Short- and long-term outcome after fetal therapy for thoracic abnormalities

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Voor Anneloes, Jet, Floor en Lotte

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PART I:

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Before the introduction of prenatal ultrasound, primary fetal lung anomalies such as congenital cystic adenomatoid malformation of the lung (CCAM), bronchopulmonary sequestration (BPS) and fetal pleural effusions (FPE) were mainly diagnosed after birth in symptomatic infants and children (1, 2).

The introduction of prenatal ultrasound enabled obstetricians to diagnose fetal lung anomalies before birth. Over the last decades the prenatal identification of these anomalies has increased, both due to the technical improvements of ultrasound equipment as well as the implementation of prenatal ultrasound screening programs. This has strongly contributed to an improved understanding of the underlying pathology and natural history of these lesions.

Various studies have since then showed that fetal lung lesions often tend to regress during the course of pregnancy and may therefore lead to a more favourable outcome than previously expected (3) In some cases, however, the space occupying effect of the lesion causes progressive cardiac failure leading to fetal hydrops. In these cases the risk of fetal demise is very high when left untreated (4-6) .

After the introduction of intrauterine fetal blood transfusion in the early 1960s (7), fetal therapy by direct in-utero intervention was developed for a number of fetal disorders including severe cases of CCAM, BPS and FPE. In the Netherlands, the Leiden University Medical Center (LUMC) is the national referral center for fetal therapy and the only hospital where direct in-utero interventions are performed.

The first intrauterine intervention in fetuses with primary lung lesions was prenatal thoracocentesis to drain the pleural effusion in a case of FPE (8). The use of TA shunts was first described about 30 years ago (9). and has since then led to a considerable improvement in the outcome of fetuses with FPE and other fetal lung anomalies.

Despite the major improvement, mortality and morbidity rates in fetuses and neonates with primary lung lesions remains considerable. Increased knowledge of the pathogenesis, optimal detection and management in the various types of congenital lung lesions may further help reduce the high rates of perinatal mortality and morbidity.

Fetal Pleural Effusion

FPE is a condition characterized by fluid collections in the fetal pleural spaces. In secondary FPE serous fluid fills the pleural space. Serous fluid effusion in secondary FPE can occur in fetuses with congenital infection, aneuploidy and congenital disorders, such as congenital heart disease or congenital diaphragmatic hernia.

In primary FPE, also called congenital chylothorax, lymphatic fluid fills up the pleural spaces. The exact cause of the development of pleural effusion in primary FPE is still unclear. Various theories have been postulated including leakage from the thoracic

duct, overproduction or impaired drainage of lymph fluid in the pleural cavity. Primary FPE is often found in association with genetic abnormalities such as trisomy 21, Turner syndrome, Noonan syndrome, and mucopolysaccharidoses. The incidence of primary FPE is approximately 1:10.000 pregnancies (10).

The outcome in fetuses with primary FPE may vary widely. In some cases spontaneous antenatal resolution has been described leading to a favourable outcome. In other cases, progression or persistence of pleural effusion may occur, leading to an increased intrathoracic pressure, impaired fetal swallowing and polyhydramnios. This can ultimately lead to reduction of venous return, causing decreased cardiac output and subsequently to fetal hydrops. In addition, prolonged antenatal compression of the lungs can lead to pulmonary hypoplasia.

In hydropic fetuses, antenatal removal of pleural effusion can lead to increased cardiac output and resolution of hydrops. Antenatal pleural effusion can be achieved by needle thoracocentesis or by TA shunts. Needle thoracocentesis is often a transient or temporary solution as pleural fluid usually re-accumulates. In contrast, TA shunting can permanently drain FPE and therefore allow for recovery of hydrops, unobstructed lung growth and prolongation of the pregnancy.

CCAM and BPS

Most prenatally detected lung lesions are CCAM, BPS or so called 'hybrid' lesions, containing features of both (11). CCAMs are histologically characterized by overgrowth of terminal bronchioles without corresponding alveoli. The arterial blood supply comes from the pulmonary circulation. BPS lesions are traditionally characterized by arterial blood supply from the systemic circulation. On histologic examination, BPS often show immature lung tissue. BPS can be positioned either intralobar of extralobar.

The incidence of CCAM and BPS is estimated between 1:25000 and 1:35000 pregnancies.

Traditionally CCAMs are described according to the pathologic classification by Stocker (12). More recently the classification based on ultrasound appearance was accepted for prenatal classification (13).

Most CCAM and BPS are detected at ultrasound screening around 20 weeks gestation. The great majority of these lesions do not grow and may even regress in size during the third trimester of pregnancy. Some lesions however continue to grow, leading to massive intrathoracic occupying lesions and causing fetal hydrops in the same manner as FPE.

Prenatal interventions can be used to alleviate the mass effect, allowing for increased cardiac output and regression of hydrops. In macrocystic lesions needle thoracocentesis and TA shunt placement can both be used. In microcystic lesions, management with open fetal surgery has been described. More recently maternal steroid treatment was

reported to lead to reduction in size of these microcystic lesions and even regression of hydrops in several cases.

Neonatal and long-term outcome in primary fetal lung lesions

Improved prenatal care strategies and management options for primary fetal lung lesions have led to a significant increase in perinatal survival. As a result of the decrease in perinatal mortality, attention is now gradually shifting towards short-term and long-term management and outcome in these infants. A few short–term cohort studies have been described in literature, but detailed reports are scarce and the interpretation of the results is often limited by the small sample size.

Reporting of long-term respiratory and neurodevelopmental outcome is also essential in evaluating the impact of survival after fetal therapy on the quality of lives of these children. However, long-term outcome studies are virtually non-existent. Long-term follow-up studies in children born after fetal therapy for primary lung lesions are difficult to perform and hampered by the small number of survivors.

The aim of this thesis is to describe the management and outcome in primary lung lesion, focusing on the neonatal and long-term outcome in these children.

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PART II:

FETAL THERAPY OPTIONS FOR PRIMARY LUNG LESIONS

Chapter 1

Single-needle laser treatment with drainage of hydrothorax in fetal bronchopulmonary sequestration with hydrops

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Ultrasound Obstet Gynecol 2009; 34:355-357

ABSTRACT

Bronchopulmonary sequestration (BPS) is sometimes associated with hydrothorax and hydrops in utero. In the absence of fetal hydrops, perinatal outcome is favourable and justifies expectant management. In the presence of fetal hydrops, perinatal outcome is reported to be extremely poor and intervention should be considered. Therapeutic options include open fetal surgery, minimally invasive coagulation of the blood supply or thoracoamniotic shunting.

We present the first case of fetal hydrops and a large hydrothorax due to BPS treated successfully with one ultrasound-guided thin needle insertion, through which both laser coagulation of the feeding artery and drainage of the hydrothorax were performed.

Following the procedure the hydrothorax and hydrops gradually disappeared and the BPS diminished in size. A healthy baby was delivered uneventfully at term. We describe the case and discuss the different therapeutic options.

Case report

A 35-year-old woman, gravida 2, para 0, was referred to our unit at 23 weeks' gestation for suspected congenital cystic adenomatoid malformation (CCAM). Ultrasound examination showed a hyperechogenic mass in the left side of the thorax, measuring 3.5 x 3.9 x 4.1 cm. An artery originating from the aorta just below the diaphragm and supplying the mass was identified with colour Doppler ultrasound (figure 1a). The lesion was thus assumed to be a BPS. Massive left-sided hydrothorax, cardiac deviation to the right, ascites and moderate skin edema were present. Polyhydramnios was present with a maximum vertical pocket of 13 cm. No other structural abnormalities were seen. Doppler investigations showed pulsatile umbilical venous flow and abnormal ductus venosus flow, interpreted as signs of cardiac decompensation. Karyotyping performed earlier in pregnancy was normal (46, XY).

Because of the presence of fetal hydrops and the concomitant poor prognosis the various management options were discussed with the parents, including expectant management, termination of pregnancy, referral to a centre in the United States for open fetal surgery and inserting a thoracoamniotic shunt with or without intrauterine laser coagulation of the feeding artery. The parents opted for the latter. We then discussed a new and thus experimental alternative, using the needle through which the laser fibre was passed to also drain both the fetal thorax and the polyhydramnios. We assumed that successful coagulation of the feeding artery with shrinkage of the lesion would also prevent recurrence of the hydrothorax. The parents consented to this approach.

The procedure was performed under local anesthesia and premedication with 50 mg indomethacin p.r. An 18-G needle was introduced under ultrasound guidance into the fetal thorax. The tip was placed 4-5 mm from the arterial vessel wall A 0.6 mm laser fiber was then inserted, its tip clearly visible just outside the needle tip, approaching the vessel wall (figure 1b). The Nd:YAG (neodymium:yttrium-aluminium-garnet) laser was fired 4 times for 5 to 10 sec, at 20 W for an overall total of 35s with a total energy delivered of 1310 kJ. The fetal heart rate and blood flow in the aorta remained normal during the procedure. Colour Doppler ultrasound imaging clearly showed absence of flow in the vessel (figure 1c).

Following cessation of blood flow in the artery, the laser fiber was removed and withdrawn to within the pleural effusion. Bright yellow fluid spurted from the needle under high pressure. With the aid of a syringe, a total of 40 ml was drained from the left side of the thorax. The needle was then pulled back to within the amniotic fluid, of which a total of approximately 400 ml was removed using a 50 ml syringe.

In the weeks following the procedure frequent ultrasound examinations continued to show absence of blood flow in the intrathoracic mass. Fetal hydrothorax reappeared in the first week following the procedure, but resolved completely thereafter over a

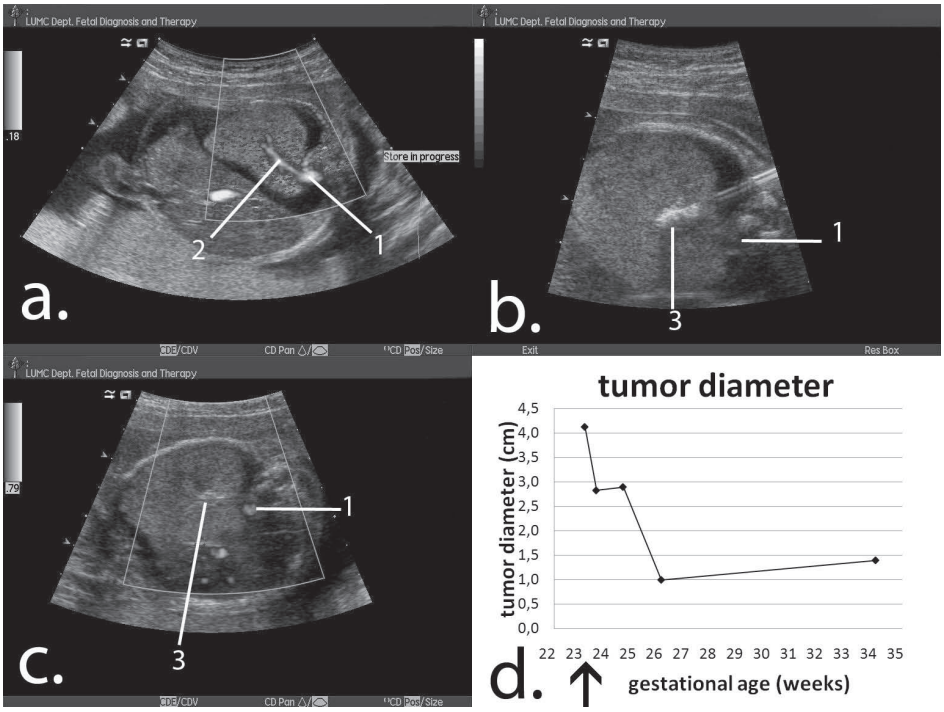

Figure 1. (a) Doppler ultrasound image showing a cross-section through the fetal thorax. A systemic artery (2) feeding the lesion and originating from the aorta (1) can be seen. (b) Gray-scale ultrasound image showing a cross-section through the fetal thorax during the laser procedure. (1) indicates the position of the aorta. The tip of the 18-G needle (3) containing the laser fiber can be seen at the site of the feeding vessel. (c) Doppler ultrasound image showing a cross-section through the fetal thorax after the procedure. Flow in the aorta (1) can be identified. No flow is seen at the position of the feeding vessel (3). (d) graph showing the largest tumor diameter before and after the laser procedure (arrow indicates timing of laser procedure)

period of 3 weeks. The mass's size and echodensity gradually decreased. At 34 weeks' gestation the lesion was hardly visible on ultrasound (figure 1d).

The remaining course of the pregnancy was uneventful. The patient delivered spontaneously at 41 weeks' gestation. An apparently healthy boy, weighing 3410 grams was born, with Apgar scores of 9 at 1 minute and 10 at 5 minutes. There were no respiratory symptoms or other complications postnatally. A computed tomography (CT) scan at the age of 4 months only showed small fibrotic lesions in the left basal thorax without arterial blood supply (figure 2). Because of the almost complete resolution of the lesion and the lack of respiratory symptoms postnatally, surgical resection of the lesion was not performed. At the time of writing the boy is alive and well at 20 months of age.

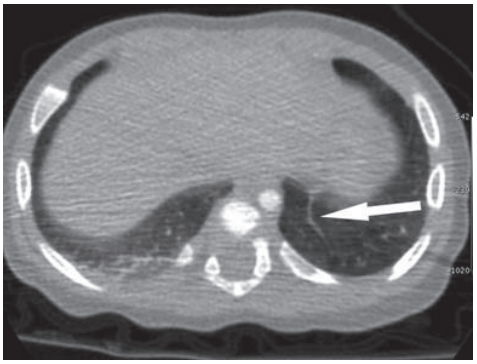

Figure 2. Computed tomographic scan of the child's thorax at years of age showing a small remnant of the original lesion (arrow).

DISCUSSION

Bronchopulmonary sequestration (BPS) is a rare congenital malformation of the lower respiratory tract, consisting of a non-functioning mass of lung tissue lacking normal communication with the tracheobroncheal tree. Appearance on fetal ultrasound mimics a congenital cystic adenomatoid malformation (CCAM) of the microcystic type. The diagnosis however can be made by identifying a separate systemic artery feeding the sequestration (1).

A large microcystic fetal lung tumor with hydrops is one of the few currently accepted indications for open fetal surgery, although this is offered in only a few centres (2, 3). For a large BPS, the presence of the systemic artery however, opens a less invasive treatment option: minimally invasive coagulation of the blood supply. This may result in shrinking of the tumor and recovery of the fetus. We describe the first case of a fetus with BPS complicated by hydrothorax and hydrops treated successfully with minimally invasive ultrasound-guided laser coagulation of the feeding artery in combination with needle-drainage of the hydrothorax and the hydramnios. The blood flow to the lung tumor was successfully arrested and hydrops reversed. Another successful case of laser treatment of a BPS combined with thoraco-amniotic shunting was done by the Toronto group (Greg Ryan, personal communication)

Successful laser coagulation of a fetal BPS was first described by our group in 2007 (4). The blood flow to the lung tumor was successfully arrested and hydrops reversed. In that case, no hydrothorax was present. The infant was born at term and is still alive and well at 4 years of age. Recently, Ruano et al reported another case of BPS treated similarly, using an even smaller diameter needle (5). However, blood flow in the abnormal vessel reappeared at 36 weeks' gestation and mass volume increased without reappearance of hydrops. The infant, born after caesarean section had no respiratory symptoms at birth, but required a thoracotomy and lobectomy for respiratory distress on day 15.

Successful arresting of blood flow in fetuses with BPS has also been described using injection of pure alcohol (6) and polidocanol, a sclerosing agent (7). In fetuses with BPS and severe unilateral hydrothorax, thoraco-amniotic shunting has been reported to result in survival, either as a single treatment (8, 9) or in combination with arresting the arterial blood flow (6). Insertion of a thoraco-amniotic shunt however requires the use of a significantly larger instrument. The most commonly used shunt, Rodeck's double pigtail shunt, requires a 3 mm introducer shaft. The technique we describe here for BPS with hydrops and a large unilateral hydrothorax only requires one insertion of an 18 G or even smaller diameter needle. This treatment is based on the assumption that cessation of blood flow in the feeding artery of a BPS results both in a reduction in size of the tumour as well as in decreased production of pleural fluid. Whether this is always the case is currently unknown, more experience with this method is needed. Prospective trials with sufficient power, testing the efficacy of various treatment modalities are unlikely to be feasible, given the rarity of the disease. Pooling of the experience by fetal treatment centres, e.g. with the use of web-based registries, and publication of all treatments - including failures - are options that may advance our knowledge and benefit our patients.

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Chapter 2

Prenatal interventions for fetal lung lesions

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ABSTRACT

The widespread availability of high resolution ultrasound equipment and almost universal routine anatomy scanning in all pregnant women in the developed world has lead to increased detection of abnormalities in the fetal thorax. Already in the 1980s, large pleural effusions and significant macrocystic lesions in the fetus were easily detected on ultrasound. However, smaller lung tumours were often missed. Nowadays, fetal medicine centres receive many referrals for evaluation of fetal lung lesions, of which the most common are congenital cystic adenomatoid malformation (CCAM) and bronchopulmonary sequestration (BPS). Almost invariably, both the parents and the referring physicians experience anxiety after detection of large lung masses in the fetus. However, the vast majority of the currently detected fetal lung lesions have an excellent prognosis without the need for prenatal intervention. In the small group of fetuses in which the prognosis is poor, almost exclusively those with concomitant fetal hydrops and cardiac failure, several options for fetal therapy exist, often with a more than 50% survival rate. Indications, techniques, complications and outcomes of these interventions will be described in this review.

INTRODUCTION

The increased use of obstetric ultrasound and advances in ultrasound technology have allowed an increase in the prenatal identification of fetal lung lesions.

Most prenatally detected lung lesions are congenital cystic adenomatoid malformations (CCAMs), bronchopulmonary sequestrations (BPS) or so called "hybrid" lesions, containing features of both (1).

Fetal lung lesions are rare and occur in 1 in 10.000 to 1 in 35.000 pregnancies (2, 3).

Most lesions have a favourable outcome without antenatal intervention, despite often impressive appearance at mid-gestation. Many lesions regress during pregnancy, some disappear completely. Conservative management with watchful waiting is commonly most appropriate. In some cases however, secondary physiologic derangements occur due to mass effect or hemodynamic changes. This can lead to progressive cardiac failure, hydrops and intrauterine demise. Prenatal intervention may be warranted to improve outcome.

This review focuses on possible prenatal interventions for CCAM and BPS, indications, techniques and results. For the also interesting debate on whether or not postnatal resection of asymptomatic lung tumours in the neonate or infant should be performed, we refer to a recent review by Bush (4). Diagnosis and treatment of isolated fetal pleural effusion also falls beyond the scope of this review.

Prenatal assessment and surveillance

Most fetal lung lesions are nowadays detected on routine ultrasound screening at 18-20 weeks' gestation. The most common appearances are a solid-appearing echogenic tumour or a tumour containing anechogenic macrocysts surrounded by echogenic soft tissue. Pleural effusion may or may not be present. Occasionally, such a tumour is located below the diaphragm. Fetal therapy has never been described in subdiaphragmatic lesions. Therefore they will not be addressed further in this review.

Differential diagnosis of fetal lung tumours includes CCAM, BPS, congenital high airway obstruction (CHAOS), bronchogenic cysts, congenital lobar emphysema, congenital diaphragmatic hernia and mediastinal tumours (5, 6). Once the lesion is detected, the location, volume, size and appearance (i.e. macrocystic or microcystic) should be evaluated. In the past, ultrasound appearance was often described similar to the pathology classification by Stocker, with Stocker type I lesions showing only large cysts (figure 1), type III showing only small cysts (<0.5mm, figure 2) and type II a mix of both (7). More recently, the group from Children's Hospital of Philadelphia proposed a more practical classification using only microcystic (solid appearance on fetal ultrasound) and macrocystic types (8). Colour Doppler (2D and 3D) should be used to look for systemic arterial blood supply to the lesion. CCAMs derive their blood supply from pulmonary

vessels. BPS can be diagnosed when a feeding systemic artery originating directly from the descending aorta can be identified (9), although this occasionally proves difficult before birth.

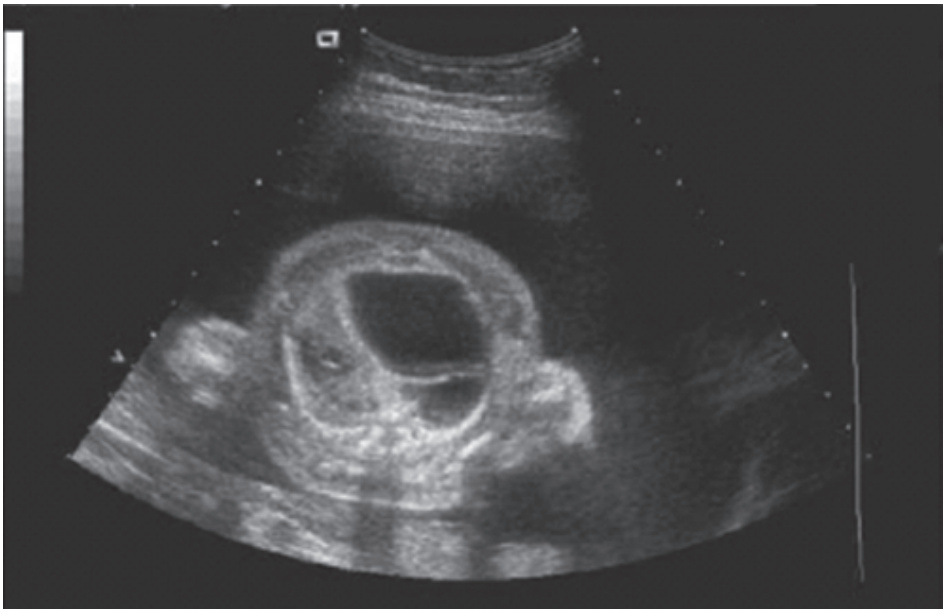

Figure 1. Transverse view of the fetal chest showing a macrocystic CCAM

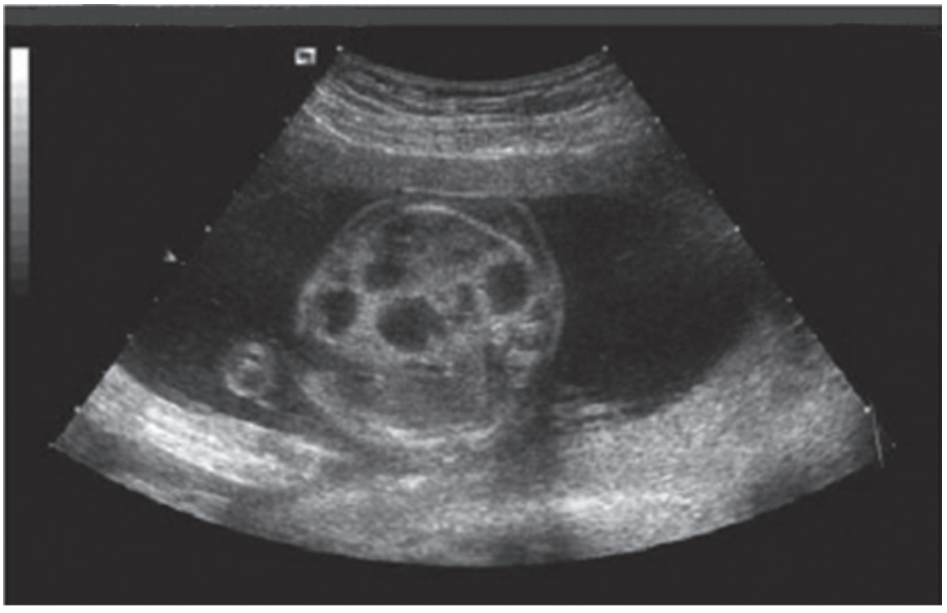

Figure 2. Transverse view of the fetal chest showing a microcystic CCAM

BPS occurs in two, anatomically distinct, subtypes (10). Intralobar sequestration (ILS) is located within the lung and covered by the visceral pleura of the lung. Extralobar sequestration (ELS) is located outside the normal lung and covered by its own visceral pleura. ELS can also be located below the diaphragm. Distinction between ILS and intrathoracic ELS is very difficult prenatally.

