ORIGINAL ARTICLE

Preterm twin gestation and cystic periventricular leucomalacia

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Objective: To identify risk factors for the development of cystic periventricular leucomalacia (PVL) in twin gestation.

Design: Retrospective case-control study.

Setting: Tertiary care university hospital, Department of Paediatrics, Division of Neonatology, Graz, Austria.

Patients: Preterm twin gestations with one sibling having developed cystic PVL, diagnosed by ultrasound scans, compared with their co-twins without PVL, in hospital between 1988 and 2000.

Main outcome measures: Perinatal and postnatal risk factors for the development of PVL.

Results: Eighteen preterm twin gestations were included. Monochorionicity was evident in 47% of the pregnancies, and twin to twin transfusion syndrome occurred in two cases (11%). Fetal distress correlated inversely with PVL (15% v 53%, p = 0.019, relative risk (RR) = 2.057, 95% confidence interval (CI) = 1.067 to 3.968). Hypocarbia with PCO_2 levels below 30 mm Hg (4 kPa) was diagnosed in 29% of the cases compared with 6% of the controls (p = 0.038, RR = 1.944, 95% CI = 1.113 to 3.396). There were no significant differences between groups with regard to premature rupture of the membranes, early onset infection, respiratory distress syndrome, mechanical ventilation, arterial hypotension, persistent ductus arteriosus, and hyperbilirubinaemia. Asphyxia was only evident in three controls. Three infants died and another three were lost to follow up. None of the cases compared with 62% of the controls were diagnosed as having developed normally (p < 0.001), and 14 cases (82%) compared with two controls (15%) developed cerebral palsy (p < 0.001).

Conclusion: Hypocarbia was the only risk factor strongly associated with cystic PVL. The general outcome of the infants was poor.

C ystic periventricular leucomalacia (PVL) is the most severe and common cause of cerebral palsy in children surviving preterm birth. Although the pathogenesis of PVL is not completely understood, most theories consider the necroses of the white matter in their typical periventricular distribution to be hypoxic-ischaemic lesions resulting from impaired perfusion at the vascular border zones between the ventriculopedal and ventriculofugal arteries.[1] A contrasting view focuses on the role of intrauterine infection with direct toxic effects on fetal oligodendrocytes and astrocytes by cytokines (interleukin 1β, interleukin 6, and tumour necrosis factor α).[2] Many risk factors for the development of cystic PVL have been identified including prematurity, asphyxia, respiratory distress,[3 4] septicaemia,[3–6] chorioamnionitis and premature rupture of the membranes (PROM),[2 4 6–13] maternal haemorrhage, arterial hypotension,[3 14] persistent ductus arteriosus,[3 15] hypocarbia,[16–20] and multiple gestation.[7 10 13 21]

During the last decade, multiple gestations have increased, mainly because of medically assisted reproductive techniques.[22] Multiple pregnancy has been identified as an important risk factor for the development of cystic PVL and cerebral palsy.[7 10 13 21 23–25] The increased risk of cerebral palsy in the case of multiple gestations is not entirely explained by the increased risk of prematurity or low birth weight.[25] Other explanations include intrauterine growth retardation,[24] vascular factors, such as imbalanced placental blood supply,[26] and specific problems such as twin to twin transfusion and intrauterine death of the co-twin.[23 26 27]

The aim of the study was to identify various perinatal and postnatal factors that may contribute to the development of cystic PVL by comparing the preterm twin with PVL with the co-twin without PVL.

MATERIALS AND METHODS

This study is a retrospective analysis of preterm twin gestations admitted to the Division of Peripartal Paediatrics and Division of Neonatology of the Department of Paediatrics of the University Hospital of Graz, Austria, between 1988 and 2000. Inclusion criteria were diagnosis of cystic PVL by ultrasound (US) examination in one twin and no evidence of periventricular echodensities (PVEs) or cystic PVL in the co-twin within 10 days of life. The medical records, US scans, and data from our neurodevelopmental follow up outpatient clinic were reviewed. Patients were diagnosed by our local computer assisted diagnosis system (installed since 1988) by coding PVEs, PVL, and multiple gestation.

