Treatment of Primary Fetal Hydrothorax with OK-432 (Picibanil): Outcome in 14 Fetuses and a Review of the Literature

Brooke O'Brien^a Greg Kesby^a Robert Ogle^a Ingrid Rieger^{b,c} Jon A. Hyett^{a,c}

Departments of ^aHigh-Risk Obstetrics and ^bNewborn Care, RPA Women and Babies, Royal Prince Alfred Hospital, and ^cDiscipline of Obstetrics, Gynaecology and Neonatology, Faculty of Medicine, University of Sydney, Sydney, N.S.W., Australia

Key Words

Picibanil · OK-432 · Chylothorax · Fetal hydrothorax · Thoraco-amniotic shunting

Abstract

Background: Primary fetal hydrothorax (PFHT) is an uncommon condition with an estimated prevalence of 1 in 10,000/15,000 pregnancies. Therapeutic interventions include thoracocentesis, thoraco-amniotic shunting (TAS), and pleurodesis using OK-432. **Methods:** A review of the literature was performed to identify all cases of PFHT treated with TAS and OK-432. All cases of PFHT referred to the Fetal Maternal Unit at Royal Prince Alfred Hospital between 2002 and 2012 were retrospectively reviewed. In the cohort of fetuses treated with OK-432, the main perinatal outcomes evaluated were termination of pregnancy, live birth, neonatal death, and fetal death in utero. Secondary outcomes included gestational age (GA) at diagnosis, GA at treatment, GA at resolution, birth weight, and GA at birth. The development of the children was screened using the Ages and Stages Questionnaires, Version 3 (ASQ-3, 2009). **Results:** Primary hydrothorax was diagnosed in 31 fetuses, of which 14 had treatment with OK-432. One pregnancy terminated after treatment with OK-432. Survival was 85% (11/13): 100% in fetuses treated with OK-432 without hydrops, and 78% in

those treated with hydrops. This compares well to the cases of TAS in the literature with an average survival of 63%: 85% in fetuses without hydrops and 55% with hydrops. The mean GA at birth was 36⁺⁴ weeks and mean birth weight 3,007 g. Eight of the 9 children screened with ASQ-3 scored well within the normal range. **Conclusion:** OK-432 appears to be a valid treatment option in fetuses with PFHT, particularly in those diagnosed at early GAs.

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Introduction

Primary fetal hydrothorax (PFHT) is uncommon, with an estimated prevalence of 1 in 10,000/15,000 pregnancies [1]. PFHT results from lymphatic fluid accumulation in the pleural space due to anomalies in the lymphatic system. PFHT is described as chylothorax postnatally, once neonatal feeding is established and the lymphatic fluid contains chyle. The diagnosis is made antenatally by a process of exclusion of other underlying immune and non-immune pathologies that can lead to the development of (secondary) pleural fluid collections.

Hydrothoraces vary in volume but as a space-occupying lesion they act to limit lung development and, if large, may cause mediastinal shift (if unilateral) or mediastinal

compression (if bilateral), with adverse outcomes including pulmonary hypoplasia, the development of hydrops and polyhydramnios (due to limitations on fetal swallowing), which may result in preterm delivery [2]. Presentation of PFHT varies [3]; some will be noted incidentally at the time of routine obstetric morphology ultrasound assessment, with others detected either incidentally or as a result of investigation of pregnancies considered large for dates, with polyhydramnios, or with reduced fetal movements in the third trimester. Some hydrothoraces will resolve spontaneously in utero [4], whilst others will become progressively more significant [5]. Most commonly, neonates born with a diagnosis of PFHT at or close to term will be effectively treated by simple chest drainage and attention to fluid balance with expectations of resolution within approximately 5–10 days with good long-term outcome. However, in circumstances of long-standing effusions or those complicated by hydrops, the neonatal course may be prolonged and stormy, requiring ventilation, medium-chain fatty acid diets, multiple chest drain insertions and associated higher rates of mortality and morbidity.

