



# Clinical or Radiological Findings Suggestive of Spontaneous Intestinal Perforation in Extremely Low Birth Weight Infants with Gasless Abdomen

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## ABSTRACT

**Purpose:** This study aimed to evaluate the clinical and radiologic findings suggestive of spontaneous intestinal perforation (SIP) in extremely-low-birth-weight infants (ELBWIs) with persistent gasless abdomen, and to investigate the usefulness of abdominal ultrasonography for the diagnosis of SIP.

**Methods:** In total, 22 infants with birth weights less than 1,000 g who showed persistent gasless abdomen on simple abdominal radiography were included. Perinatal, neonatal, and perioperative clinical findings were retrospectively reviewed, and the risk factors for intestinal perforation were evaluated. Abdominal sonographic findings suggestive of intestinal perforation were also identified, and postoperative short-term outcomes were evaluated.

**Results:** In total, eight of the 22 infants (36.4%) with gasless abdomen had SIP. The number of infants with patent ductus arteriosus who were treated with intravenous ibuprofen or indomethacin was significantly higher in the SIP group than in the non-SIP group ( $P<0.05$ ). Greenish or red gastric residue, abdominal distension, or decreased bowel sound were more frequent in infants with SIP ( $P<0.05$ ), in addition to gray or bluish discoloration of abdomen, suggestive of meconium peritonitis ( $P<0.05$ ). Pneumoperitoneum on simple abdominal radiography was found in only one of the eight infants (12.5%) with SIP. Intramural echogenicity and echogenic extramural material on abdominal ultrasonography were exclusively observed in infants with SIP. Four infants (50%) with SIP died after surgical intervention.

**Conclusion:** Intestinal perforation may occur in ELBWIs with gasless abdomen. As intramural echogenicity and extraluminal echogenic materials on abdominal ultrasonography are indicative of SIP, this technique could be useful for diagnosing SIP.

**Key Words:** Spontaneous intestinal perforation; Ultrasonography; Infant, extremely low birth weight

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## INTRODUCTION

Gasless abdomen has been defined as a state of scanty or invisible intestinal gas on simple abdominal radiography<sup>1)</sup>. Until recently, the incidence of gasless abdomen in premature infants has not been well-documented. A recent study reported that 57 (11.5%) of 496 extremely-low-birth-weight infants (ELBWIs) with birth weight less than 1,000 g showed gasless abdomen on radiography, and 12 (21.1%) of them had been confirmed to have spontaneous intestinal perforation (SIP)<sup>1)</sup>. However, the incidence of SIP in ELBWIs with gasless abdomen remains unclear. Several other studies have reported that gasless abdomen may commonly present in ELBWIs with SIP (52.0% to 67.0%)<sup>1-6)</sup>.

SIP is a common complication observed in ELBWIs with birth weight less than 1,000 g, and it has been described as a distinct clinical entity that differs from necrotizing enterocolitis (NEC), in terms of both clinical and histologic presentation<sup>1,4,5)</sup>. Unlike NEC that accompanies radiologic hallmarks on simple abdominal radiography, such as pneumatosis intestinalis, or portal vein gas, and fixed bowel loop, SIP does not show distended, fixed bowel loops, pneumatosis intestinalis, or portal venous gas on abdominal radiography, and the most common radiological finding in infants with SIP has been gasless abdomen<sup>1,4,6)</sup>. In addition, SIP associated with gasless abdomen in ELBWIs may occur without any signs suggestive of intestinal perforation, such as pneumoperitoneum, which can be found in only 33.3% to 50.0% of cases<sup>4,6)</sup>. This low rate of intraperitoneal free air in SIP could be explained by the fact that perforation in SIP occurs as a more gradual process with slow spillage of meconium or bile-stained intraluminal material into the peritoneum rather than as a sudden event caused by rupture of subserosal cavity in NEC<sup>1,4,6)</sup>.

Moreover, intestinal structures other than the perforation site usually tend to be relatively well preserved<sup>4,6)</sup>. Thus, it is often difficult to diagnose SIP in infants with gasless abdomen by simple abdominal radiography in the absence of pneumoperitoneum<sup>2,7)</sup>.