Cranial US scans were routinely obtained in all preterm infants on days 1, 3, and 5, and thereafter once a week in the case of pathological findings, and always at discharge (36–40 weeks corrected age). Real time US scans were performed with a commercially available unit (Advanced Technology Laboratories Inc, Bothell, Washington, USA) using a 7.5 MHz transducer, and multiple images were obtained in the coronal and sagittal planes through the anterior fontanelle. The US scans were reviewed for the diagnosis and onset of PVEs and cystic PVL, according to the classification of de Vries *et al*.[28] PVEs were defined as confluent areas of increased echogenicity comparable to the echogenicity of the choroid plexus. The diagnosis of cysts was confirmed in both the coronal and sagittal planes. Unilateral or bilateral location and anterior

(A), parietal (P), and occipital (O) location were documented, and the maximum diameter of the single largest cyst was measured. In addition, day of diagnosis of PVEs, day of diagnosis of cysts, number of US examinations up to the first diagnosis of cysts, and total number of US examinations were recorded.

For the analysis of risk factors, twins with cystic PVL were compared with their co-twins without PVL. Perinatal characteristics included birth weight, birth weight discordance, small for gestational age (SGA), sex, birth order, breech presentation, caesarean section, risks during labour including abruptio placentae, umbilical cord anomalies, and fetal distress (pathological intrapartum cardiotocography, meconium stained amniotic fluid), type of placentation, PROM, chorioamnionitis, twin to twin transfusion syndrome, Apgar scores, umbilical artery pH, and capillary pH less than 30 minutes after birth. Postnatal characteristics included asphyxia, early onset infection, arterial hypotension, persistent ductus arteriosus, hyperbilirubinaemia, days of mechanical ventilation, hypocarbia, respiratory distress syndrome, apnoeas, neonatal seizures, hypoxic-ischaemic encephalopathy, cerebral infarction, intra/periventricular haemorrhage (I/PVH) and posthaemorrhagic hydrocephalus.

Birth weight discordance (percentage) was defined as follows:[29]

((Birth weight of larger twin − birth weight of smaller twin)/birth weight of larger twin) × 100.

PROM was defined as onset before labour. Clinical chorioamnionitis was diagnosed according to the definition of Baud et al.[9] Monochorionic placentation was diagnosed by the obstetrician by placental examination after birth. Twin to twin transfusion syndrome was diagnosed by antenatal US examination as described by Wittmann et al.[30] Asphyxia was characterised by fetal distress, an Apgar score of 5 or less after five minutes, and an umbilical artery pH less than 7.10. Diagnosis of early onset infection included clinical signs of sepsis with positive blood culture and/or a positive sepsis score[31] within the first 72 hours of life. Arterial hypotension was defined as a mean arterial blood pressure, measured with a Dinamap, below 95% limits[32] and requiring treatment. Hypocarbia was defined as an arterial carbon dioxide partial pressure (P_{CO_2}) less than 30 mm Hg for at least one hour. Diagnosis of hypoxic-ischaemic encephalopathy included neurological abnormalities occurring during the first 24 hours of life as described by Sarnat and Sarnat[33] following asphyxia as described above. Neonatal seizures were defined as paroxysmal alterations in neurological function (subtle, tonic, clonic, or myoclonic), with autonomic nervous system changes and different from the symmetrical tremor of jitteriness.

For neurodevelopmental outcome, infants were examined at the corrected for prematurity age of 4, 8, 12, 18, and 24 months, and thereafter once a year. Outcome was assessed using developmental tests as described by Griffith[34] in the first 2 years of life and those described by Kaufman and Kaufman[35] above this age, and neurological examinations as described by Amiel-Tison and Stewart[36] and Touwen.[37] Classification of mental outcome included normal, developmental delay, and mental retardation. Classification of neurological outcome included normal, minor neurological abnormalities (dystonia, hypotonia, asymmetry), and cerebral palsy including hemiplegia (one side of body, arm more than leg), diplegia (minimal upper extremity involvement, legs more impaired), and tetraplegia (severe involvement of all extremities, legs more than arms). Classification of visual disorders included normal, strabismus, and severe visual impairment. Hearing deficiency and dyslalia were also diagnosed. Other findings included microcephaly and dystrophy.

