stool passage time according to sex and gestational age after excluding patients with serious medical conditions that may affect the meconium passage.

Statistics

Categorical variables were analysed using the chi-square test or, when applicable, Fisher's exact test. Continuous variables were reported as mean ± standard deviation (SD) or median and range, and analysed using Student's t-test or the Mann-Whiney U test. Factors affecting the time to meconium passage were evaluated by logistic regression analysis. All statistical analyses were performed using Predictive Analytics Software (PASW statistics 18.0), with a $p<0.05$ considered statistically significant.

Results

Comparisons of Baseline Demographics, Clinical Presentation, and Outcome Between Early and Late Groups

A study population consisted of 564 ELBWIs, 285 (50.5%) boys and 279 (49.5%) girls. Their mean ± SD gestational age was 26.9±2.4 weeks, and their mean birth weight was 800.0±156.1 g. Of these 564 ELBWIs, 127 (22.5%) were the result of multiple births.

The patients were divided into half according to meconium passage time; meconium release within 72 hours after birth as the early passage group, and after 72 hours as the late passage group. It showed that the late passage group had a higher percentage of males, earlier gestational age, and lower birth weight than the early passage group.

Also, the late passage group had a lower APGAR score and was associated with increased maternal factors of multiparty and magnesium administration. There was no difference between gastrointestinal or extra-gastrointestinal anomaly, duration of NPO, parenteral nutrition-associated cholestasis, and meconium plug syndrome. However, the late group showed an increase in the length of hospital stay (Table 1).

Time of First Stool Passage in ELBWIs and Associated Factors of Delayed Passage

Of the 564 ELBWIs, only 146 (25.9%) passed their first stool within 24 hours and 304 (55.5%) within 72 hours. The mean age at the first stool passage was 2.64±4.2 days (63.4±100.8 hours). Thereafter, there was a steady daily cumulative increase in the percentage of ELBWIs who defecated, with 90% of these infants passing stool by nine days after birth (Figure 1).

Univariate logistic regression showed that sex, gestational age, 1-, and 5-minute APGAR score, severe sepsis, maternal magnesium administration, multiparty, ICH, renal anomaly, and haemodynamically significant

Table 1 Demographic and clinical characteristics of study populations

	Total (n=564)	Early (<3 days) group (n=304)	Late (≥3 days) group (n=260)	P-value
Infant chracteristics				
Gestational age (weeks)	26.9±2.4	27.6±2.6	25.9±1.9	<0.001
Birth weight (grams)	800.0±156.1	840.0±155.1	771.0±155.9	0.063
Male gender	285 (50.5%)	137 (45.0%)	148 (56.9%)	0.013
Multiple gestation	127 (22.5%)	56 (18.4%)	71 (27.3%)	0.003
1 minute APGAR score	3.8±1.8	4.1±1.9	3.3±1.7	<0.001
5 minutes APGAR score	6.1±1.6	6.4±1.6	5.7±1.6	<0.001
Congenital malformation				
Gastrointestinal anomalies(1)	154 (27%)	84 (28%)	70 (27%)	0.775
Extra-intestinal anomalies(2)	208 (37%)	118 (39%)	90 (35%)	0.723
Genetic disorder(3)	5 (0.9%)	3 (0.5%)	2 (0.4%)	0.784
Antenatal drug exposure				
Maternal $MgSO_4$ administration	285 (51%)	144 (47%)	141(54%)	0.016
Maternal opioid administration	210 (37%)	115 (38%)	95 (37%)	0.791
Clinical course				
Time to first oral feed (days)	11.6±10.3	11.2±11.0	12.5±9.5	0.153
Meconium plug syndrome	25 (4%)	9 (3%)	16 (6%)	0.062
Parenteral nutrition-induced cholestasis	50 (9%)	28 (9%)	22 (8%)	0.947
Hospital days	79±40	76±38	89±40	<0.001

(1) GI anomalies consisted of 143 inguinal hernias, 4 intestinal obstructions, 2 Hirschsprung's disease, 2 ventral hernia, 1 diaphragmatic hernia, 1 imperforate anus, 1 malrotation, and 1 Meckel's diverticulum.
(2) Extra-GI anomalies consisted of 109 urologenital, 87 cardiovascular, 86 pulmonary, 25 nephrologic, 22 musculoskeletal, 16 head and neck, 10 hepatobiliary, 10 neurologic, and 3 ophthalmologic anomalies.
(3) Genetic disorder consisted of 1 Down syndrome, 1 Edwards syndrome and 1 Klinefelter syndrome in early group, and 1 Wilson-Mikity syndrome and 1 cystic fibrosis in late group.