Due to the significant morbidity and mortality associated with PFHT, intrauterine therapy is judiciously offered with reference to gestational age (GA), the size of the pleural collections, and the presence of secondary fetal effects, with the aim being one of improving neonatal outcome [6, 7]. Potential therapeutic interventions include thoracocentesis (either single and multiple procedures), thoraco-amniotic shunting (TAS) [8–13] and, more recently, pleurodesis using OK-432 (Picibanil) [14–22]. The primary aim of all these interventions is to remove fluid from the chest and reduce the adverse effects of the space-occupying collection on pulmonary development, cardiovascular function and fetal swallowing. OK-432 has the additional advantage of being able to directly inhibit and possibly cease the fluid production by lymphatic vessels, and additionally effect pleurodesis, which may obviate the need for admission to the neonatal intensive care unit and neonatal drainage. We aim to report our experience using OK-432 as a therapeutic intervention for PFHT and include data on the developmental outcomes of those infants that had a successful neonatal course.

Methods

To review the literature we evaluated all published studies and case reports of PFHT in peer-reviewed journals over the period 2000–2012. The relevant literature was identified by using PubMed, Embase, and Cochrane databases. In addition, a search was performed of all the reference lists of all identified articles. The key

words in the search were fetus, foetus, fetal in combination with hydrothorax, chylothorax, pleural effusion(s), shunting, OK-432, and Picibanil.

The cohort of fetuses treated with OK-432 in this study were identified by retrospective review of consecutive singleton pregnancies complicated by fetal pleural effusion diagnosed at or referred to the Fetal Medicine Unit at Royal Prince Alfred Hospital, Sydney, between 2002 and 2012. Pregnancies complicated by fetal pleural effusion were identified by search of our fetal database (ViewPoint, GE).

PFHT was a working diagnosis defined by the presence of fetal pleural effusions in the absence of other identifiable causes. Secondary pleural effusions were defined as a pleural effusion associated with any fetal malformation, recognised genetic or chromosomal anomaly or other pathology known to result in pleural effusion. Hydrops was defined as the presence of a pleural fluid collection associated with either skin oedema, ascites and/or pericardial effusions. Polyhydramnios was defined as an amniotic fluid index >25 cm or maximal single vertical pocket >8 cm. Effusions were noted to be either unilateral or bilateral and were graded according to size: mild (<1 cm of fluid outlining lungs), moderate (>1 cm of fluid outlining lungs), or severe (>1 cm of fluid outlining lungs with deformation of the mediastinum and/or diaphragm).

Maternal investigations included full blood count, blood group and antibody screen, Kleihauer, serology for parvovirus B19, toxoplasmosis, syphilis, rubella, cytomegalovirus and herpes infections. All fetuses had a morphology ultrasound assessment and echocardiography by a certified maternal fetal medicine specialist. The presence of fetal anaemia was screened for by assessment of middle cerebral artery Doppler peak systolic velocity. Amniocentesis was performed for karyotype and culture/PCR for infective agents (where indicated based on maternal serology). At the same procedure, a (near) complete unilateral fetal thoracocentesis was performed by 20–22 G needle single-puncture aspiration for the purposes of fluid cytology and to assess for recollection prior to embarking on more definitive therapy.

In those fetuses with a working diagnosis of PFHT, both TAS and pleurodesis were discussed with parents as available therapeutic interventions. Intrauterine fetal therapy was offered at a GA of <35 weeks in fetuses that were either (1) hydropic where the pleural effusion was suspected as the primary problem or (2) non-hydropic fetuses with recurrent pleural effusion following drainage causing mediastinal deviation or found to be increasing in volume on serial assessment. The therapeutic intervention used in each case was determined by clinical circumstance and the preference of both the treating clinician and the patient who was informed about the potential advantages and risks of each therapy. There was a trend over the period of the study, to move from TAS to OK-432, as clinicians developed more experience with OK-432 as a therapeutic agent. The parents were informed that there were limited reports using OK-432 and gave written consent for the administration of OK-432 as an experimental treatment. Administration involved the transamniotic ultrasound-guided introduction of a 20 G spinal needle into the fetal thoracic cavity. After drainage of the pleural effusion, 0.1–0.3 KE/kg EFW of OK-432 (Chugai Pharmaceutical Co., Tokyo, Japan) reconstituted in 1.5–2 ml of sterile water was instilled into the pleural space. The procedure was then repeated by separate entry directly into the contralateral hemithorax in the setting of bilateral disease. Ultrasounds were then repeated to monitor the evolution of the effusions at 1–2 weekly in-