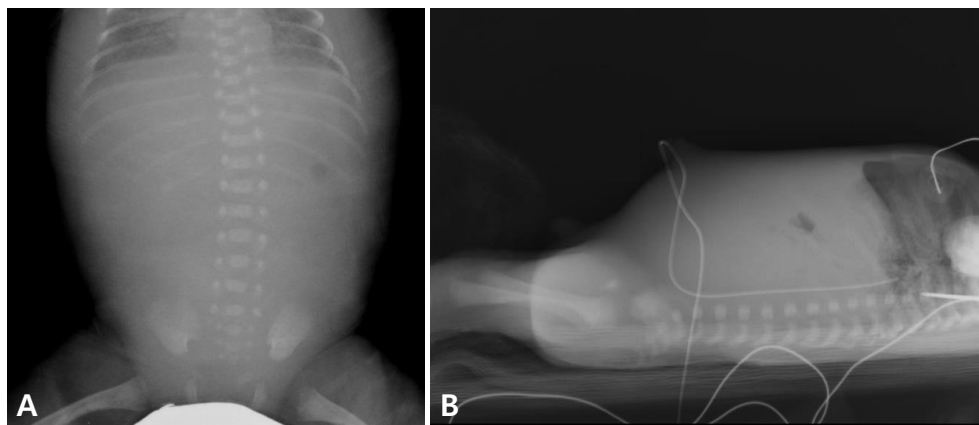
Given that the delayed treatment of SIP in ELBWIs owing to difficulty in early diagnosis may increase the likelihood of subsequent dismal outcomes, a more careful clinical and radiologic assessment is required if the gasless abdomen is persistently observed in these infants<sup>3)</sup>. In this regard, previous studies have reported that abdominal ultrasonography had an important role in the early diagnosis of SIP in ELBWIs with gasless abdomen<sup>1,7)</sup>.

Thus, in this study, we intended to evaluate the clinical and radiologic findings for early diagnosis of SIP in ELBWIs with persistent gasless abdomen, and to determine the risk factors associated with SIP. We also aimed to evaluate the usefulness of abdominal ultrasonography for the diagnosis of SIP in ELBWIs with gasless abdomen.

## MATERIALS AND METHODS

### 1. Subjects

This study included 22 ELBWIs with birth weight less than 1,000 g, whose simple abdominal radiography showed persistently gasless abdomen lasting for more than 3 days (Figure 1). All infants had been admitted to the neonatal intensive unit (NICU) of Dankook University Hospital between 2008 and 2015. Perinatal, neonatal, and perioperative clinical and radiologic findings were retrospectively reviewed and compared between infants without and with SIP, and the risk factors associated with



**Figure 1.** Gasless abdomen on simple abdominal radiography supine (A) and cross-table lateral (B) views show gasless or scanty gas abdomen.

SIP were determined. Postoperative neonatal outcomes were also evaluated. Infants with a perforation secondary to other etiologies such as congenital gastrointestinal anomalies or congenital meconium peritonitis were not included. All infants suspected of having clinical or radiological signs suggestive of intestinal perforation underwent surgical intervention. SIP was defined at laparotomy as the presence of isolated intestinal perforation surrounded by normal-appearing bowel and the absence of characteristic gross or microscopic features of NEC.

## 2. Abdominal ultrasonography

Abdominal ultrasonography was conducted in infants who showed gasless abdomen on simple abdominal radiography for at least 3 consecutive days or in infants with clinical symptoms suggestive of meconium peritonitis or intestinal perforation, such as gray or bluish abdominal discoloration and/or free air on simple abdominal radiography. Abdominal ultrasonography was performed in the NICU, and the findings were evaluated by a pediatric radiologist.

## 3. Statistical analysis

Statistical analysis was performed using SPSS version 23.0 (IBM Co., Armonk, NY, USA). Variables were compared between the SIP and non-SIP groups using the independent *t*-test, chi-square test, Fisher's exact test, and Mann-Whitney *U*-test. *P*-values less than 0.05 were considered significant. This study was approved by the Institutional Review Board (IRB File No. DKUH 2019-05-025). Informed consent was waived by the board.

# RESULTS

## 1. Perinatal and neonatal characteristics

In total, eight of the 22 infants (36.4%) with gasless abdomen on simple abdominal radiography had SIP. Mean gestational age and mean birth weight did not significantly differ between infants without and with SIP (25.0±1.0 weeks vs. 23.9±1.6 weeks, 793.6±143.9 g vs. 743.8±166.6 g, respectively; *P*>0.05). The number of infants with patent ductus arteriosus (PDA) who were treated with intravenous ibuprofen or indomethacin was significantly higher in the SIP group (87.5%) than in the non-SIP group (42.9%; *P*<0.05). Indomethacin was administered in only one infant without SIP. Other perinatal and postnatal factors including twin pregnancy, premature rupture of membrane (>18 hours),

