Lymphology 45 (2012) 91-102

CONGENITAL FETAL AND NEONATAL VISCERAL CHYLOUS EFFUSIONS: NEONATAL CHYLOTHORAX AND CHYLOUS ASCITES REVISITED. A MULTICENTER RETROSPECTIVE STUDY

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ABSTRACT

This retrospective study was carried out at eight Neonatal Intensive Care Units (NICU) Centers worldwide on 33 newborns presenting at birth with pleural, pericardial, or abdominal chylous effusions. Diagnosis of chylous effusion is based on findings of fluid with a milk-like appearance, a concentration of triglycerides in pleural effusion >1.1 mmol/l, and a total cell count >1,000 cells/ml with a predominance of >80% lymphocytes. Thirty-three newborns met the inclusion criteria and were studied. Six subjects who presented at birth with fetal effusion were treated by in-utero pleuro-amniotic shunt. Five of these patients are alive at follow-up. At birth, pleural drainage was performed in 29/33 patients and abdominal drainage was carried out in 3/33. Total parenteral nutrition (TPN) was given to 32/33 patients; 19/23 patients were fed a medium-chain triglycerides (MCT). No adverse effects were observed. Eight patients were treated with Octreotide at dosages ranging from 1 to 7 mcg/kg/hour for 8 to 35 days. All patients showed decreased chylous production. Two patients were treated by pleurodesis. Twenty-two babies are alive after at least 6 months follow-up, 9/33 are deceased, and 2 were lost to follow-up. Clinical conditions of survivors are basically good except for lung involvement [chronic lung disease (CLD) or lung lymphangiectasia] and lymphedema. All patients were using a MCT diet at follow-up with good control of chylous effusion. Visceral chylous effusions of

the fetus and neonate are rare disorders, and there currently is only partial agreement on decision-making strategies. We suggest the need for an international prospective trial in an effort to establish the efficacy and effectiveness of diagnostic and therapeutic options described in this article.

Keywords: non-immune hydrops fetalis, fetal hydrops, edema of the fetus, congenital visceral effusion, chylothorax, hydrothorax, chylous ascites, lymphatic abnormalities, MCT diet, Octreotide

Accumulation of fluid in the visceral compartment during the neonatal period is rare, and data on pathogenesis and treatment modalities are limited and contradictory (1-4). During the intrauterine period, occurrence of these conditions alone or in combination may configure the end-stage process leading to hydrops formation (4, 5). Chylothorax is defined as an accumulation of chyle in the pleural space and is a common endpoint for a variety of pathologic processes including intrinsic abnormalities of the lymphatic system, or disruption of the thoracic duct via trauma, surgery, malignancy, or cardiovascular disease. Chylothorax in the neonate is the most common cause of pleural effusion (6). Congenital duct defect, either isolated or associated with generalized lymphatic vessel dysplasia, is the most common cause of congenital chylothorax, and rarely it is the result of direct trauma at birth. Primary chylous ascites in the neonatal period is also a rare occurrence which is caused by inadequate lymphatic drainage from the intestine resulting from maldevelopment of the intra-abdominal lymphatic system leading to extravasation of chyle into peritoneal cavity (7,8). Hypoplastic or hyperplastic lymphatic systems may lead to obstruction of the lymphatic flow and an increase in the intestinal lymphatic pressure, which eventually causes lymph to leak into the abdomen. Primary chylous ascites is relatively easy to recognize, although diagnosing the underlying pathology may be difficult (9). The reported incidence of congenital chylothorax ranges from 1:8,600 to 1:10,000 live births (1). The true incidence of primary chylous ascites has never been well established (10), and it can only be estimated at approximately one in 20,000 admissions from a large university-based hospital (11). The incidence of congenital chylopericardium has never been truly established and it is considered extremely rare (1-3).

This study describes our experience on 33 newborns affected by congenital chylous effusions based on a large number of newborns that were enrolled from eight tertiary level NICUs worldwide.

