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The long-term outcome following thoraco-amniotic shunting for congenital lung malformations

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ABSTRACT

Aim of the Study: Insertion of a thoraco amniotic shunt (TAS) during fetal life is a therapeutic option where there is a high risk of death secondary to large congenital lung malformations (CLM). The aim of this study is to present our center's long-term experience.

Methods: Retrospective single center review of the period (Jan 2000–Dec 2020). We included all fetuses that underwent TAS insertion for CLM with detailed analysis of those live newborns managed in our center. Data are quoted as median (range).

Main results: Thirty one fetuses underwent 37 TAS insertions at a 25 (20–30) weeks gestational age. This was successful on 1st attempt in 30 (97%) fetuses. In 6 cases a 2nd shunt was required at 6.5 (2–10) weeks following the 1st insertion. Twenty-eight survived to be born.

Sixteen (9 male) infants were delivered in our center at 39 (36–41) weeks gestational age and birth weight of 3.1 (2.6–4.2) kg. All infants underwent surgery at 2 (0–535) days (emergency surgery, $n = 9$; expedited $n = 4$; elective surgery, $n = 3$). Final histopathology findings were CPAM Type 1 ($n = 14$, n.b. associated with mucinous adenocarcinoma, $n = 1$), CPAM Type 2 ($n = 1$) and an extralobar sequestration ($n = 1$). Postoperative stay was 16 (1–70) days with survival in 15/16 (94%). One infant died at 1 day of life secondary to a combination of pulmonary hypoplasia and hypertension. Median follow up period was 10.7 (0.4–20.4) years. Nine (60%) children developed a degree of chest wall deformity though none have required surgical intervention. Clinically, 14/15 (93%) have otherwise normal lung function without limitations of activity, sporting or otherwise. One child has a modest exercise limitation (FVC – 70% predicted).

Conclusions: TAS insertion is associated with high perinatal survival and should be considered in fetuses at risk of hydrops secondary to large cystic lung malformation. Their long term outcome is excellent although most have a mild degree of chest wall deformity.

1. Introduction

Congenital lung malformation (CLM) is an umbrella term used for a heterogenous group including congenital pulmonary airway malformations (CPAMs) (formerly congenital cystic adenomatoid malformation) [1], bronchopulmonary sequestrations (BPS), hybrid lesions, congenital pulmonary emphysema, segmental emphysema [2] and bronchogenic cysts. The current classification of CPAM, developed by Stocker [1], is based on resected surgical specimens and histological features. Therefore, it has obvious limitations when trying to apply it antenatally. To overcome this and provide a simpler more pragmatic classification, Adzick et al. [3] divided ultrasound observed lesions on the basis of size and appearance, as either macrocystic (>5 mm) or microcystic (<5 mm).

A high proportion of CLM are identified on antenatal ultrasound screening, now almost universally offered within the UK. This allows antenatal intervention for that small proportion which are felt to have life threatening features. These are typically large CPAMs (usually macrocystic) where there is significant mediastinal shift, leading to hydrops and then fetal demise secondary to cardiac failure [4,5].

Insertion of a thoraco-amniotic shunt (TAS) was pioneered in 1987 at Kings College Hospital, London in a 24 weeks gestational age fetus with type I CPAM [6,7]. These were subsequently used for the management of fetal chylothorax and pleural effusion [8,9] and massive pleural effusion [9]. Now, more than 35 years after its first use, TAS placement is a well established procedure with published indications and guidance in the form of a UK NICE review [10].

Abbreviations: CPAM, congenital pulmonary airway malformation; CCAM, congenital cystic adenomatoid malformation; BPS, bronchopulmonary sequestration; TAS, thoraco-amniotic shunt; CPAP, continuous positive airway pressure.

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The aim of this study is to present not only the short-term outcome from our center's current use of TAS for CLM, but, most importantly its long-term outcomes.

2. Methods

This was a retrospective review of all fetuses managed with TAS for CLM, in the period 2000–2020 at the Harris Birthright center for Fetal Medicine co-located with King's College Hospital, London. This institution was first established in 1984 and acts as a supra regional and international referral center for fetuses diagnosed with potential CLM.