Fetal magnetic resonance imaging (MRI) provides more detailed imaging of the lesion and might therefore aid in a more definite diagnosis (11-14). Precise indications for additional MRI have not been described in the literature.

The amount of amniotic fluid as described by the amniotic fluid index (AFI) or deepest vertical pocket should be measured. Mass effect of the lesion can lead to esophageal compression causing impaired fetal swallowing (15, 16). This can lead to polyhydramnios. In case of polyhydramnios, cervical length should be measured and taken into consideration when assessing the necessity of intervention.

An essential part of the evaluation is a full and detailed anatomical survey of all fetal organs and structures, including echocardiography. Combined occurrence with e.g. diaphragmatic hernia is not uncommon. The occurrence of other anomalies in association with CCAM has been reported in 10 - 20% of cases (16, 17). In BPS associated anomalies have been reported to occur in up to 10% of cases of ILS and up to 50% of cases of ELS (18). Cardiac evaluation may be hampered by displacement of the heart. Aneuploidy has been reported occasionally in fetuses with lung lesions (3, 19), but it is not regularly associated with isolated fetal lung lesion (18, 20). We do suggest offering karyotyping, or in the near future possibly array Comparative Genomic Hybridization (array CGH), to all women carrying a fetus with anomalies on ultrasound. In fetuses with multiple congenital anomalies or chromosomal aberrations, the prognosis is often considerably worse. Fetal interventions are generally not offered in this group. In the remainder of this article, we will focus on the management of the fetus with isolated lung lesions.

Natural history

The natural history of fetal lung lesions is variable. Spontaneous regression is not uncommon. CCAM/BPS growth generally peaks at 26 to 28 weeks' gestation. In the weeks thereafter spontaneous regression is regularly described (21-23). As a consequence the lesions can be hard to find on ultrasound in the third trimester. Postnatal computed tomography (CT) or MRI can identify to what extent the lesion is still present (24, 25). The precise mechanism leading to spontaneous regression is not clear and may be due to outgrowing of the vascular supply of the CCAM or to spontaneous resolution of the underlying bronchial obstruction (23, 26).

Reported rates of spontaneous regression of CCAM vary from 15 to 65% (3, 20, 23, 24, 26-28). The largest published series describes sonographic evidence of regression in 76

of 154 CCAMs (49%) (24). Spontaneous regression of BPS is also regularly described, in up to 68% of cases (26).

On the other hand, secondary physiological derangements can occur, mostly due to the mass effect of the lesion in the fetal thorax. Oesophageal compression can interfere with fetal swallowing causing polyhydramnios (15, 16). The mass effect of the lesion can cause mediastinal shift and may, although surprisingly rare, restrict lung growth causing pulmonary hypoplasia (29, 30). The mass effect can also cause obstruction of the vena cava, impairment of venous return and cardiac compression ultimately leading to fetal hydrops.

Serial ultrasonographic assessment is important to follow the, often unpredictable, growth pattern of fetal lung lesions and to identify the early occurrence of fetal hydrops.

To aid in the prediction of occurrence of fetal hydrops, a prognostic tool using sonographic measurement of the CCAM volume was developed. The CCAM volume ratio (CVR) is obtained by dividing the CCAM volume (length x width x height x 0.52) by head circumference. A CVR greater than 1.6 is predictive of increased (75%) risk of the development of fetal hydrops (31).

Indications for prenatal intervention

An important conclusion from the existing literature is that the prognosis for a fetus with a lung lesion is generally favourable. A clear distinction needs to be made between lung lesions with and without fetal hydrops.

Cavoretto et al. reviewed the literature on the outcome of fetal lung lesions and found a survival of more than 95% in cases of CCAM without hydrops and cases of BPS without pleural effusion (24). When fetal hydrops does develop, however, mortality rates increase dramatically. Cavoretto *et al.* (24) reported death before or after birth in 95% of cases with CCAM and hydrops managed expectantly.

Knox et al. systematically reviewed the literature trying to determine the effect of in-utero drainage on perinatal survival in fetuses with congenital cystic lung lesions (32). No randomised studies were found. The available studies showed that treatment had a negative association with outcome overall (odds ratio (OR) for survival 0.56, 95% confidence interval (CI) 0.32-0.97). However in cases accompanied by fetal hydrops, a significantly higher chance of survival in treated cases was reported (OR 19.28 95% CI 3.67 -101.27).

Several case reports also suggest that in BPS with pleural effusion, outcome is very poor without prenatal treatment (33-37).

Fetuses that develop hydrops are therefore candidates for prenatal intervention.

Several centres advocate that hydropic fetuses at or after 32 weeks' gestation can best be delivered, with or without an ex-utero intrapartum treatment (EXIT) procedure, with reasonable chances of survival. This could imply that fetal interventions, with their

inherent risks of ruptured membranes, preterm birth and other complications may be restricted to hydropic fetuses below 32 weeks' gestation. However, a severely hydropic neonate with a large lung tumour born at 33 or 34 weeks can be very hard to resuscitate, and urgent lobectomy in such a baby is a high-risk procedure. In addition, although (extracorporeal membrane oxygenation (ECMO) certainly can be a life-saving technique, there are many drawbacks and complications. Fetal therapy, with the outlook for the fetus to remain in utero on placental support while recovering from hydrops in our view is preferable over preterm birth of a very sick child. Therefore, we and others believe that fetal interventions in potentially treatable fetal hydrops, due to lung lesions or in fact any other treatable condition, should be seriously considered up to 37 weeks' gestation (38). Successful intervention and postponing of delivery should lead to reduction of hydrops and increasing maturation of the lungs and other organs, making postnatal surgery much less risky. In addition, the possible complications of minimally invasive interventions such as rupture of membranes lose much of their importance after 32 weeks' gestation.

Prenatal interventions

Prenatal interventions for fetal lung lesions aim to alleviate the mass effect by decompression or resection of the lesion. A number of surgical and non-surgical options have been reported.

In macrocystic lesions decompression can be attempted by single needle thoracocentesis or permanent drainage via ultrasound guided thoraco-amniotic shunt placement (32).

In microcystic lesions, cysts are too small for drainage. In these cases open fetal surgery has been performed. When a systemic feeding vessel is found, percutaneous laser coagulation or injection of a sclerosing agent can be successful. Recently, maternal betamethasone treatment, often used to promote lung maturity, was suggested to have beneficial effects on large CCAMs. We will evaluate the literature on these treatment modalities in more detail.

Prenatal steroid therapy

Fetuses with microcystic CCAM are not amenable for thoracocentesis and cyst aspiration or thoraco-amniotic shunting. Open fetal surgery with lobectomy seemed to be the only available option. Resolution of a large CCAM after steroid therapy given for lung maturation was first described by Higby *et al.* in 1998 (39). In 2003, Tsao *et al.* reported on 3 fetuses with large, solid fetal lung lesions showing unexpected resolution of hydrops shortly after injection of the mother with betamethasone to promote lung maturity for expected preterm birth (40). They postulated that steroids could have a beneficial effect on large CCAMs. Since then, several others have indeed observed the

same effect, after giving the standard dose of 2 times 12 mg betamethasone, 24 hours apart.

Peranteau et al reported on a series of 11 patients, with microcystic CCAM and fetal hydrops and/or CVR > 1.4 treated with maternal betamethasone therapy (41). Resolution of hydrops was seen in 4 of 5 patients with fetal hydrops. The non-responding fetus was treated by fetal surgery. All patients survived.

Later series showed a more variable response on maternal betamethasone treatment. Morris et al treated 15 high risk fetuses (macro- and microcystic CCAM with fetal hydrops and / or CVR >1.8) (42). They found resolution of hydrops in only 54% of cases and a survival rate of 53%.

Curran et al. treated 13 fetuses with predominantly microcystic CCAM and hydrops and/or CVR>1.6 (43). They found resolution of hydrops in 78% of what they described as high-risk cases, with a survival rate of 85%. Their group, from University of California, San Francisco, who also published the first three cases, plans to find more evidence for the quite promising effects of steroids by a randomised controlled trial (clinicaltrials.gov NCT00670956) In the mean time, current evidence suggests that in large CCAMs with hydrops, a course of steroids appears to be a reasonable first line therapy, also because of the virtual absence of maternal side-effects. A slight concern remains due to a case report from Hong Kong, of a fetus with a large CCAM and hydrops, that resolved after steroids followed by sudden and unexplained intrauterine demise of the fetus at 34 weeks' gestation (44). Whether steroids should also be used in CCAMs without hydrops is more questionable, since the prognosis without intervention is generally good and spontaneous regression often occurs.

Thoracocentesis

Thoracocentesis with aspiration of fluid can be used to reduce the size of dominant cysts in macrocystic CCAM or to remove pleural effusions (PE) occurring from BPS or hybrid lesions. This mode of treatment can therefore be used to allow for lung expansion and/or resolution of hydrops (45). After single thoracocentesis the fluid usually reaccumulates in the macrocyst or pleural cavity over a period of days to weeks. Serial aspirations have been described resulting in resolution of hydrops and survival of the fetus (46). Single thoracocentesis can be used to evaluate the amount of shrinkage of CCAM or resolution of PE, followed by thoracoamniotic shunting if hydrops reappears.

In total thirteen hydropic fetuses with macrocystic CCAM only treated by single or multiple thoracocenteses are described in the literature (20, 31, 46-52).

A minimum of one and an maximum of six serial aspirations per case were reported. Median gestational age of treatment was 27 weeks where mentioned. All fetuses were live born. Neonatal survival at discharge was 9/13 (69%).

Table 1. Outcome of 68 fetuses with CCAM treated by thoraco-amniotic shunt placement. Publications describing more than one case are shown separately. Publications describing only one single case are combined, this includes cases from the following publications: (Asabe *et al.*, 2005; Bunduki *et al.*, 2000; Chow *et al.*, 2007; Clark *et al.*, 1987; Golaszewski *et al.*, 1998; Gornall *et al.*, 2003; Isnard *et al.*, 2007; Laberge *et al.*, 2001; Miller *et al.*, 1996; Ruano *et al.*, 2005; Ruano *et al.*, 2008; Ryo *et al.*, 1997; Sugiyama *et al.*, 1999; Viggiano *et al.*, 2006; Vu *et al.*, 2007)

	Number of cases		Outcome					
			hydropic cases			non-hydropic cases		
Reference	hydropic	non-hydropic	fetal death	neonatal death	survival	fetal death	neonatal death	survival
Bernaschek *et al.*, 1994	2	2	-	1 (50%)	1 (50%)	-	-	2 (100%)
Thorpe-Beeston and Nicolaides, 1994	0	5	-	-	-	-	-	5 (100%)
Dommergues *et al.*, 1997	5	3	-	2 (40%)	3 (60%)	-	2 (67.7%)	1 (33.3%)
Adzick *et al.*, 1998	3	3	1 (33.3%)	-	2 (67.7%)	-	-	3 (100%)
Crombleholme *et al.*, 2002	6	0	-	-	6 (100%)	-	-	-
Adzick *et al.*, 2003	3	0	1 (33.4%)	-	2 (67.7%)	-	-	-
Morikawa *et al.*, 2003	1	1	-	-	1 (100%)	-	-	1 (100%)
Wilson *et al.*, 2004	3	1	-	1 (33.3%)	2 (67.7%)	-	1 (100%)	-
Illanes *et al.*, 2005	2	0	1 (50%)	1 (50%)	0 (0%)	-	-	-
Ierullo *et al.*, 2005	1	1	-	-	1 (100%)	-	-	1 (100%)
Cavoretto *et al.*, 2008	5	6	1 (20%)	-	4 (80%)	-	-	6 (100%)
Combined single cases	13	2	1 (7,7%)	4 (30.8)%)	8 (61.5%)	-	-	2 (100%)
Total (n=68)	44	24	5/44 (11.4%)	9/44 (20.5%)	30/44 (68.2%)	0	3/24 (12.5%)	21/24 (87.5%)

Thoraco-amniotic shunting

Drainage of fetal fluid-filled spaces using a drain towards the amniotic cavity was first described in the 1980s for fetal bladder drainage. In 1986, Seeds and Bowes described this procedure in the treatment of fetal hydrothorax (53). Many fetal therapy centres worldwide still use this technique, insertion through a 2-3 mm diameter needle of a double pigtail catheter under ultrasound guidance, for these two indications. In a recent review article, techniques and complications were described in detail (38). Figure 3 shows a neonate with a thoraco-amniotic shunt still in place. Insertion of such a catheter in a large cyst of a CCAM has been successful too, first reported by Nicolaides et al. in 1987 (54).

Thereafter several case reports and small series describe the results of this technique in hydropic and non-hydropic fetuses with CCAM or BPS.

Thoraco-amniotic shunting with the aim of decompressing a large cyst in macrocystic CCAM has been described in 68 cases in the literature. This includes 44 hydropic fetuses. In addition 24 non-hydropic fetuses with a large cyst causing major mediastinal shift were described. Outcome is summarized in Table 1.

Of the hydropic foetuses 89% (39/44) were liveborn and 9 infants died in the neonatal period. Overall perinatal survival in this group was thus 68% (30/44)

Of the non-hydropic fetuses (n=24) all were liveborn. Three infants died in the neonatal period due to pulmonary hypoplasia. Overall survival was therefore 87.5%.

Thoraco-amniotic shunting can also be used to drain pleural effusions in BPS with or without prior thoracocentesis. Adzick et al. describe two hydropic fetuses with BPS treated by thoraco-amniotic shunt placement. In both hydrops resolved after treatment and both survived after birth, all requiring ventilatory support and surgical excision of the lesion (21). Lopoo et al. describe two hydropic fetuses with BPS treated by thoraco-amniotic shunt placement. In both hydrops resolved and both did well after birth (55). Hayashi et al. describe three hydropic fetuses with BPS treated by thoraco-amniotic shunt placement (56). All received thoracocentesis first, but the hydrothorax reaccumulated necessitating further treatment. In all three cases hydrops resolved and all survived after birth, requiring ventilatory support and surgical excision of the lesion.

In addition seven single cases of hydropic fetuses with BPS treated by thoracoamniotic shunt placement have been described (57-63). In one case pleural effusion reaccumulated probably due to shunt occlusion (63). In all other cases hydrops resolved and fetuses survived after birth.

Laser and sclerosing agents in the treatment of CCAM and BPS

Attempts at percutaneous ablation of a microcystic CCAM in a hydropic fetus using Nd:YAG laser have been described four times in the literature (29, 64-66). In all cases a Nd:YAG laser was passed through the lumen of an 18G needle after which the tumour

itself was photocoagulated. In one case (66) hydrops resolved and the fetus survived needing postnatal respiratory support and surgical resection the lesion. In one case (64) the fetus died prenatally. In one case (29) the fetus died four days after birth. In the last case resolution of hydrops was described but no further outcome was reported (65).

The group of Quintero reported on three cases of CCAM complicated by fetal hydrops and treated with percutaneous insertion of a sclerosing agent directly into the CCAM (67). In all cases hydrops resolved and all fetuses were born alive. One neonate died after ten days because of nosocomial sepsis.

Interruption of flow in the systemic feeding vessel of a BPS has been described as a treatment option in hydropic fetuses with BPS. Successful ultrasound guided laser coagulation of the feeding artery of BPS using Nd:YAG laser through a 18G-needle was described by our group in 2007 and 2009 (68, 69). Figures 4-7 show images of the second case. In both cases hydrops resolved after treatment and the fetuses survived uneventfully. In the last case, only one puncture with the 18 G needle was used first to insert the laser fiber for coagulation of the vessel, then for drainage of the unilateral hydrothorax and lastly for drainaige of the polyhydramnios.

One technically successful case was performed by Nicolaides, unfortunately ending in neonatal demise (29). Ryan et al. used the same laser technique combined with placement of a thoraco-amniotic shunt in a hydropic fetus with BPS, with success (70). This combined procedure makes it difficult to assess which of the two interventions contributes most to the success. Mass size reduced in both cases.

Ruano et al. described a case in which coagulation of the vessel was incomplete after laser therapy (71). The mass's volume increased without reappearance of hydrops. The child needed ventilatory support in the neonatal period and thoracotomy and lobectomy were performed.

Rammos et al. described resolution of hydrops in two hydropic fetuses with BPS treated with laser (72). In both cases the feeding vessel remained open after laser treatment. One fetus needed thoracoamniotic shunting for residual hydrothorax. The other child needed a thorax shunt after birth. Both lesions were resected after birth, in one child respiratory distress was noted after birth.

Interruption of blood flow in the feeding vessel of BPS has also been described using injections of pure alcohol in one case (73), polidocanol in three cases (74) and N-butyl-2-cyanoacrylate in one case (75). In all cases the agent was injected directly into the feeding vessel of the BPS. Nicolini combined this treatment with placement of a thoraco-amniotic shunt. Hydrops resolved in all cases after treatment. The pregnancies continued uneventfully and the children were born asymptomatic. One child, treated with polidocanol sclerotherapy died in the neonatal period from operative complications after resection of the remaining lesion

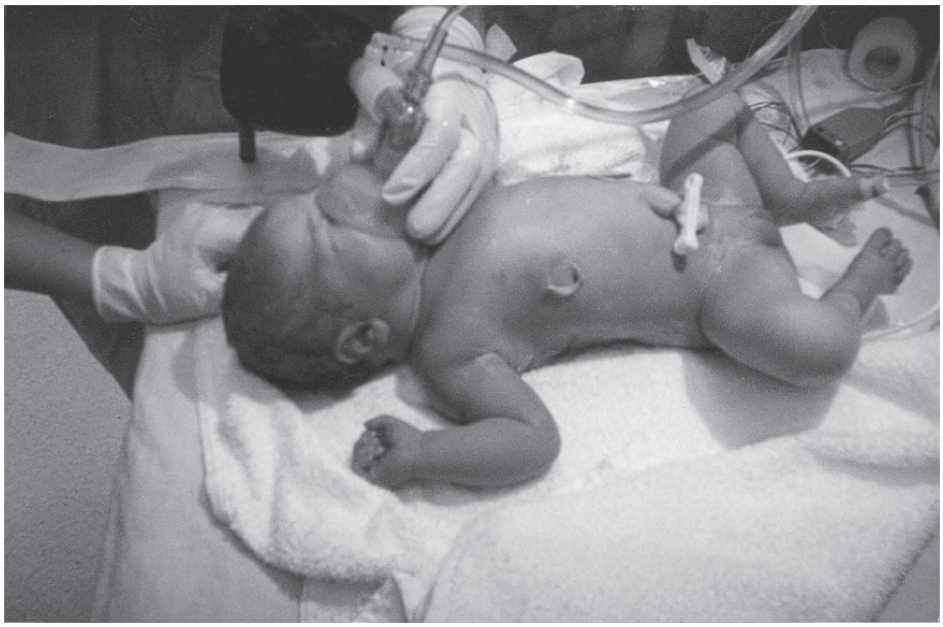

Figure 3. Neonate with thoraco-amniotic shunt still in place

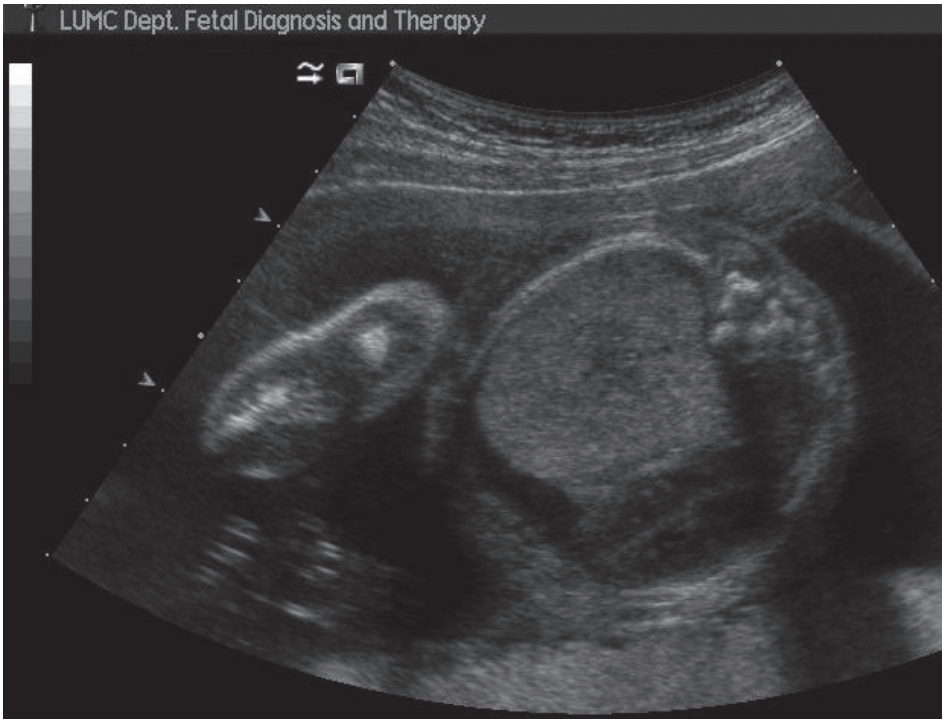

Figure 4. Ultrasound image of a large lung lesion with pleural effusion

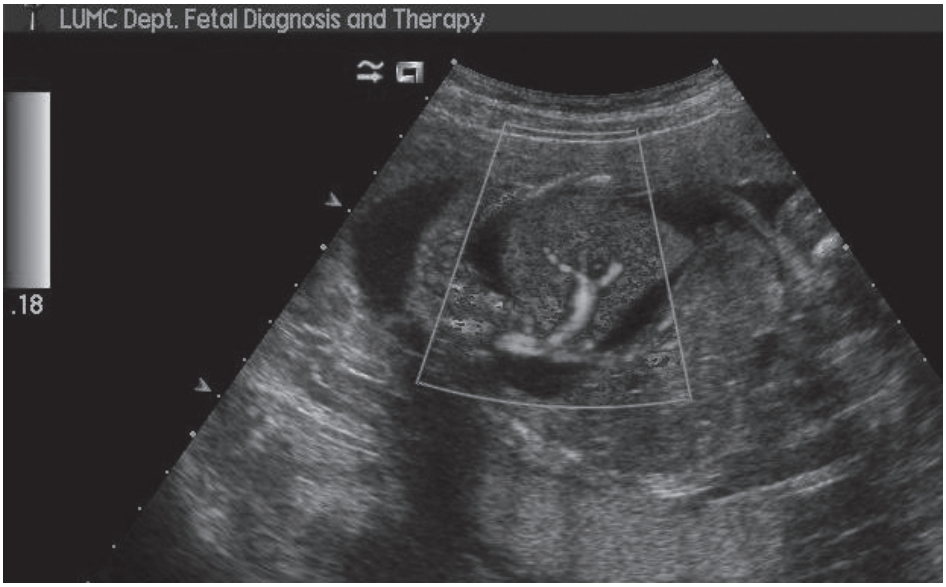

Figure 5. Color Doppler showing systemic artery, thus diagnosis of pulmonary sequestration