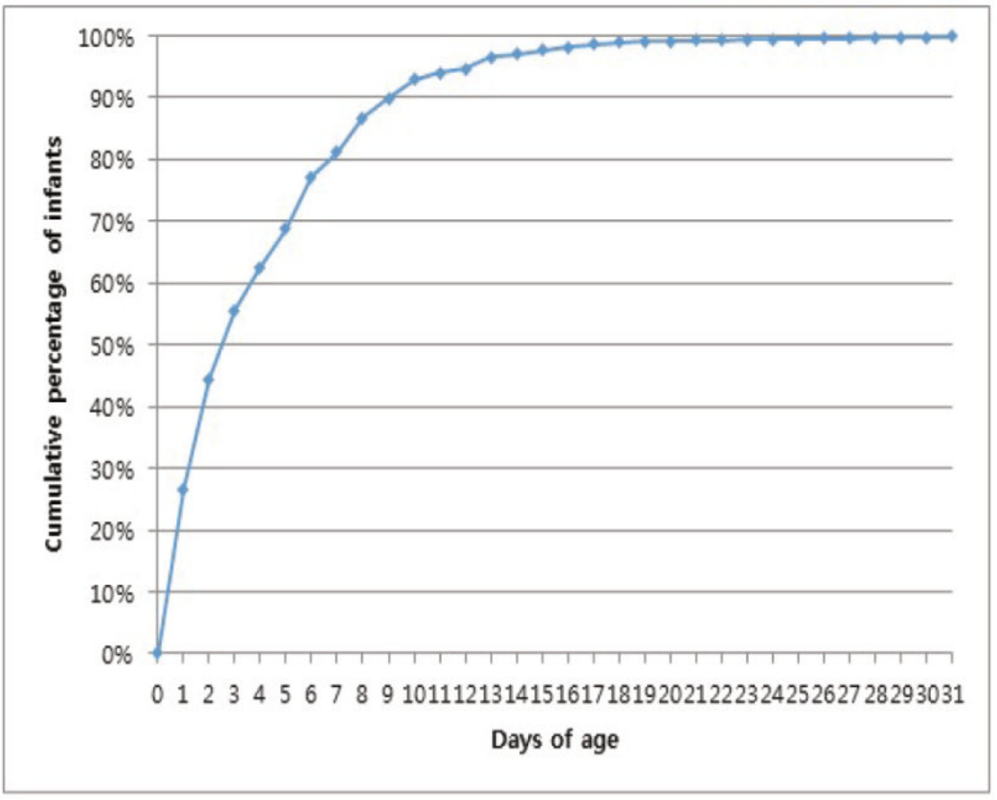

Figure 1. Cumulative percentage of first stool passage in ELBWIs.

PDA were associated with delayed passage (Table 2). Multivariate analysis showed that sex, gestational age, severe sepsis, and ICH were significantly associated with meconium passage ($p<0.05$, Table 3)

Time of First Stool Passage in ELBWIs Without a Serious Medical Condition

ELBWIs without other serious medical conditions such as congenital anomalies, sepsis, and ICH were categorised according to gender and gestational age to assess the stool passage time (Figure 2).

In male infants, the median time of meconium passage was 2.5 (±4.5) days, and 90% of patients passed meconium within ten days. In female infants, the median time of meconium passage was 1.0 (±3.9) days, and 90% of patients passed meconium within eight days.

Neonates of gestational age less than 27 weeks showed a median time of 4.0 (±4.7) days in meconium passage, and 90% of patients passed meconium within ten days. Neonates of gestational age greater than 27 weeks showed a median time of meconium passage in 1.0 (±3.3) days, and 90% of patients passed meconium within eight days.