Statistical analyses were performed using the *t* test and Wilcoxon test for numerical data and the χ^2 test using Yates correction and Fisher's exact test as appropriate for categorical data. For all statistical tests, a level of significance of 0.05 was used. Multivariate analysis was performed with a logistic regression model (Sysstat 8.0; SPSS Inc, Chicago, Illinois, USA, 1998). Relative risks and 95% confidence intervals were calculated using the software package CIA (Confidence Interval Analysis; version 2.0.0: *Statistics with confidence*; London: BMJ Publishing Group, 2000).

RESULTS

During the study period, 276 twin gestations ($\leqslant$ 35 weeks gestational age) were admitted to one of our two neonatal wards. Their mean (SD) gestational age was 32 (2.8) weeks (range 24–35), and their mean (SD) birth weight was 1614 (542) g (range 450–3000). Twenty one preterm twin gestations (7.6%) had a diagnosis of cystic PVL. Eighteen twins fulfilled the inclusion criteria. In three cases both twins had developed cystic PVL.

Diagnosis of PVEs occurred at median day 2 (range 1–6), and diagnosis of cysts at median day 20 (range 10–32). The total median number of US examinations per patient was 10 (range 6–14), the median number of examinations up to the diagnosis of cysts was 4 (range 2–7). The median latency period between last US examination and diagnosis of cysts was five days (range two to seven). Bilateral location of the cysts was diagnosed in 15 infants (88%), and cysts were predominantly located parieto-occipital (APO/PO) in 13 infants (72%). The median maximum diameter of the single largest cyst was 10 mm (range 4–24). Five infants developed cysts within 14 days, suggesting an antenatal origin of the cerebral damage, a perinatal origin was suspected in four cases (diagnosis of cysts between 13 and 20 days), and a postnatal origin in the remaining nine cases including those with hypocarbia.

Table 1 shows the prenatal and maternal characteristics of the 18 preterm twin gestations. There was a birth weight discordance of more than 30% in three cases (57%, 44%, and 33%). The infants with higher birth weight (1840 g, 2100 g, and 1090 g respectively) were all diagnosed as having cystic PVL and all developed cerebral palsy. The infants with lower birth weight (790 g, 1180 g, and 726 g, respectively) did not develop cerebral palsy (two of them were SGA). Twin to twin transfusion syndrome occurred in two of the seven monochorionic pregnancies (29%). In both cases, the recipient developed cystic PVL and cerebral palsy. One of the donors died at day 18 following multiorgan failure caused by early onset sepsis, and the other one developed normally. In two cases (11%) the co-twins also developed cerebral palsy, one as the result of cerebral infarction, the other one because of I/PVH.

Table 1 Prenatal and maternal characteristics of the study population

Gestational age (weeks)	30 (2.7) (26–35)
Maternal age (years)	29.7 (4.7) (20–35)
Number of pregnancies	2.6 (1.1) (1–4)
History of abortion	7 (39)
In vitro fertilisation	3 (17)
Maternal haemorrhage	3 (17)
Pre-eclampsia	2 (11)
Maternal steroids	13 (72)
Chorioamnionitis	6 (33)
Monochorionic placentation	7/15 (47)
Birth weight discordance (>30%)	3 (17)
Twin to twin transfusion syndrome	2 (11)

Data are presented as number (%) or mean (SD) (range).

Table 2 Perinatal characteristics of 18 preterm twins with cystic PVL compared with their 18 co-twins without cystic PVL

Characteristic	PVL group	Controls	p Value	Relative risk (95% CI)
Birth weight	1459 (550)	1290 (507)	ns	–
SGA	0	3(17%)	nc	–
Male	10 (56%)	12 (67%)	nc	–
1st twin	11 (61%)	7 (39%)	0.1	1.571 (0.791 to 3.122)
2nd twin	7 (39%)	11(61%)	–	–
Breech presentation	4 (22%)	7(39%)	ns	–
Caesarean section	10 (56%)	10 (56%)	nc	–
Risks during labour	2 (11%)	5 (28%)	ns	–
PROM	4 (22%)	6 (33%)	ns	–
Hours (PROM–birth)	61 (72)	25 (19)	ns	–
Fetal distress	2/13 (15%)	8/15 (53%)	0.019	2.057 (1.067 to 3.968)
Apgar 1 minute	6.6 (2.4)	5.9 (2.9)	ns	–
Apgar 5 minutes	8.8 (1.1)	8.3 (1.4)	ns	–
Apgar 10 minutes	9.4 (0.7)	8.9 (1.3)	ns	–
Umbilical artery pH	7.30 (0.08)	7.26 (0.11)	ns	–
Capillary pH	7.19 (0.05)	7.21 (0.07)	ns	–

Data are presented as n (%) or mean (SD).
ns, Not significant; nc, not calculated; SGA, small for gestational age; PROM, premature rupture of the membranes; PVL, periventricular leucomalacia.