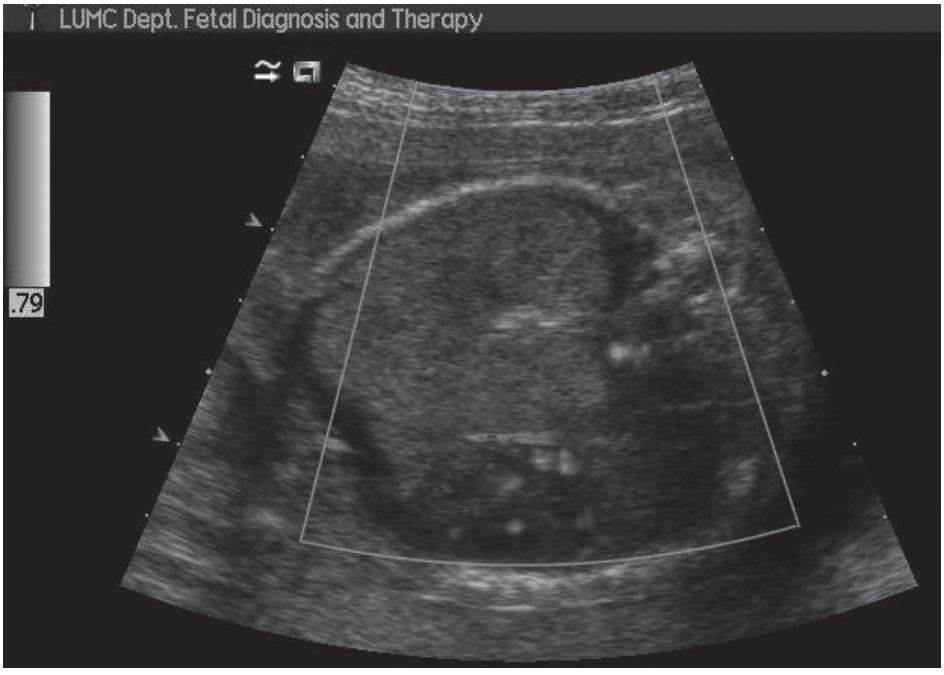

Figure 6. Color Doppler after laser therapy showing absence of flow to the lung lesion

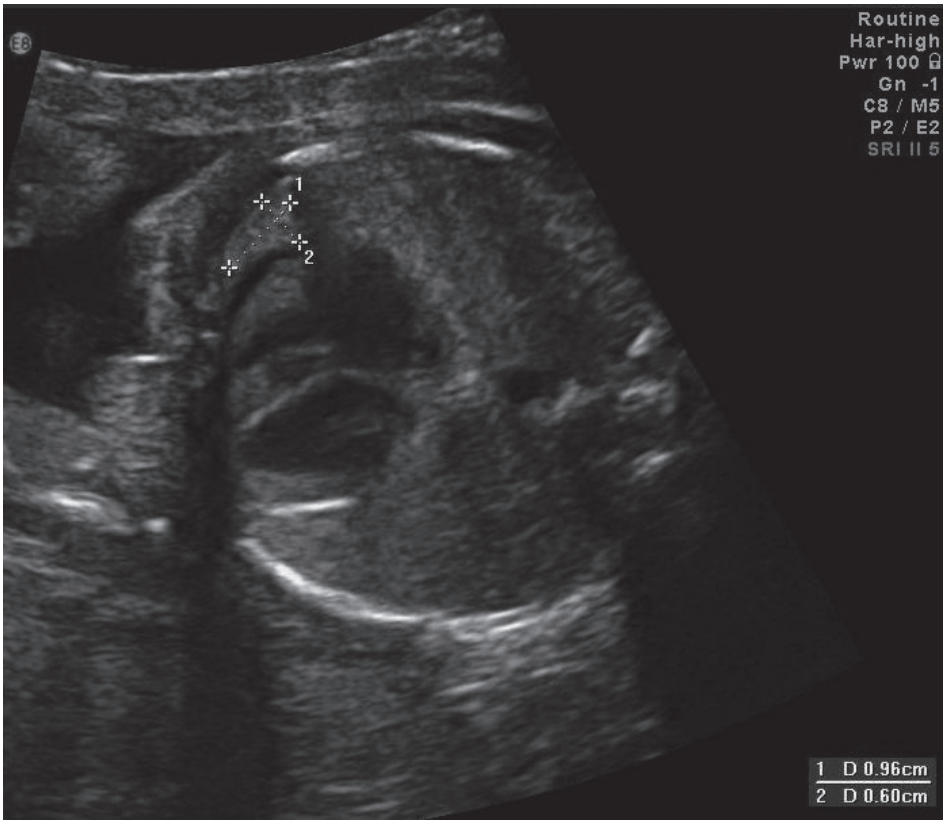

Figure 7. Ultrasound image 10 weeks after laser showing tiny remaining lesion

Open fetal surgery

Open surgical resection of fetal lung lesions has been performed in a small number of fetal treatment centers, mainly in the USA. The largest series to date has been published by the group from Children's Hospital of Philadelphia (76).

Adzick describes outcome after fetal lobectomy for massive multicystic or predominantly solid CCAMs in 24 cases between 21 and 31 weeks' gestation. Thirteen (54%) healthy survivors were reported with uneventful follow-up at 1 to 16 years of age. Resolution of hydrops was seen within 1 to 2 weeks in these cases.

Of the 11 nonsurvivors seven died intraoperatively due to cardiovascular collapse during surgery, two became bradycardic and died within the first day after surgery and three died of maternal problems (mirror syndrome, postoperative chorioamnionitis and preterm contractions).

Recently Cass et. al reported on three other hydropic fetuses with large fetal lung lesions (2 CCAMs, 1 BPS) that underwent fetal surgery (77). In two fetuses hydrops resolved and children were liveborn. One child had no problems after birth and is growing

and developing well. One infant suffered from significant tracheobronchomalacia and respiratory insufficiency requiring tracheostomy and ventilation. The third fetus died intraoperatively, probably because the disease process had developed too far at the time of intervention.

SUMMARY

We conclude that in the majority of pregnancies where the fetus is diagnosed with an isolated lung lesion, the parents can be reassured that the outcome is likely favourable. In the absence of hydrops, even large lesions can be treated expectantly, obviously with frequent (weekly) monitoring and selection of an appropriate site for delivery. In CCAMs with hydrops, a course of steroids may be beneficial when gestational age is under 32 weeks. Evidence of effect, however, is limited. Minimally invasive fetal interventions such as thoracoamniotic shunting of large cysts, or occlusion of the feeding artery in pulmonary sequestrations often lead to good outcome. In utero resection of large life-threatening solid or microcystic fetal lung tumours, in case of failure of the steroid treatment, is probably the currently best application or open fetal surgery in experienced centres.

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PART III:

NEONATAL AND LONG-TERM OUTCOME AFTER FETAL THERAPY FOR PRIMARY FETAL LUNG LESIONS

Chapter 3

Neonatal outcome after prenatal interventions for congenital lung lesions

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ABSTRACT

Congenital lung lesions, mostly congenital cystic adenomatoid malformations (CCAMs) and bronchopulmonary sequestrations (BPSs), are uncommon disorders. Prenatal intervention in severely affected (hydropic) fetuses has drastically improved perinatal survival. Not much is known, however, on the short-term and long-term respiratory and neurodevelopmental outcome. Several small case series have been reported and suggest an increased incidence of neonatal morbidity, mainly associated with prematurity and respiratory failure at birth. Overall, neonatal mortality and morbidity after prenatal interventions for CCAM seems to be worse than for BPS. This review focuses on the neonatal outcome after prenatal intervention for congenital lung lesions and summarizes the results reported in the literature.

1. INTRODUCTION

Congenital lung lesions are estimated to occur in 1 in 10,000 to 1 in 35,000 pregnancies [1] and can be divided in two major groups: congenital cystic adenomatoid malformations (CCAMs) and bronchopulmonary sequestrations (BPSs). CCAMs are characterized by hamartomous growth of terminal respiratory structures [2]. CCAMs derive their blood supply form the pulmonary vasculature. On prenatal ultrasound they usually present as a cystic or solid intrapulmonary mass, usually confined to one lobe. They are sonographically classified according to the size of the cysts as macrocystic or microcystic [3]. BPSs are masses of non-functioning lung tissue wich have a blood supply originating from the systemic vasculature. They can be divided into intralobar and extralobar forms where intralobar BPSs are enveloped in the pleura of the lung and extralobar BPSs have a visceral pleura of their own. On prenatal ultrasound they are identified by color flow Doppler detection of the feeding artery from the aorta to the lung lesion. So called "hybrid lesions" containing features of CCAM with a systemic vascular supply have also been described [4]. Most congenital lung lesions have a favorable outcome without antenatal intervention and regress during pregnancy, some disappear completely [5]. Conservative management with watchful waiting in these cases is commonly most appropriate. In a minority of cases however, secondary physiologic derangements occur due to mass effect or hemodynamic changes, leading to progressive cardiac failure and the development of fetal hydrops. In these cases prenatal intervention may be warranted to prevent further deterioration and intrauterine demise [6]. Several prenatal treatment options have been described, including single or repeated thoracocentesis, placement of a thoraco-amniotic shunt, laser coagulation, injection of sclerosing agents and open fetal surgery [7]. The optimal management is not clear as none of these treatments has been evaluated in a controlled study design.

The short-term and long-term outcome in survivors with congenital lung lesions treated with fetal interventions is not well known. Premature delivery and respiratory failure are not uncommon in live-born neonates after prenatal intervention. However, most case series focus on prenatal survival and describe associated neonatal morbidity only summarily. No well-designed studies have yet been published on the long-term neurodevelopmental outcome to determine the incidence of psychomotor developmental delay in survivors.

The aim of this review is to investigate and summarise the associated neonatal morbidity and mortality after prenatal interventions for CCAM and BPS.

Methods of the Review

We performed a systematic literature search to retrieve all articles for this review. Relevant articles were identified using electronic bibliographic databases: PubMed, Embase

and Web of Science, using the following MESH terms: congenital cystic adenomatoid malformation, bronchopulmonary sequestration, fetal therapies. The computer aided searches were limited to English language articles and included the period from 1985 to May 2011. All reference lists of primary articles and reviews were examined to search for additional references. Then, a manual search of identified articles was conducted. All articles (including case reports) mentioning the perinatal outcome after prenatal intervention were included in this review, even if the neonatal outcome was not, or only summarily reported. Incidence of neonatal mortality and morbidity was calculated based on available data. We excluded evident duplicate cases and cases reported only as abstracts.

Bronchopulmonary sequestration (BPS)

In fetuses with BPS without concomitant pleural effusion or development of hydrops, perinatal outcome has generally been reported to be favourable. Cavoretto et al. reviewed the literature on the outcome of fetal lung lesions and found a perinatal survival of more than 95% in cases of BPS without pleural effusion [6]. In contrast, when pleural effusion or fetal hydrops develops, outcome is reported to be very poor without prenatal treatment [8, 9]. However, perinatal outcome data in these cases is based on small case series and a few case reports only.

Several modes of prenatal treatment of BPS have been described in fetuses with pleural effusion or hydrops [7]. Treatment can be aimed at decompressing the pleural effusion by single or repeated thoracocentesis [10, 11] or placement of a thoraco-amniotic shunt [10, 12]. Another aim of the prenatal intervention can be arresting further growth of the lesion by ultrasound guided laser ablation of the feeding artery [13] or injection of a sclerosing agent in the feeding artery [14].

Table 1 shows details of 49 liveborn cases with BPS and pleural effusion that were treated with single or repeated thoracocentesis (n=6) [10, 11, 15-18], thoraco-amniotic shunts (n=14) [10-12, 19-25], laser coagulation (n=15) [6, 13, 26-29] or injection of a sclerosing agent (n=4) [14, 30]. Prenatal survival of published cases was 100%. Mean gestational age at intervention was 27.4 weeks (19-34 weeks) and at birth 35.7 weeks (29-41 weeks). The rate of neonatal survival was 92% (34/37). Most neonates (56%, 14/25) had respiratory failure at birth and required mechanical ventilation. Postnatal resection of the lesion was performed in 74% (25/34) of cases.

Description of neonatal morbidity for the individual cases was sporadic and incomplete, mainly focusing on respiratory problems in the first week after birth. In 13 of 49 cases (27%) the postnatal course was not described at all. No formal neurodevelopmental long-term follow up data have been published for any of the cases.

Congenital Cystic Adenomatoid Malformation (CCAM)

In cases of prenatally detected CCAM without fetal hydrops survival without interventions has been reported to be excellent [6, 31, 32]. When fetal hydrops does develop, however, mortality rates increase dramatically [1, 6]. Cavoretto *et al.* reported death before or after birth in 95% of cases with CCAM and hydrops managed expectantly [6]. Several modes of treatment have been described for fetuses with CCAM [7]. Both non-hydropic and hydropic fetuses have been treated prenatally. In macrocystic lesions, cyst decompression can be attempted by single needle thoracocentesis [33, 34] or permanent drainage via ultrasound guided thoraco-amniotic shunt placement [35, 36]. In microcystic lesions, cysts are too small for drainage. In these cases open fetal surgery has been performed [10]. Injection of sclerosing agents in the lesion [37] , ultrasound guided laser ablation of the lesion [38] or its feeding vessels [6], and radiofrequent laser ablation [39] have also been described in microcystic CCAM. Next to these invasive management options, in recent years prenatal corticosteroid administration to the mother has been shown to be effective in reducing CCAM size and reversing fetal hydrops in mainly microcystic CCAM sometimes [40-42]. In large CCAMs with hydrops maternal corticosteroid therapy therefore seems to be a reasonable first line therapy before more invasive interventions are considered.

Table 2 shows results of 32 liveborn CCAM cases without hydrops that were treated antenatally. Prenatal intervention consisted of single or repeated thoracocentesis of the dominant cyst of macrocystic CCAM in 5 cases [3, 34, 43-45] or thoraco-amniotic shunting in 27 cases [6, 10, 35, 36, 46-54]. Prenatal survival of published cases was 100%. Mean gestational age at intervention was 27.2 weeks (range 21-35 weeks) and at birth 37.0 weeks (28-40 weeks). Data on postnatal outcome were not available for all cases. The rate of neonatal survival after live birth was 87% (27/31). The reported rate of respiratory failure at birth and need for mechanical ventilation was 42% (8/19). Postnatal resection of the lesion was reported in 93% (25/27) of cases. Description of neonatal morbidity was found in 19 of 32 cases (59%). No formal neurodevelopmental long-term follow up data have been reported for any of the cases.

The largest group of congenital lung lesions treated with prenatal intervention consists of hydropic fetuses with CCAM. Treatment modalities used in macrocystic CCAM were thoracocentesis (n=13) [18, 33, 49, 55-60] or thoraco-amniotic shunting (n=43) [1, 6, 10, 36, 39, 42, 47, 50-52, 57-67] (see Tables 3 and 4). In microcystic CCAM, reported treatment interventions were ultrasound guided laser coagulation or sclerosing agent injection (n=9) [6, 37, 38, 68, 69] and resection through open fetal surgery (n=26) [10, 59, 70, 71] (see Tables 5 and 6). Prenatal survival of published cases was 80% (73/91). Demise occurred in 42% (11/26) of fetuses after open fetal surgery, 88% (38/43) of cases after thoracoamniotic shunting and 22% (2/9) of cases after laser therapy or injection of a sclerosing agent. Prenatal survival of published cases after single or serial thoracocentesis was 100%.

Table 1. Outcome of liveborn children after fetal intervention for bronchopulmonary sequestration with pleural effusion.

Reference	Intervention	GA at intervention (weeks)	GA at delivery (weeks)	Postnatal survival	Respiratory failure at birth	Neonatal morbidity	Postnatal surgery
Hernanz-Schulman 1991 [8]	thoracocentesis, single	NA	31	yes	yes	thoracic drain	yes
Jones 1992 [12]	thoracocentesis, single	24	29	no	yes	death day 1 due to hydrops	
Adzick 1998 [7]	thoracocentesis, weekly	27	33-35	yes	yes	mechanical ventilation	yes
Anandakumar 1999 [13]	thoracocentesis and iv furosemide and digoxin	28	32	yes	no	digoxin and furosemide iv for 2 weeks	planned
Morville 2003 [14]	thoracocentesis, single	27	32	yes	no	thoracic drain	NA
Pumberger 2003 [15]	thoracocenteses, repeated	NA	NA	yes	yes	HFOv, thoracic drain, surfactant, BPD	yes
Weiner 1986 [16]	thoracoamniotic shunt after thoracocentesis	24	29	no	yes	death due to pulmonary hypoplasia	yes
Slotnick 1990 [17]	thoracoamniotic shunt	33	33	yes	yes	1 day mechanical ventilation, thoracic drain	yes
Hernanz-Schulman 1991 [8]	thoracoamniotic shunt	27	36	yes	no	none	yes
Adzick 1998 [7]	thoracoamniotic shunt	29	33-35	yes	yes	mechanical ventilation	yes
Adzick 1998 [7]	thoracoamniotic shunt	30	33-35	yes	yes	mechanical ventilation	yes
Becmeur 1998 [18]	thoracoamniotic shunt	30	38	yes	no	none	yes
Lopoo 1999 [19]	thoracoamniotic shunt	30	33	yes	no	did well postnatally	no
Lopoo 1999 [19]	thoracoamniotic shunt after thoracocentesis	23	33	NA	no	NA	NA
Salomon 2003 [20]	thoracoamniotic shunt	34	36	yes	yes	4 days mechanical ventilation, single drainage pleural effusion	no
Picone 2004 [21]	thoracoamniotic shunt	19-36	28-40	yes	NA	NA	NA

Table 1. Outcome of liveborn children after fetal intervention for bronchopulmonary sequestration with pleural effusion. (continued)

Reference	Intervention	GA at intervention (weeks)	GA at delivery (weeks)	Postnatal survival	Respiratory failure at birth	Neonatal morbidity	Postnatal surgery
Hayashi 2006 [9]	thoracoamniotic shunt after thoracocentesis	30	35	yes	yes	HFOv, thoracic drain	yes
Hayashi 2006 [9]	thoracoamniotic shunt after thoracocentesis	28	33	yes	yes	HFOv, thoracic drain	yes
Hayashi 2006 [9]	thoracoamniotic shunt after thoracocentesis	30	35	yes	yes	nCPAP, thoracic drain	yes
Odaka 2006 [22]	thoracoamniotic shunt	28	37	yes	yes	mechanical ventilation, thoracic drain	yes
Ryan 2003 [23]	laser coagulation feeding vessel	23	NA *				
Ryan 2003 [23]	laser coagulation + thoraco-amntico shunt	19	39	yes	no	none	yes
Oepkes 2007 [10]	laser coagulation feeding vessel	23	39	yes	no	none	no
Ruano 2007 [24]	laser coagulation feeding vessel	29	38	yes	yes	progressive pulmonary hypertension requiring mechanical ventilation	yes
Cavoretto 2008 [3]	laser coagulation feeding vessel	31	38	yes	NA	NA	yes
Cavoretto 2008 [3]	laser coagulation feeding vessel	30	38	yes	NA	NA	yes
Cavoretto 2008 [3]	laser coagulation feeding vessel	32	34	yes	NA	NA	no
Cavoretto 2008 [3]	laser coagulation feeding vessel	27	41	yes	NA	NA	no
Cavoretto 2008 [3]	laser coagulation feeding vessel	24	40	yes	NA	NA	no
Cavoretto 2008 [3]	laser coagulation feeding vessel	31	34	yes	NA	NA	yes
Cavoretto 2008 [3]	laser coagulation feeding vessel	23	35	yes	NA	NA	yes
Cavoretto 2008 [3]	laser coagulation feeding vessel	28	39	yes	NA	NA	yes
Witlox 2009 [25]	laser coagulation + drainage pleural effusion	23	41	yes	no	none	no
Rammos 2010 [26]	laser coagulation + drainage pleural effusion	30	term	yes	no	residual hydrothorax	yes
Rammos 2010 [26]	laser coagulation + drainage pleural effusion	31	NA	yes	NA	residual hydrothorax, respiratory distress	yes

Table 1. Outcome of liveborn children after fetal intervention for bronchopulmonary sequestration with pleural effusion. (continued)

Reference	Intervention	GA at intervention (weeks)	GA at delivery (weeks)	Postnatal survival	Respiratory failure at birth	Neonatal morbidity	Postnatal surgery
Nicolini 2000 [27]	alcohol injection + thoracoamniotic shunt	27	term	yes	no	none	no
Bermudez 2007 [11]	polidocanol injection	24	38	no	NA	NA	yes
Bermudez 2007 [11]	polidocanol injection	26	38	yes	NA	NA	yes
Bermudez 2007 [11]	polidocanol injection	26	38	yes	NA	NA	no

GA: gestational age, NA: data not available, HFOv: High Frequency Oscillatory ventilation, BPD: Bronchopulmonary Dysplasia, nCPAP: nasal Continuous Positive Airway Pressure

*Pregnancy was ongoing at the time of publication

Table 2. Outcome of liveborn children after fetal intervention for congenital cystic adenomatoid malformation without hydrops