MATERIALS AND METHODS

This is a retrospective study that was carried out at eight NICU Centers worldwide on newborns presenting at birth with pleural, pericardial, or abdominal chylous effusions. Prenatal and postnatal clinical courses and baseline maternal variables were collected. A previously published flow-chart for non-immune hydrops fetalis was used (12). Diagnosis of chylous effusion was based on the findings of fluid with a milk-like appearance, a concentration of triglycerides in visceral effusion >1.1 mmol/l, and a total cell count >1,000 cells/ml with a predominance of >80% lymphocytes (13).

RESULTS

Thirty-three newborns met the inclusion criteria. Our study results are summarized in *Table 1*. A history of each subject, together with clinical data and a description of therapeutic features are provided in *Table 2*. Six subjects who presented at birth with fetal effusion were treated by in-utero pleuro-amniotic shunt. Five of these patients are alive at follow-up. No significant side effects to the procedures were observed except for one case of a stuck pigtail catheter which had to be extracted.

TABLE 1
Summary of Main Clinical Features of Patients Studied

Cases	Median GA at birth (weeks) (Min/Max)	Median BW at birth (grams) (Min/Max)	Gender (M/F)	Prenatal therapy	Postnatal therapy						Outcome after 6 months follow-up		
				Thoracic drainage	Pleural drainage	Abdominal drainage	MV	TPN	MCT diet	Octreotide Dosage (mcg/kg/h) Duration (Days: Min/Max)	Alive	Deceased	Lost (Alive when lost)
33	34 + 2 (28+0/40+6)	2,722 (830/3,960)	20/13	6/33	29/33	2/33	31/33	32/33	29/33	10/33 1 up to 10 9/38	26/33	7/33	2/33

GA=gestational age; BW=birth weight; MCT=medium chain triglyceride; MV=mechanical ventilation; TPN=total parenteral nutrition

At birth, pleural drainage was performed in 29/33 patients (22 bilateral, 5 right, and 2 left chest drains) and abdominal drainage was carried out in 2/33. Thirty-one patients underwent mechanical ventilation (29 SIPPV, 2 HFOV) and surfactant was administrated to 20/33 patients. Total parenteral nutrition (TPN) was given to 32/33 patients and 28/32 patients were fed a Medium-Chain Triglycerides (MCT) diet with varied MCT content[(Pregestimil® 55% (6/28), Caprilon® 75% (2/28), Portagen® 87% (12/28), and Monogen® 90% (8/28)]. No side effects were observed. None of the patients who died ever reached suitable general clinical conditions allowing enteral feeding. Ten patients were treated with Octreotide, at dosages ranging from 1 to 10 mcg/kg/hour for 8 to 38 days. All Octreotide-treated patients showed decreased chylous production. Although one patient died of severe respiratory distress syndrome (RDS) due to pulmonary hypoplasia, she experienced a mild reduction of pleural effusion during Octreotide therapy. Bile sludge and mild cholestasis were observed in one patient who spontaneously recovered within one month. Two patients were treated by pleurodesis. Twenty-six babies are alive after at least 6 months follow-up, 7/33 are deceased, and 2 further were lost to follow-up. Clinical conditions of survivors are basically good, except for lung involvement (CLD or lung lymphangiectasia) and lymphedema. All patients were using a MCT diet at follow-up with good control of chylous effusion.

DISCUSSION

We present our experience on diagnosis and management of 33 newborns affected by various combinations of congenital visceral chylous effusions presenting at birth *(Tables 1 and 2*). There are several points of interest in these data and some limitations. Our study allowed us to collect a large number of newborns affected by congenital visceral chylous effusions. The sample size is quite

large considering the rarity of the described conditions, making this study exemplary in our opinion, and allowing us sufficient data to compare different diagnostic and therapeutic approaches. Although we are aware that our approach might be limited by methodological and/or clinical heterogeneity, we believe that collecting such patients is currently the best approach possible due to the rarity of these disorders and the lack of multi-center, prospective, controlled trials.

Consistency was found regarding the need for exclusive level III intensive care and the need for mechanical ventilation and chest drainage at birth as well as the use of TPN and MCT diet. Disagreement was found on a) use of intrauterine pleural shunt, b) MCT content, c) Octreotide therapy, and d) pleurodesis.

It is beyond the scope of this article to discuss the various types of ventilatory support that may be used, including SIPPV, HFOV, and nCPAP, with or without iNO supplementation, or specific diagnostic protocols or procedures (14,15). We briefly discuss some of the debated topics.