Table 2 shows the perinatal data comparing the cases with their controls. PVL grade 2 was diagnosed in two cases (11%), grade 3 in 15 cases (83%), and grade 4 in one case (6%).

Table 3 shows postnatal characteristics and neurodevelopmental follow up. Three infants without signs of PVEs or PVL died within 28 days of life, two after severe I/PVH, and one after multiorgan failure. Table 4 shows the association of ultrasound findings with motor deficits in the cases. Two infants (7%) developed seizure disorders combined with cerebral palsy; one of them had had neonatal seizures. Visual disorders were diagnosed in seven infants (23%), three of them with strabismus (43%) and four with severe visual impairment (57%). Hearing deficiency was diagnosed in one infant without cerebral palsy, and dyslalia in another one. Other findings were microcephaly in one control with hemiplegia following cerebral infarction, and dystrophy in five infants. Neurodevelopmental outcome differed significantly between the groups. None of the cases developed normally. Fourteen of 17 cases (82%) compared with two of 13 controls (15%) had a diagnosis of cerebral palsy (p < 0.001), and eight (44%) versus none had a diagnosis of mental retardation (p < 0.001) (table 3). In the case of cerebral palsy, infants always had cysts located parietal and/or occipital. In eight cases there was a history of I/PVH (germinal matrix haemorrhage in seven cases, IVH grade 2 in one case), of whom six (75%) developed cerebral palsy in contrast with seven controls with I/PVH, of whom only one infant (14%) developed cerebral palsy (this infant developed posthaemorrhagic hydrocephalus). Cerebral infarction occurred in one control developing hemiplegia.

Risk factor analysis by multivariate regression analysis revealed significant differences between cases and controls with regard to fetal distress (15% v 53%) and hypocarbia (29% v 6%); see tables 2 and 3. The mean Apgar scores at 1, 5, and 10 minutes tended to be lower in the controls. The mean birth weight of the cases tended to be higher, and more controls were SGA. Apnoeas and seizures were more common in the cases.

DISCUSSION
Our study is the first to analyse selected risk factors for the development of cystic PVL in preterm twin gestations by directly comparing infants with cystic PVL with their co-twins without PVL. Therefore we studied selected perinatal factors and focused especially on postnatal factors that may possibly influence the development of cystic PVL. We found a strong association between the occurrence of hypocarbia and the development of cystic PVL, with a twofold increased relative risk (95% CI 1.113 to 3.396). The rates of respiratory distress syndrome and days of mechanical ventilation did not differ between the groups. The timing of first detection of cysts by US in these cases strongly supports a postnatal origin of cerebral damage. However, these results are somewhat limited by the fact that only a few infants were prone to hypocarbia. Thus, in most of the infants, no overt risks were found despite the fact of preterm twin gestation.

Several authors have described an association between hypocarbia and cystic PVL.[16–20 38] A decrease in the arterial partial pressure of carbon dioxide causes a reduction in cerebral blood flow in both humans and most animals. Interestingly, a relation between hypocarbia and brain injury has not been observed in adults and full term newborn infants. The immature brain may be more sensitive to hypocarbia because of less developed regulation of cerebral blood flow.[19] Thus hypocarbia in preterm infants is thought to cause vasoconstriction and a decrease in cerebral blood flow with subsequent hypoxic brain tissue injury[16 17 19] Kubota et al[20] found a weaker relation between hypocarbia (values below 25 mm Hg) and PVL in infants with birth weights less than 1000 g than in infants with birth weights above 1000 g. They suggest that these very low birthweight infants may have decreased sensitivity to hypocarbia because of their treatment, including mechanical ventilation and the frequent use of indomethacin. Wiswell et al[16] described an association between hypocarbia (below 25 mm Hg during the first day of life) and cystic PVL in preterm infants treated with high frequency jet ventilation. They reported that a high rate (31%; 18 of 58 surviving infants) developed cystic PVL with cysts more than 5 mm in size. There were no differences in mean $PaCO_2$ values between the groups. However, there was a significantly greater cumulative hypocarbia below a threshold of 25 mm Hg in infants with cystic PVL (odds ratio 5.43). Okumura et al[38] raised the question of whether hypocarbia is a cause or a result of PVL. They found no differences in ventilator settings between the groups. They suggested that the rate of spontaneous respiration in infants with PVL may be greater than in those without, assuming that respiratory coordination may be deranged in infants with PVL. In addition, they recently reported decreased resistance indices measured by Doppler ultrasonography of the pericallosal artery in patients with PVL on the first and third day of life compared with infants without PVL, but no differences in