maternal diabetes, complete dose of antenatal corticosteroid, respiratory distress syndrome treated with surfactant, bronchopulmonary dysplasia (BPD), use of postnatal dexamethasone for BPD, use of inotropics or hydrocortisone for hypotension, intraventricular hemorrhage greater than stage 2, periventricular leukomalacia, and retinopathy of prematurity (ROP) greater than stage 2 were not significantly different between infants without and with SIP (*P*>0.05). There were four cases of sepsis presumed to be temporally related to gasless abdomen, two (14.8%) in the non-SIP and two (20.0%) in the SIP groups, which was not significantly different (*P*>0.05). *Enterococcus* species and group B *Streptococcus* (GBS) were detected on blood culture in two infants with SIP, and *Candida* and *Serratia* species were detected in two infants without SIP. In-hospital death was not significantly different between the non-SIP and SIP groups (*P*>0.05). In addition, age of death and duration of hospital stay were not significant different between the non-SIP and SIP groups (*P*>0.05) (Table 1).

## 2. Perioperative feeding history and clinical findings suggestive of intestinal perforation

Trophic feedings before onset of gasless abdomen were performed in seven (50.0%) and five infants (62.5%) of the non-SIP and SIP groups, respectively (*P*>0.05), and breast feeding was performed in six (42.9%) and five infants (62.5%) of the non-SIP and SIP groups, respectively (*P*>0.05). Age of initiation of trophic feeding was not significantly different between the two groups (*P*>0.05). Greenish or red gastric residue, abdominal distension, or decreased bowel sound were more frequent in infants with SIP (*P*<0.05). In particular, gray or bluish discoloration of the abdomen suggesting meconium peritonitis was that observed in six infants (75%) of the SIP group, which was significantly more frequent compared to that observed in the two infants (14.3%) in the non-SIP group (*P*<0.05). Infants in the non-SIP group who had bluish discoloration of the abdomen did not reveal radiologic or clinical evidence that is attributable to NEC. The age of perforation in infants with SIP was 11.6±4.4 days (Table 2).

## 3. Radiologic findings suggestive of intestinal perforation

Ages at which gasless abdomen was detected on simple abdominal radiography were 5.9±4.7 and 7.3±3.2 days of life in the non-SIP and SIP groups, respectively (*P*>0.05). The durations of gasless abdomen on simple abdominal radiography were 8.7±6.8 and 8.3±5.4 days of life in the non-SIP and SIP groups, respectively (*P*>0.05). Pneumoperitoneum on simple abdominal

**Table 1.** Perinatal and Neonatal Characteristics of Enrolled Infants

Characteristic	Infants without SIP (n=14)	Infants with SIP (n=8)	P-value
Gestational age (wk)	25.0±1.0	23.9±1.6	0.062
Birth weight (g)	793.6±143.9	743.8±166.6	0.469
Twin birth	2 (14.3)	4 (50.0)	0.070
PROM	3 (21.4)	3 (37.5)	0.416
Cesarean section	8 (57.1)	3 (37.5)	0.375
SGA	0	0	-
Preeclampsia	1 (7.1)	0 (0.0)	
Maternal diabetes	1 (7.1)	1 (12.5)	0.674
Antenatal corticosteroid, complete	4 (28.6)	1 (12.5)	0.387
RDS treated with surfactant	12 (85.7)	7 (87.5)	0.907
PDA treated with IV ibuprofen or indomethacin	6 (42.9)	7 (87.5)	0.040
BPD	5 (35.7)	2 (25.0)	0.887
Postnatal dexamethasone for BPD	4 (28.6)	2 (25.0)	0.865
Inotropic for hypotension	8 (57.1)	7 (87.5)	0.070
Hydrocortisone for hypotension	0	1 (12.5)	0.176
IVH grade ≥3	2 (14.3)	4 (50.0)	0.070
Periventricular leukomalacia	1 (7.1)	0	0.439
ROP stage ≥3	4 (28.6)	0	0.095
Sepsis during gasless abdomen	2 (14.3)	2 (25.0)	0.240
Death, in-hospital	6 (42.9)	4 (50.0)	0.746
Age of death (d)	29.3±26.7	16.6±10.9	0.404
Duration of hospital stay (d)	82.3±52.8	85.7±79.7	0.915

Values are expressed as mean±standard deviation or number (%).