A previous experience (1994–2006) from our center reported the outcome of 193 fetuses with antenatally diagnosed echogenic fetal lung lesions [11]. Within this series were 6 fetuses who were treated with TAS and these have also been included in the current study.

The indication for TAS was CLM with a large and growing cystic component, significant mediastinal shift with either actual or significant risk of developing pulmonary hypoplasia and/or hydrops. Insertion of TAS for other indications such as chylothorax and pleural effusion were excluded.

A thoraco amniotic shunt (double pigtail catheter, KCH pattern fetal bladder drainage catheter, Rocket Medical PLC, Watford, WD24 4XX, UK) was inserted under local anaesthesia using a 15 cm long, 3 mm diameter trocar inserted under ultrasound-guidance by a single operator (KN). Serial ultrasound examinations was performed every 1–2 weeks to monitor the progress of pregnancy and the response to the fetal intervention. The paediatric surgical team, as part of a multidisciplinary team, was involved after the diagnosis of CLM was established to assist with antenatal counselling and postnatal management [12].

Delivery was planned at term in the referring regional neonatal surgical center, if there were no other complications. Infants were managed locally thereafter. Indications for further diagnostic investigation and subsequent intervention in our own infant cohort has been published previously [5,13]. Briefly, this included surgical resection for all those shown to have symptoms during the neonatal period following a CT scan. Asymptomatic infants were investigated by CT at 3 months and typically offered elective resectional surgery (since 2008, thoracoscopically) before 12 months of age.

Antenatal records were reviewed for all fetuses that underwent TAS placement. For the cases of live newborns managed at KCH, data on postnatal findings, management and long-term outcome was obtained.

Formal ethical review was not required as it was regarded as an audit of outcome.

GraphPad Prism 9.0.0 software was used for statistical analysis. Data are quoted as median(range).

3. Results

3.1. Prenatal course

The fetal medicine database search identified 31 fetuses that underwent 37 TAS insertions for CLM (Fig. 1). Median GA at the first TAS placement was 27 (20–35) weeks. Insertion of TAS was successful on the first attempt in 30 (97%) fetuses. The shunt could not be advanced beyond the fetal oedematous skin in just one case, but a second attempt in the same session was successful. Insertion of a second shunt was required after 6.5 (2–10) weeks in 6 cases. The reasons were: shunt displacement ($n = 2$), TAS blockage ($n = 2$), residual/recurrent macrocystic component ($n = 2$). There were no maternal complications. The overall fetal survival rate to delivery was 90.3% ($n = 28$), there was one intrauterine death and two families elected for termination of pregnancy in the view of the worsening hydrops (Fig. 2).

3.2. Postnatal course (n = 16)

Sixteen live infants were delivered at our institution at a GA of 39 (36–41) weeks. There were 3 preterm births (GA between 36 and 37 weeks). Median interval from shunting to delivery was 13 (15–17) weeks. The delivery modes were spontaneous vaginal delivery ($n = 2$), induced vaginal delivery ($n = 9$), elective caesarian-section ($n = 4$) and emergency caesarian-section ($n = 1$). Birth weight was 3080 (2560–4200) g and 9 (56%) were males.

Seven infants did not require any type of respiratory support at the time of birth; 5 patients were intubated; 1 infant required as continuous positive airway pressure (CPAP) and 3 infants had oxygen delivered via nasal canulae.

In one case born at 40 weeks GA, it was noted that the intrauterine end of the shunt coiled around the baby's arm resulting in a constricting band without ischaemic changes.

The CLM was left-sided in 9 (56%) infants; there were no cases with bilateral involvement. Preoperatively, 4 infants developed pneumothorax, bilateral in one case, and all required chest tube drainage.