Table 1. Summary of published pleural effusion series reporting intervention

	Number of cases ^a		GA intervention, weeks	GA at delivery, weeks	Perinatal survival, n	
	hydropic	non-hydropic			hydropic	non-hydropic
Shunting						
Petersen and Nicolaides [8], 1997	41 (60)	28 (41)	29	36	19 (46)	28 (100)
Picone et al. [9], 2004	47 (100)	–	31	34	31 (66)	–
Smith et al. [10], 2005	16 (76)	5 (24)	24	32	7 (44)	3 (60)
Rustico el al. [4], 2007	43 (81)	10 (19)	–	–	25 (58)	9 (90)
Yinon et al. [12], 2012	59 (67)	29 (33)	28	34	31 (53)	21 (72)
	206 (74)	72 (26)	29*	34*	113 (55)	61 (85)
Pleurodesis OK-432						
Chen et al. [20], 2007	3 (33)	6 (67)	22	33	0 (0)	6 (100)
Nygaard el al. [21], 2007	1 (14)	6 (86)	21	38	1 (100)	6 (100)
Yang el al. [22], 2012	27 (60)	18 (40)	24	32	4 (15)	12 (67)
This study	9 (69)	4 (31)	24	36	7 (78)	4 (100)
	40 (54)	34 (46)	23	33	17 (30)	35 (82)
Numbers in parentheses are percentages. GA = Median gestational age. * Calculated from studies where data was available.						

tervals. The procedure was repeated if there was no evidence of a convincing trend to resolution of the effusion after 2 weeks.

The main outcome measures were resolution of the collection, termination of pregnancy (TOP), live birth (LB), neonatal death (NND), fetal death in utero (FDIU), and childhood developmental outcome. Secondary outcomes included birth weight, GA at diagnosis, GA at treatment, GA at resolution and GA at birth. Childhood developmental outcome was screened using the Ages and Stages Questionnaires, Version 3 (ASQ-3; 2009), a validated developmental assessment tool consisting of a set of 21 questionnaires, each of which has 30 questions adjusted for age groups of children between 1 month and 5.5 years. The questionnaire is completed by parents or primary caregivers and the information sought covers five developmental domains: communication, gross motor, fine motor, problem-solving and personal-social. Administration of the ASQ was performed in consultation with a developmental paediatrician (I.R.). Because the ASQ-3 is a screening tool, completed questionnaires with scores outside the range of normal were scrutinised with a view to further assessment and referral if necessary.

Perinatal outcomes for fetuses with PFHT were analysed for statistical significance using SPSS version 17 (SPSS, Inc., Chicago, Ill., USA), with a *p* value <0.05 considered statistically significant.

This study has ethics approval granted by the Sydney Local Health District Ethics Committee (Protocol No. X12-0130 and HREC/12/RPAH/221).

Results

Literature Review

The prognosis for fetuses with PFHT without hydrops is usually good, with up to 75% survival and up to a 22%

spontaneous regression rate [3]. However, 57% of fetuses present with PFHT complicated by hydrops where the prognosis is recognised as being poor, with anticipated survival rates of 24% without treatment [3]. The presence of severe effusions, bilateral effusions or the development of polyhydramnios are poor prognostic indicators for survival in fetuses that present without hydrops. Thus whilst some authors recommend that intervention should be reserved for hydropic fetuses [23], a justification can be made for therapeutic intervention in cases without hydrops that present with very large or progressive effusions with mediastinal shift and/or demonstrate rapid accumulation of pleural fluid after diagnosis or therapeutic thoracocentesis [11].