Point a). In our experience, only 6/33 cases presenting with fetal effusion were treated by pleuro-amniotic shunt (cases 1, 3, 21, 22, 23, and 30; cases 22 and 23 did not present hydrops), within a range of 31 to 37 weeks of gestational age at birth. All patients, except case 22, are alive at follow-up. No significant side effects to the procedures were observed except for one case of a stuck pigtail catheter which had to be extracted. The National Institute for Health and Clinical Excellence (NICE) (16) provided guidelines concerning the insertion of pleuro-amniotic shunts for treatment of fetal pleural effusion. The report highlights that there are several uncertainties about patient selection and natural history of fetal pleural effusion. A recent systematic review (17) reported that currently available treatment options in isolated fetal hydrothorax with hydrops included single or serial thoracocentesis, thoraco-amniotic shunt placement or a combination of thoracocentesis and shunting, pleurodesis with OK-432, and intrapleural injection of autologous blood. This review, together with others which were recently published (17-22), estimated that a 60% perinatal survival rate may be expected in treated subjects. These papers, together with the NICE report concluded that there is a lack of hard proof regarding effectiveness of intrauterine pulmonary drainage and that, although improved outcome in treated fetuses seems to be demonstrable, the procedure is not completely safe nor free of severe complications. There is consensus that invasive fetal therapy should be reserved for hydropic fetuses without additional anomalies. Further, it must be taken into account that pleural effusion may resolve spontaneously, thus making it necessary to evaluate the detailed balance between treatment risks and natural history-progression outcome of the effusion.

In our experience, subjects who did not undergo intrauterine pleural drainage were usually born by planned cesarean section (CS vs VD, 20 vs 4; CS group GA from 28 to 40 weeks; VD group GA from 34 to 37 weeks). Although our results seem to show that premature birth can protect the fetus from injuries caused by progressive fluid accumulation, we cannot provide definitive data supporting the effectiveness of performing a premature delivery to avoid the risks of large visceral effusions, and especially large pleural effusions eventually leading to lung hypoplasia. A comparison among the participating centers concerning the balance between premature delivery vs intrauterine pleural drainage seems to indicate that a reasonable, although empirical approach thus needing confirmation, might be to drain the fluid up to as late as 32-34 weeks gestational age. If the fetus reaches 34 weeks with large effusion, the benefit of extrauterine drainage and treatment exceeds the problems of prematurity. If the fetus has a large effusion, we also suggest administering antenatal steroids to the mother.

TABLE 2
Main Clinical Features of 33 Patients in the Study

Case	Gender	GA (wk)	BW (g)	Prenatal history	Mode of Delivery	Clinical Findings at birth	Clinical course, Treatment	Etiologic Classification, Diagnosis	Outcome after 6 months
1	M	31+5	2,290	Hydrops fetalis at 29 ws, chest drain in utero, VEGFR3 gene mutation	CS	Severe RDS, PPHN, pleural chylous effusion	Bilateral chest drain, surfactant, HFOV, iNO, SIPPV, nCPAP, Octreotide 1up to 8 mcg/kg/hour (26 days), TPN, Portagen®, *Serratia* sepsis, renal failure	Pulmonary lymphangiectasia. Confirmation of VEGFR3 gene mutation	Alive. CLD
2	F	31+1	2,120	Family history of swelling of the limbs, 2 previous spontaneous abortions, fetal ascites at 24 ws, karyotype 46XX	CS	Severe RDS, Ascites, pleural chylous effusion, lymphedema of the limbs	Bilateral chest drain, paracentesis, surfactant, SIPPV, nCPAP, TPN, Portagen®	Hereditary primary lymphedema (Milroy's Disease) No VEGFR3 gene mutation	Alive, well; Lymphedema fibrosis of the limb tissues, cellulitis.
3	M	35+5	3,117	Hydrops fetalis at 29 ws, chest drain in utero	CS	Mild RDS, aortic arch hypoplasia, pleural chylous effusion	Left chest drain, nCPAP; PNX, TPN, Portagen®	Noonan syndrome suspected; no mutations in: PTP11, SOS 1, KRAS, RAF1, VEGFR3 genes	Alive. CLD
4	F	32+4	2,200	Hydrops fetalis at 30 ws	CS	Severe RDS, pleural chylous effusion, chylous ascites	Bilateral chest drain, SIPPV, surfactant, nCPAP, TPN, Portagen®	Primary lymphatic dysplasia	Alive, well. Mild and soft lymph-edema upper right limb
5	M	38+1	3,960	Bilateral pleural effusion at 35 ws	CS	Severe RDS, pleural chylous effusion, chylous ascites	Left chest drain, SIPPV, nCPAP, TPN, Portagen®	Primary lymphatic dysplasia	Alive, well.
6	F	34+0	2,800	Polyhydramnios at 30 ws, Hydrops fetalis at 32 ws, pleural effusion	VD	Severe RDS, pleural chylous effusion	Right chest drain, SIPPV, surfactant, CPAP, TPN, Portagen®	Primary lymphatic dysplasia	Alive, well. Mild and soft lymphedema lower right limb
7	F	33+2	2,400	Bilateral pleural effusion at 31 ws	CS	Severe RDS, pleural chylous effusion	Bilateral chest drain, surfactant, SIPPV, nCPAP, TPN, Portagen®	Primary lymphatic dysplasia. Hennekam syndrome	Alive, well, lymphedema lower right limb, mild mental retardation