Discussion

Whereas most healthy full-term infants pass their first stool by 48 hours after birth,[1] 10-22% of preterm infants tend to have delayed meconium passage.[2,3,5] Delays in meconium passage are thought to be due to underdevelopment of the gastrointestinal system and poor general condition due to younger gestational age and lower birth weight, but factors affecting delays in meconium passage remain unclear.[2,3,6,7] Meconium passage after 48

Table 2 Univariate analysis of risk factors associated with delayed meconium passage

	P-value	Odds ratio	95% confidence interval	
Gestational age	0.000	0.716	0.657	0.781
Birth weight	0.064	0.999	0.998	1.000
Male gender	0.011	1.549	1.104	2.174
Multiple gestation	0.002	1.847	1.249	2.732
1 minute APGAR score	0.000	0.791	0.720	0.871
5 minutes APGAR score	0.000	0.751	0.673	0.838
Maternal $MgSO_4$ administration	0.014	1.531	1.090	2.149
Maternal opioid administration	0.768	1.053	0.640	1.500
Severe sepsis	0.001	3.864	1.696	8.800
Congenital infections	0.237	1.701	0.546	4.134
Fetal hydrops	0.783	1.253	0.062	2.648
Hypothyroidism	0.680	0.888	0.602	2.389
Intracranial haemorrhage	0.000	2.280	1.087	2.423
Respiratory distress syndrome	0.294	1.424	0.421	1.922
Duration of mechanical ventilation	0.449	0.993	0.974	1.012
PDA, haemodynamically significant	0.001	2.178	1.354	3.503
Twin-to-Twin Transfusion syndrome	0.339	1.630	0.583	6.482
Gastrointestinal anomalies	0.766	1.058	0.735	1.875
Cardiovascular anomalies	0.309	0.799	0.589	1.661
Head and neck anomalies	0.722	1.255	0.255	3.922
Hepatobiliary anomalies	0.287	0.559	0.189	2.148
Musculoskeletal anomalies	0.149	2.130	0.776	6.918
Nephrologic anomalies	0.028	2.789	1.118	6.952
Neurologic anomalies	0.438	1.374	0.394	2.411
Urogenital anomalies	0.143	0.702	0.469	1.498
Genetic disorders	0.784	1.130	0.646	1.525

PDA: patent ductus arteriosus

hours was reported in 20% of low birth weight infants and 33% of VLBWIs, with delayed passage associated with gastrointestinal immaturity and severe disease condition.[2] A study of 144 VLBWIs found that the median time to first meconium passage was three days, with 90% passing meconium within 12 days after birth.[8] That study found, however, that time to first passage was significantly longer in male than in female neonates, but was not associated with gestational age.

In comparison, the present study found that the median time to first meconium passage was 2.6 days, with 90% of ELBWIs passing meconium by nine days after birth. Moreover, the present study found that male gender and earlier gestational age were significantly associated with delayed meconium passage. Because our study included more ELBWIs, their mean gestational age was younger than in previous studies. Younger gestational age was accompanied by more immature gastrointestinal systems.[9,10] As earlier studies also reported similar results,[3,6] low gestational age can be a major factor of delayed meconium passage.

Development of the fetal gastrointestinal tract starts during the first trimester of pregnancy. Starting at gestational age 13 weeks, Auerbach's plexi and Meissner's plexi are found in the small and large intestines, respectively. By the gestational age of 20 weeks, neuroblasts finish migrating into the gastrointestinal tract. The fetal gastrointestinal muscular and neurohormonal systems are established long before the gastrointestinal tract absorbs nutrients after birth.[9] Bowel movements of the small intestine are irregular up to gestational age 31 weeks, with some regular waves appearing as fetal-type movements by weeks 31-34 of gestation. During weeks 34-36, longer and stronger waves of movement appear. After week 37 of gestation, gastrointestinal tract movements resemble those of adults, being regular, long

Table 3 Multivariate analysis of risk factors associated with delayed meconium passage

	P-value	Odds ratio	95% confidence interval	
Gestational age	0.000	0.785	0.715	0.861
Male gender	0.040	1.476	1.017	2.143
Multiple gestation	0.248	1.299	0.833	2.024
1 minute APGAR score	0.596	0.956	0.809	1.129
5 minutes APGAR score	0.548	0.943	0.778	1.143
Maternal $MgSO_4$ administration	0.152	1.322	0.902	1.937
Severe sepsis	0.026	2.691	1.123	6.445
Intracranial haemorrhage	0.016	1.617	1.094	2.390
PDA, haemodynamically significant	0.154	1.460	0.868	2.456
Nephrologic anomalies	0.050	2.673	0.999	7.154