Reference	Intervention	GA at intervention (weeks)	GA at delivery (weeks)	Postnatal survival	Neonatal morbidity	Respiratory failure at birth	Postnatal surgery
Adzick 1985 [37]	thoracocentesis, repeated	34	37	yes	mechanical ventilation, persistent hypercapnia, mediastinal shift until surgery	yes	Yes
Nugent 1989 [38]	thoracocentesis, single	28	40	yes	none	no	yes
Alegre 2007 [31]	thoracocentesis, repeated	21	38	yes	mild, transient respiratory distress	no	yes
Tran 2008 [39]	thoracocentesis, single	30	NA	NA	NA	NA	NA
Lecomte 2009 [40]	thoracocentesis, single	26	40	no	mechanical ventilation. Resection CCAM day 1 postnatally. Died day 15 because of postoperative airleak	yes	yes
Nicolaides 1987 [41]	thoracoamniotic shunt	24	38	yes	re expansion cyst postnatally. mechanical ventilation until resection CCAM	yes	yes
Bernaschek 1994 [42]	thoracoamniotic shunt	24	36	yes	NA	NA	yes
Bernaschek 1994 [42]	thoracoamniotic shunt	35	40	yes	NA	NA	yes
Thorpe-Beeston 1994 [32]	thoracoamniotic shunt	24	40	yes	NA	NA	yes
Thorpe-Beeston 1994 [32]	thoracoamniotic shunt	25	39	yes	NA	NA	yes
Thorpe-Beeston 1994 [32]	thoracoamniotic shunt	26	38	yes	NA	NA	yes
Thorpe-Beeston 1994 [32]	thoracoamniotic shunt	31	37	yes	NA	NA	yes
Thorpe-Beeston 1994 [32]	thoracoamniotic shunt	32	33	yes	NA	NA	yes
Miller 1996 [43]	thoracoamniotic shunt	25	NA	yes	NA	NA	yes
Dommergues 1997 [33]	thoracoamniotic shunt	30	31	no	died day 1 due to pulmonary hypoplasia	yes	no
Dommergues 1997 [33]	thoracoamniotic shunt	23	36	no	died day 6 due to pulmonary hypoplasia	yes	yes
Dommergues 1997 [33]	thoracoamniotic shunt	27	36	yes	RDS	NA	yes
Adzick 1998 [7]	thoracoamniotic shunt after thoracocentesis	25	NA	yes	NA	NA	NA

Table 2. Outcome of liveborn children after fetal intervention for congenital cystic adenomatoid malformation without hydrops (continued)

Reference	Intervention	GA at intervention (weeks)	GA at delivery (weeks)	Postnatal survival	Neonatal morbidity	Respiratory failure at birth	Postnatal surgery
Adzick 1998 [7]	thoracoamniotic shunt after thoracocentesis	28	38	yes	HFOv, 4 days ECMO postoperatively, then another 7 days ventilation	yes	yes
Adzick 1998 [7]	thoracoamniotic shunt after thoracocentesis	30	32	yes	bilateral pneumothorax, 2 weeks HFOv, surgical ligation bronchopulmonary fistula.	yes	NA
Roggin 2000 [44]	failed thoracoamniotic shunt placement	28	28	yes	NA	NA	NA
Morikawa 2003 [45]	thoracoamniotic shunt after thoracocentesis	29	37	yes	no morbidity	no	yes
Wilson 2004 [46]	thoracoamniotic shunt	24-29	27-30	no	NA	yes	NA
Ierullo 2005 [47]	thoracoamniotic shunt	30	40	yes	NA	NA	yes
Viggiano 2006 [48]	thoracoamniotic shunt	28	38	yes	none	no	yes
Cavoretto 2008 [3]	thoracoamniotic shunt	25	39	yes	none	no	no
Cavoretto 2008 [3]	thoracoamniotic shunt	22	36	yes	none	no	yes
Cavoretto 2008 [3]	thoracoamniotic shunt	24	39	yes	none	no	yes
Cavoretto 2008 [3]	thoracoamniotic shunt	24	37	yes	none	no	yes
Cavoretto 2008 [3]	thoracoamniotic shunt	25	38	yes	none	no	yes
Cavoretto 2008 [3]	thoracoamniotic shunt	27	37	yes	none	no	yes
Ruano 2008 [49]	thoracoamniotic shunt	33	38	yes	none	no	yes

GA: gestational age, NA: data not available in publication, HFOv: high frequency oscillatory ventilation, RDS: respiratory distress syndrome, ECMO: extracorporeal membrane oxygenation

Table 3. Outcome of liveborn children after thoracocentesis for macrocystic congenital cystic adenomatoid malformation with hydrops

Reference	Intervention	GA at intervention (weeks)	GA at delivery (weeks)	Postnatal survival	Neonatal outcome	Respiratory failure at birth	Postnatal surgery
Chao 1990 [50]	thoracocentesis, repeated	27	35	no	died day 1 due to pulmonary hypoplasia	yes	
Neilson 1991 [51]	thoracocentesis, single	30	34	no	died day 1 due to pulmonary hypoplasia	yes	
Brown 1995 [30]	thoracocentesis, repeated	28	34	yes	supplementary oxygen needed	no	yes
Sugiyama 1999 [52]	thoracocentesis, single	29	29	no	died day 1 due to hydrops	yes	yes
Bunduki 2000 [53]	thoracocentesis, single	25	38	no	asymptomatic at birth, died of sepsis post elective lobectomy at age 2 months	no	yes
Roggin 2000 [44]	thoracocentesis, single	30	30	yes	NA	NA	yes
Crombleholme 2002 [54]	thoracocentesis, single	NA	NA	NA	NA	NA	NA
Crombleholme 2002 [54]	thoracocentesis, single	NA	NA	NA	NA	NA	NA
Crombleholme 2002 [54]	thoracocentesis, repeated	NA	NA	NA	NA	NA	NA
Crombleholme 2002 [54]	thoracocentesis, repeated	NA	NA	NA	NA	NA	NA
Pumberger 2003 [15]	thoracocentesis, repeated	NA	NA	yes	NA	NA	yes
Gornall 2003 [55]	thoracocentesis, single	20	38	yes	NA	NA	yes
Gornall 2003 [55]	thoracocentesis, single	22	37	yes	NA	NA	yes

GA: gestational age,

Table 4. Outcome of liveborn children after thoraco-amniotic shunt placement in macrocystic congenital cystic adenomatoid malformation with hydrops.

Reference	Intervention	GA at intervention (weeks)	GA at delivery (weeks)	Postnatal survival	Neonatal morbidity	Respiratory failure at birth	Postnatal surgery
Avni 1986 [56]	thoracoamniotic shunt after thoracocentesis	28	29	no	died day 1 due to pulmonary hypoplasia	yes	
Clark 1987 [57]	thoracoamniotic shunt	20	37	yes	NA	NA	yes
Bernaschek 1994 [42]	thoracoamniotic shunt	22	33	no	died day 1 due to pulmonary hypoplasia	yes	
Bernaschek 1994 [42]	thoracoamniotic shunt	29	39	yes	NA	NA	yes
Dommergues 1997 [33]	thoracoamniotic shunt	28	36	yes	none	no	yes
Dommergues 1997 [33]	thoracoamniotic shunt	26	37	yes	respiratory distress syndrome	yes	yes
Dommergues 1997 [33]	thoracoamniotic shunt	26	35	yes	respiratory distress syndrome	yes	yes
Dommergues 1997 [33]	thoracoamniotic shunt	27	34	no	died day 1 due to pulmonary hypoplasia	yes	no
Dommergues 1997 [33]	thoracoamniotic shunt	18	39	no	died day 1 due to pulmonary hypoplasia	yes	yes
Ryo 1997 [58]	thoracoamniotic shunt	27	37	yes	none	no	yes
Adzick 1998 [7]	thoracoamniotic shunt after thoracocentesis	24	34	yes	HFOv	yes	NA
Adzick 1998 [7]	thoracoamniotic shunt after thoracocentesis	30	34	yes	ECMO	yes	NA
Sugiyama 1999 [52]	thoracoamniotic shunt	27	37	yes	mechanical ventilation	yes	yes
Bunduki 2000 [53]	thoracoamniotic shunt	22	33	yes	mild left lung hypoplasia.no dependency oxygen	no	yes
Laberge 2001 [1]	thoracoamniotic shunt after thoracocentesis	23	36	no	died day 1 due to pulmonary hypoplasia	yes	
Crombleholme 2002 [54]	thoracoamniotic shunt	NA	NA	NA	NA	NA	NA
Crombleholme 2002 [54]	thoracoamniotic shunt	NA	NA	NA	NA	NA	NA
Crombleholme 2002 [54]	thoracoamniotic shunt	NA	27	yes	pulmonary hypoplasia and RDS. mechanical ventilation. Severe BPD requiring tracheostomy and chronic mechanical ventilation	yes	NA
Crombleholme 2002 [54]	thoracoamniotic shunt	NA	NA	NA	NA	NA	NA
Crombleholme 2002 [54]	thoracoamniotic shunt	NA	NA	NA	NA	NA	NA
Crombleholme 2002 [54]	thoracoamniotic shunt	NA	NA	NA	NA	NA	NA

Table 4. Outcome of liveborn children after thoraco-amniotic shunt placement in macrocystic congenital cystic adenomatoid malformation with hydrops. (continued)

Reference	Intervention	GA at intervention (weeks)	GA at delivery (weeks)	Postnatal survival	Neonatal morbidity	Respiratory failure at birth	Postnatal surgery
Gornall 2003 [55]	thoracoamniotic shunt	NA	40	yes	NA	NA	yes
Morikawa 2003 [45]	thoracoamniotic shunt after thoracocentesis	21	40	yes	NA	NA	yes
Wilson 2004 [46]	thoracoamniotic shunt	NA	22-39	no	NA	NA	NA
Wilson 2004 [46]	thoracoamniotic shunt	NA	22-39	yes	NA	NA	yes
Wilson 2004 [46]	thoracoamniotic shunt	NA	22-39	yes	NA	NA	yes
Asabe 2005 [59]	thoracoamniotic shunt	29	37	no	day 1 emergency left pneumonectomy folllowed by postpneumonectomy syndrome and death at age 13 months	yes	yes
Ierullo 2005 [47]	thoracoamniotic shunt	27	40	yes	NA	NA	yes
Illanes 2005 [60]	thoracoamniotic shunt	27	30	no	died due to pulmonary hypoplasia	yes	
Chow 2007 [61]	thoracoamniotic shunt	28	33	no	died day 1 due to pulmonary hypoplasia	yes	yes
Isnard 2007 [62]	thoracoamniotic shunt	25	37	yes	mechanical ventilation, thoracic drain	yes	yes
Vu 2007 [36]	thoracoamniotic shunt	25	34	no	died day 1 due to pulmonary hypoplasia	yes	yes
Cavoretto 2008 [3]	thoracoamniotic shunt	21	38	yes	NA	NA	yes
Cavoretto 2008 [3]	thoracoamniotic shunt	24	41	yes	NA	NA	yes
Cavoretto 2008 [3]	thoracoamniotic shunt	26	38	yes	NA	NA	yes
Cavoretto 2008 [3]	thoracoamniotic shunt	26	38	yes	NA	NA	yes
Morris 2009 [63]	thoracoamniotic shunt after steroids	23	34	yes	NA	NA	NA
Morris 2009 [63]	thoracoamniotic shunt after steroids	22	36	yes	NA	NA	NA

GA: gestational age, NA: data not available in publication, HFOv: high frequency oscillatory ventilation, ECMO: extracorporeal membrane oxygenation, RDS: respiratory distress syndrome, BPD: bronchopulmonary dysplasia

Table 5. Outcome of liveborn children after laser coagulation or injection of sclerosing agents in microcystic congenital cystic adenomatoid malformation with hydrops

Reference	Intervention	GA at intervention (weeks)	GA at delivery (weeks)	Postnatal survival	Neonatal morbidity	Respiratory failure at birth	Postnatal surgery
Ong 2006 [35]	laser coagulation lesion	21	38	yes	mechanical ventilation	yes	yes
Bermudez 2008 [34]	polidocanol injection in lesion	25	38	no	died day 19 after birth due to nosocomial sepsis post elective surgery	no	yes
Bermudez 2008 [34]	ethanolamine injection in lesion	21	39	yes	mild respiratory distress, no intervention	no	no
Bermudez 2008 [34]	polidocanol injection in lesion	26	38	yes	none	no	no
Cavoretto 2008 [3]	laser coagulation major vessels	19	37	no	died postnatally due to pulmonary hypoplasia	yes	
Flores Acosta 2010 [64]	polidocanol injection in lesion	30	39	no	pulmonary hypertension, died day 4 after birth	yes	
Sepulveda 2010 [65]	histoacryl injection feeding vessel	22	39	yes	none	no	no

GA: gestational age

Table 6. Outcome of liveborn children after fetal resection of microcystic congenital cystic adenomatoid malformation with hydrops.

Reference	Intervention	GA at intervention (weeks)	GA at delivery (weeks)	Postnatal survival	Neonatal morbidity	Respiratory failure at birth
Harrison 1990 [66]	fetal lobectomy	27	28	no	died day 2 due to respiratory failure	yes
Harrison 1990 [66]	fetal lobectomy	23	30	yes	mechanical ventilation	yes
Adzick 1998 [7]	fetal lobectomy	26	33	yes	mechanical ventilation for 2 days	yes
Adzick 1998 [7]	fetal lobectomy	24	30	yes	mechanical ventilation for 10 days	yes
Adzick 1998 [7]	fetal lobectomy	22	35	yes	none	no
Adzick 1998 [7]	fetal lobectomy	22	35	yes	none	no
Adzick 1998 [7]	fetal lobectomy	29	37	yes	none	no
Adzick 1998 [7]	fetal lobectomy after failed shunt	26	34	yes	mechanical ventilation for 6 days (RDS), persistent ductus arteriosus requiring indomethacin therapy, Necrotising Enterocolitis	yes
Adzick 1998 [7]	fetal lobectomy after serial thoracocentesis	24	26	yes	mechanical ventilation for 4 weeks, right pneumothorax, surgical ligation of persistent ductus arteriosus	yes
Crombleholme 2002 [54]	fetal lobectomy	NA	35	yes	mechanical ventilation	yes
Crombleholme 2002 [54]	fetal lobectomy	NA	36	yes	mechanical ventilation	yes
Crombleholme 2002 [54]	fetal lobectomy	24	24	no	died day 1 due to the prematurity	yes
Crombleholme 2002 [54]	fetal lobectomy	NA	32	no	NA	NA
Cass 2011 [67]	fetal lobectomy	22	32	yes	NA	NA
Cass 2011 [67]	fetal lobectomy	24	33	yes	tracheobronchomalacia, treacheostomy ventilation	yes

GA: gestational age, NA: not available, RDS: respiratory distress syndrome

Mean gestational age at intervention was 24.9 weeks (range 18-30 weeks) and at birth 34.9 weeks (range 24-39 weeks). Neonatal survival rate was 69% (44/64). The incidence of respiratory failure at birth was high (73%, 32/44). Postnatal resection was performed in 89% (31/35) of available cases. Description of neonatal morbidity was found in 55% (40 of 73) liveborn cases.

Two small studies describing results of fetal surgery for microcystic CCAM briefly describe long-term neurodevelopmental outcome in survivors [10, 71]. Adzick et al. describe that developmental testing at 6 to 12 month intervals was normal in all 8 survivors of fetal surgery (range of age at follow-up: 6 months- 7 years) [10]. Cass et al. describe long term follow up of two children after fetal surgery including one child with normal neurodevelopmental and pulmonary outcome at 4 years of age and another child with mild motor delay and no cognitive neurodevelopmental deficit at 3 years of age [71]. The methods to assess neurologic and psychomotor development were not described in both studies.

Overall outcome in all reported liveborn infants after fetal intervention for CCAM or BPS are pooled together and summarized in Table 7.

Table 7. Outcome in liveborn neonates with BPS and CCAM, according to type of prenatal intervention
GA: gestational age

		Mean GA at intervention - weeks (n)	Mean GA at birth - weeks (n)	Postnatal survival - n (%)	Respiratory failure at birth - n (%)	Postnatal surgery - n (%)
BPS	thoracocentesis	26.5 (4)	31 (4)	5/6 (83)	4/6 (67)	4/4 (100)
	shunt	28.9 (13)	34.4 (11)	12/13 (92)	9/13 (69)	10/12 (83)
	laser	26.9 (15)	38 (12)	14/14 (100)	1/5 (20)	9/14 (64)
	sclerosing agent	25.8 (4)	38 (3)	3/4 (75)	0/1 (0)	2/4 (50)
	TOTAL	**27.4 (36)**	**35.7 (30)**	**34/37 (92)**	**14/25 (56)**	**25/34 (74)**
CCAM without hydrops	thoracocentesis	27.8 (5)	38.8 (4)	3/4 (75)	2/4 (50)	4/4 (100)
	shunt	27.1 (26)	36.7 (24)	24/27 (89)	6/15 (40)	21/23 (91)
	TOTAL	**27.2 (31)**	**37.0 (28)**	**27/31 (87)**	**8/19 (42)**	**25/27 (93)**
CCAM with hydrops	thoracocentesis	26.4 (8)	34.4 (8)	5/9 (56)	3/5 (60)	7/7 (100)
	laser/sclerosing agent	23.4 (7)	38.3 (7)	4/7 (57)	3/7 (43)	2/5 (40)
	shunt	25.0 (28)	35.8 (30)	23/33 (70)	16/19 (84)	22/23 (96)
	surgery	24.4 (12)	32.0 (15)	12/15 (80)	10/13 (77)	-
	TOTAL	**24.9 (55)**	**34.9 (60)**	**44/64 (69)**	**32/44 (73)**	**31/35 (89)**

5. DISCUSSION

Perinatal survival in fetuses with congenital lung lesions has increased with the use of prenatal interventions. This systematic review demonstrates that increased perinatal survival is associated with a significant risk of neonatal morbidity and mortality.

Table 7 shows that respiratory failure at birth and postnatal demise were highest in the group treated for CCAM with hydrops (69% postnatal survival compared to 87% and 92% in the groups with CCAM without hydrops and BPS respectively) The hydropic fetuses with CCAM can be considered to be more severly affected than the non-hydropic ones. That could explain the higher rates of mortality and respiratory failure in that group. Most patients with CCAM without hydrops were treated in the 1990's. Some of these patients might not have been treated now, because regression of even very large lesions in the last trimester of pregnancy is often seen and treatment now is usually reserved for fetuses developing hydrops.

In BPS a trend is seen towards lower postnatal respiratory failure in the group treated by laser ablation or injection of a sclerosing agent in the feeding artery (Table 7). This might be due to the fact that thoracocentesis and thoracoamniotic shunting only treats a symptom of the BPS (pleural effusion), whereas laser therapy and injecting sclerosants leads to growth arrest or even considerable size reduction of the lesion [28]. Gestational age at birth in the group treated with laser or sclerosant therapy was longer compared to the other groups which may reflect the more effective "treatment" of the lesion. The lower rate of prematurity probably contributes to the lower rate of respiratory failure.

Given the increased incidence of neonatal morbidity, neonates with congenital lung lesions after fetal therapy should be regarded by neonatologists as a high-risk population. Awareness and knowledge of the underlying condition is required to offer both patients and parents, the best available care and support.

Morbidity includes on one hand complications related to prematurity (often inherent to prenatal interventions) and on the other hand respiratory failure related to the congenital lung lesion. Mean gestational age at delivery was < 37 weeks in both subgroups of neonates with either BPS or CCAM.

Although some patients have no respiratory symptoms after delivery, the majority have severe respiratory failure, requiring mechanical ventilation (including high frequency oscillatory ventilation). Respiratory failure at birth occurred particularly in hydropic fetuses with CCAM. Neonates born after thoraco-amniotic shunting usually have the shunt still in place at birth. The shunt should be clamped directly after birth to prevent air from entering the thorax.

Some neonates may require temporary drainage of persisting pleural effusion through a newly placed thoracic drain. Incidence of neonatal pleural effusion or pneumothorax requiring shunting after birth is not clearly reported in the literature.

In fetuses with persistent large congenital lung lesions or hydrops at a gestational age over 32 weeks, ex-utero intrapartum (EXIT) treatment can be considered. EXIT procedures allow partial fetal delivery through cesarian section with subsequent establishment of a safe fetal airway by either intubation or bronchoscopy, while fetal oxygenation is maintained by the placental circulation. Meanwhile the airway is secured by intubation and the baby is born for further treatment. EXIT to resection (meaning that the lung lesion is resected while the child is still on placental support) has also been described [72].

Postnatal surgical resection of the lung lesion was performed in the vast majority of cases, irrespective of the type of lesion. Although there is international consensus that symptomatic neonates with congenital lung lesions require immediate surgical resection, the management of asymptomatic infants with congenital lung lesions is controversial. Some authors advocate preventive surgical resection of the lung lesion during the first year of life while others prefer a "wait-and-see" policy. The main arguments in favor of postnatal resection of asymptomatic lesions are prevention of possible malignant transformation and prevention of infection of mainly cystic lesions [73]. The actual risk of complications, however, is not exactly known and complications have been described in asymptomatic children after elective surgery [58, 74] as well as in asymptomatic children where the lesion was left in situ [75]

Overall postnatal mortality rates in live-born neonates were increased and highest in the subgroup of hydropic fetuses with CCAM (31%). Unfortunately, the published data on neonatal outcome is often incomplete and summarily reported. Detailed information on the severity of respiratory failure and crucial data on incidence of chronic lung disease was often omitted, limiting our conclusions.

Our data should be interpreted with care due to the lack of high quality evidence and major heterogeneity between the various studies. Most studies included in this review are small case series or case reports. Controlled studies or RCT have not been performed, which prevents accurate comparison of perinatal and neonatal outcome between the various types of prenatal interventions. The risk of publication bias is also substantial, as successes are generally more often published than failures. Neonatal morbidity and mortality rates reported in the literature and summarized in this review might be under-reported.

CONCLUSIONS

In contrast with the fairly large amount of evidence showing the beneficial role of prenatal interventions (in particular minimally invasive procedures) for congenital lung lesions in terms of perinatal survival, data on neonatal morbidity is limited. Lack of evidence on neonatal outcome prevents reaching reliable conclusions to guide neo-

natologists in deciding the optimal postnatal management and counseling of parents on short- and long-term outcome. Large studies on long-term neurodevelopmental and respiratory outcome are urgently needed. Given the rarity of prenatal interventions for congenital lung lesions, international cooperation between fetal therapy centers is of paramount importance.

Key Guidelines:

- Prenatal survival in congenital lung lesions has drastically improved with the use/ development of minimally invasive fetal interventions.
- Neonates born after fetal therapy for congenital lung lesions are at high risk of (respiratory) morbidity after birth
- Increased awareness in perinatologists participating in the care of these neonates is is of paramount importance.

Research Directions:

- Large studies on neonatal morbidity and mortality in survivors after fetal therapy for congenital lung lesions are required to determine the exact rates of neonatal complications and the optimal management after delivery.
- Well-designed long–term follow-up studies in survivors of fetal therapy for congenital lung lesions are urgently needed to determine the incidence of neurodevelopmental impairment and identify risk factors for adverse outcome.

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Chapter 4

Neonatal management and outcome after thoracoamniotic shunt placement for fetal hydrothorax

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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's-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).

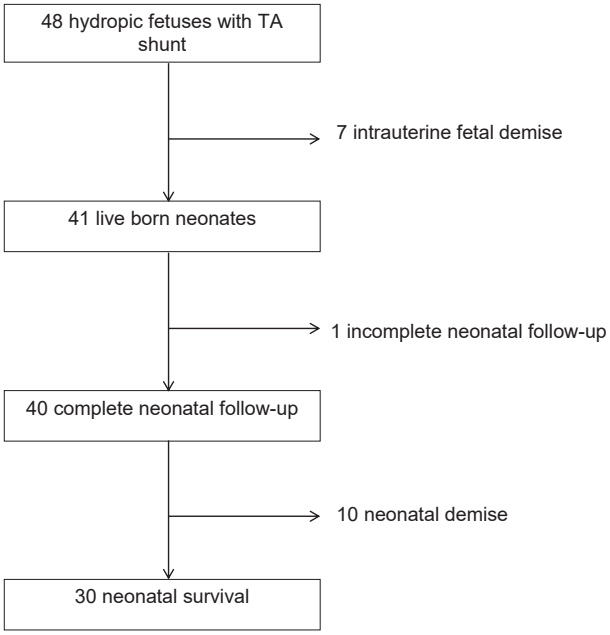

Figure 1. Flowchart showing the derivation of our population.