Abbreviations: SIP, spontaneous intestinal perforation; PROM, premature rupture of membrane; SGA, small for gestational age, RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; IV, intravenous; BPD bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity.

**Table 2.** Perioperative Feeding History and Clinical Findings Suggestive of Intestinal Perforation

Variable	Infants without SIP (n=14)	Infants with SIP (n=8)	P-value
Feeding before gasless abdomen			
Trophic feeding	7 (50.0)	5 (62.5)	0.571
Brest milk feeding	6 (42.9)	5 (62.5)	0.375
Age of start of trophic feeding (d)	3.2±4.0	4.5±4.2	0.720
Clinical findings suggestive of perforation			
Greenish or red gastric residue	2 (14.3)	5 (62.5)	0.020
Abdominal distension	2 (14.3)	5 (62.5)	0.020
Decreased bowel sound	4 (28.6)	8 (100)	0.001
Gray or bluish discoloration of abdomen	2 (14.3)	6 (75.0)	0.004
Age of perforation (d)	-	11.6±4.4	-

Values are expressed as number (%) or mean±standard deviation. Abbreviation: SIP, spontaneous intestinal perforation.

radiography was found in only one of the eight infants (12.5%) with SIP. Abdominal ultrasonography showed ascites or focal fluid collection in three infants (21.4%) in the non-SIP group; otherwise, the findings were mostly unremarkable. Meanwhile, abdominal ultrasonography of the infants in the SIP group showed bowel wall thickening (50.0%), intramural echogenicity (75.0%), and echogenic extramural material (50.0%;  $P<0.05$ ); ascites or focal fluid collection was also detected in four infants (50%) in the SIP group (Table 3, Figure 2).

#### 4. Operative findings and postoperative outcomes

All infants with SIP had isolated focal intestinal perforations surrounded by a normal-appearing bowel (100%). Perforation occurred in the terminal ileum in five infants (62.5%); in the proximal ileum, in one infant (12.5%); in the transverse colon, in one infant (12.5%); and in the cecum, in one infant (12.5%). None of the surgical specimens were compatible with the gross or microscopic features of NEC. Primary peritoneal drainage was

performed in three infants (37.5%), and primary laparotomy with resection of perforated segments of the intestine was performed in five infants (62.5%). All three infants treated with primary peritoneal drainage required salvage laparotomy. Four infants (50%; one who underwent primary peritoneal drainage [33.3%] and three who underwent primary laparotomy [60.0%]) died at 0, 4, 6, and 12 days after operation (Table 4). Three of them died owing to problems related to postoperative bleeding, and there was no additional neonatal death in the SIP group.

## DISCUSSION

This study showed the clinical and radiological findings

**Table 3.** Radiologic Findings Suggestive of Spontaneous Intestinal Perforation

Variable	Infants without SIP (n=14)	Infants with SIP (n=8)	P-value
Simple abdominal radiography			
Age of onset of gasless abdomen (d)	5.9±4.7	7.3±3.2	0.605
Duration of gasless abdomen (d)	8.7±6.8	8.3±5.4	0.807
Pneumoperitoneum	0	1 (12.5)	0.176
Abdominal ultrasonography			
Bowel wall thickening	0	4 (50.0)	0.008
Intramural echogenicity	0	6 (75.0)	0.001
Extra-luminal echogenic material	0	4 (50.0)	0.008
Ascites or intra-abdominal focal fluid collection	3 (21.4)	4 (50.0)	0.311

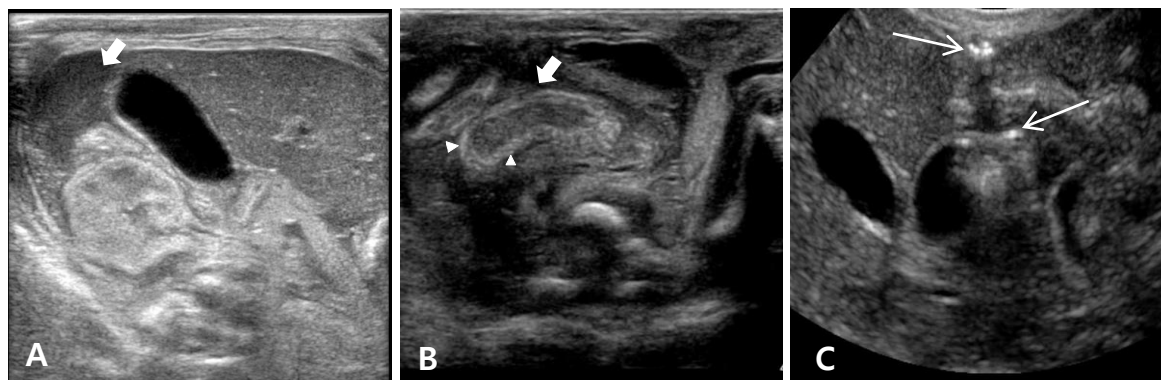
Values are expressed as mean±standard deviation or number (%). Abbreviation: SIP, spontaneous intestinal perforation.