All infants came to surgical resection at age of 2 (0–535) days [emergency surgery ($n = 9$); expedited intervention ($n = 4$) or as an elective procedure ($n = 3$)]. A muscle-sparing thoracotomy was used in 15 (one infant with bilobar involvement underwent a second thoracotomy as decision was made to only remove one lobe during this first procedure because of the high risk of respiratory compromise) and a thoracoscopic converted to open approach in the other. Resection was single lobectomy ($n = 10$), bi lobectomy ($n = 2$), left lower lobectomy and lingular segmentectomy ($n = 3$) and an excision of an extralobar sequestration ($n = 1$). A TAS that was retained in the chest secondary to intrauterine displacement was also removed during surgery (Fig. 3).

In the early postoperative period, 5 infants developed 8 complications. According to the Clavien-Dindo classification [14] they were stratified in grade I ($n = 2$ wound infections), grade IIIa ($n = 5$, pneumothorax after drain removal that required reinsertion of chest drain, with 2 events in the same patient) and grade IVa ($n = 1$ aspiration pneumonia that required reintubation). Extubation was achieved at 3 (0–17) days post-operatively.

Histopathology examination showed CPAM Type 1 ($n = 14$), CPAM Type 2 ($n = 1$) and extralobar sequestration ($n = 1$). One case of CPAM Type 1 was associated with mucinous adenocarcinoma with a somatic *KRAS* point mutation [15].

Time to discharge was 20 (6–71) days. The overall survival was 15/16 (94%), with one infant dying on postoperative day one because of a combination of pulmonary hypoplasia and hypertension, despite being on high frequency oscillatory ventilation and maximal ionotropic and nitric oxide support.

3.3. Long-term follow-up

The median follow up period was 10.7 (0.4–20.4) years. A total of 15 complications were noted in 9 (60%) children. These long term complications mainly involved chest wall deformities: scoliosis ($n = 5$), pectus excavatum ($n = 4$), mild chest wall asymmetry ($n = 4$), winging of the scapula that later resolved ($n = 1$), and a raised left diaphragm most likely because of phrenic nerve injury ($n = 1$) (Fig. 4). Only one child was referred for possible intervention for scoliosis, but this was not thought necessary and is currently only under observation.

Clinically, 14/15 (93%) of children and young adults have an otherwise normal lung function without limitations of activity, sporting or otherwise, compared to their peers. Only one child has a

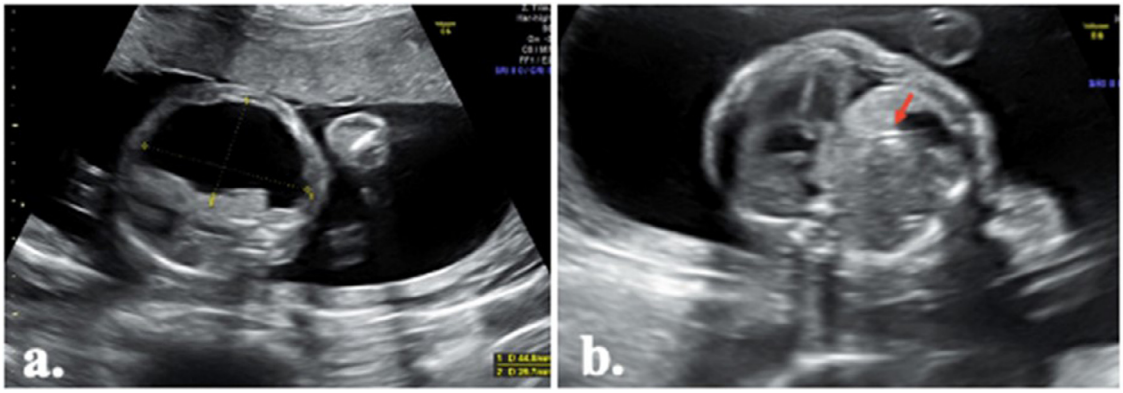

Fig 1. a. Transverse section of fetal scan showing a very large right lung cyst (approximately 5 × 3 cm) with significant mediastinal shift and severely displaced cardiac axis. b. Transverse section of same fetus after the shunt was placed (red arrow) - the cyst resolved almost entirely and there is significant improvement in the mediastinal shift and cardiac axis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