PDA: patent ductus arteriosus

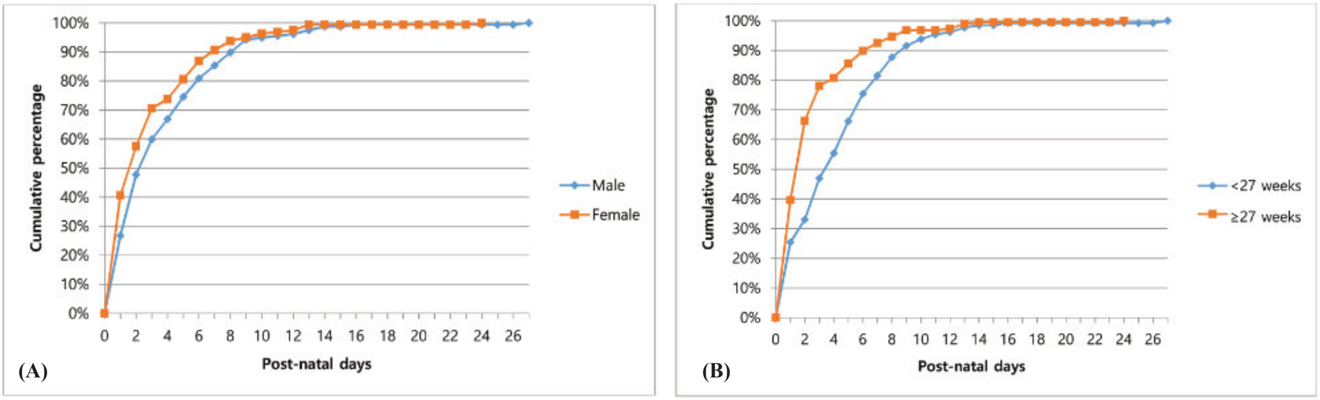

Figure 2. Cumulative percentage of first stool passage in ELBWIs stratified (A) by sex, and (B) by gestational age.

bowel movements.[10] Amniography showed that gastrointestinal tract mobility became more active with increasing gestational age.[11] The time for contrast media to reach the colon after swallowing was 9 hours in preterm infants, compared with 4-5 hours in term infants. Therefore, intestinal obstruction observed in preterm infants may be due to the functional immaturity of the gastrointestinal tract.

In male neonates, the cause of delayed meconium passage was uncertain. As opposite to neonatal patients, in the adult population, females showed slower bowel transit time and higher rates of constipation.[12] Considering the higher rate of expression in the gene mutation responsible for the erroneous gastrointestinal nervous system in male infants, leading to a higher proportion of male patients in Hirschsprung disease, it can be speculated that male infants have slower development during the transitional phase between neonatal and adult phase.[13]

Unexpectedly, other gastrointestinal anomalies and maternal administration of magnesium or morphine did not affect meconium passage. However, severe sepsis with organ dysfunction or ICH was associated with a significant delay of meconium passage.

Faster enteral feeding in neonates was found to promote gastrointestinal motility and meconium passage,[6,7] with enteral feeding stimulating the secretion of gastrointestinal stimulating hormones, such as gastrin, motilin, secretin, and enteroglucagon in both term and preterm infants.[14] This effect, however, is likely diminished in VLBWIs with delayed enteral feeding, as many of these infants have an unstable general condition requiring ventilator treatment or administration of inotropic agents that could compromise gastrointestinal blood flow. In addition, 78% of preterm infants were found to pass meconium before starting enteral feeding, suggesting that enteral feeding may be more effective in promoting defecation after first meconium passage.[3]

Of the 240 ELBWIs with delayed meconium passage >72 hours after birth, 105 (40%) underwent enemas. Although gastrograffin enemas can be used to treat meconium plug syndrome with obstructive symptoms,[15] stable preterm infants without gastrointestinal obstruction may not benefit from enemas. In these infants, enemas may not promote gastrointestinal motility or enteral feeding, but may increase the risk of necrotising enteritis.[16] Thus, enemas are not in these clinical settings.

Since, the delayed passage group did not show an increase in time to feeding, the incidence of parenteral nutrition-associated cholestasis, or meconium plug syndrome, delayed stool passage should be considered for observation as a benign clinical course even when these risk factors are present.

This study had several limitations, including its retrospective design. However, the present study included more VLBWIs than previous studies. Moreover, we used the electronic medical records from a single institution to increase the reliability of the data. Prospective follow-up studies are required to confirm these results.

Conclusions

In this study, we analysed risk factors associated with delayed passage and time to first stool passage in ELBWIs. Time to first meconium passage was associated with gestational age and male gender. Severe sepsis and ICH could delay the time of the first stool passage. Associated factors and clinical signs should be considered before choosing the appropriate method of treatment for ELBWIs with delayed meconium passage.

Conflict of Interest

The authors have no conflict of interest to disclose in relation to this work. There was no funding received.

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