associated with SIP occurring in ELBWIs with persistent gasless abdomen on simple abdominal radiography. PDA treated with intravenous ibuprofen or indomethacin might be regarded as a significant risk factor associated with SIP in ELBWIs with gasless abdomen. Pneumoperitoneum was found in only one of the eight infants (12.5%) with SIP on simple abdominal radiography; abdominal ultrasonography in the non-SIP group showed ascites or focal fluid collection in three infants; the other findings were mostly unremarkable. Meanwhile, abdominal ultrasonography of infants in the SIP group exclusively showed findings suggestive of intestinal perforation such as intramural echogenicity (75.0%), echogenic extraluminal material (50.0%) and ascites (50%), with or without bowel wall thickening (50.0%). Thus, this study suggested that abdominal ultrasound might help detect intestinal

**Table 4.** Operative Findings and Postoperative Outcomes

Variable	Perforation (n=8)
Focal intestinal perforation	8 (100)
Perforation site	
Terminal ileum	5 (62.5)
Proximal ileum	1 (12.5)
Cecum	1 (12.5)
Transverse colon	1 (12.5)
Surgical intervention	
Primary peritoneal drainage followed by salvage laparotomy	3 (37.5)
Primary laparotomy with resection	5 (62.5)
Postoperative death	4 (50.0)
Primary peritoneal drainage	1/3 (33.3)
Primary laparotomy with resection	3/5 (60.0)

Values are expressed as number (%).



**Figure 2.** Abdominal ultrasonographic findings suggestive of intestinal perforation in extremely low-birth-weight infants with gasless abdomen on simple abdominal radiography. (A) Fluid collection with heterogeneous echogenicities is observed in the extraluminal space (short arrow). (B) Bowel wall thickening (short arrow) and increased intramural echogenicity (arrowheads) are observed. (C) Two tiny echogenic air bubbles are observed in the extraluminal space (long arrows).

perforation when SIP is suspected in ELBWIs with gasless abdomen.

Several causes of SIP in extremely premature infants have been suggested. Multifocal partial or complete defects of musculature in the intestinal muscular layer have been frequently observed in the histologic findings of SIP<sup>8-12</sup>. Thus, defects in the muscle layer owing to immaturity in premature infants might be considered as one of the causes of SIP. Additionally, ischemia caused by stress, hypoxia, and/or hypotension before or after birth may lead to disruptions in both musculature and mucosa followed by the regeneration of mucosa, which results in total or partial absence of musculature<sup>13,14</sup>. Thus, SIP occurs typically in the terminal ileum, also known as the “watershed zone,” which is vulnerable to ischemia<sup>15,16</sup>. In this study, similar to the results of previous studies, the most common perforation site was the terminal ileum. However, it is not fully understood whether perforation occurs in other parts of the intestine, such as the colon or proximal ileum, which have more blood supply, as well as in multiple sites.

SIP of the newborn occurs primarily in ELBWIs with an incidence of approximately 3% in this specific population<sup>17-19</sup>. The median age at presentation of SIP ranges from 7 to 15 days<sup>4,15,19-22</sup>, which was 11.6±4.4 days in this study. It is well-known that prostaglandin inhibitors such as indomethacin used for the treatment of PDA in premature infants could reduce blood flow to the intestinal tract and induce bowel wall ischemia, subsequently leading to SIP<sup>4,23-25</sup>. Combined with indomethacin for treating PDA, administration of glucocorticoids is commonly reported to be a risk factors for SIP, and exposure to both indomethacin and hydrocortisone in the first week of life might significantly increase the risk of SIP in very-low-birth-weight infants<sup>26</sup>. Moreover, a study reported that the use of ibuprofen could be related to the occurrence of SIP in premature infants<sup>27</sup>. Similarly, this study suggested that PDA treated with intravenous ibuprofen or indomethacin might be a risk factor associated with the occurrence of SIP. However, we were unable to investigate whether hydrocortisone might be a risk factor for SIP, because it was used in only one infant with SIP in this study. Other risk factors reported in previous studies associated with SIP, such as exposure to inotropic agents and surfactants<sup>28</sup>, were not significant. Immature gastrointestinal motility and thickening of the meconium would exert mechanical compression on the bowel wall, making the patient susceptible to mucosa damage, ischemia, and perforation<sup>6,13</sup>. In addition, various infections, especially those caused