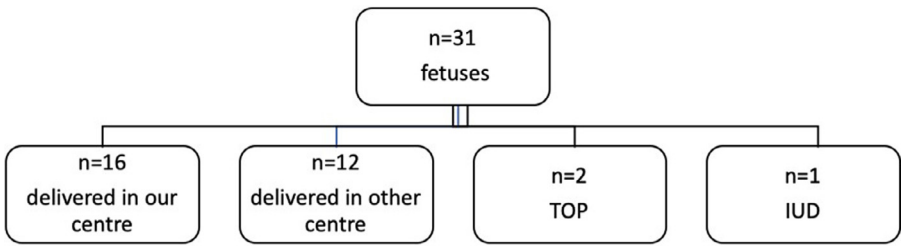

Fig. 2. Outcome of fetuses that underwent TAS insertion (TOP - termination of pregnancy; IUD - intrauterine death).

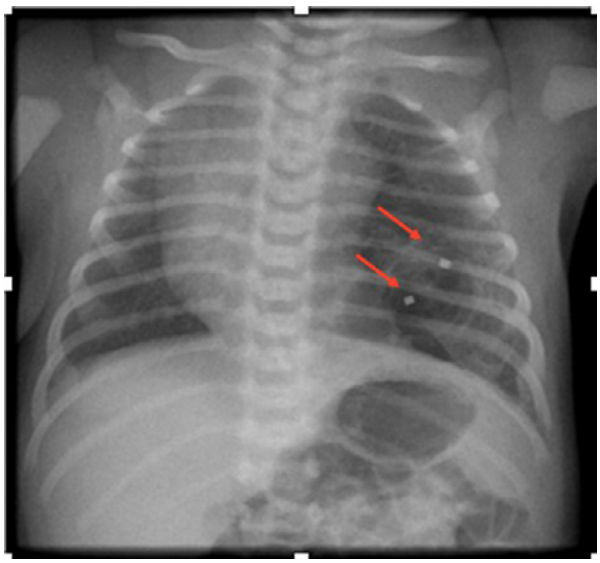

Fig. 3. Intrathoracic retained TAS - pigtail catheter radiopaque markers (red arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

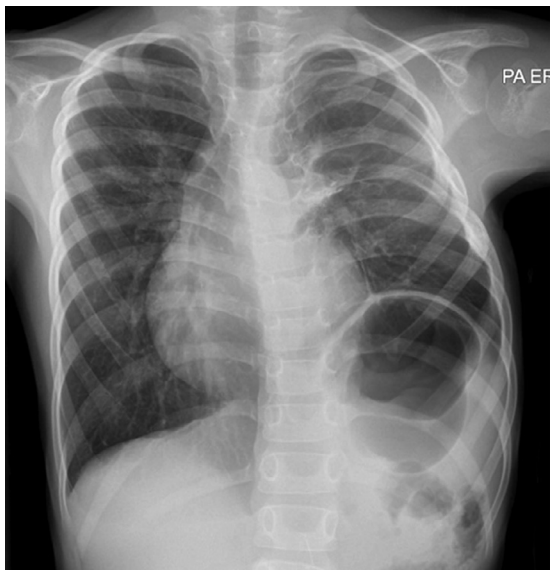

Fig. 4. Chest x-ray depicting raised left diaphragm postoperatively, most likely because of phrenic nerve injury (patient underwent redo-thoracotomy).

modest exercise limitation which on investigation with formal lung function showed an FVC – 70% predicted.

4. Discussion

The natural history of antenatally diagnosed CLM is variable, with most pregnancies being uneventful. However, the prognosis changes markedly and is significantly worse if the fetus develops hydropic changes. Fetal intervention should be considered in these cases, as adopting an expectant management will result in a mortality rate that approaches 100% [4,16].

