Neonatal management and outcome after thoracoamniotic shunt placement for fetal hydrothorax

Witlox, R.S.G.M.; Klumper, F.J.C.M.; Pas, A.B. te; Zwet, E.W. van; Oepkes, D.; Lopriore, E.

Abstract

Aim: To evaluate the short-term neonatal outcome after fetal thoracoamniotic shunt placement for isolated hydrothorax.

Methods: Retrospective evaluation of infants with isolated hydrothorax treated with thoracoamniotic shunt placement at our fetal therapy centre between 2001 and 2016.

Results: In total 48 fetuses were treated with a thoracoamniotic shunt. All fetuses had signs of hydrops at the time of intervention. Median (interquartile range (IQR)) gestational age at shunting was 28.7 (24.4 – 31.3) weeks. Forty-one of 48 (85%) fetuses were born alive at a median (IQR) gestational age of 34.4 (31.1-36.7) weeks. In one child the course of disease after birth was unknown (this child was excluded from further analyses). After birth, 24/40 (60%) children had signs of pleural effusion and 12/40 (30%) needed a thoracic shunt for continuous pleural drainage. Twenty-one (53%) children required mechanical ventilation of which 13 (33%) needed high frequency ventilation as rescue therapy. Overall 30/40 (75%) infants survived the neonatal period. Neonatal survival rate was significantly higher when infants were born ≥ 32 weeks' gestation as compared to < 32 weeks, 93% (26/28) versus 33% (4/12); $P < 0.01$).

Conclusion: Postnatal course of hydropic fetuses treated with thoracoamniotic shunt for isolated hydrothorax is often complicated by respiratory failure and persistent pleural effusions. Neonatal survival is good provided delivery occurs at or after 32 weeks' gestation.

Introduction

Isolated fetal hydrothorax is an uncommon congenital abnormality, occuring in approximately 1:10.000 pregnancies (1). Fetal hydrothorax is thought to be due to leakage of lymphatic fluid in the pleural space either caused by direct leakage of lymphatic fluid from the thoracic duct, overproduction or impaired drainage of lymph (2, 3).

Fetal hydrothorax is a heterogeneous condition and the outcome may vary from spontaneous resolution without postnatal morbidity to severe fetal hydrops and perinatal death. Fetal hydrops results from compression of the heart and obstruction of venous return due to the space occupying effect of the hydrothorax.

Fetal hydrothorax can be treated prenatally with fine needle aspiration or permanent drainage through thoracoamniotic shunts. The aim of both interventions is to remove accumulated fluid and improve fetal condition (4).

Perinatal survival in hydropic fetuses with primary fetal hydrothorax is approximately 30% if left untreated and increases to 65% after thoracoamniotic shunt placement (5-12).

Previous case series with isolated fetal hydrothorax focussed primarily on perinatal survival and only few reports evaluated the neonatal outcome and long-term neurodevelopmental outcome.

The aim of this study was to evaluate the short-term neonatal management, outcome and risk factors after thoracoamniotic shunting for primary fetal hydrothorax.

Methods

In this retrospective study we included all patients with hydrothorax treated with thoracoamniotic shunts at our centre between January 2001 and May 2016. Patients throughout the Netherlands were referred to our centre in case of fetal hydrothorax with or without fetal hydrops. The Leiden University Medical Centre (LUMC) is the national referral centre for invasive fetal therapy in the Netherlands. All fetuses with congenital chylothorax, but without other structural abnormalities were included. As per our Institutional Review Board-approved protocol, our criteria for shunting are: likely isolated uni- or bilateral

hydrothorax with hydrops and a gestational age between 16 and 37 weeks. Hydrops was defined as accumulation of fluid in two or more compartments, including pleural effusion, skin oedema, ascites and/or pericardial effusion. We exclude fetuses with structural abnormalities detectable by ultrasound or chromosomal anomalies detectable by QF-PCR for trisomy 13, 18 and 21. We perform chromosomal microarray in all fetuses as well, but since it generally lasts two weeks until the results are known, shunting is performed when the results of QF-PCR are normal. In most cases, we perform a single needle drainage of the hydrothorax first, together with sampling of the amniotic fluid for diagnostic purposes. In the rare event that there is no recurrence of the hydrothorax, we obviously do not insert a shunt.