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.

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)

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.

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.

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

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

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.

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

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.

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Chapter 5

Long-term neurodevelopmental and respiratory outcome after fetal therapy for congenital thoracic malformations

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ABSTRACT

Introduction: The aim of this study is to evaluate long-term neurodevelopmental and respiratory outcome after fetal therapy for fetal pleural effusion, congenital cystic adenomatoid malformation and bronchopulmonary sequestration.

Methods: Children ≥18 months of age underwent an assessment of neurologic, motor, and cognitive development. Medical records were reviewed to determine respiratory outcome. Behavioral outcome was assessed using the Child Behavioral Checklist.

Results: Between 2001 and 2016, 63 fetuses with fetal hydrops secondary to thoracic abnormalities were treated at our center. Overall perinatal survival was 64% (40/63). Twenty-six children were included for follow-up (median age 55 months). Severe neurodevelopmental impairment (NDI) was detected in 15% (4/26). Three out of 4 children with severe NDI had associated causes contributing to the impairment. Overall adverse outcome, including perinatal mortality or NDI, was 55% (27/49). Fifteen percent (4/26) had severe respiratory sequelae. Parents did not report more behavioral problems than Dutch norms.

Discussion: Our results suggest that severe NDI in this specific high-risk cohort occurs in 15%, which is above the range of the incidence of NDI reported in case series treated with other fetal therapies (5–10%). Large multicenter studies and an international web-based registry are warranted to prospectively gather outcome data at fixed time points.

INTRODUCTION

Congenital thoracic malformations present in different forms prenatally. Fetal pleural effusion (FPE) presents as pleural fluid on prenatal ultrasound, probably due to leakage of lymphatic fluid in the pleural space(1, 2).

Congenital cystic (or pulmonary) adenomatoid malformation (CCAM) and bronchopulmonary sequestration (BPS) present as cystic or solid lung masses. CCAMs are classified as being microcystic or macrocystic based on ultrasound appearance(3). A BPS is a solid lung mass characterised by an arterial feeding vessel originating from the systemic vasculature.

The outcome in FPE, CCAM and BPS is heterogeneous and varies from spontaneous resolution to severe fetal hydrops and perinatal death. Perinatal outcome is particularly poor in cases complicated by severe fetal hydrops. Perinatal survival rate in hydropic foetuses with FPE or CCAM ranges from 5 to 30%(4-8). Prenatal fetal intervention is therefore primarily indicated in cases with fetal hydrops and is associated with an increased survival rate up to 65%(4, 7). Fetal intervention for these lesions is aimed at permanently reducing the space occupying effect of the lesion and includes thoracoamniotic shunt placement in FPE and macrocystic CCAM and BPS with pleural effusion(8-10). BPS can also be treated by laser coagulation of the feeding vessel(11).

One of the concerns of the successful use of fetal therapy is that an increase in perinatal survival may be associated with an increase of children with long-term handicaps.

Long-term follow-up studies are lacking and counselling of parents prior to fetal interventions is limited to information on perinatal survival.

The aim of this study was to report on the long-term neurodevelopmental, behavioral and respiratory outcome after fetal therapy for congenital thoracic malformations including FPE, CCAM and BPS.

METHODS

In this observational cohort study we included all patients with FPE, CCAM or BPS treated with thoracoamniotic shunting or laser occlusion of the feeding vessel of BPS at our center between January 2001 and May 2016. The Leiden University Medical Center (LUMC) is the national referral center for invasive fetal therapy in the Netherlands. Patients throughout the Netherlands are referred to our center for these therapies.

The indication for fetal therapy was hydrops, defined as an accumulation of fluid in two or more compartments, including pleural effusion, skin edema, ascites, and/or pericardial effusion. For the purpose of this study we invited all families with their surviving children at least 16 months of age (corrected for prematurity) to participate

in this follow-up study. The study was approved by the ethics committee of the Leiden University Medical Center. Informed consent was obtained from all participating families.

A follow-up visit was performed at a minimum age of 18 months corrected for prematurity and included a neurologic examination according to Touwen(12) and an assessment of cognitive and motor development using the Bayley Scales of Infant and Toddler Development third edition (Bayley-III) in children between 21 and 36 months of age(13). Cognitive development of children between 3 and 7 years of age was tested with the Wechsler Preschool Primary Scale of Intelligence third edition (WPPSI-III) (14). Children at the age ≥ 7 years were tested with the Wechsler Intelligence Scale for Children third edition (WISC-III)(15). Both the WPPSI and WISC provide a Total IQ (TIQ) score including a Verbal IQ (VIQ) and a Performance IQ (PIQ). Bayley-III, WPPSI and WISC scores follow a normal distribution curve with a normed mean of 100 and a standard deviation (SD) of 15. A test score that is, a Bayley-III cognitive or motor composite score, WPPSI or WISC TIQ, VIQ or PIQ score, below 70 (< -2 SD) indicates severe delay and scores below 85 (< -1 SD) indicate mild-to-moderate delay. Children who could not be tested due to severe cognitive impairment were assigned a nominal score of 49 to reflect severe developmental delay.A trained psychologist (JMMvK), performed the psychometric tests in all children.

Cerebral palsy was defined according to the European CP Network and classified as spastic bilateral, spastic unilateral, dyskinetic (dystonic or choreo-athetotic), ataxic, or mixed.(16) Severity was classified according to the Gross Motor Function Classification System (GMFCS) for Cerebral Palsy(17). Minor neurological dysfunction (MND) was defined as a moderate abnormality of tone, posture and movement leading to only minor functional impairment or minor developmental delay(12).

The Achenbach's Child Behavior Checklist (CBCL) versions 1½–5 and 6–18 years(18, 19) was used to measure the occurrence of problem behavior. For the purpose of this study the Total problem scale, and the two broadband syndrome scales Internalizing (withdrawn, somatic complaints, anxious/depressed) and Externalizing (delinquent or rule-breaking, aggressive) behavior problems were used. T scores were computed from raw scores with higher scores on the syndrome scales indicating greater severity of problems. T scores of the normative sample have a mean of 50 ± SD 10. A clinical score in 10% of the children for the Total, Internalizing and Externalizing behavior problem scales (T score ≥ 64) served as cut-off points for comparison with Dutch normative data(19).

The primary outcome measure was a composite outcome termed severe neurodevelopmental impairment (NDI) including cerebral palsy (GMFCS II-V), cognitive or motor test score of less than 70, bilateral blindness, or bilateral deafness requiring amplification. Mild-to-moderate impairment was defined as MND, a cognitive or motor test score

< 85, mild hearing impairment, or mild visual impairment with good functional vision when corrected with glasses. An "overall adverse outcome" was calculated including perinatal mortality or severe NDI. Secondary outcomes included behavioral problem scores and respiratory outcome, including discharge on home oxygen and hospital readmissions for respiratory problems in the first 24 months after birth.

STATISTICAL ANALYSIS

All data were analysed using SPSS version 20.0 (IBM, Armonk, NY, USA). Categorical data are presented as numbers and percentages while continuous variables are presented as median with interquartile range (IQR). The percentages of children with a clinical CBCL score (T score ≥ 64) were compared with normative percentages (10% with clinical score) using a binomial test. The level of statistical significance for all analyses was set at $P < 0.05$.

RESULTS

In the study period 63 fetuses with thoracic abnormalities were treated antenatally. The antenatal and neonatal outcome of the 48 fetuses with FPE has been described earlier(20). A flowchart showing the derivation of all patients is shown in Figure 1.

Median gestational age at shunt placement or laser coagulation was 28.0 weeks (IQR 22.9-30.8 weeks). Fetal demise occurred in 16% (10/63) of pregnancies after the intervention. Eighty-four percent (53/63) of neonates were liveborn at a median gestational age of 33.9 weeks (IQR 30.5-36.5 weeks). Thirty percent (16/53) of liveborn neonates were born very preterm below a gestational age of 32 weeks. Seventy-five percent (40/53) of liveborn fetuses survived the neonatal period. Overall perinatal survival was 64% (40/63). Perinatal survival was 63% (31/48) in fetuses with FPE, 44% (4/9) in foetuses with CCAM and 83% (5/6) in foetuses with BPS.

Neurodevelopmental outcome:

Twenty-six children were included for long-term follow up at a median age of 55 months (range 21-130). Detailed information on the results can be found in Table 1, 2 and 3. The overall incidence of severe NDI in the children included for follow-up was 15% (4/26). For the 'overall adverse outcome' assessment, 49 fetuses were included. From the 63 fetuses that were treated antenatally, 10 children were excluded from analysis and in 4 cases (13%) parents gave no consent for testing (Fig. 1). Overall adverse outcome,

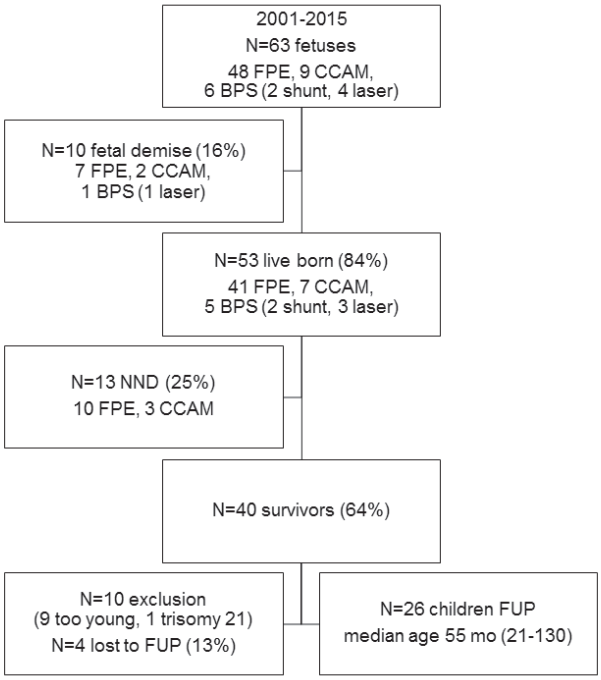

Figure 1. Flowchart showing the derivation of the study population.

including perinatal mortality (fetal demise (n=10) and neonatal death (n=13)) or long-term NDI (n=4), was 27/49 (55%).

Severe cognitive development, a score <70, was detected in 12% (3/26) of children and mild-to-moderate cognitive development <85 in 15% (4/26). Median cognitive score was 105 (range: 58-120), 102 (range: 86-118) and 87 (range: 47-103) according to Bayley-III (*n* = 8), WPPSI-III (*n* = 9) and WISC-III (*n* = 8) assessment, respectively. Overall, median cognitive score was 95 (range: 47-120). One child (case No. 15) had severe cognitive impairment and severe motor dysfunction due to congenital hypomyelinating neuropathy. She could not be assessed with formal psychometric testing and was assigned a test score of 49 in the database. Another child (case No. 19) moved with her family to another country where pediatric examinations showed age-appropriate motor and cognitive development. No score that is, a missing value, was assigned in the database. Nineteen percent (5/26) of children had mild motor dysfunction according to Touwen examination.

After birth, two children (cases No. 1 and No. 19) were diagnosed with Noonan syndrome. Case No. 1 presented with normal neurodevelopmental outcome at follow-up at age 6 years (WISC TIQ 96) and attends a regular school. Case No. 19 presented with severe cognitive and motor impairment at follow-up at 23 months of age. A tracheostomy has been placed due to severe respiratory failure probably because of Congenital

Table 1. Perinatal and long-term outcome of 20 cases of fetal pleural effusion treated with thoracoamniotic shunt placement

Case	GA at shunt placement, weeks	GA at birth, weeks	Mechanical ventilation	ICU stay, days	Age at FUP, months	Respiratory outcome		Motor development	Cognitive score	NDI	Behavioral problem
						Discharge home O2	Readmission <24 months				
1	33	33	yes	65	73	no	no	normal	95	no	no
2	18	39	yes	6	114	no	no	MND	103	no	no
3	30	34	yes	11	108	no	no	normal	84	no	no
4	32	33	yes	34	125	no	yes	normal	81	no	no
5	28	39	no	17	90	no	no	normal	78	no	yes
6	30	42	no	5	57	no	no	MND	107	no	no
7	33	33	yes	24	48	no	no	normal	86	no	no
8	25	37	no	9	29	no	no	normal	120	no	no
9	29	38	no	7	27	no	no	normal	105	no	no
10	24	28	yes	28	53	no	yes	normal	90	no	no
11	20	36	no	7	39	no	no	normal	118	no	no
12	20	38	no	7	37	no	yes	normal	102	no	no
13	34	36	no	22	25	no	no	normal	105	no	no
14	22	37	no	9	130	no	no	normal	92	no	NA
15	31	34	yes	114	88	yes	yes	neuropathy	49	yes	NA
16	21	29	yes	144	30	yes	yes	normal	105	no	no
17	31	33	yes	88	31	no	no	normal	95	no	no
18	32	34	yes	45	75	no	yes	normal	102	no	no
19	28	32	yes	282	23	yes	yes	severe	58	yes	no
20	31	36	no	12	21	no	no	severe	72	yes	NA
	29.5 (18-34)	35 (28-42)	11/20 (55%)	19,5 (6-144)	50,5 (21-130)	3/20 (15%)	7/20 (35%)	3/20 (15%)	95 (49-120)	3/20 (15%)	1/17 (6%)

Data are summarized as median (range) or percentage (n/N)

GA, gestational age; ICU, intensive care unit; FUP, follow-up; NDI, neurodevelopmental impairment; FPE, fetal pleural effusion; NA, not assessed; MND, minor neurologic dysfunction.

Table 2. Perinatal and long-term outcome of 4 cases of BPS treated with fetal therapy.

Case	Indication	Therapy	GA at therapy, weeks	GA at birth, weeks	Mechanical ventilation	ICU stay, days	Age at FUP, months	Respiratory outcome		Motor development	Cognitive score	NDI	Behavioral problem
								Discharge home O2	Readmission <24 months				
21	BPS	shunt	32	36	yes	7	31	no	no	normal	113	no	yes
22	BPS	laser	23	39	no	3	110	no	yes	normal	102	no	no
23	BPS	laser	29	41	no	0	61	no	no	normal	90	no	no
24	BPS	laser	25	38	no	4	48	no	no	normal	NA	no	NA
			27 (23-32)	38.5 (36-41)	¼ (25%)	3.5 (0-7)	54.5 (31-110)	0/4 (0%)	1/ 4 (25%)	0/4 (0%)	102 (90-113)	0/4 (0%)	1/3 (33%)

Data are summarized as median (range) or percentage (n/N)
GA, gestational age; ICU, intensive care unit; FUP, follow-up; NDI, neurodevelopmental impairment; NA, not assessed; MND, minor neurologic dysfunction.

Table 3. Perinatal and long-term outcome of 2 cases CCAM treated with thoracoamniotic shunt placement..

Case	Indication	Therapy	GA therapy	GA birth	Mechanical ventilation	ICU stay	Age FUP	Respiratory outcome		Motor development	Cognitive score	NDI	Behavior
								Discharge home O2	Readmission <24 months				
25	CCAM	shunt	23	38	no	7	109	no	no	MND	89	no	no
26	CCAM	shunt	22	26	yes	98	123	yes	no	MND	47	yes	no
			22.5 (22-23)	32 (26-38)	1 / 2 (50%)	52.5 (7-98)	55 55 (16-130)	1 / 2 (50%)	0/2 (0%)	0/2 (0%)	68 (47-89)	1 / 2 (50%)	0/2 (0%)

Data are summarized as median (range) or percentage (n/N)
GA, gestational age; ICU, intensive care unit; FUP, follow-up; NDI, neurodevelopmental impairment; NA, not assessed; CCAM, congenital cystic adenomatoid malformation; MND, minor neurologic dysfunction.

Pulmonary Lymphangiectasia (CPL) and a percutaneous endoscopic gastrostomy was performed to maintain nutrition. Recent ventilation tube insertion for both ears has resulted in better hearing that is, from a hearing loss of approximately 80 decibels to a loss less than 20-50 decibels. He attends a medical daycare facility. Twenty-seven percent (7/26) of children had mild visual impairment with good functional vision when corrected with glasses. Mild-to-moderate impairment, including MND, test scores below 85, and mild hearing and/or visual impairments, was present in 25% (9/26) of survivors.

Behavioral outcome:

Complete behavioral questionnaires were obtained from the parents of 85% (22/26) of children (n=1 ≤ 16 months of age and n=4 questionnaires not returned). According to the CBCL 1½-5 (*n* = 13), mean total problem score was 48.4 ± 12.2. Mean internalizing and externalizing problem scores were 46.6 ± 15.1 and 50.5 ± 10.0, respectively. According to the CBCL 6-18 (*n* = 9), mean scores were 56.67 ± 9.1, 51.4 ± 11.4 and 53.0 ± 11.8, respectively. T scores of the normative sample have a mean of 50 ± 10. Overall, behavioral problems within the clinical range were reported in 9% (2/22) of cases, with internalizing problems in 9% (2/22) and externalizing problems in 9% (2/22) of cases. No differences compared with normative percentages (10% with clinical score) were reported ($P > .05$).

Respiratory outcome:

Fifteen percent (4/26) of children still received oxygen therapy at discharge from the hospital. One child (case No. 15) was born at 29 weeks' gestation and was diagnosed with a severe neuropathy. One child (case No. 19) was diagnosed with Noonan syndrome after birth and appeared to suffer from CPL requiring long-term ventilation through a tracheostomy. The two other children requiring home oxygen were born premature at a gestational age of 26 and 29 weeks. Thirty-one percent (8/26) of children was readmitted to the hospital for respiratory problems (mainly respiratory tract infections) after discharge home and within 24 months after birth.

DISCUSSION

In this study we evaluated the long-term outcome in survivors after fetal therapy for fetal thoracic malformations including FPE, CCAM, and BPS. Overall adverse outcome, including perinatal mortality or severe long-term impairment was high (55%) but was mainly due to a relative high risk of perinatal death. Severe NDI in long-term survivors was detected in 15%. Mild-to- moderate impairment was present in 25% of survivors.

Compared with normative data, the parents of the children did not report more behavioral problems.

This is the first detailed analysis of a relatively large cohort of long-term survivors after fetal interventions for FPE, CCAM and BPS. We employed standardized psychometric tests in all children performed by a certified child psychologist. Importantly, the lost to follow-up rate was low (13%), reducing the risk of selection bias.

To date, only one long-term follow-up study reporting on the respiratory outcome has been published. Caserio et al. report on respiratory morbidity in a group of 15 survivors after congenital chylothorax(7). They found recurrent respiratory infections and signs of asthma in 27% of survivors. However, not all patients received fetal treatment, and some of the survivors were diagnosed with chylothorax only postnatally. In our study, we did not record the percentage of children with respiratory infections or signs of asthma as we think these parameters are not specific for respiratory problems in this selective population of children. However, some children (15%) had severe respiratory sequelae, with the need of home oxygen therapy after hospital discharge. This appeared to be related to premature birth, CPL and severe demyelinating neuropathy. Unfortunately, we do not have the facilities to perform lung function testing in children below age 5 years in our hospital. Lung function testing would have been a more objective measure to quantify respiratory outcome in this population.

Neurodevelopmental outcome in children treated with fetal therapy for fetal pleural effusion or congenital thoracic abnormalities has not been reported before. Our results suggest that long-term NDI in this specific high-risk cohort occurs in 15% of survivors, which is above the range of the incidence of NDI reported in case series treated with other fetal therapies (5-10%)(21-24). The rate of NDI in children treated with intrauterine transfusion (IUT) for alloimmune hemolytic disease was reported in 5%(21). In children treated with fetoscopic laser surgery for twin-twin transfusion syndrome (TTTS), long-term NDI occurs in 10% in most recent series(25). NDI has been reported in 7% of children treated with selective reduction in complicated monochorionic twin pregnancies(22). In most studies, prematurity and severe neonatal morbidity were identified as potential risk factors for NDI. Unfortunately, in this study, the sample size was too small to perform a risk factor analysis which would allow results to be adjusted for, e.g., the underlying cause of hydrops and prematurity. In addition, three out of four children with severe NDI had associated causes contributing to the impairment, that is, hypomyelinating neuropathy, Noonan syndrome, and NAA10-gene mutation. These associated anomalies might therefore contribute more to this relatively high rate of NDI than the thoracic abnormality and/or the associated hydrops.

Care should be taken when interpreting our results. In our cohort, different techniques were used depending on different clinical factors and the indications for intervention varied. Therefore, our study group is relative inhomogeneous and difficult to compare

to other studies. Furthermore, the interpretation of our results is limited by the lack of an appropriate control group. It would be interesting to assess long-term neurodevelopment in all children who have had fetal hydrops, whether or not they received fetal therapy. The most important limitation is the relatively small sample size which is inherent with the rarity of the disease and the fetal intervention. To reach reliable conclusions, large multicentre studies are warranted and an international web-based registry should be installed to prospectively gather outcome data in this high-risk group of children. It is important to continuously assess the neurodevelopment of the children, at fixed time points, e.g., at 2, 5, and 8 years, using standardized psychometric tests with increasing reliability of results with increasing age of the children. Only then, parents with an hydropic fetus with thoracic abnormalities can be accurately counselled including not only information on survival, but most importantly also with reliable information on long-term outcome in case of survival.

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PART IV:

DISCUSSIONS AND SUMMARY

Chapter 6

General discussion

GENERAL DISCUSSION

Primary fetal lung and airway anomalies are rare. Recognition and understanding of these lesions has improved over the last decades mainly due to improvements in prenatal ultrasound. With the introduction of fetal therapy options an increasing number of children survive with larger and more severe forms of fetal pleural effusion (FPE), congenital pulmonary airway malformations (CPAM) and bronchopulmonary sequestrations (BPS). In this chapter I will discuss the current views on etiology and pathophysiology of fetal lung lesions, the various pre- and postnatal management options (including fetal interventions) and report on the perinatal and neonatal outcome as well as what is known on long-term outcome. The first part focuses on FPE and the second part on CPAM and BPS.

FETAL PLEURAL EFFUSION

Etiology

Primary fetal pleural effusion (FPE) or congenital chylothorax is the accumulation of lymphatic fluid in the pleural space of the fetus. Despite increased recognition of this abnormality in recent years, the etiology remains uncertain. The thoracic duct is the major channel of the lymphatic system. It transports lymph before birth (1, 2) which changes to chyle after the introduction of enteral feeding and transport of free fatty acids (FFAs) after birth. The thoracic duct ascends through the mediastinum to drain in the left subclavian and internal jugular veins and crosses the posterior mediastinum from left to right at the level of the fifth thoracic vertebra (Th5). Therefore leakage of lymph from the thoracic duct below Th5 can lead to a right-sided chylothorax whereas leakage above Th5 can lead to a left-sided chylothorax (3).