Table 3 Postnatal characteristics and outcome of 18 preterm twins with cystic PVL compared with their 18 co-twins without cystic PVL

Characteristic	PVL group	Controls	p Value	Relative risk (95% CI)
Asphyxia	0	3 (17%)	nc	–
HIE	0	0	–	–
Early onset sepsis	5 (28%)	4 (22%)	ns	–
Arterial hypotension	1 (6%)	2 (11%)	ns	–
PDA	6 (33%)	5(28%)	ns	–
Hyperbilirubinaemia	6 (33%)	6 (33%)	ns	–
RDS	9 (50%)	10 (56%)	ns	–
Days on ventilator	6.9 (10.1)	7.4 (8.7)	ns	–
Hypocarbia*	5/17 (29%)	1/17 (6%)	0.038	1.944 (1.113 to 3.396)
Apnoeas	12 (67%)	8 (44%)	0.09	1.600 (0.774 to 3.309)
Neonatal seizures	5 (28%)	2 (11%)	0.1	1.607 (0.856 to 3.019)
Cerebral infarction	0	1 (6%)	nc	–
I/PVH	8 (44%)	7 (39%)	nc	–
PHH	0	1 (6%)	nc	
Follow up (months)	52 (31)	29 (27)	nc	–
Normal development	0	8 (62%)	< 0.001	∞
MNA	2 (12%)	2 (15%)	nc	–
Developmental delay	2 (12%)	1 (8%)	nc	–
Mental retardation	8 (44%)	0	< 0.001	∞
Cerebral palsy	13/17 (76%)	2/13 (15%)	< 0.001	3.250 (1.372 to 7.699)

Data are presented as n (%) or mean (SD).
*P_{CO_2} values < 30 mm Hg for at least one hour.
ns, Not significant; nc, not calculated; HIE, hypoxic-ischaemic encephalopathy; PDA, persistent ductus arteriosus; RDS, respiratory distress syndrome; I/PVH, intra/periventricular haemorrhage; PHH, posthaemorrhagic hydrocephalus; MNA, minor neurological abnormalities; PVL, periventricular leucomalacia.

resistance index and associated hypocarbia between groups.[39] Thus they could not confirm the speculation that cerebral vasoconstriction and decreased cerebral blood flow may be induced by hypocarbia.

As previously reported,[7] Apgar scores and umbilical artery pH tended to be lower in the controls, and there was a diagnosis of asphyxia only in some controls. Some authors have reported similar observations on the occurrence of cystic PVL in infants with a relatively benign postnatal course.[40 41] We found apnoeas and seizures more often in the cases, as described elsewhere.[7] In contrast with our results, some studies have identified male sex as a risk factor for the development of cystic PVL.[17 42–44] Fetal distress occurred significantly more often in our controls, in contrast with the findings of Ito et al.[45] Intrauterine growth retardation has been thought to be associated with cerebral palsy in twins,[24] but in neither this nor another recent study[7] could we confirm this association between SGA and cerebral palsy. In this study, we found no significant effects of risk factors well known to be associated with cystic PVL in singletons, such as chorioamnionitis and PROM,[2 4 13 6–11 46] hyperbilirubinaemia,[6 7 18] asphyxia,[3 4] arterial hypotension,[3 14] persistent ductus arteriosus,[3 15] acidosis at birth,[47] and SGA and low birth weight.[23 25] The incidence of PVL and additional I/PVH (50%) was comparable to that reported recently.[7]

Monochorionic placentation was observed in seven of 15 (47%) twin gestations. Several authors have described a strong correlation between monochorionic placentation in twin pregnancies and cystic PVL or cerebral palsy.[26 27 46] Placental vascular anastomoses are common in monochorionic