8	M	33+3	1,795	Bilateral pleural effusion, Hydrops fetalis at 32 ws	CS	Severe RDS, pleural chylous effusion	Bilateral chest drain, surfactant, SIPPV, nCPAP, TPN, septic shock on day 53 of life	Primary lymphatic dysplasia	Dead due to septic shock
9	F	32+3	2,300	Polyhydramnios at 29 ws, Hydrops fetalis, bilateral pleural effusion, and ascites at 31 ws	CS	Severe RDS, pleural chylous effusion, chylous ascites	Bilateral chest drain, surfactant, SIPPV, nCPAP, TPN, Portagen®	Primary lymphatic dysplasia	Alive, well, lymphedema lower right limb
10	M	30+0	1,850	Hydrops fetalis, bilateral pleural effusion, and ascites at 29 ws	CS	Severe RDS, pleural chylous effusion, chylous ascites	Bilateral chest drain, surfactant, SIPPV, nCPAP, TPN. Bilateral PNX, acute pneumopericardium	Primary lymphatic dysplasia	Dead due to acute pneumoperi-cardium
11	F	35+1	2,900	Polyhydramnios at 29 ws, aortic coartaction, pleural effusion	CS	Severe RDS, pleural chylous effusion, aortic coartaction	Bilateral chest drain, SIPPV, surfactant nCPAP, TPN, Portagen®. Cardiac surgical correction.	Primary lymphatic dysplasia with heart defect	Alive, well; lymphedema lower limbs; mild mental retardation. Pleurodesis (2 years old)
12	M	32+1	3,150	Fetal ascites at 28 ws	CS	RDS due to severe abdominal distension, chylous ascites, bilateral hydrocele	Paracentesis, SIPPV, nCPAP, surfactant,TPN, Octreotide 1 up to 5 mcg/kg/hour (15 days), Portagen®, cholestasis, bile sludge	Primary lymphatic dysplasia	Alive, well; lymphedema lower limbs
13	F	28+0	1,670	Hydrops fetalis at 27 ws; IVF-ICSI (in vitro fertilization-intra cytoplasm spermatozoon injection)	CS	Severe RDS, hypoplastic lungs	Bilateral chest drain, SIPPV, surfactant TPN, Octreotide 1 up to 5 mcg/kg/hour (9 days)	Possible primary lymphatic dysplasia	Dead due to acute, severe RDS caused by pulmonary hypoplasia
14	F	32+5	2,900	Hydrops fetalis, bilateral pleural effusion, and ascites at 30 ws	CS	Severe RDS, pleural chylous effusion, chylous ascites	Bilateral chest drain, SIPPV, surfactant nCPAP, TPN, Portagen®, sepsis	Primary lymphatic dysplasia	Alive, well; lymphedema lower limbs
15	M	34+6	2,800	Pleural effusion at 34 ws	VD	RDS, hypoplastic lungs, bilateral pleural chylous effusion	Bilateral chest drain, SIPPV, surfactant,TPN, Pregestimil®, sepsis	Klinefelter syndrome and lymphatic dysplasia, transitory hypothyroidism	Alive, well. Mild mental retardation