Diagnosis

In FPE the exact anatomical cause of lymph leakage is hardly ever identified. It is even hard to identify the exact cause of the pleural effusion before birth. After birth chylothorax is diagnosed when pleural effusion contains > 1.1 mmol/l triglycerides (with oral fat intake) and has a total cell count ≥ 1000 cells/µl, with a lymphocyte fraction ≥ 80% (4). Before birth, when no enteral fat intake is present, lymphocyte count obtained by thoracocentesis has been proposed as diagnostic method to identify chylothorax and rule out other causes of fetal pleural effusion (5, 6). However, lymphocyte fractions < 80% were repeatedly found in antenatal pleural fluid samples from patients that were diagnosed with chylothorax after birth (7, 8). Therefore, a lymphocyte fraction lower than 80% before birth does not rule out the presence of chylothorax. Another diagnos-

tic test using contemporaneous measurement of IgG in fetal serum and pleural fluid is described. In one study in 13 cases of FPE, antenatal pleural fluid/serum IgG ratio > 0.6 was found in patients diagnosed with chylothorax after birth compared to patients with other causes of antenatal pleural effusion (8). However, this diagnostic method necessitates an additional intrauterine intervention as it requires fetal cord blood in addition to pleural fluid analysis.

In the absence of an exact diagnostic test, primary FPE is usually diagnosed by ruling out other, secondary, causes of pleural effusion. Secondary pleural effusion is usually part of a generalized picture of fluid retention in non-immune fetal hydrops. Secondary causes of pleural effusion include structural cardiac defects, immune or non-immune severe fetal anaemia, congenital infections and aneuploidy. In table 1 etiology and evaluation of possible causes of fetal pleural effusion are summarised.

Secondary causes of pleural effusion are usually ruled out through detailed Doppler ultrasound analysis, including fetal echocardiography (to rule out structural cardiac defects or arrhythmias and fetal anaemia) and maternal viral serology testing to rule out congenital infections (9) , blood type and antibody screen to rule out immune hydrops. Fetal chromosome analysis is also performed often to rule out aneuploidy which is associated with secondary FPE in about 35% of cases and with primary FPE in 5-12% of cases (10-12). Structural anomalies are frequently associated with fetal pleural effusion (13). Therefore detailed ultrasound evaluation should be performed to rule out pulmonary malformations, such as CCAM and BPS, congenital diaphragmatic hernia (CDH) or mediastinal tumours.

In primary FPE the pleural effusion starts unilateral and may then progress to bilateral involvement. When cardiac compression occurs secondary heart failure occurs. Usually the upper body becomes oedematous first after which generalized hydrops can develop (14). Primary FPE is associated with genetic abnormalities in up to 15% of cases (15). Associated abnormalities include Turner syndrome, Down syndrome, Noonan syndrome, Klippel-Trenaunay-Weber syndrome, Simpson-Golabi-Behmel syndrome and Costello syndrome (15-17).

Natural History

The natural history of FPE is unpredictable. Effusions can regress, remain stable or progress. Spontaneous regression is reported in up to 22% of cases (14), but this can be an underestimation because many spontaneously regressed cases may not have been reported. Features favouring spontaneous regression were reported to be: early diagnosis, unilateral effusion, absence of polyhydramnios and absence of hydrops (14).

Progression of unilateral pleural effusion usually leads to contralateral extension first, causing an increase in intrathoracic pressure, impaired fetal swallowing occurs and subsequent polyhydramnios can develop. When the intrathoracic pressure increases

Table 1. Fetal pleural effusions: etiology and diagnostic evaluation

Etiology	Diagnostic test / evaluation
Pulmonary	
primary chylothorax	lymphocyte count in pleural fluid
CCAM / BPS	ultrasound aspect lungs and Doppler feeding vessel
Congenital diaphragmatic hernia (CDH)	ultrasound aspect thorax
Congenital Pulmonary Lymphangiectasia	lymphoscintigraphy, genetic testing (ref Wilson 2006)
Cardiac	
Structural heart defect	prenatal echocardiography
Cardiac Tumour	prenatal echocardiography
Cardiomyopathy	prenatal echocardiography
Arrhythmia	prenatal echocardiography
Chromosomal / genetic	
45, X Turner syndrome	prenatal chromosome analysis
Down syndrome (trisomy21)	prenatal chromosome analysis
Noonan syndrome	pre- / postnatal mutation analysis
Congenital infections	
TORCH	maternal serology testing and fetal culture and PCR
parvoB19	maternal serology testing and fetal culture and PCR
Haematological/fetal anaemia	Doppler evaluation of peak systolic velocity (PSV) in middle cerebral artery (MCA)
red blood cell immunisation	MCA-PSV Doppler and blood type and antibody screen
fetomaternal haemorrhage	MCA-PSV Doppler and Kleihauer-Betke test
other causes of fetal anaemia	MCA-PSV Doppler and maternal haemoglobin electrophoresis
Metabolic	
lysosomal storage disease	Lysosomal enzyme evaluation in fetal cord blood
glycogen storage disease	Postnatal metabolic screening
mucopolysaccharidosis	Postnatal metabolic screening
Congenital Disorder of Glycosylation (CDG)	Postnatal metabolic screening

further secondary fetal hydrops can develop. This process is thought to be caused by direct compression of the fetal heart and resulting impairment of cardiac function (18). Severe and longstanding compression of the lungs can also lead to pulmonary hypoplasia (19, 20).

Multiple studies have tried to determine prognostic factors in primary fetal hydrothorax. Premature delivery and the presence of hydrops consistently appear as poor prognostic indicators; gestational age at diagnosis and presence of polyhydramnios do not seem to have an impact on outcome. When effusions are bilateral, outcome has been reported to be worse in some studies (6, 14) but not in others (13, 21).

Antenatal Management and outcome

Various antenatal management strategies have been reported for FPE including conservative management, thoracocentesis, thoracoamniotic shunting and pleurodesis.

Conservative management

When the amount of pleural effusion is small and no signs of lung compression or hydrops are present, conservative management is appropriate. In these cases there is no direct risk to the fetus and spontaneous regression might occur. When no further progression occurs the prognosis is good, with reported survival rates ranging from 70-100% (14, 16).

Frequent ultrasound evaluation is needed to detect further progression of FPE and allow for further treatment if necessary.

Antenatal thoracocentesis

Thoracocentesis can have both a diagnostic and therapeutic role in the management of FPE. When FPE progresses and hydrops or polyhydramnios develop, thoracocentesis allows for decompression of the pleural fluid collection.

After removal of the pleural fluid, underlying cardiac or pulmonary abnormalities might become apparent. When fetal hydrops is secondary to the mass effect of the pleural effusion, it is more likely to resolve after the intervention. In cases of generalized hydrops not secondary to FPE, hydrops is less likely to resolve (22). The fluid aspirated from the fetal thorax can be used for fetal chromosome analysis using fluorescent in-situ hybridization (FISH) as it usually contains a high rate of lymphocytes (23).

In some cases single decompression of the thorax is not followed by recurrence of pleural fluid and thus is a definitive treatment (24). In most cases, however, pleural fluid reaccumulates in a few days. In these cases repeated thoracocenteses could be considered (13, 14). Because of the cumulative risks of repeated procedures and the usually rapid reaccumulation of fluid in most cases, a more definitive form of thoracic draining is chosen by placement of a permanent thoracoamniotic shunt (TA shunt).

When a fetus presents with a considerable amount of pleural fluid at near-term equivalent age, single needle thoracocentesis should be envisaged even shortly before delivery to allow for lung expansion after birth and facilitate transition and neonatal resuscitation (25, 26). There is no consensus on the gestational age after which TA

shunting is no longer warranted and delivery after single needle thoracocentesis is the better option.

Thoracoamniotic shunting

Placement of a TA shunt should be considered in case of reaccumulation of fluid after thoracocentesis. The following criteria for TA shunting have been reported in the literature (27, 28):

- fetal pleural effusion likely to be isolated chylothorax
- normal fetal karyotype with no significant other fetal anomalies
- rapid re-accumulation of fluid after initial thoracocentesis
- fetal hydrops and/or symptomatic / progressive polyhydramnios

The procedure has been described elsewhere (29, 30). It is carried out under sterile circumstances. Maternal sedation can be used but is not obligatory. A local anaesthetic is used at the site of insertion. Maternal broad-spectrum antibiotics are given prior to the insertion and continued until after the procedure. Some authors have advocated the use of tocolytic around the procedure but it is not necessary in every case (15). The procedure is carried out under continuous ultrasound guidance. The trocar and cannula are introduced transabdominally into the amniotic cavity. The trocar is then inserted into the fetal pleural cavity through the chest wall as close as possible to the mid-axillary line at the base of the scapula. After removal of the trocar, the double pigtail shunt is inserted into the cannula. The distal part is advanced into the fetal pleural cavity. After withdrawal of the cannula into the amniotic fluid the proximal part of the shunt is pushed out of the cannula. When effusions are bilateral a second shunt can be placed in the contralateral pleural cavity. In Japan only double-basket catheters are approved for fetal shunting procedures.(31) This catheter is thinner than the, more widely used, double pigtail catheters.

Perinatal outcome after TA shunting for primary fetal pleural effusion has been reported in numerous series. Care should be taken when comparing the perinatal outcome between these series due to differences in inclusion criteria and heterogeneity between the series: not all pleural effusions were documented chylothorax and not all cases were hydropic or had documented high-risk criteria at the time of treatment. Furthermore multiple series were published in which cases where invasive fetal therapy was performed are described together with cases where no fetal therapy was performed (32-34). Only the series where TA-shunting was performed or series where the cases with TA-shunting could easily be identified are described in this chapter.

Outcome of the different studies is summarized in Table 2 including a total of 519 cases. The overall perinatal survival after shunt placement was 60%, ranging from 33 to 79%. Survival was generally better when there was no associated hydrops. Importantly,

most authors agree that without signs of hydrops or clinically relevant polyhydramnios, fetal shunting is not indicated. In a recent systematic review, the authors concluded that the highest survival rates for hydropic FPE were reported using a protocol of one initial thoracocentesis, followed by shunting, but the difference compared to the group managed by primary shunt placement was small (35).

Table 2. Perinatal outcome after TA shunt

First author, year (ref)	number of cases	Hydrops (%)	mean GA at delivery - wks (range)	Perinatal survival % (range)
Rodeck, 1988 (36)	8	63	32 (32-39)	75
Nicolaides, 1990 (37)	47	64	36 (24-40)	62
Bernaschek, 1994 (38)	9	100	31 (22-36)	33
Picone, 2004 (39)	54	100	36 (28-40)	57
Smith, 2005 (22)	21	76	32 (22-40)	48
Rustico, 2007 (16)	53	81	21% ≤ 24 wks 25% 25-28 wks 47% 29-32 wks 7% ≥ 32 wks	64
Yinon, 2010 (15)	88	67	34 (19-42)	59
Caserio, 2010 (40)	6	66	33.5	67
Walsh, 2011 (41)	15	60	35	53
Pellegrinelli, 2012 (42)	27	75	34	52
Takahashi, 2012 (43)	24	71	34.8	79
Petersen, 2013 (44)	6	50	34	67
Peranteau, 2015 (45)	35	60	34	60
Mallmann, 2017 (46)	78	36	33	59
Witlox, 2017 (47)	48	100	34 (26-42)	63
Hidaka, 2018 (31)	10	100	33 (29-38)	70
TOTAL	529	71		60 (33-79)

All the reported series are descriptive and retrospective in nature. All series are described by referral centers that offer fetal therapy where patients are often referred to by other hospitals. In most series only cases that received fetal therapy are described. No randomized controlled trials comparing different treatment modalities or comparing treatment to conservative management have been performed. The risk of selection bias is therefore very high and the superiority of TA shunting over conservative management or thoracocentesis cannot be established.

Shunt related complications include shunt migration into the amniotic fluid or fetal thorax (6, 48), migration into the maternal peritoneal cavity (37) and shunt obstruction (15, 49). Shunt migration into the amniotic fluid is the most frequent complication. Lateral or ventral shunt placement can result in easier shunt dislocation because of traction on the shunt by fetal limb movements. Therefore dorsal shunt placement is preferred.

In some cases, a second shunt may be required if there is significant re-accumulation of pleural fluid. After migration of the shunt into the fetal thorax different approaches are adopted after birth. Some advocate postnatal surgical shunt removal (50, 51), but conservative management has also been described without long-term complications (48, 52). We have seen multiple cases of shunt migration into the fetal thorax where we left the shunt in situ after birth without complications. Shunt occlusion can occur, either due to the proteinaceous content of the pleural fluid, or from thrombus following bleeding at the time of insertion. Again, in cases where there is significant re-accumulation with persistence or recurrence of hydrops, re-insertion may be indicated. For these reasons, close ultrasound surveillance after shunt placement is required.

As a consequence of the invasive nature of the procedure, PPROM has been reported in several series after TA shunt placement, and in two large series was reported in 6-17% (15, 39). Overall, the rate of preterm birth is reasonably high following shunt placement, partly due to PPROM. The extent to which the procedure versus the underlying pathology and associated polyhydramnios contributes to this outcome is not clear.

Less common complications have been reported following shunt placement including a case of a constriction band due to the shunt wrapping around the fetal arm(53), fetal demise secondary to umbilical cord laceration at the time of shunt insertion (15),lung hilum compression (54) and amniotic band syndrome (55).

Pleurodesis

Another approach to the treatment of FPE is in utero pleurodesis. This is used as an alternative to shunting or as an adjunct after shunt failure. The procedure requires the same equipment and approach as thoracocentesis, but a sclerosing agent is instilled in the fetal pleural space after drainage of the effusion. Most often, OK-432, an inactivated strain of group A streptococcus pyogenes, is used as the sclerosing agent. It generates a local inflammatory response which increases vascular permeability and thereby increases lymph drainage (56). Adhesion of the pleural membrane and lung surface can also be responsible for the effect of this technique (57). The largest series published to date describes 45 fetuses treated with OK-432 pleurodesis. The overall long-term survival was 35.6% and for hydropic fetuses this was only 14.8% (58), i.e. much lower compared to the series with cases managed with thoracocentesis and TA shunting. In addition, the safety of the agent has been questioned in animal experiments (59, 60). Although the technique seems promising because pleurodesis can potentially reduce pleural leakage and inhibit the possibility of pleural effusion, the low success rate and potentially toxic nature of the substance used warrant caution. Therefore this approach is highly questionable and should not be adopted, not even in studies in human subjects, until a safe agent has been established in animal studies.

Antenatal clinical approach

An algorithm describing the decision analysis in cases of FPE is shown in Figure 3. As the course of FPE can vary from spontaneous regression to deterioration leading to heart failure and hydrops, the decision to treat, deliver prematurely or follow conservatively can be difficult. After exclusion of other structural or chromosomal anomalies, management will depend on the gestational age, rate of progression or regression of the pleural effusion and presence of hydrops. When the amount of pleural effusion is small or moderate and no signs of cardiac decompensation or hydrops are present, a conservative approach with close follow-up is reasonable, given the favourable prognosis. Single thoracocentesis before birth can be considered to facilitate pulmonary transition after birth.

Most authors suggest TA-shunting should be reserved for fetuses with signs of hydrops (35, 39). Others advocate intervention even without hydrops when rapid worsening of the effusion is seen, especially in the presence of polyhydramnios or mediastinal shift (16, 22, 61).

Different opinions exist about the gestational age until which TA-shunting should be performed. Some suggest TA-shunting should be performed only < 32 (14) or < 34 (16) weeks' gestation. Others suggest shunting may be beneficial until 36 weeks' gestation (30). In our experience, shunt placement between 34 and 36 weeks' gestation allows for reversal of fetal hydrops and improvement of fetal condition before birth, therefore facilitating transition and resuscitation at birth (47). It also allows for birth at later gestation, reducing the risks associated with premature delivery. The risks associated with shunt placement at a later gestational age are not exactly known.

Maternal complications of hydrothorax

Maternal mirror syndrome can occur in the presence of fetal hydrops of any etiology. This has also been described related to fetal pleural effusions. The maternal condition can improve following fetal therapy (62).

Neonatal management and outcome

Antenatal and perinatal outcome after TA-shunting for FPE have been reported in numerous publications. However, reports on postnatal management and outcome are much more scarce and long-term follow up has only been reported in a few papers (16, 29, 40, 63) Evaluation of outcome is hampered by the heterogeneity of the described populations in the various series. We described for the first time the postnatal management and outcome in a homogeneous cohort of only hydropic fetuses treated with TA-shunting before birth (chapter 4) (47). Most series describe a mix of hydropic and non-hydropic fetuses treated with thoracocentesis and/or TA-shunts(15, 16, 37, 46) In other series, neonates treated for congenital chylothorax after birth are also included

(34, 40, 44). Therefore the following description is based on studies describing a heterogeneous group of neonates with varying fetal clinical course and fetal treatment history.

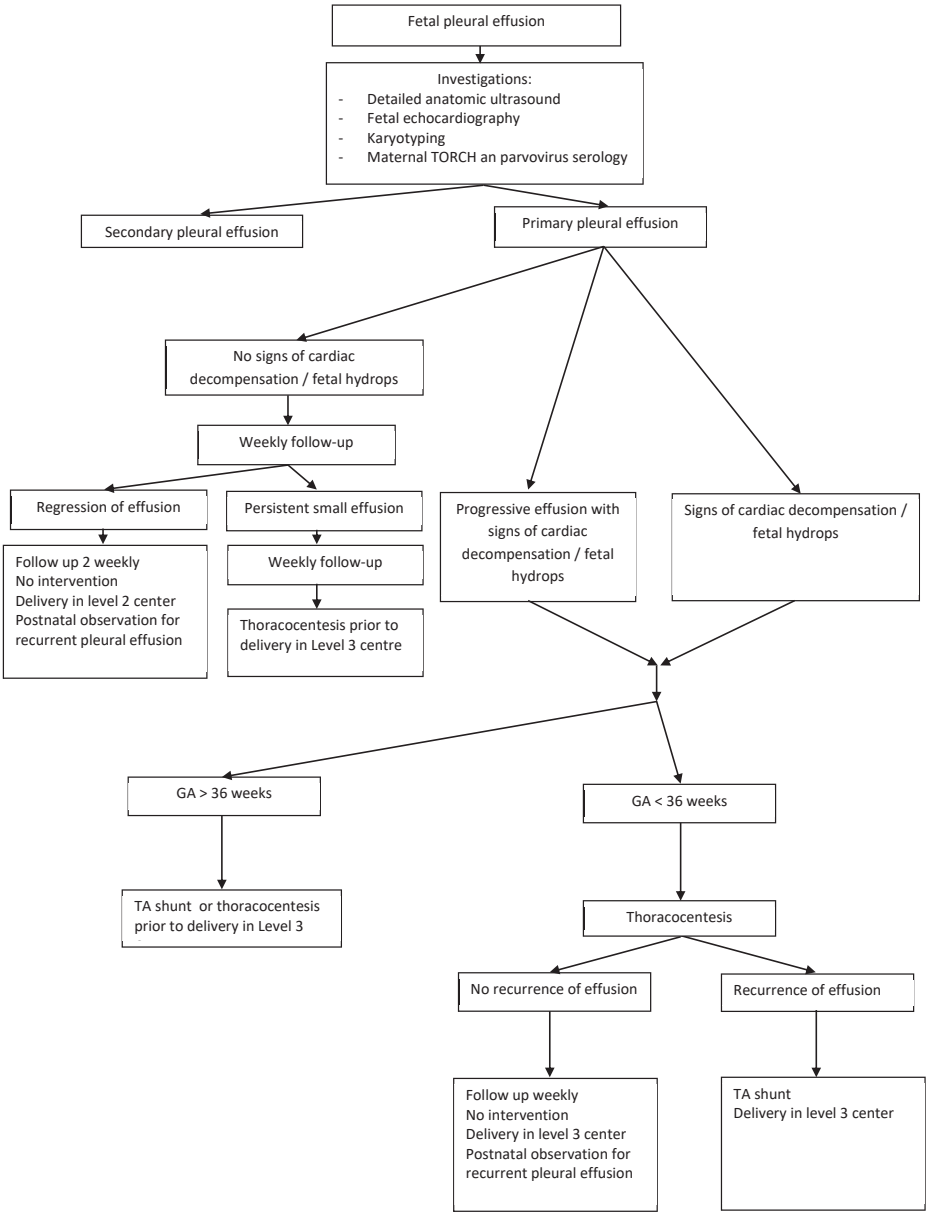

Figure 3. Decision analysis in cases of FPE

Respiratory management

Direct postnatal treatment is mainly aimed at providing adequate respiratory support and allowing for maximal lung expansion. When a TA-shunt is still in situ, it should be clamped directly after birth to reduce the risk of air entering the pleural space after onset of spontaneous breathing. Adequate respiratory support according to the international resuscitation guidelines should be given (64). When pleural effusion is still present, thoracocentesis or placement of a new pleural drain might be necessary to reduce intrathoracic pressure and allow for adequate lung expansion.

A subset of children can be affected by pulmonary hypoplasia due to inadequate prenatal lung growth and development caused by the space occupying effect of the FPE. These children often need extensive respiratory support after birth, including High Frequency Ventilation (HFV) and Nitric Oxide (NO) therapy because of Persistent Pulmonary Hypertension of the Newborn (PPHN). Neonatal mortality in this subgroup of children is high and demise often occurs within 48 hours after birth due to intractable respiratory failure (45, 47).

Pleural effusion is still present at birth in about 60% of cases (47). In some cases pleural effusion reappears after birth, but evacuation of these pleural effusions is not always necessary since the effusion may also regress spontaneously over time. Spontaneous regression is probably due to the lung expansion after birth which is a counterforce against leakage of chyle into the pleural cavity. In our experience, thoracocentesis or more permanent pleural drainage is generally not required when the amount of pleural effusion is small and/or the child does not need respiratory support.

Medical and dietary management

In cases with large pleural effusions and/or when increasing respiratory support is needed after birth, evacuation of pleural fluid is indicated. Single thoracocentesis can be attempted first. Lung expansion after the removal of pleural fluid can tamponade the thoracic duct or lymphatic leakage leading to reduction and cessation of pleural fluid production. When the pleural fluid reappears fast or increases in amount more permanent drainage through a chest tube can be considered.

In most children, pleural fluid production stops within a few days or weeks after birth. Multiple treatment options are available after birth to reduce chyle production and reduce the amount of pleural fluid and/or the need for drainage. After birth and after introduction of enteral feeding, the composition of chyle changes. Lymph fluid is mixed with emulsified free fatty acids that are formed in the intestine during the digestion of fatty foods and are taken up by intestinal lymph vessels. Therefore the clear and yellow fluid that is found before birth changes to an opalescent, milky fluid after the introduction of fat in the neonate's diet. This can be used to make a definite diagnosis of chylothorax in a neonate with persisting pleural effusions after birth. Chylothorax

is diagnosed when pleural effusion contains > 1.1 mmol/l triglycerides (with oral fat intake) and has a total cell count ≥ 1000 cells/µl, with a lymphocyte fraction ≥ 80% (4). When the diagnosis chylothorax is reached, dietary modification can be used to try to reduce the production of chyle while waiting for spontaneous closure of the defect.