Patients underwent a thorough prenatal work-up including ultrasound examination of the fetal anatomy, fetal echocardiography and Doppler studies to exclude fetal anemia, as well as the above-described chromosomal assessment. Thoracoamniotic shunt placement was performed using a double pigtail Silastic catheter under local analgesia, using a technique described before by Rodeck et al[5]. All fetuses that received a thoracoamniotic shunt were included in the study.

During the study period, the following neonatal management was adopted after birth. At delivery, shunts were immediately clamped to prevent the development of pneumothorax. Neonatal thoracocentesis was performed when pleural effusion was apparent and compromising the respiratory function of the infant. After birth normal enteral feeding was started. When pleural effusion persisted or reappeared, pleural fluid was analysed for lymphocyte fraction and triglyceride level. When chylothorax was diagnosed, initially Medium Chain Triglyceride (MCT) formula was started to reduce chyle flow, but when no improvement was observed nil per os (NPO) and total parenteral nutrition (TPN) was started. Octreotide treatment was reserved for the infants where pleural effusion production continued despite the previous regimen.

Several antenatal variables were recorded including gestational age at diagnosis, gestational age at intervention and type of intervention

For infants born in our hospital, postnatal records were reviewed. For infants born in other hospitals, discharge letters were reviewed after parental consent was obtained. Neonatal management regimen was not standardised between the various hospitals.

Several neonatal variables were recorded including gestational age at birth, birth weight, presence of hydrothorax at birth, development of hydrothorax during the neonatal period, , (type of) mechanical ventilation severe persistent pulmonary hypertension of the neonate (PPHN) (defined as inhaled nitric oxide (iNO) administration because of clinical or echocardiographic evidence of right to left shunt), surfactant-treatment, postnatal thoracocentesis, postnatal chest drainage (duration), appearance of pleural fluid when obtained after birth, feeding management and use of octreotide

The neonatal outcome was also evaluated in association with very preterm birth (< 32 weeks of gestation) (13).

Statistical analysis

Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. Student-t-test and Mann-Whitney test were used for continuous variables. A *P* value < 0.05 was considered statistically significant. Logistic regression was used to assess the impact of three variables (gestational age at birth, resolution of hydrops after shunt placement and interval in days between first shunt placement and birth) on the likelihood of survival after birth. Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, Il, USA).

RESULTS

In the study period 48 fetuses were identified with pleural effusions in which one or more thoracoamniotic shunts were placed (figure 1).

Prenatal course

Antenatal characteristics are described in Table 1. All fetuses included in this study had signs of hydrops. Thirteen (27%) fetuses had fluid overload in 2 compartments, the other 35 (73%) in 3 compartments. None of the fetuses had pericardial effusion. Accompanying structural anomalies were not present.

All treated cases were from singleton pregnancies. Median gestational age at diagnosis was 27.4 weeks (IQR 20.5 – 30.5 weeks).

In the course of the pregnancy six (13%) women were treated for mirror syndrome. In these six cases, delivery occurred before 34 weeks' gestation, 3 of these foetuses died in utero, 2 died the first day after birth and only one baby survived until discharge.

Procedure characteristics are also described in Table 1. Needle thoracocentesis was performed as initial procedure in 29 (60%) fetuses. After recurrence of pleural effusion thoracoamniotic shunt placement was considered when the results of QF-PCR for trisomy 13, 18 or 21 were known.

The karyotype was abnormal in three cases. One case of partial trisomy 4 was only detected after shunt placement. The baby died in the first 24 hours after birth. In two cases trisomy 21 was detected. After extensive counselling and on repeated parental request, bilateral shunts were placed in both cases.

Thoracoamniotic shunt placement in the 48 fetuses included in this study was performed at a median gestational age of 28.7 weeks (IQR 24.4 – 31.3 weeks). In seven cases (15%) the shunt became dislodged after initial successful insertion. In five cases (10%) multiple shunt insertions were performed due to incomplete disappearance of hydrothorax after first shunt insertion.

In 36 (75%) cases hydrops improved after shunt insertion. In the 6 cases with mirror syndrome fetal hydrops persisted in 4 (75%) cases.

Fetal demise occurred in 7 (15%) pregnancies after fetal intervention. In one case, demise occurred within 1 day after shunt placement at a gestational age of 21 weeks, probably due to traumatic rupture of a thoracic vessel during the procedure as seen on ultrasound. Autopsy was not performed in the cases of fetal demise.