Comparison in outcomes between TAS and pleurodesis with OK-432 are shown in table 1. There were 278 cases of TAS published in five case series [8–12], with an overall survival rate of 63% and survival of 55 and 85% in hydropic and non-hydropic fetuses, respectively. The mean GA at insertion of shunt was 29 weeks, with a GA delivery of 34 weeks. Three case series involving 61 fetuses with PFHT were treated with OK-432 [20–22]. The largest, most recent series of 45 fetuses with PFHTs reported neonatal survival of only 36% and survival of 15 and 67% in hydropic and non-hydropic fetuses, respectively. The mean GA of treatment with OK-432 was 24 weeks in the series by Yang et al. [22], with a median GA at delivery of 32 weeks, which was less

Table 2. Management of 31 fetuses diagnosed with primary fetal hydrothorax

Intervention	Total	TOP	FDIU	NND	LB
No treatment	5	0	1	2	2
Pleurocentesis	6	0	0	1	5
Thoracoamniotic shunt	6	0	1	0	5
OK-432	14	1	0	2	11
	31	1 (3%)	2 (6%)	5 (16%)	23 (74%)

than previously published studies of OK-432, and the current series.

Intervention

Pleural effusions were diagnosed in 51 fetuses, of which 31 were diagnosed with PFHT. The study cohort consisted of the 14 fetuses treated with OK-432 described in table 2. There was one TOP at 21+ weeks after a single dose of OK-432 at 19⁺⁶ weeks in a woman with anxiety disorder due to concern regarding the possible association of the hydrothorax with an undiagnosed syndrome. Subsequent autopsy demonstrated successful pleurodesis and no other fetal anomaly. Of the 13 remaining fetuses treated with OK-432, the number of treatments needed varied, but overall 9/13 (69%) had a repeat procedure either on one or both sides. The median age for treatment with OK-432 was 24⁺⁵ weeks, and the mean time between first treatment and delivery was 12 weeks.

Pregnancy Outcomes

Perinatal outcomes of fetuses treated with OK-432 are shown in table 3. Of 13 fetuses treated with OK-432, 11 were born at a GA ranging from 31 to 41 weeks, with mean GA 36⁺⁴ weeks. Resolution of hydrothorax occurred in utero in 8 of 13 infants. The mean birth weight was 3,007 g (range 1,650–3,795). The mean age at diagnosis of fetal hydrothorax was 23⁺¹ weeks (range 18–31). Fetuses with hydrops were more likely to be diagnosed and delivered at an earlier gestation than those without, although this trend did not reach statistical significance ($p = 0.22$).

There were 2 (15%) NNDs in fetuses that did not have resolution in utero. One infant (case 8) was diagnosed with bilateral hydrothoraces and hydrops at 24⁺¹ weeks, and had bilateral treatment with OK-432 at 25⁺¹ and 27⁺¹ weeks. From then the pregnancy was seen at the original referral hospital and had persistent small pleural hydro-

thoraces with signs of ascites and polyhydramnios seen on ultrasound, and had an amnioreduction performed at 30⁺⁴ weeks. The mother developed preterm labour at 31⁺⁶ weeks, and given her history of more than one previous caesarean delivery, a repeat emergency caesarean was performed. The infant died at 12 h of life from pulmonary hyperplasia and fetal hydrops, with the cause of death confirmed on autopsy. The second NND occurred in an infant (case 9) with unilateral hydrothorax with hydrops treated at 20⁺⁵ weeks and with subsequent resolution of the hydrothorax documented at 24 weeks' gestation. The infant was found to have recurrence of pleural fluid collections at 31 weeks at the original referral hospital, followed by spontaneous rupture of the membranes at 32 weeks. The infant was delivered electively by caesarean at 32⁺⁴ weeks after administration of antenatal steroids, and had bilateral chest tube insertion but died from pulmonary sepsis in the late neonatal period. Autopsy found bilateral pulmonary consolidation but did not demonstrate any evidence of pulmonary hypoplasia. Both infants had a birth weight >95th percentile, consistent with persistent hydrops.

One child (case 4) was found to have mild left-sided ventriculomegaly and an area of mixed echogenicity in left anterior cerebral hemisphere on ultrasound 3 weeks following the initial treatment with OK-432. MRI at 28⁺⁴ and 32⁺³ weeks confirmed a 10 × 9 × 10 mm focal rounded area of increased T2 signal intensity in the deep white matter of the left frontal lobe at the superolateral angle of the frontal horn of the lateral ventricle associated with very mild enlargement of left lateral ventricle, with no other brain abnormality being evident.