by *Candida* species, have been reported to be related to SIP<sup>6</sup>. In this study, one case of *Enterococcus* and one case of GBS were detected in the blood cultures of infants in the SIP group. However, the relationship between sepsis and the occurrence of SIP in ELBWIs with gasless abdomen could not be evaluated in this study because of the small number of cases. Further research in this aspect is warranted.

In general, infants with SIP have no typical symptoms or signs of NEC, such as abdominal distension, abdominal rigidity, tenderness, abdominal wall edema, or erythema<sup>29</sup>. These infants do not meet the traditionally accepted Bell’s criteria for NEC<sup>6</sup>. They are often strikingly stable in the early stage and have no signs of severe illness or peritonitis<sup>5,15</sup>. Their abdominal radiography commonly shows gasless abdomen<sup>6</sup>. Hence, perforation may be difficult to diagnose, particularly in ELBWIs with gasless abdomen, which may delay prompt and adequate surgical intervention<sup>1,2,4,5,29</sup>. Gray or bluish discoloration of the abdominal wall, resulting from peritoneal staining by spillage of meconium into the peritoneal cavity, that it should be regarded as a typical sign of perforation, and this discoloration usually starts in the groin or scrotum<sup>5,16</sup>. In this study, these findings were observed in six of the infants (75%) with SIP, and non-specific findings such as greenish or red gastric residues, abdominal distension, and decreased bowel sounds, were common in infants with SIP.

Previous studies have reported that abdominal ultrasonography may be a very useful tool for diagnosis of SIP<sup>1,2</sup>. In particular, the presence of extraluminal free-floating hyperechogenic materials could suggest the occurrence of intestinal perforation in ELBWIs with gasless or scanty gas abdomen<sup>1</sup>. Extraluminal echogenic materials and intraluminal echogenicity were observed in four (50%) and six infants (75%) with SIP, respectively, in this study. However, these findings should not be interpreted as definite signs of intestinal perforation, because their specificity was reported to be only 89.0%<sup>1</sup>. All infants with the above-mentioned abdominal ultrasonographic findings were operated on, and the presence of SIP was confirmed.

Treatment options for SIP in ELBWIs are primary laparotomy with resection or primary peritoneal drainage<sup>19,30-33</sup>. Although previous studies did not reveal a clear difference in prognosis between infants who underwent peritoneal drainage and those who underwent primary surgical repair<sup>32</sup>, there is compelling evidence that infants who underwent peritoneal drainage show inferior neurologic outcomes at 18 to 22 months of age<sup>33</sup>. In this study, three patients underwent peritoneal drainage followed

by salvage laparotomy. These three infants had unstable vital signs at the first intervention, and peritoneal drainage was preferred over primary laparotomy with resection of perforated segments. Primary laparotomy was performed in the other five infants. However, despite the surgical treatment and subsequent intensive care, four infants (50.0%) died after operation. It was presumed that three of them died owing to postoperative bleeding resulting from disseminated intravascular coagulation occurring during the surgery. Therefore, early diagnosis and surgery are required.

This study has several limitations. First, this study was conducted retrospectively in a single center, and included only a small number of ELBWIs with persistent gasless abdomen on abdominal radiography. Thus, the exact incidence and prognosis of SIP in ELBWIs with gasless abdomen could not be predicted. Second, because the clinical and radiologic findings suggestive of SIP in ELBWIs in this study would be non-specific and might present in other gastrointestinal disorders, such as NEC, the results indicating that these clinical findings may be associated with intestinal perforation in ELBWIs with gasless abdomen should be interpreted with caution. However, despite the above limitations, the findings of abdominal ultrasonography in this study such as extraluminal echogenic materials and intraluminal echogenicity may be helpful for early detection of a slowly progressive intestinal perforation in ELBWIs with gasless abdomen.

In conclusion, this study showed that SIP could commonly occur in ELBWIs who show persistent gasless abdomen on simple abdominal radiography, and gray or bluish discoloration of the abdomen suggestive of meconium peritonitis was frequently observed in infants with SIP. Moreover, this study showed that abdominal ultrasound could be a highly useful for the diagnosis of SIP.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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