Table 4 Ultrasound documentation and neurological outcome (motor deficits) of 18 preterm twins with cystic PVL

Patient/Year	PVEs (day)	Cysts (day)	Latency period (days)*	Location (A/P/O; L/R/B)†	Max DM (mm)‡	Number of US exams	GMH/IVH¶	Follow up (age in years)	Outcome§
1/1988	2	26	6	APO; B	24	11	1	11.5	DP
2/1991	1	24	4	APO; B	19	11	1	2	Ataxia
3/1993	2	30	5	PO; L	10	14	1	7.5	HP
4/1994	2	24	7	PO; B	8	10	0	7	Dystonia
5/1994	1	32	6	P; B	10	9	0	3	DP
6/1994	2	26	5	O; B	8	8	0	6.5	DP
7/1995	1	19	6	APO; B	6	6	1	6.5	DP
8/1995	1	20	5	O; B	6	8	0	4.5	DP
9/1995	2	22	4	APO; B	12	9	0	Lost to follow-up	
10/1996	1	11	3	P; B	4	13	0	2.25	DP
11/1996	2	19	6	PO; B	9	10	1	3	DP
12/1996	6	23	7	O; B	8	6	1	3.5	DP
13/1997	3	23	3	APO; B	22	12	0	4	DP
14/1997	2	20	5	PO; L	6	10	1	2	normal
15/1999	1	15	6	APO; B	12	7	0	3	DP
16/1999	1	15	8	APO; B	14	7	0	2.5	DP
17/2000	3	17	5	APO; B	15	8	0	3	TP
18/2000	1	10	3	APO; B	15	13	1	2	DP

*Period between last US examination and first diagnosis of cysts.
†A, Anterior; P, parietal; O, occipital; L, left sided; R, right sided; B, bilateral.
‡Maximum diameter of a single cyst.
¶Germinal matrix/intraventricular haemorrhage.
§Motor deficits: DP, diplegia; HP, hemiplegia; TP, tetraplegia.
PVL, Periventricular leucomalacia; PVE, periventricular echodensity.

infants.[26] These anastomoses can lead to twin to twin transfusion syndrome, which we observed in two of seven (29%) monochorionic pregnancies, as compared with 15% reported by Sebire et al.[48] Our findings confirm that the recipient twin is at increased risk of developing cystic PVL and cerebral palsy.[49][50] Even if there are no clinical signs of twin to twin transfusion syndrome, placental vascular connections, especially vein to vein anastomoses, may produce transitory cardiovascular compromise in one or both twins, resulting in impaired cerebral perfusion and brain damage.[26]

We observed a significant birth weight discordance of more than 30% in three twin pairs. The infants with higher birth weight all developed cystic PVL and subsequently cerebral palsy. The infants with the lower birth weight did not develop cystic PVL or cerebral palsy. Cheung et al[29] found a higher incidence of PVL in the group of infants with birth weight discordance, but not in the groups of smaller and larger birth weight. They proposed that the difference in growth between the fetuses may be associated with changes in their haemodynamic status, and that may affect the oxygen supply to the fetal brain.

In contrast with Baud et al,[9] we found no association between mode of delivery and the development of cystic PVL. Furthermore we found no association between breech presentation and cystic PVL, which was in accordance with Baud et al. We found no effect of birth order on subsequent risk of brain damage, in accordance with other authors.[24][25] There have been many suggestions about the influence of various risk factors on the development of cystic PVL, but we were unable to show a correlation between the possible timing of PVL and its cause except for hypocarbia and postnatal origin of cerebral damage.

Our results suggest that postnatal factors such as hypocarbia may have an important role in the development of cystic PVL in preterm twin gestations. Therefore mechanical ventilation of infants at high risk of PVL should be monitored carefully to avoid low Pco_2 levels. On the other hand, we do not know exactly to what extent prepartal factors such as placentation contribute to its pathogenesis, which requires further investigation.

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IMAGES IN NEONATAL MEDICINE..

A complication worth remembering

This neonate developed progressive abdominal distension after long line insertion requiring high ventilating pressures. A linogram revealed leakage of contrast into the peritoneum. After long line removal, the child was extubated in 48 hours.

This complication should be considered when abdominal distension occurs without convincing evidence of necrotising enterocolitis.

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Figure 1 Linogram showing contrast leakage into peritoneum.