Long-Term Outcome

Nine of the 11 surviving children's parents completed the ASQ-3 developmental screened at ages shown in table 3. Two children were unable to be screened due to their age. However, both are attending school and are performing at an expected level with no concerns expressed by their parents. Eight of the 9 screened children scored well within the normal range. The remaining child (case 12), screened at the age of 60 months, was already known to have both an expressive and receptive language disorder and was receiving intervention.

The child (case 4) that had antenatal ultrasound and MRI changes on CNS examination was followed up within the neonatal department after delivery. An MRI at 1 month of age showed a well-defined cystic cavity measuring 10 × 5 × 10 mm; however, there was no evidence of brain abnormality. It was the opinion of the treating neo-

Table 3. Outcomes and characteristics of cases of fetal hydrothorax treated with OK-432

Case	Diagnosis	GA diagnosis	GA OK432	GA birth	Birth weight, g	Outcome	ASQ, age
1	Left hydrothorax	31+4	31+6	37+5	3,285	LB	Normal, 6 months
2	Bilateral hydrothorax	19+5	21+5	39+5	3,365	LB	Normal, 12 months
3	Bilateral hydrothorax	30+0	31+0	32+1	1,650	LB	Normal, 60 months
4	Bilateral hydrothorax	23+0	25+1	41+2	3,468	LB	Normal, 12 months
Without hydrops		26+1	27+3	37+5	2,942	100% survival	
5	Bilateral hydrothorax with hydrops	19+3	21+2	38+0	3,200	LB	NA ^a , 10 years
6	Right hydrothorax with hydrops	19+2	19+5	36+5	2,802	LB	Normal, 18 months
7	Left hydrothorax with hydrops	18+0	19+1	41+1	3,500	LB	Normal, 48 months
8	Bilateral hydrothorax with hydrops	24+1	25+1	31+6	2,795	NND	–
9	Left hydrothorax with hydrops	18+5	20+5	32+4	2,555	NND	–
10	Bilateral hydrothorax with hydrops	18+5	19+4	38+0	3,795	LB	Normal, 12 months
11	Bilateral hydrothorax with hydrops	31+3	31+5	33+1	2,160	LB	Normal, 24 months
12	Bilateral hydrothorax with hydrops	20+0	22+4	41+1	3,730	LB	Below ^b , 60 months
13	Bilateral hydrothorax with hydrops	30+3	32+1	32+6	2,782	LB	NA ^a , 9 years
With hydrops		22+0	23+5	36+1	3,035	75% survival	
All cases		23+1	24+5	36+4	3,007	85% survival	

^a Not applicable, above the age for screening with ASQ-3.

^b Known to have an expressive and receptive language disorder and verbal dyspraxia.

natologist that this most likely represented a frontal horn cyst [24], which are present in up to 1% of fetuses <32 weeks' gestation and are not associated with any increased risk for adverse neurodevelopmental outcome. ASQ-3 screening in this infant was normal for age, and assessment by the developmental paediatrician (I.R.) at 12 months of age using Bayley-III Scales of Infant Development found normal cognition, language and motor skills and there were no other developmental concerns.

Discussion

Summary of Findings and Comparison of Interventions

This cohort provides further evidence for the potential value of OK-432 as a therapeutic agent in the management of primary hydrothoraces. 85% of infants survived after treatment with OK-432; 100% of those that were not hydropic and 78% of those that were hydropic at the time of intervention. GA at diagnosis and treatment with OK-432 in this series was 23⁺¹ and 24⁺⁵ weeks, respectively, which is lower than the reported mean of 25⁺² and 27⁺⁶ weeks for TAS [12]. Earlier onset of primary hydrothorax is known to be associated with a poorer prognosis [3], yet

despite this, overall GA at delivery and survival in this cohort was similar to that described in those series where shunts were introduced at later gestations. The less invasive nature of OK-432 may have lowered the author's threshold for intervention, which would benefit the fetus in terms of optimising fetal lung growth and expansion.