Table 2 (continued)

Case	Gender	GA (wk)	BW (g)	Prenatal history	Mode of Delivery	Clinical Findings at birth	Clinical course, Treatment	Etiologic Classification, Diagnosis	Outcome after 6 months
16	M	35+6	3,080	Pleural effusion at 33 ws	CS	Severe RDS, bilateral pleural chylous effusion	Bilateral chest drain, SIPPV, TPN, Pregestimil®	Noonan syndrome suspected; no mutations in: PTP11, SOS1, KRAS, RAF1, VEGFR3 genes	Alive when lost at follow-up
17	F	34+4	2,380	Hydrops fetalis at 32 ws	CS	Severe RDS, bilateral pleural chylous effusion, chylous ascites	Bilateral chest drain, SIPPV, surfactant,TPN, Pregestimil®	Possible primary lymphatic dysplasia	Alive, well
18	M	37+2	3,450	Intrauterine diagnosis of pulmonary sequestration at 30 ws	VD	Severe RDS, right pleural chylous effusion, PPHN	Right chest drain, SIPPV, TPN, Pregestimil®, sepsis	Lung sequestration	Alive, well
19	M	39+1	2,420	No prenatal diagnosis	CS	Severe RDS, right pleural chylous effusion	Right chest drain, SIPPV,TPN, Pregestimil®, sepsis	Down syndrome, tetralogy of Fallot and AV canal	Alive when lost at follow-up
20	F	32+6	2,610	Hydrops fetalis at 31 ws	CS	Severe RDS, bilateral pleural chylous effusion, chylous ascites	Bilateral chest drain, SIPPV, surfactant,TPN, Monogen®, Octreotide 1 up to 10 mcg/kg/hour (23 days), cranial ventriculomegaly, hypothyroidism, sepsis	Primary lymphatic dysplasia, possible lung lymphangiectasia	Alive. Overall motor and mental retardation, deafness. Still suffering from recurrent pneumonia, had a cochlear transplant and started talking
21	M	33+0	2,680	Hydrops fetalis at 29 ws, intrauterine pleural drain	VD	Severe RDS, bilateral pleural chylous effusion, chylous ascites	Bilateral chest drain, SIPPV, Pregestimil®, sepsis	Possible primary lymphatic dysplasia	Alive, well; lymphedema lower limbs
22	F	35+4	2,300	Pleural effusion at 30 ws, intrauterine pleural drain	CS	Severe RDS, bilateral pleural chylous effusion; brain hypoplasia, seizures, limb contractures, sepsis	Bilateral chest drain, SIPPV, TPN, Monogen®	Possible primary lymphatic dysplasia	Dead due to septic shock