After birth, feeding the baby with mother's milk could be considered as the first-line diet as this is the optimal diet for a newborn (65). When the pleural fluid is diagnosed as chyle and the production is progressive after thoracocentesis, a diet containing medium-chain triglycerides (MCT) should be initiated. MCTs are absorbed directly into the portal venous system and therefore bypass the drainage through the lymphatic system. MCT formulas lack essential fatty acids. Supplementation of these is needed when prolonged therapy with MCT based formulas is given (66). An alternative to the use of MCT formula is the use of processed mother's milk. Solidified-fat is removed from the human milk after centrifugation. Successful use of this method in infants with chylothorax has been described (67).

When a MCT-diet is not successful in reducing the pleural fluid production, complete enteric rest is often used as next treatment step. Some advocate this option directly after birth. The neonate can be fed by total parenteral nutrition waiting for the chyle production to decrease.

As a next step in treatment of persisting chyle production Somatostatin or Octreotide can be considered. Somatostatin is an endogenous hormone while octreotide is a synthetic, long-acting somatostatin. The mechanism of action of Somatostatin and octreotide is not completely clear, but it is thought to cause a reduction in intestinal blood flow by vasoconstriction of the splanchnic circulation, leading to reduction of chyle production (68). Octreotide has a longer half-life and can be given both intravenously and subcutaneously (69). It is usually administered intravenously in a dose of 0.3 to 10 mcg/kg/hour (70-72). The optimal duration of treatment is unknown. Most studies report a decrease in chylous effusion within a week time (72-74). Side-effects of treatment are also reported and include hyperglycemia, hypothyroidism (75), pulmonary hypertension (74), necrotizing enterocolitis (76) and liver dysfunction.

Surgical management

If all medical options have failed, surgery should be considered as a last-resort treatment option. There is no international consensus on the timing of surgery. Most recommend a period of at least 3-4 weeks of conservative treatment before surgery is considered (4). Several surgical options are available including direct surgical ligation in case of clearly identified thoracic duct rupture (by lymphangiography), thoracoscopic duct ligation, obliteration of the pleural space by injection of a sclerosing agent and placement of a pleuroperitoneal shunt.

Complications of chylothorax

Prolonged drainage of chyle from the thorax can lead to complications due to the loss of proteins and electrolytes. Malnutrition, hyponatremia, fluid imbalance, increased risk of thrombosis and secondary immunodeficiency have been described (77, 78)

Long-term follow-up

Only few reports have been published describing long-term follow-up after TA shunting for FPE. The series that have been published usually give limited data and focus mainly on respiratory/pulmonary outcome without evaluating the neurodevelopmental outcome. An overview of all published reports on long-term outcome after FPE (with or without fetal therapy) is presented here below.

The first report on placement of a TA-shunt for FPE was made by Seeds and Bowes in 1986 (29). The child was born around 30 weeks' gestation and needed ventilator support and continuous drainage after birth. The infant was reported to do well at one year of age with only an episode of acute bronchiolitis as a complication.

Booth et al. describe two hydropic fetuses of which one was treated with a TA-shunt (5). They were born at 34 and 36 weeks' gestation and the chylous effusion disappeared after dietary restrictions. They were reported to develop normally at the age of one year.

Murbayashi et al. describe a fetus with FPE in which a TA shunt was placed at 23 weeks' gestation. The child was born at 40 weeks' gestation and had no pleural effusion after birth. At 6 months after delivery she was developing normally.

Rustico et al. report on a series of 53 fetuses treated with TA-shunting of which 81% were hydropic (16). Overall, 34 infants survived the neonatal period (58% of hydropic fetuses survived, compared to 90% of non-hydropic foetuses). At follow-up, ranging from 1 to 7 years after birth, 10 infants had clinical abnormalities that were not further specified.

Caserio et al. describe a group of 29 neonates with congenital chylothorax (40) of which 27 were diagnosed antenatally. Hydrops was found in 18 (67%) and 11 received an intrauterine intervention of which 6 were TA-shunt placements. 15 infants survived the neonatal period. Four of the survivors, that were also born prematurely between 32 and 34 weeks had recurrent respiratory tract infections during infancy and were diagnosed with asthma. The remaining 11 were reported to have a normal clinical situation. Neurodevelopmental outcome was not formally assessed.

In 2012 Resch described long-term follow-up of six patients with congenital chylothorax (79). In three patients, antenatal thoracocentesis was performed and in two a TA-shunt was placed. One child was diagnosed with Noonan syndrome. The neonatal course was relatively complicated with 5/6 needing inotropic support, three cases needing octreotide and one case needing surgical intervention for persisting chylotho-

rax. Long-term follow-up at a mean (range) age of 7 (3.5-12) years revealed no recurrence of chylothorax. Height and weight growth was normal in all except for the child with Noonan syndrome. Four children were re-hospitalised due to infectious diseases and three had recurrent respiratory infections. Five out of six children were classified as having normal development. One child developed autism with neurodevelopmental delay and muscular hypotonia. Pulmonary function testing was performed in five children and showed mildly abnormal results in three of them. The authors conclude that neurodevelopmental outcome is mainly dependent on associated anomalies or prematurity.

Thompson et al. describe respiratory function in infancy after TA-shunting for FPE (80). 48 fetuses had shunts inserted (12 were hydropic). 28 children survived the neonatal period, one infant died at the age of 6 months of septicaemia following severe necrotizing enterocolitis (NEC) in the neonatal period. In seventeen of the 27 survivors lung function was assessed by measurement of functional residual capacity (FRC) using a helium dilution technique and were compared to measurements of FRC in healthy control infants. No infants were symptomatic at the time of examination. Fifteen of the patients had FRCs within the normal ranges. Two infants had low FRCs, but neither had recurrent respiratory symptoms. The authors conclude that TA-shunting may prevent serious respiratory morbidity in survivors of fetal pleural effusion.

Reiterer describe a boy, treated with TA-shunts at 26 weeks' gestation and born at 34 weeks and 6 days gestation (81). The boy had severe and prolonged respiratory insufficiency. The pleural fluid showed low lymphocyte counts and did not show the typical findings of chylothorax. A lung biopsy was performed confirming the diagnosis primary pulmonary lymphangiectasis (PPL). He was discharged home at the age of 7 months and still required assisted ventilation through tracheostomy at the age of 3 years and 7 months. The infant was reported to have mild global developmental delay.

Mallmann et al. described a series of 78 fetuses with FPE treated with TA-shunt (46). 28 fetuses (36%) were hydropic. 31 fetuses (40%) had additional anomalies, of which 14 (20%) had trisomy 21 and 11 (14%) other genetic abnormalities. 69 (89%) children were live born of which 46 (59%) were born premature. 46 children survived the neonatal period. Long-term follow up was performed at a mean age of 20.1 months (0-60 months). Of the 46 survivors, 27 (59%) were largely free of long-term health problems. The remaining 19 children had genetic syndromes: 13 cases of Down syndrome, 3 cases of unknown syndromes and one each of Noonan, Opitz-G/BBD and Kabuki syndrome.

The only study that performed standardized neurodevelopmental follow-up in survivors after TA-shunting was from our own group (chapter 5). 48 hydropic fetuses with FPE were treated with TA-shunts (47). 41 (85%) neonates were live born and 31 (76%) survived the neonatal period. A follow-up visit was planned at a minimum age of 18 months to allow for thorough neurodevelopmental testing using Touwen neurologic

examination (82) and cognitive and motor development assessment using the Bayley Scales of Infant and Toddler Development (83). Of the 31 survivors, 20 were tested. Eight had an age below 18 months, one had trisomy 21 and two were lost to follow-up. Mean age at the follow-up visit was 50.5 months. Three children (15%) needed respiratory support at discharge from the hospital. Seven children (35%) were readmitted because of respiratory problems within the first two years of life. One child was diagnosed with Congenital Pulmonary Lymphangiectasia (CPL) and still requires assisted ventilation through a tracheostomy at the age of 2 years. Three children (15%) had severe motor development delay, of which one was diagnosed with a congenital neuropathy. Severe neurodevelopmental impairment was detected in 3/20 (15%) of survivors.

CONGENITAL PULMONARY AIRWAY MALFORMATIONS (CPAM) AND BRONCHOPULMONARY SEQUESTRATIONS (BPS)

Etiology

Most prenatally detected lung and airway malformations are congenital pulmonary airway malformations (CPAM) or bronchopulmonary sequestrations (BPS). CPAM (originally and alternatively called Congenital Cystic Adenomatoid Malformation CCAM) is a developmental anomaly of the lung characterized by overgrowth of terminal bronchioles and a lack of normal alveoli (84). The pathogenesis remains largely unknown. Stocker histologically classified CPAM into three types (84): type I single or large cysts, where the largest cyst is >2mm, type II with multiple small cysts usually less than 10 mm in greatest diameter and type III with very small cysts with a homogeneous aspect. For prenatal description, a more practical ultrasound-derived classification was developed by Adzick(85). Lesions are classified as macrocystic or microcystic by ultrasound appearance where macrocystic lesions contain one or more cysts measuring ≥5mm.

The incidence of CPAM is estimated to be between 1:25.000 and 1:35.000 pregnancies (86) or 1 per 12.000 live births (87).

Bronchopulmonary sequestration (BPS) lesions appear as immature lung tissue on histology (88). This mass of lung tissue is non-functioning and has no communication with the bronchial tree. A BPS is supplied by an anomalous systemic blood vessel, often originating from the descending aorta. BPS lesions form as a supernumerary lung bud, arising distal to the lung and can develop intralobar or extralobar, depending on whether the supernumerary bud migrates before or after pleural development (89).

More recently hybrid lesions have been described with histologic and pathologic features of CPAM and arterial supply similar to BPS (90, 91). With advancing imaging accuracy hybrid lesions are found more often, accounting for about 20% of congenital lung malformations (92).

Diagnosis

CPAM are usually diagnosed on prenatal ultrasound when a cystic parenchymal lung mass is found. The differential diagnosis includes bronchogenic cysts, mediastinal teratoma, congenital lobar emphysema, thoracic neurenteric cysts and mainstem bronchial atresia (93). A detailed anatomical ultrasound and echocardiography is required to exclude diaphragmatic hernia or congenital heart disease. Associated anomalies can be found and are present in up to 15% of cases (87, 94). CPAM are most often diagnosed at the time of routine ultrasound screening at 18-20 weeks' gestation.

Fetal magnetic resonance imaging (MRI) can help reaching the definite diagnosis by providing more detailed imaging of the lesion and help distinguish, for example, between microcystic CPAM and BPS (95).

Aneuploidy has been reported occasionally in fetuses with CPAM and genetic screening is often performed in these fetuses (86, 96).

Natural History

The natural history of CPAM varies greatly and is difficult to predict. Spontaneous regression is most common. The mechanism leading to spontaneous regression is not known, but it may be because of outgrowing of the vascular supply of the CPAM or spontaneous resolution of the underlying bronchial obstruction (97, 98). CPAM growth usually peaks at 26-28 weeks' gestation, whereafter no further growth and often even spontaneous regression occurs (99). Reported rates of spontaneous regression vary. The largest published series describes sonographic evidence of regression in 49% of cases (100). After regression the lesions can be hard to find in the third trimester. Postnatal computed tomography can identify these lesions (101). The majority of fetuses survive until birth without intervention and have no problems after birth.

Large CPAM lesions can cause secondary physiological derangements primarily because of mass effect of the lesion in the fetal thorax. Mediastinal shift and compression of the vena cava and oesophagus can lead to fetal hydrops with or without polyhydramnios (85, 94). This progression is reported in 12 to 40% of cases (87, 102, 103). This is likely to be an overestimation because these reports are from fetal treatment centres likely to receive referrals of more severe cases leading to selection bias.

A large lesion on ultrasound and secondary mediastinal shift may predict the progression to hydrops. The CCAM volume ratio (CVR) was developed as an objective measurement to define prognosis (104). A CVR > 1.6 predicted the development of hydrops in 75% of cases. These cases should be monitored more closely with ultrasound surveillance twice weekly. However, in the group with a CVR < 1.6, 17% still developed hydrops. Complete reassurance based on ultrasound features is therefore not possible and ultrasound surveillance is indicated throughout pregnancy.

The CVR can also be used to predict outcome after birth in non-hydropic cases. Ehrenberg-Buchner et al. showed that all cases that experienced hydrops at any time in gestation had respiratory morbidity after birth (105). For fetuses with a maximum CVR >1.0 during gestation the likelihood of respiratory problems and need for neonatal lung resection was 75%. For fetuses with a CVR < 1.0 the likelihood of being asymptomatic after birth was 98%.

Antenatal management and outcome

In general the prognosis for a fetus with a CPAM is favourable as it usually stops growing or regresses in size during the third trimester. A survival of more than 95% was described in the largest series on the outcome of fetal lung lesions (100). Conservative management with close monitoring of the lesion is therefore appropriate in most cases.

When fetal hydrops does develop, the mortality rate increases dramatically with a reported mortality rate of more than 95% before or after birth (100). A systematic review of the literature by Knox et al. in 2006 found significantly higher odds of survival in hydropic fetuses treated with TA-shunt (106). The presence or development of hydrops could therefore form the indication for fetal therapy. Cass et al. added fetal echocardiography to the assessment of fetal condition in large lung masses. An abnormal echocardiogram and findings of fetal heart failure appeared to be more specific predictors of impending fetal demise than the presence of fetal hydrops alone (107).

When hydrops develops above a gestational age of 32 weeks the option of delivery followed by postnatal surgery should be evaluated and is advocated by some. The possibility of recovery of hydrops after fetal therapy may lead to prolongation of the pregnancy and postpone delivery leading to the birth of a more mature baby in a much better condition without hydrops. We therefore think that fetal interventions that can potentially reverse hydrops and improve the condition of the fetus should be considered even up to 37 weeks' gestation.

Available modes of therapy include administration of corticosteroids, thoracocentesis, TA shunting, laser therapy and sclerotherapy. The different fetal treatment options will be discussed below.

Maternal corticosteroid therapy

Maternal intramuscular corticosteroid administration has been shown to reduce the size of CPAM and has become the first-line treatment of large CPAM because of its non-invasive nature; especially in microcystic or solid lesions where decompression of the dominant cyst is not an option. Usually 2 doses of 12 mg betamethasone, 24 hours apart, are given. Resolution of hydrops and shrinkage of the CCAM after maternal steroid administration was first described by Higby et al. in 1998 (108). It is usually used for cases of microcystic CPAM where invasive therapy decompressing the major

cysts is not an option. Since the first report several series have reported resolution of fetal hydrops in 54-80% of cases after this treatment (109-112). An increase in CPAM size after the steroid course has been observed and the repeated effect of multiple steroid courses has been described (112, 113).

In BPSs maternal betamethasone therapy has also shown to be effective in treatment of large lesions in utero.(114)

Antenatal thoracocentesis

The dominant cyst in macrocystic CPAM can be reduced in size by needle thoracocentesis. Pleural effusion, occurring in cases of BPS or microcystic CPAM can also be drained by needle thoracocentesis. This allows for increased cardiac function and can therefore lead to resolution of hydrops. However, the fluid within the cyst usually reaccumulates within days and repeated procedures may then be needed. Serial thoracocenteses have been described allowing for prolongation of pregnancy and live birth of the fetuses (115).

Thoraco-amniotic shunting

More permanent drainage of the dominant cyst in macrocystic CPAM can be achieved by placement of a thoracoamniotic shunt. In hydropic foetuses we reported live birth in 89% of cases after TA shunting (115). Overall perinatal survival was 68%.

Other groups have also published small series of thoracoamniotic shunting in macrocystic CPAM (45, 116-119) and have found comparable results.

TA shunting can also be used to drain pleural effusion associated with BPS or microcystic CPAM and leading to hydrops. Resolution of hydrops, live birth and neonatal survival was reported in 100% of 14 cases (115) and (114). However, the risk of overestimation of the positive effect is large due to publication bias since these were all case reports or small case series.

Because of the non-invasive nature of treatment with betamethasone, this can be used as first-line therapy in macrocystic CPAM too. When reversal of hydrops does not occur, invasive fetal therapy is indicated.

Laser and sclerosing agents

Percutaneous laser therapy can be used to ablate CPAM and has been reported only in a few cases (120-123). The outcome was diverse with 2 cases of fetal or neonatal demise. Percutaneous insertion of a sclerosing agent into the CPAM was reported in 11 cases (124, 125). In four cases IUFD occurred, in one case directly related to the procedure, in one case because one day after the procedure due to severe hydrops and in two other cases several weeks later due to enlarging or non-shrinking CPAM. The other 8 cases showed reduction in CPAM size, resolution of hydrops and delivery at term. One baby

died in the neonatal period of nosocomial sepsis. One baby had a prolonged intensive care period after CPAM resection and was shown to have delays in motor and language development and recurrent respiratory problems at 18 month follow-up.

Interruption of flow in the systemic feeding vessel of a BPS or hybrid lesion has been described as a treatment option in hydropic fetuses with BPS. Laser ablation of the feeding vessel has been described in a few small series and case reports and generally shows reversal of hydrops and shrinkage of the lesion when successful laser ablation of the feeding vessel can be applied (126-129).

Interruption of blood flow in the feeding vessel of BPS has also been described using injections of pure alcohol in one case (130), polidocanol in three cases (131) and N-butyl-2-cyanoacrylate in one case (132).

Open fetal surgery

In open fetal surgery the uterus of the pregnant woman is opened and the fetus is exposed. The affected lung lobe is resected and the fetus is returned to the womb and the uterus is surgically closed. Maternal fetal surgery is considered when there is a large microcystic lesion and associated fetal hydrops, which could not be treated by medical or less invasive fetal surgical treatment. Therefore, this procedure is not primarily considered for macrocystic lesions where decompression of the dominant cyst through thoraco-amniotic shunting is generally considered to be the preferred initial approach to reverse the mediastinal shift and fetal hydrops. The most experience in maternal fetal surgery of pulmonary adenomatous lesions with fetal hydrops, with 30 cases, is described by two American centers (104, 133).

The criteria for open fetal surgery are:

- 20-30 weeks' gestation
- No additional fetal anomalies (not associated with the primary lung lesion)
- Normal fetal karyotype (banded resolution standard for amniocentesis or CVS)
- No maternal medical or surgical contraindications to surgery (including maternal BMI >35)
- No maternal contraindications to general anesthetic
- No obstetrical risks for preterm delivery or previous preterm delivery

The surgical technique is well described (134) with continuous surgical and obstetrical quality improvement over time.

Single center pregnancy outcomes are reported among the survivors, in-utero hydrops resolved within 2 weeks and mediastinal decompression within 3 weeks of the surgery. The most significant risk is preterm labour, with more than 50% delivering prior to 34 weeks (98). Data from a larger series of pregnancies exposed to fetal surgery, in most cases for meningomyelocele without hydrops, indicates that 34% have

evidence of chorioamnion separation after the procedure, 40% have premature rupture of membranes (PROM), and 28% deliver prior to 33 weeks' gestation (135). It is this risk of preterm labour, which provides the impetus to develop less invasive techniques.

In a retrospective review comparing treatment with steroids versus open fetal surgery, 83% of fetuses in the steroid group survived until neonatal discharge compared to 56% in the open fetal surgery group (136). After fetal surgery mean gestational age at delivery was significantly earlier (mean 31 vs 34 weeks in the steroid group). Importantly, fetal surgery was only performed before 2001, whereas steroid treatment had only been used after 2001.

Finally, fetal surgery has significant implications on future pregnancies. Subsequent pregnancies have an increased risk of preterm birth (25%), uterine dehiscence at the hysterotomy site (12%), uterine rupture (6%), and maternal hemorrhage requiring transfusion (9%) (137).

Open fetal surgery is only offered in a few centers worldwide mainly in the US. Because of the significant implications for the mother and the availability of multiple less invasive therapeutic options, open fetal surgery is not envisaged in cases with CPAM or BPS in Europe.

EXIT to resection

When significant neonatal respiratory compromise is anticipated at birth, Ex Utero Intrapartum Therapy (EXIT) delivery may be considered. This procedure is used in some very high-risk lesions, as it takes advantage of the placental bypass to facilitate fetal thoracotomy by controlled resection without respiratory decompensation and subsequent intubation prior to umbilical cord clamping.

In a single series, EXIT was performed on 9 fetuses at an average gestational age 35 weeks for high risk lesions, defined as persistently elevated CVR (mean 2.2 at time of EXIT), with significant mediastinal shift and/or hydrops (138). The average time on placental bypass was 65 minutes. Overall survival was 90%, with one neonatal death from bleeding and prematurity. Maternal risks of the procedure are comparable to caesarian section under general anesthetic (139).

Neonatal management and outcome

A systematic review of the literature on neonatal outcome after prenatal interventions for congenital lung lesions is described in chapter 3(47). Respiratory failure is common after birth and is described in 73% of cases of hydropic fetuses with CPAM after fetal therapy and in 56% of cases of BPS after fetal therapy (115). Postnatal survival occurred in in 69% of cases of hydropic fetuses with CPAM after fetal therapy and in 92% of cases of BPS after fetal therapy.

After publication of this review, Schrey et al. recently reported on the outcome of 11 fetuses treated with TA shunting for isolated large macrocystic CCAM. Six fetuses were hydropic and the others had severe polyhydramnios, and/or rapidly increasing lesions. Mean gestational age at delivery was 38.2 weeks. The overall survival rate was 10/11 fetuses (91%) and 5/6 (83%) of hydropic fetuses survived. All but two newborns needed respiratory support after birth. All newborns had uneventful total lobectomy, nine of them in the first weeks after birth and one at the age of 3.5 months. All 10 newborns had no significant surgical complications and were discharged home soon after surgery. Six children were followed up on until 12 to 24 months of age. Four were reported to have normal development and two had mildly delayed language development (119).

The optimal postnatal management of congenital lung lesions is not well known and highly controversial. Management options include conservative/expectant approach and surgical intervention; i.e. removal of the lesion. Consensus exists that postnatal surgical resection of the affected lobe/cyst is warranted in symptomatic lesions, causing respiratory symptoms after birth. In asymptomatic neonates, some surgeons advocate routine postnatal resection to reduce the risks of lung infection and malignancy (140-142). However, the true benefits and potential complications of the various approaches are not well known as randomized studies have never been performed.

No specific management guidelines exist for postnatal management of congenital lung lesions after fetal therapy. In general, macrocystic CPAMs after TA-shunt placement are large lesions that will become symptomatic after birth. Therefore postnatal resection is indicated in these cases as it is in all symptomatic cases. In cases of microcystic CPAM that decreased in size after maternal steroid treatment or cases of BPS where the feeding vessel was ablated, the same management regimen can be followed as in asymptomatic cases. In our hospital, neonates with asymptomatic congenital lung lesions after birth are not primarily referred to a pediatric surgeon for lesion resection. If no symptoms occur after birth, patients are discharged from the hospital. In the first year of life, when no further symptoms occur, a CT scan of the thorax is made to further evaluate the lesion and obtain more detailed information about the exact position and size. The parents are counselled by a pediatric pulmonologist and, if necessary, by a pediatric surgeon, before a decision about resection of the lesion is made.