Postnatal course

A total of 41 (85%) neonates were live-born, of which 10 died in the neonatal period (24%, 10/41). In two neonates intensive care treatment was not initiated because of a known chromosomal abnormality (partial trisomy 4) in one and massive hydrops in the other case. The other eight cases with neonatal demise had signs of pulmonary hypoplasia and persistent pulmonary hypertension at birth. Six of these cases died within 48 hours after birth, one died after 31 days and another one after 12 days, both due to intractable respiratory failure. Autopsy was not performed in any of these cases. The overall rate of perinatal survival was 63% (30/48).

All children were born at a tertiary care centre, either at our centre (n=30 or at another national tertiary care centre (n=10). Complete data on postnatal management and outcome was obtained in all but one case (40/41, 98%) as parents did not consent the use of medical data and this neonate was excluded from further analyses on neonatal morbidity and mortality.

Characteristics of the 40 live-born children with complete neonatal follow-up are presented in Table 2.

Median gestational age at birth was 34.4 weeks. Median time interval between first shunt insertion and delivery was 34 days. The majority (75%) of children was born premature (< 37 weeks' gestation), mostly due to spontaneous preterm delivery. Pleural effusion was still present at birth in 24 cases (60%) or reappeared after birth in 2 cases. Seven of these cases were managed by single thoracocentesis. In 12 cases (30% of live-born children) a thoracic shunt was placed for continuous pleural drainage for a median duration of 3.5 days (IQR 1-13 days).

In eleven of these 19 cases where pleural drainage was performed, the fluid was analysed biochemically. In ten cases the results were compatible with the diagnosis chylothorax because of a triglyceride level above 1.1 mmol/l and a lymphocyte fraction greater than 80%.

In 12 cases an MCT diet was started, either prophylactically directly after birth to reduce the chance of worsening of chylothorax (n=4) or therapeutically as a treatment of persistent chylothorax (n=8). In 33% (4/12) of cases this treatment had insufficient effect and NPO and TPN was given for a median duration of 9 days. In two of these cases treatment with Octreotide was administered to stop the pleural effusion. In all 8 cases with persistent pleural effusion the effusion eventually stopped after treatment.

A majority of children (28/40, 70%) needed respiratory support during the neonatal period. Twenty-one (53%) children required mechanical ventilation, of which thirteen (33%) needed high frequency ventilation (HFOv). In 6 (15%) cases severe PPHN requiring iNO was present. Seven children (18%) required only nasal continuous positive airway pressure (nCPAP). Seven (18%) children developed bronchopulmonary dysplasia (BPD) . All seven had severe respiratory insufficiency after birth. No cases with severe Intraventricular Hemorrhage (IVH) or cystic Periventricular Leucomalacia (PVL) were detected. Detailed information on neonatal morbidity and mortality of the 40 live-born children with complete follow-up is presented in Table 3.

Routine testing of Noonan syndrome was not performed. Two children were diagnosed with Noonan syndrome after birth, because of characteristic dysmorphic features. The diagnosis was confirmed by mutation analysis. The first of these two was born at a gestational age of 34^{+6} weeks, six days after thoracoamniotic shunt placement. He was ventilated for 43 days after birth and had persistent chylothorax that only stopped after Octreotide treatment. The second child with Noonan syndrome was born at a gestational age of 32^{+2} weeks, 24 days after thoracoamniotic shunt placement. After birth only a small amount of pleural fluid was detected and he needed 8 days of CPAP. At 3 weeks of age, myelodysplasia was suspected and mechanical ventilation was required in order to perform a bone marrow biopsy. After the procedure he could not be weaned off the ventilator because of suspected lymphangiectasia. At 10 months of age he is still ventilated through a tracheostomy.

The likelihood of survival was assessed in a logistic regression model using three independent variables (gestational age at birth, resolution of hydrops after shunting and time interval between shunting and birth). The full model containing all predictors was statistically significant, χ^2 (3, n=40) = 21.29, p<0,0001. Only two of the three independent variables made a unique statistically significant contribution to the model; gestational age at birth and resolution of hydrops after shunting. The strongest predictor of survival was gestational age at birth (in weeks) recording an odds ratio of 1.7 (95% confidence interval 1.1 – 2.7). Persistence of hydrops after shunting recorded an odds ratio of 0.039 (95% confidence interval 0.002-0.768), indicating that in children where hydrops persisted perinatal survival has 0.039 times less odds than in children in whom hydrops resolved after shunting. The neonatal mortality and morbidity in in relation to premature delivery is shown in Table 4. Survival rate in children born <32 weeks was 33% (4/12). Of the surviving four infants born < 32 weeks three had a prolonged course of intensive care treatment and mechanical ventilation. In contrast, survival rate in children born ≥ 32 weeks' gestation was 93% (26/28), of which in one case intensive care treatment was not started because of a partial trisomy 4, and the other infant died of severe respiratory insufficiency at birth suggestive of pulmonary hypoplasia.