23	F	37+0	3,170	Pleural effusion at 31 ws, intrauterine pleural drain	VD	Severe RDS, bilateral pleural chylous effusion	Bilateral chest drain, SIPPV, TPN, Monogen®	Possible lymphatic dysplasia	Alive, well
24	M	35+4	3,000	Pleural effusion at 31 ws, polyhydramnios	CS	Severe RDS, bilateral pleural chylous effusion	Bilateral chest drain, SIPPV, TPN, Monogen®	Possible lymphatic dysplasia	Alive, well
25	M	31+5	2,885	Hydrops fetalis, bilateral pleural effusion at 31 ws	CS	RDS, bilateral pleural chylous effusion, chylous ascites	Bilateral chest drain, SIPPV, surfactant,TPN, Monogen®, umbilical catheter related aortic thrombosis	Down syndrome, heart defect, lymphatic dysplasia	Dead
26	M	35+0	2,190	Bilateral pleural effusion at 30 weeks, polyhydramnios	VD	Severe RDS, bilateral pleural chylous effusion	Bilateral chest drain SIPPV, TPN, Monogen®, bilateral PNX	Possible lymphatic dysplasia, lingual thyroid.	Alive, well. Hypothyroidism-L thyroxin
27	M	32+2	2,850	Bilateral pleural effusion at 31 ws, polyhydramnios	CS	RDS, severe PPHN, pleural chylous effusion, chylous ascites, sepsis	Bilateral chest drain, SIPPV, iNO, surfactant, TPN, Octreotide 2 mcg/kg/hour (35 days)	Down syndrome, sepsis. Possible lymphatic dysplasia	Dead due to septic shock
28	M	28+2	830	Oligohydramnios, intrauterine growth restriction, acute fetal distress	CS	Cranial ventriculomegaly, severe RDS, subcutaneous edema, pleural chylous effusion, chylous ascites	Surfactant, HFOV, SIPPV, nCPAP, Octreotide 1 up to 6 mcg/kg/hour (12 days), TPN, Portagen®	Possible lymphatic dysplasia	Alive, well; lymphedema lower limbs
29	M	40+6	3,900	Hydrops fetalis, chylous ascites, edema, pericardial effusion, mild pleural effusion. Polyhydramnios at 30 ws	CS	Chylous ascites, pericardial effusion, lymphedema of the lower limbs, hydrocele, hypospadia; portal cavernoma, portal hypertension	Spironolactone, porto-systemic shunt, TPN, Portagen®	Lymphodysplasic syndrome	Alive, well; lymphedema lower limbs
30	M	34+0	2,850	Hydrops fetalis, pleural effusion at 30 ws. In utero bilateral chest drain. Karyotype 46XY	CS	Severe RDS, chylous ascites, pleural effusion limb lymphedema	Bilateral chest drain, SIPPV, surfactant,TPN, Monogen®, Octreotide 3 mcg/kg/hour (11 days). Stuck pigtail catheter extraction	Possible lymphatic dysplasia. Sepsis	Alive, well

Table 2 (continued)

Case	Gender	GA (wk)	BW (g)	Prenatal history	Mode of Delivery	Clinical Findings at birth	Clinical course, Treatment	Etiologic Classification, Diagnosis	Outcome after 6 months
31	M	39+0	3,220	Parents are 1st degree relatives. Pleural effusion at 36 ws	VD	Severe RDS, PPHN, right pleural chylous effusion, sepsis, dysmorphism	Right chest drain, SIPPV, surfactant, TPN, Octreotide 3 mcg/kg/hour (38 days), Monogen®	Trisomy 21. Congenital pulmonary lymphangiectasia	Dead at 52 days due to respiratory failure
32	M	32+0	3,855	Abdominal effusion at 30 ws	VD	RDS, chylous ascites	IPPV, abdominal drain, Octreotide 3 up to 6 mcg/kg/hour (20 days), TPN, Caprilon®, diuretics	Abdominal lymphatic dysplasia	Alive; underwent partial surgical correction; waiting for definitive surgery
33	F	39+5	3,920	Uneventful	VD	At age10 day progressive RDS, chylous pleural effusion	IPPV, right chest drain, TPN, Octreotide 3 up to 5 mcg/kg/hour (25 days), thoracic duct ligature, pleurodesis, Caprilon®	Lymphatic dysplasia	Alive, good control of lymph effusion

GA=gestational age; BW=body weight; ws=weeks; CS=cesarean section; VD=vaginal delivery; RDS=respiratory distress syndrome; CLD=chronic lung disease

Point b). In our series, 29/33 patients were fed an MCT diet for varying lengths of time. We observed no side effects with the MCT diet. Patients were fed formulas that varied in MCT content (Pregestimil® 55%, Caprilon® 75%, Portagen® 87%, and Monogen® 90%). It is well known that the intestinal production of lymph exacerbates and worsens chylothorax and chylous ascites (23). Thus, fat provided by enteral feeding must be avoided and the recommended approach is to feed the patient by total parenteral nutrition alone. The use of MCT for enteral feeding during the re-feeding period, which usually follows a variably long period of chest drainage, mechanical ventilation, and TPN is now accepted. Conflicting data have been reported on the use of prolonged MCT diets in newborns. A high degree of gastrointestinal intolerance as well as necrotizing enterocolitis have both been affirmed and negated. No definitive data are available on the use and duration of the MCT diet and long-term growth or neurodevelopmental outcomes (23). In our experience, the reasons why some types of MCT formula were chosen over others are not altogether clear. We observed that availability of the formulas in the countries involved in our study varied. Personal preferences on the part of the physicians may also be one of the reasons. It is important to note that the MCT-contents in the various formulas differ considerably, thus leading to the conclusion that we need to come to an agreement regarding the duration and the dose of MCT. Fat-free human milk has been suggested for infants with chylothorax, and this may add immunologic benefits of human milk that other feedings cannot provide (24).