Long-term follow-up

Long-term follow up in children with fetal lung lesions that received fetal treatment has hardly been reported. Only two small studies have been published where formal neurodevelopmental testing has been performed in these children.

Danzer et al. reported on neurodevelopmental outcome of infants with high-risk fetal lung lesions after fetal intervention (n=2) or EXIT (n=6) (143). Neonates requiring emer-

gent resection of the lesion because of acute respiratory decompensation were also included (n=5). 13 patients were included and neurodevelopmental status was evaluated using the Bayley Scales of Infant Development-III (n=12) and the Wechsler Preschool and Primary Scale of Intelligence -III (n=1). Average scores for cognitive development were found in all children assessed under 3 years of age. The one child tested at 6 years of age scored in the borderline range of intellectual functioning. For language outcome, 15% scored above average, 54% scored within the average range, and 31% had mild deficits. Overall, 77% scored within the average range for neuromotor outcome, while 23% scored within the mildly delayed range.

In the second study performed at our center, we described long-term outcome in 4 cases of BPS and 2 cases of CCAM after fetal therapy (144). The outcome after TA-shunting or laser occlusion of the feeding vessel in BPS was good with normal cognitive outcome in the 4 children tested. The outcome in the CCAM was normal in one child, while the other child was born premature at 26 weeks' gestation and had a prolonged intensive care admission with multiple complications. At the age of 10 years months he had severe neurodevelopmental impairment.

In conclusion the knowledge and experience with fetal interventions for thoracic abnormalities has increased over the last years. The number of patients where comprehensive neonatal and long-term follow up has been described is very limited however. In the next chapter I will describe knowledge gaps and I will propose future research directions.

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Chapter 7

Future research perspectives

FUTURE RESEARCH PERSPECTIVES.

The number of children that have survived after invasive fetal therapy for congenital thoracic abnormalities has steadily increased over the last decades. Knowledge on the natural history of fetuses with these conditions has gradually improved and we have become more informed about their perinatal outcome. However, the number of publications on neonatal outcome and structured long-term follow-up is still very limited. Studies including standardized neurodevelopmental testing and clearly specified criteria for impairment are lacking and are urgently needed, for parents and for medical professionals.

For optimal counselling before potential fetal treatment, parents require detailed information not only on the chances of survival but also on the risks of short-term and long-term morbidity, in particular on the long-term development. This crucial information will enable parents to make an informed decision on whether or not to start invasive fetal treatment. Information on the short and long-term outcome will also help medical professionals identify risk factors for an adverse outcome and help in case selection before treatment. Since the number of patients is limited, follow-up should be an integrated part of fetal therapy where all survivors are included in a long -term follow-up program and data on their neonatal and long-term outcome are collected in a structured way, and ideally included in an international web-based registry.

This chapter focuses on future perspectives and research proposals on the neonatal and long-term outcome of fetuses with congenital thoracic abnormalities. Because of the different nature of the abnormalities fetal pleural effusion and congenital lung abnormalities will be discussed separately.

Fetal pleural effusion

The exact pathophysiologic mechanism behind the origin of primary fetal pleural effusion (FPE) is unknown. It is even questionable whether the cause is the same in different cases of FPE. Knowledge about the anatomy and function of the pleura and pleural liquid mechanics are all derived from adult and animal studies (1). To date, no studies regarding pleural fluid dynamics have been performed in fetuses or neonates. More research into the anatomy of fetal and neonatal pleura and pleural fluid dynamics in fetuses and neonates could lead to better understanding of the different causes of FPE and might lead to new treatment modalities both pre- and postnatally. As a first step, autopsy studies in fetuses and neonates that died after FPE could lead to better understanding of the underlying pathophysiology.

In some cases FPE is associated with genetic abnormalities such as Down syndrome, Noonan syndrome and Costello syndrome (2-4). The causal mechanisms behind these associations are unknown. By performing whole exome sequencing or whole genome

sequencing in a large group of patients with FPE possible links between genetic abnormalities and FPE can be found (5). Better knowledge of the genetic abnormalities associated with FPE can also allow for more advanced genetic testing before treatment and thus better case selection. There is also a need for more genetic tests where results are available after a few days. Fetuses often present with advanced disease where hydrops is already present or imminent. Thoracocentesis can releave thoracic pressure for a short time. But pleural effusion usually reappears within days (6). When results of advanced genetic tests can be available within a week, the results can be taken into account when deciding on more definitive treatment.

A subset of children present after birth with severe respiratory insufficiency and severe persistent pulmonary hypertension of the newborn (PPHN). Neonatal mortality in this subgroup of children is high and demise often occurs within 48 hours after birth (7, 8). This could be due to pulmonary hypoplasia caused by inadequate fetal lung growth. The PPHN could also be caused by failed circulatory adaptation at birth due to a delay in the normal fall in pulmonary vascular resistance (PVR) (9). Persistent pleural effusion at birth could have a role in the delay in the fall of PVR. The use of Physiologically based cord clamping (PBCC) could allow for a more gradual transition (10) which could lead to a better fall in PVR in these neonates leading to less severe PPHN.

The course of disease after treatment differs widely between patients. Various factors such as the occurrence of hydrops, premature birth and short interval between treatment and birth seem to have an important impact on survival(11). To date, only the occurrence of hydrops has clearly been shown to be an independent prognostic factor of survival. All series that reported on treatment and outcome of FPE are relatively small and are heterogeneous. The occurrence of hydrops differs widely between series showing that the criteria for offering treatment differ between centres. Moreover the detail of the reporting of neonatal and long-term follow up is very poor. Also, the neonatal treatment regimen varies greatly between different centres. Registrations using clear inclusion criteria and a robust and uniform set of outcome parameters combining both obstetric and neonatal outcome are urgently required. Ideally, given the low prevalence of the disease, multicentre/multinational registries should be set up to allow for the collection of sufficient data to further improve our knowledge about prognostic factors and optimal treatment for these patients.

Ideally all patients that received fetal treatment are entered in a structured long-term follow up program. This would include formal neurodevelopmental testing up until school age. Also pulmonary function testing at school age should be added to assess the effect of prenatal abnormalities on lung development and function.

CPAM and BPS.

In most cases of CPAM and BPS, spontaneous regression of the lesion occurs already in the third trimester and fetal therapy is therefore not necessary. Even very large lesions in the second trimester of pregnancy can regress and remain asymptomatic after birth. Fetal therapy should therefore be reserved to a selected number of fetuses with persistent signs of hydrops.

The discovery of the beneficial effect of antenatal corticosteroids in inducing reduction of CPAM size has further reduced the number of cases where invasive fetal therapy is considered necessary. In our centre the number of CPAM / BPS cases treated with invasive fetal therapy has decreased significantly from an average of 2 per year in 2003-2004 to only 1 in the last 8 years.

The rarity of the disease makes it very hard for individual fetal centres to collect sufficient patient data to draw firm conclusions about the best indication for invasive fetal therapy or attempt to predict about the course of prenatal, neonatal and long-term outcome. In CPAM and BPS, such as in FPE, collection of cases in global multicentre registries is urgently needed in order to improve our knowledge on optimal management and short- and long-term outcome, and improve the quality of prenatal counselling. The key to reach this ultimate goal is international cooperation and centralization of treatment for these extremely rare but severe diseases.

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Chapter 8

Summary

SUMMARY

After the introduction of prenatal ultrasound abnormalities in the fetal thorax have been detected more frequently. Primary fetal lung abnormalities such as congenital cystic adenomatoid malformation of the lung (CCAM), bronchopulmonary sequestration (BPS) and fetal pleural effusions (FPE) are regularly diagnosed before birth nowadays. In most cases spontaneous regression occurs during pregnancy and fetal intervention is not indicated. In some cases, however, the space occupying effect of the lesion leads to progressive cardiac failure leading to fetal hydrops which is often followed by fetal demise.

In the 1980s permanent decompression of the fetal thoracic abnormality using a thoraco-amniotic (TA) shunt was developed. With this treatment fetal hydrops could be reversed in these cases leading to an improvement in the condition of the fetus, ongoing pregnancies and live born children surviving the neonatal period.

Since then multiple studies have described outcome after fetal therapy for primary thoracic abnormalities. These studies have mainly focussed on pregnancy outcome. In this thesis several studies describing treatment options for fetal thoracic abnormalities are described mainly focussing on the neonatal and long-term outcome of these children.

Fetal therapy options for primary lung lesions

In *chapter 1* a hydropic fetus with large hydrothorax due to BPS is described. Through ultrasound-guided thin needle insertion both laser coagulation of the feeding artery and drainage of the hydrothorax were performed. After this procedure the hydrothorax and hydrops gradually resolved and eventually the BPS considerably diminished in size. A healthy neonate was delivered uneventfully at term. Long term follow-up of the child showed no sign of developmental delay.

In *chapter 2* an overview of the literature on prenatal assessment, natural history and prenatal interventions for fetal lung lesions is presented. CCAM and BPS are usually detected on routine ultrasound screening at 18-20 weeks' gestation. Detection of a feeding artery from the systemic circulation can be identified through colour doppler imaging. Classification into different subtypes can be performed based upon ultrasound findings. The natural history of fetal lung lesions is usually benign as spontaneous regression or slow growth is most often described. Ongoing growth can lead to mass effect of the lesion in the fetal thorax. As a consequence cardiac compression leading to fetal hydrops can occur. The prognosis for a fetus with a lung lesion is generally favourable. The occurrence of hydrops however significantly reduces chances of survival. Therefore fetal hydrops is generally considered to be the indication for fetal intervention. The different fetal treatment options are described. Prenatal steroid therapy is mainly used

in microcystic CCAM. Thoracocentesis is used in macrocystic CCAM but usually leads to rapid reaccumulation of fluid and recurrence of the mass effect of the lesion. Thoracoamniotic shunting to drain macrocystic CCAM or concurring hydrothorax is used as a more permanent means of drainage. Laser ablation or injection of sclerosing agents can be used to either occlude the systemic feeding vessel or directly damage the lung lesion itself. Lastly open fetal surgery has been used accidentally for large predominantly solid CCAMs.

In *chapter 3* an overview of the literature on neonatal outcome after prenatal interventions for fetal lung lesions is described. In non-hydropic cases conservative management with watchful waiting seems most appropriate. Prenatal intervention increases perinatal survival in hydropic fetuses with fetal lung lesions. The increased perinatal survival is associated by an increased risk of neonatal morbidity and mortality. The rates of respiratory failure at birth and postnatal demise are highest in the group treated for CCAM with hydrops. In patients with BPS and hydrops the rates of neonatal morbidity and demise are lower, especially after laser ablation or injection of a sclerosing agent in the feeding artery. Morbidity includes on one hand complications related to prematurity (often inherent to prenatal interventions) and on the other hand respiratory failure related to the congenital lung lesion. Given the increased incidence of neonatal morbidity, neonates with congenital lung lesions after fetal therapy should be regarded by neonatologists as a high-risk population. Unfortunately, the published data on neonatal outcome is often incomplete and summarily reported. Detailed information on the severity of respiratory failure and crucial data on incidence of chronic lung disease was often omitted, limiting our conclusions. The cause of neonatal mortality is often unclear, but is sometimes suggested to be associated with lung hypoplasia.

In *chapter 4* neonatal management and outcome after thoracoamniotic shunt placement for fetal hydrothorax is described in a cohort of patients that was treated at our centre between 2001 and 2016. 48 fetuses, all with signs of hydrops, were treated with TA shunt placement at a median gestational age (GA) of 28.7 weeks. Forty-one of 48 (85%) fetuses were born alive at a median GA of 34.4 weeks. 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 whom 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 with <32 weeks. We conclude that the 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.

In *chapter 5* the long-term outcome after fetal therapy for the different thoracic abnormalities is described, focussing on long-term neurodevelopmental and respiratory outcomes. Twenty-six children were included for follow-up at a median age of 55 months. Severe neurodevelopmental impairment (NDI) was detected in 15% (4/26), which is above the range of the incidence of NDI reported in case series treated with other fetal therapies (5–10%). Three out of 4 children with severe NDI had associated causes contributing to the impairment. Overall adverse outcome, including perinatal mortality or NDI, was 55% (27/49). Fifteen percent (4/26) had severe respiratory sequelae. Parents did not report more behavioral problems than Dutch norms.

In *chapter 6* we discuss the results of our studies and review the literature on neonatal management and outcome after fetal therapy for thoracic abnormalities. The diagnostic process and criteria are described as well as the natural history of fetal thoracic abnormalities. The different treatment options, their indications and outcome and are also covered. Detailed description on neonatal morbidity and possible postnatal treatment options are also given. Finally the scarce literature on long-term outcome is reviewed.

In *chapter 7* a perspective on future research directions is given.

Chapter 9

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Sinds de introductie van prenatale echografie worden afwijkingen in de foetale borstholte steeds vaker ontdekt. Primaire foetale longafwijkingen, zoals congenitale cysteuze adenomatoïde malformatie van de long (CCAM), bronchoplumonale sequestratie (BPS) en foetale pleura-effusie worden tegenwoordig regelmatig voor de geboorte gediagnostiseerd. In de meest gevallen vindt spontane regressie plaats tijdens de zwangerschap en is ingrijpen bij de foetus niet geïndiceerd. In enkele gevallen leidt het ruimte-innemende effect van de laesie tot toenemend hartfalen, wat op zijn beurt weer leidt tot foetale hydrops wat vaak gevolgd wordt door overlijden van de foetus.

In de jaren 80 van de vorige eeuw werd een vorm van permanente decompressie van de foetale thorax ontwikkeld door gebruik te maken van een thoraco-amniotische (TA) shunt. Door deze behandeling kon de foetale hydrops worden teruggedraaid in dit soort gevallen, leidend tot een verbeterde conditie van de foetus, een doorgaande zwangerschap en levendgeboren kinderen die ook de neonatale periode overleven.

Sindsdien hebben meerdere studies de uitkomst na foetale therapie voor primaire borstkasafwijkingen beschreven. Deze studies waren met name gericht op de uitkomst van de zwangerschap. In dit proefschrift worden meerdere studies beschreven waarin wordt ingegaan behandelmogelijkheden voor afwijkingen in de foetale borstkas met name gericht op neonatale en lange-termijn uitkomsten van deze kinderen.

Foetale therapiemogelijkheden bij primaire longafwijkingen

In *hoofdstuk 1* wordt een hydropische foetus met een forse hydrothorax veroorzaakt door een BPS beschreven. Door middel van echogeleide dunnenaaldinsertie werden zowel lasercoagulatie van de aanvoerende slagader als drainage van de hydrothorax verricht. Na deze procedure trokken de hydrothorax en de hydrops langzaam weg en uiteindelijk werd ook de BPS kleiner van grootte. Rond de a terme datum werd een gezond kind geboren zonder problemen na geboorte. Lange-termijn follow-up van het kind toonde geen tekenen van ontwikkelingsachterstand.

In *hoofdstuk 2* wordt een overzicht van de literatuur over prenatale beoordeling, natuurlijk beloop en prenatale interventies voor foetale longafwijkingen beschreven. CCAM en BPS worden gewoonlijk ontdekt bij routinematige echografische controle rond een zwangerschapsduur van 18 tot 20 weken. Detectie van een voedende slagader uit de systeemcirculatie kan middels kleurendoppleronderzoek gebeuren. Classificatie in verschillende subtypes vindt plaats op basis van de echografische bevindingen. Het natuurlijk beloop van foetale longafwijkingen is gewoonlijk goedaardig omdat meestal spontane regressie of langzame groei wordt beschreven. Doorgaande groei kan leiden tot een massa-effect van de afwijking in de foetale thorax. Door verdrukking van het hart kan zo foetale hydrops ontstaan. De prognose van een foetus met een longafwij-

king is meestal gunstig. Wanneer hydrops ontstaat wordt de kans op overleven echter veel kleiner. Daarom wordt foetale hydrops in het algemeen gezien als de indicatie voor foetale therapie. De verschillende foetale behandelopties worden beschreven. Prenatale bijnierschorshormoontherapie wordt vooral gebruikt bij microcysteuze CCAM. Thoracocentese wordt met name bij macrocysteuze CCAM gebruikt, maar wordt meestal gevolgd door snelle reaccumulatie van vocht waardoor het massa-effect van de laesie terugkeert. Plaatsing van een TA shunt om de macrocysteuze CCAM of de bijkomende hydrothorax te draineren, wordt gebruikt als meer permanente manier van drainage. Laserablatie of injectie van een scleroserend agens kan zowel gebruikt worden om de aanvoerende systemische slagader te occluderen of om de laesie zelf direct te beschadigen. Als laatste optie bestaat de mogelijkheid van open foetale chirurgie die met name gebruikt is voor grote, vooral solide CCAMs.

In *hoofdstuk 3* wordt een overzicht van de literatuur betreffende neonatale uitkomst na prenatale interventies voor foetale longafwijkingen gegeven. In gevallen zonder hydrops lijkt een conservatief beleid met goede controles meest passend. Prenataal ingrijpen verhoogt de perinatale overleving bij hydropische foetus met foetale longafwijkingen. De verhoogde perinatale overleving is wel geassocieerd met een verhoogd risico op neonatale morbiditeit en mortaliteit. Respiratoir falen en sterfte na geboorte komen het vaakst voor in de groep waar foetaal sprake was van CCAM met hydrops. In patiënten met BPS en hydrops kwam neonatale morbiditeit en sterfte minder vaak voor, met name wanneer laserablatie of injectie van een scleroserend agens had plaatsgevonden. De morbiditeit wordt aan de ene kant gevormd door complicaties gerelateerd aan de vroeggeboorte (die vaker voorkomt na prenatale interventies) en aan de andere kant door respiratoir falen gerelateerd aan de aangeboren longafwijking. Vanwege het verhoogde voorkomen van neonatale morbiditeit moeten neonaten met een congenitale longafwijking na foetale therapie door neonatologen beschouwd worden als hoogrisicopopulatie. Helaas worden gegevens over neonatale uitkomst vaak spaarzaam en incompleet gerapporteerd in de literatuur. Gedetailleerde informatie over respiratoir falen en cruciale data over de incidentie van chronische longziekte ontbreekt vaak, wat het trekken van duidelijke conclusies beperkt. De oorzaak van neonatale sterfte is vaak onduidelijk, maar wordt regelmatig geduid als passend bij longhypoplasie.

In *hoofdstuk 4* worden het neonatale beleid en uitkomst na TA shuntplaatsing vanwege foetale hydrothorax beschreven in een cohort patiënten die in ons centrum werd behandeld tussen 2001 en 2016. 48 foetussen, allemaal met tekenen van hydrops, werden behandel met TA-shuntplaatsing bij een mediane zwangerschapsduur van 28,7 weken. 41 van de 48 (85%) foetussen werden levend geboren bij een mediane zwangerschapsduur van 34,4 weken. Na de geboorte hadden 24 van de 40 (60%) kinderen tekenen van pleura-effusie en 12 van de 40 (30%) hadden en thoraxshunt nodig voor continue pleuradrainage. 21 (53%) van de kinderen had mechanische ventilatie nodig,

waarvan 13 (33%) hoogfrequente beademing als rescuetherapie. Overall overleefden 30 van de 40 (75%) kinderen de neonatale periode. De mate van neonatale overleving was significant hoger bij kinderen die geboren werden bij een zwangerschapsduur van groter of gelijk aan 32 weken. Wij concluderen dat het postnatale beloop van foetusen die behandeld zijn geweest met een TA-shunt voor geïsoleerde hydrothorax vaak gecompliceerd wordt door respiratoir falen en persisterende pleura-effusie. Overleving na geboorte is goed wanneer de bevalling bij of na 32 weken plaatsvindt.

In *hoofdstuk 5* worden langetermijnuitkomsten na foetale therapie voor verschillende afwijkingen in de borstkas beschreven, waarbij met name gekeken wordt naar langetermijnontwikkeling en respiratoire uitkomsten wordt gekeken. 26 kindere werden geincludeerd voor follow-up op een mediane leeftijd van 55 maanden. Een ernstige ontwikkelingsachterstand werd gevonden in 15% (4/26) van de kinderen, wat hoger is dan de incidentie (5-10%) die beschreven wordt in groepen kinderen die vanwege een andere indicatie foetale therapie ondergingen. 3 van de 4 kinderen met een ernstige ontwikkelingsachterstand hadden bijkomende afwijkingen die bijdragen aan de ontwikkelingsachterstand. Een algehele slechte uitkomst, waaronder vallen perinatale sterfte of ernstige ontwikkelingsachterstand, kwam voor in 55% (27/49) van de gevallen. 15% (4/26) van de kinderen had ernstige respiratoire problemen in het langetermijnbeloop. Ouders rapporteerden niet meer gedragsproblemen dan de Nederlandse normen.

In *hoofdstuk 6* bespreken we de resultaten van ons onderzoek en beoordelen we de literatuur over neonataal beleid en uitkomst na foetale therapie voor afwijkingen in de borstkas. Het diagnostisch proces en diagnostische criteria worden beschreven evenals het natuurlijk beloop. De verschillende behandelopties, hun indicatie en uitkomst worden ook beschreven. Een gedetailleerde beschrijving van neonatale morbiditeit en mogelijke postnatale behandelopties worden ook gegeven. Tenslotte wordt de schaarse literatuur over longetermijnuitkomsten beoordeeld.

In *hoofdstuk 7* worden toekomstige onderzoeksrichtingen beschreven.

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CURRICULUM VITAE

Ruben Witlox werd op 9 juli 1974 geboren in 's-Hertogenbosch.

In 1992 haalde hij zijn diploma aan het Stedelijk Gymnasium in 's-Hertogenbosch. Datzelfde jaar begon hij aan de studie geneeskunde aan de Universiteit Utrecht. Daar behaalde hij in 2001 zijn artsexamen, waarna hij als arts-assistent kindergeneeskunde ging werken in het UMC St. Radboud in Nijmegen.

Van 2002 tot 2007 specialiseerde hij zich tot kinderarts in het Leids Universitair Medisch Centrum in Leiden (opleiders prof.dr. J.M. Wit en dr. R.N. Sukhai) en in het Spaarne ziekenhuis in Haarlem (opleider drs. J.J.E.M. de Nef). Na afronden van de opleiding tot kinderarts werd van 2007 tot 2010 een fellowship neonatologie gevolgd op de afdeling Neonatologie van het LUMC (opleider prof.dr. F.J. Walther)

Als kinderarts-neonatoloog werkte hij eerst een paar maanden in het Juliana Kinderziekenhuis in Den Haag om eind 2010 terug te keren als staflid van de afdeling Neonatologie in het LUMC, waar hij nog steeds met veel plezier werkt.

Ruben woont samen met Anneloes Kerssen in Leiden. Zij hebben drie dochters: Jet, Floor en Lotte.

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