DISCUSSION

In this study we report the short-term outcome in hydropic fetuses with isolated hydrothorax treated with thoracoamniotic shunting. We found that the postnatal course was often complicated by respiratory failure and persistent pleural effusions. However, neonatal survival was good, provided delivery occurs after 32 weeks' gestation.

Prenatal management in fetuses with primary fetal hydrothorax is based on timely intervention with thoracocentesis and thoracoamniotic shunting. Because these fluid collections tend to reaccumulate within 24-48 hours permanent drainage, thoracoamniotic shunt placement seems more appropriate in cases needing long-term drainage (11, 14). The

rationale for this intervention in fetuses with primary hydrothorax is based on the extremely poor survival rate in case of expectant management, ranging between 24 and 46% (1, 10, 15). Given the low survival rate without fetal intervention, thoracoamniotic shunt placement is usually reserved for hydropic fetuses. Impending hydrops as observed on serial ultrasounds by progression of the hydrothorax often accompanied by polyhydramnios or mediastinal shift is sometimes also considered as treatment indication (11, 14). In contrast, survival in fetuses with primary hydrothorax without hydrops is reported to be 73-100% without treatment and prenatal treatment is therefore often not indicated (10, 14, 16). Single needle thoracocentesis before birth can be considered to facilitate lung expansion at birth.

The overall rate of perinatal survival (30/48, 63%) in hydropic fetuses reported in our cohort is comparable to that in previous reports, varying from 52% to 67% (11, 14, 17).

Our data also show that neonatal mortality and morbidity was particularly high in case of preterm delivery. The association between preterm birth and worse perinatal outcome is in agreement with previous reports emphasizing the important impact of prematurity. Increased mortality in very preterm infants can be due to increased risk associated with prematurity itself. In addition, a shorter shunt-to-delivery interval could implicate less time for prenatal lung recovery. Other reported adverse prognostic criteria include bilateral pleural effusion, fetal hydrops, and absence of spontaneous regression by 28 weeks' gestation (12, 15, 18).

The most important cause of primary fetal pleural effusion was congenital chylothorax (10 of 11 (91%) analysed cases. This condition is thought to be caused by incomplete formation of lymphatic structures in the thorax leading to leakage of chylous fluid. Therefore persistence of leakage can be expected after birth. In 65% of infants, signs of recurrent or persistent pleural effusion after birth were present, requiring various treatments such as drainage, TPN and Octreotide. In the end pleural effusion gradually regressed and eventually stopped in all cases.

Care should be taken when interpreting our results due to the retrospective nature of our study and the relative small number of patients. All published series, including this cohort, are small, which limits our conclusions. In addition, results may be influenced by case selection. In our cohort all fetuses were severely affected as illustrated by the invariable presence of fetal hydrops. Less severe cases were probably not referred to our fetal treatment centre, which partly explains the relative small number of fetuses in our series.

Because of the relatively high rate of short-term morbidity and increased risk of very preterm birth, these survivors are also at risk of long-term sequelae. There is little data on long-term follow-up, but mild respiratory abnormalities in survivors have been reported (12, 19). Unfortunately, data on the neurodevelopmental outcome in long-term survivors is not available.

In conclusion, the survival of fetuses with primary hydrothorax and associated hydrops treated with thoracoamniotic shunting is high, when delivered after 32 weeks' gestation. However, the respiratory morbidity and mortality after birth remain high, especially in case of very preterm birth. In view of the potential neonatal complications, delivery of these high-risk fetuses should always occur in a specialized tertiary care centre. Larger series, including long-term follow-up, are needed to correctly identify criteria associated with adverse outcome, allowing for better patient selection at the moment of treatment. Multicentre studies or global web-based registry might aid to achieve this goal.

What is known about this topic:

- Perinatal survival in hydropic fetuses with isolated fetal hydrothorax is poor when left untreated antenatally.
- Perinatal survival appears to be improved by fetal thoracoamniotic shunt placement.
- Detailed reports on neonatal and long-term outcome after thoraco-amniotic shunt placement for fetal hydrothorax are scarce.