Point c). In our experience, 6 patients were treated with Octreotide. The indication for Octreotide treatment was presence of continuous and intractable visceral effusions despite drainage, or re-accumulation of fluid after drainage tubes were removed. All patients treated with Octreotide were severely ill, but on the other hand, other patients who

presented with a similar degree of severity were not treated with Octreotide. All treated patients benefitted from the therapy and showed a decrease in the production of chylous effusion. Although one patient (case 13) died of severe RDS due to pulmonary hypoplasia, she experienced a mild reduction of pleural effusion during Octreotide therapy. We observed only one side effect during treatment with Octreotide in a patient (case 28) who presented bile sludge and mild cholestasis that spontaneously recovered within one month. In our opinion, the cholestasis might also have been connected with a prolonged period of TPN. In general, from our experience and with discussion among participating centers, the reason(s) supporting the decision for treating these 5 patients is(are) not entirely clear. It is possible that physicians who had previously administered Octreotide therapy were less hesitant to use the drug. Octreotide is reportedly effective and in general safe. However, although our experience also seems to confirm that Octreotide is safe and effective in reducing visceral chylous effusions, the relative effect of supportive treatments, TPN, MCT diet, and Octreotide treatment in the control of chylous effusion needs to be evaluated in larger, prospective, clinical trails.

Octreotide is a somatostatin analog that decreases intestinal blood flow and inhibits lymph secretion through somatostatin receptors in the intestinal wall (25). The indication for Octreotide treatment is the presence of continuous and intractable chylous effusions despite drainage, or the reaccumulation of fluid after drainage tubes are removed (25). Somatostatin was first used in 1998 (26) to treat a 4 month old infant with postoperative chylothorax. Two series describing the use of Octreotide in post-cardiac surgery chylothorax were then published (25,27). A report on the use of Octreotide to treat congenital chylothorax in the newborn was first published in 2003 (28). Following this report, only few papers were published describing both positive and negative results (29-38). Octreotide treatment is generally well tolerated except for transient side effects such as bile sludge, hypothyroidism, and cholestasis (35). Conservative management and Octreotide infusion reportedly lead to good control of both chylous ascites and chylothorax even in the absence of valid abdominal drainage by possibly preventing excessive sufficient drainage from mesenteric varicose lymph vessels during the acute phase of chylous ascites and thus allowing adaptive changes of the mesenteric lymphatic system.

Point d). Pleurodesis with povidone-iodine, OK-432 (a lyophilized preparation of a low virulence group A Streptococcus pyogenes inactivated by heating with penicillin), fibrin glue, autologous blood, and percutaneous thoracic duct embolization were anecdotally reported to treat persistent chylothorax (34,35) primarily when other treatment modalities failed. In our experience, one patient (case 33) was treated early by pleurodesis, and a second patient (case 11) underwent pleurodesis at 2 years of age (*Table 1*). After the procedures, chylothorax never recurred.

CONCLUSION

Perinatal chylous visceral effusions are rare disorders. Agreement on treatment currently exists only in specific areas and only for specific aspects, and guidelines on this topic are currently under debate. In this study, we enrolled a large number of patients affected by perinatal visceral chylous effusion from all over the world. Our observations lead to the conclusion that intrauterine pleural-shunt, MCT diet, and Octreotide therapy are useful therapeutic options to treat congenital chylous effusions. We strongly believe that there is a need for international, prospective studies with adequate controls, and long-term follow-up. A suitable number of patients has to be collected on the basis of appropriate eligibility and recruitment

criteria in an effort to establish, and possibly confirm, the efficacy and effectiveness of diagnostic and therapeutic options, as described in this report, in the field of fetal and neonatal visceral chylous effusions.

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