Insertion of a TAS is an invasive procedure that carries a potential risk for both the mother and the fetus, complications such as premature delivery (uterine stimulation from procedure-related bleeding, premature rupture of membranes, chorioamniotic separation), traumatic haemothorax and procedure-associated fetal death have all been reported [17,18]. Gratifyingly, in our current series there were no maternal complications or indeed immediate fetal complications. Entrapment of one of the limbs in the intrauterine end of the TAS is a rare, but potentially severe complication that has been reported before [19]. In our one case, there was no real

morbidity, as the shunt, most likely because of its flexibility, did not constrict the arm in any way.

In our experience, shunt failure secondary to dislodgment or occlusion was encountered in 13% of cases (4/31), which was higher than the Philadelphia series at 7% [20]. Shunt dislodgment can be encountered in <10% of procedures, with a predilection for intrathoracic migration, often necessitating re-shunting [17,21]. Similarly, the need for multiple shunts is not uncommon – being about 10% in our series and somewhat higher in the Philadelphia series (25%) [20]. There was one case of a retained shunt at the level of the fetal thoracic cavity, which was removed during the surgery for CPAM excision. In cases where conservative management of CPAMs is preferred, leaving a foreign body in the chest might be seen as a risk factor for future complications. Still, this appears to be safe as long as postnatal imaging excludes mediastinal involvement [21].

The histopathology examination of CLM that are managed with shunting usually shows a CPAM type I or, more rarely, a bronchopulmonary sequestration (associated with pleural effusion) [18,20]. In our series >90% of cases were CPAM type I, one of which, interestingly, showed an association with mucinous adenocarcinoma with KRAS point mutation[15].

The short term survival from TAS insertion for CLM has been shown to be excellent in a number of series since its first descriptions [16-18,22-24]. For example, Peranteau et al. reported a 15-year experience from the Children's Hospital of Philadelphia with 37 fetuses with CCAM [20]. Of these there were 27 (73%) survivors to discharge with perhaps 17% requiring supplemental oxygen.

What is lacking in the literature is any sense of the long-term outcomes. So, with increasing experience it is important to try and appreciate not only short-term immediate outcome but whether fetal insertion of a TAS has longer-term implications. There is much less data available here. One study from Israel in 33 infants assessed their medium term neurodevelopmental outcome [24]. They compared two groups, those with underlying CLM ($n = 12$) and those with fetal hydrothorax ($n = 21$) and found that more than 20%, usually boys, had some degree of neurodevelopmental delay as assessed at a mean age of 4 years. Furthermore, early brain sonography was abnormal in about 16% of infants. These comparatively poor results were not reflected in our current study. A similar study on neurological outcome was reported by Witlox et al. from The Netherlands in 2019 on initially 63 fetuses subject to TAS (CLM, $n = 15$) [25]. Again, around 15% had poor outcomes when assessed around 4–5 years, although there was few actual CLM that formed this survivor cohort. The largest series of TAS for fetal pleural effusion is from Toronto [26] and in that, 85% of survivors were neurologically normal beyond 18 months.

In our center, patients are followed in a multidisciplinary CLM clinic, until transition to adult services if needed. We observed a median of about 11 years for our follow-up and were able to show that respiratory capacity was well maintained and virtually all had comparable exercise tolerance to their peers. This illustrates the potential for restitution of lung volumes post early thoracotomy [5,27]. By contrast there were evident consequences of chest wall deformity either because of the TAS, the small intrathoracic volumes post resection of abnormal lung or the actual thoracotomy used. Thus around 60% of our cohort developed some degree of chest wall deformity. This was invariably mild as no surgical correction was necessary. Still, further follow up until chest wall maturity has been reached will be required in this cohort. Certainly, previous reports have established that TA shunting may be associated with postnatal chest wall deformity [25,28], especially if the procedure occurs before 21 weeks GA [28]. This latter feature was not the norm in our cohort as only one fetus underwent TAS insertion before 21 weeks GA.

The present study has several limitations. It is of retrospective design and the data were collected by chart review. We are also aware that we have no real data on other infants treated outside of our institution.

5. Conclusion

TAS insertion is associated with high perinatal survival and an excellent long-term outcome. This should be considered in fetuses at risk of hydrops secondary to large cystic lung malformations.

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