What this study adds:

- This is the first study describing detailed neonatal management and outcome in children born after thoracoamniotic shunting for fetal hydrothorax.
- The majority of these children require mechanical ventilation after birth and/or continuous pleural drainage for persistent pleural effusion and should therefore be delivered in a tertiary care centre.
- Survival is high in children delivered after 32 weeks' gestation.

Figure 1. Flowchart showing the derivation of our population.

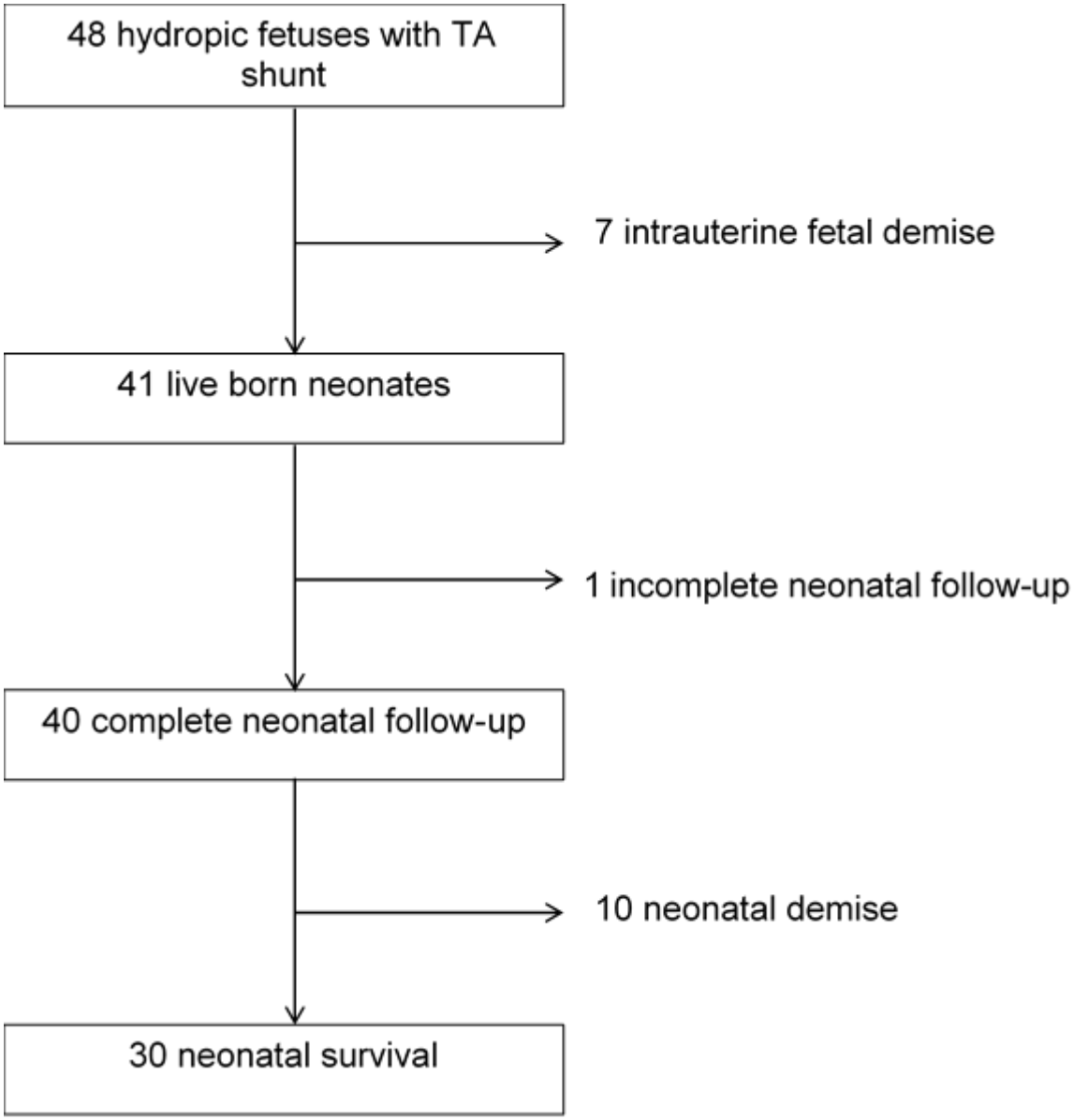

Table 1. Antenatal characteristics of the study group (n=48)

Maternal age (years)	31.0 (29-34)
Male:female ratio	1.4 : 1
Gestational age at diagnosis (weeks)	27.4 (20.5-30.5)
Hydrops at diagnosis	48 (100%)
Polyhydramnios	25 (52%)
Maternal 'mirror' syndrome	6 (13%)
Abnormal karyotype *	3 (6%)
Characteristics of intervention	
Thoracocentesis prior to shunt	29 (60%)
Gestational age at shunting (weeks)	28.7 (24.4 -31.3)
Bilateral shunt placement	29 (60%)
Procedure related fetal demise	1 (2%)
Intrauterine shunt displacement	7 (15%)
Multiple shunt placements	5 (10%)
Hydrops resolved after shunt	36 (75%)
Interval from shunt placement to delivery (days)	26 (9-56)

Data are given as median (interquartile range), ratio, or n (%)

* 2 cases of trisomy 21 (detected antenatally), 1 case of partial trisomy 4 (detected prenatally after shunt treatment)

Table 2. Perinatal characteristics of the 40 live born children with complete neonatal follow-up.

Gestational age at birth (weeks)	34.4 (31.1-36.8)
Time interval between first shunt insertion and delivery (days)	34 (16-67)
Birth weight (grams)	2490 (1943-3216)
Spontaneous preterm labour (gestation <37 weeks) (n=28)	16 (53%)
Vaginal delivery	29 (73%)
Preterm birth	
<32 weeks	12 (30%)
<34 weeks	18 (45%)
<37 weeks	30 (75%)
Causes of preterm delivery <37 weeks (n=30)*	
fetal distress	9 (29%)
worsening maternal condition	2 (7%)
spontaneous preterm birth	16 (53%)
Antenatal steroids <34 weeks (n=18)	11 (61%)
Pleural effusion at birth	24 (60%)
Bilateral	12
Unilateral	12
Neonatal survival	30 (75%)

Data are given as median (interquartile range) or n (%)
*includes 28 cases born after spontaneous preterm labour and 2 cases of cesarean section beacuase of worsening maternal condition without spontaneous preterm labour.

Table 3. Neonatal management and outcome in the 40 live born children with complete data.

Postnatal pleural effusion, at birth or during admission	26 (65%)
Thoracocentesis, without drain	7 (18%)
Continuous pleural drainage	12 (30%)
duration (days) median, (IQR)	3.5 (1-13)
Endotracheal mechanical ventilation	21 (53%)
duration (days) median, (IQR)	6 (1-22)
CPAP only	7 (18%)
High Frequency Ventilation	13 (33%)
Inhaled Nitric Oxide	6 (15%)
Inotropic support	7 (18%)
Enteral nutrition support with MCT formula	12 (30%)
NPO and TPN support	4 (10%)
Octreotide treatment	2 (5%)
Necrotising enterocolitis	0 (0%)
Culture proven sepsis	5 (13%)
Survival until discharge	30 (75%)
Early neonatal death (<48hrs)	8 (20%)

Data are given as median (interquartile range) or n (%)

CPAP: continuous positive airway pressure, MCT: medium chain triglyceride, NPO: nil per os, TPN: total parenteral nutrition

The majority of neonatal deaths occurred in very preterm neonates delivered before 32 weeks' gestation; eight of twelve (67%) neonates born < 32 weeks died after birth as compared to 2 of 28 (7%) neonates born ≥ 32 weeks ($P < .01$).

Comparison between the outcome in children born before and after a gestational age of 32 weeks is shown in Table 4.

Table 4. Analysis in children (n=40) born before and after 32 weeks' gestation

Characteristic	Delivery <32 weeks (n=12)	Delivery >= 32 weeks (n=28)	P-value
GA at shunt insertion (weeks, range)	26.6 (24.4-28.2)	29.9 (26.5-31.5)	P=0.03**
GA at delivery (weeks, range)	29.9 (29.5-30.9)	36.4 (34.3-38.0)	P<0,001**
Shunt-delivery interval (days, range)	28 (14-39)	41 (17-82)	P=0.1**
Pleural effusion at birth	50% (6/12)	64% (18/28)	P=0.49+
Endotracheal intubation after birth	90% (10/12)	32% (9/28)	P=0.005+
Survival until 48 hours after birth	50% (6/12)	93% (26/28)	P=0.005+
Survival until discharge	33% (4/12)	93% (26/28)	P<0.001+

Data are given as median (interquartile range) or n (%)

** Group differences were tested with the Mann-Whitney U test.

+ Differences between proportions were tested with Fisher's exact test

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