The mean GA at birth of OK-432-treated fetuses in this study was 36⁺⁴ weeks, compared to 34 weeks with shunting in the literature. There were 5 infants (38%) treated with OK-432 that delivered preterm; all premature deliveries occurred in the fetuses where resolution did not occur. Two of the 5 fetuses delivered preterm did not survive; 1 fetus (case 8) developed spontaneous preterm labour at 31 weeks, and a second delivered at 32 weeks following spontaneous rupture of the membranes (case 9). The 3 fetuses that survived were delivered electively at 32–33 weeks for persistent pleural effusions causing fetal compromise, and required admission to the neonatal nursery for drainage of persistent hydrothorax.

The most common complications that occur with TAS are preterm rupture of the membranes (15%), chorioamnionitis (8.5%), and preterm delivery (71%) [9]. In this series there were no cases in which treatment with OK-432 resulted in iatrogenic preterm rupture of the membranes or preterm labour within 48 h of treatment,

or in chorioamnionitis. This is an important finding as premature delivery is the leading cause of perinatal morbidity and mortality in these fetuses. Between 32 and 37 weeks, delivery of fetuses with primary hydrothorax increases the risk of death by a factor of 1.3 (1.1–1.6) for each week of prematurity [3]. The risk of death is 3.6-fold higher (1.3–10.3) for an infant born any time before 35 weeks relative to an infant born after 35 weeks. OK-432 administration is technically easier to perform than shunt placement – as it can be delivered via a standard 20 G spinal needle rather than the larger 3-mm trocar and cannula used for shunting, making it less invasive and particularly easier to perform at earlier gestations and in hydropic fetuses with significant skin oedema. The injection of OK-432 is likely to have a procedure-related risk similar to thoracocentesis and amniocentesis, with risk of premature rupture of the membranes of 1–1.6% and fetal loss of 0.5–1% [6]. The procedure-related risk of fetal loss with shunting is 5–10% [6], and up to 30% of fetuses that have TAS require more than one procedure [12].

Eight fetuses (62%) in this study had resolution of hydrothorax and/or hydrops in utero following administration of OK-432, which compares well to TAS where a 47.5% resolution rate is reported [12]. To achieve resolution, 69% of fetuses in this series required repeat treatment with OK-432. It is possible that the success of treatment in the setting of repeat procedures was in part due to the associated repeated aspirations. However, we believe that the successful outcome achieved after repeated treatment with OK-432 was primarily due to achievement of pleurodesis rather than by virtue of serial thoracocentesis. By achieving pleurodesis and cessation of fluid production, there is the possibility of avoiding postnatal chest tubes and the neonatal nursery altogether. None of the 8 fetuses which achieved resolution in utero in this study required admission to the neonatal nursery for chest drainage.

Safety of OK-432 and Neurodevelopmental Issues

OK-432 has not been shown to have any serious or permanent sequelae in the paediatric population in which it has been very widely used for treatment of head and neck lymphatic malformations [25]. However, the absolute safety of OK-432 in animal or human fetuses has not been established. There is evidence that exposure of the preterm fetus to infection and inflammation can lead to the development of neural injury and cerebral palsy, based primarily on evidence from exposure to Gram-negative bacteria lipopolysaccharide [26]. OK-432 is derived from a low-virulence Su strain of type 3 group A

Streptococcus pyogenes (a Gram-positive bacterium) treated with benzylpenicillin (penicillin G) and heat to eliminate its toxin-producing capability and ability to cause infection. OK-432 acts as an immunostimulant [27, 28], promoting a localised inflammatory response by activation of neutrophils, macrophages, lymphocytes and natural killer cells, and induction of multiple cytokines, including IL-1, IL-2, IL-6, TNF and IFN, which causes pleural inflammation and fibrosis resulting in pleurodesis. In a study of 45 pregnant Japanese white rabbits, OK-432 or saline was administered either subcutaneously behind the back of the fetal neck or into the amniotic cavity [29]. No statistical difference in fetal C-reactive protein was found between the OK-432 and saline groups after 48 h, indicating that there was no systemic inflammatory response.

In two small studies of 10 and 13 sheep fetuses [30, 31], intrathoracic administration of OK-432 under general anaesthesia was found to be associated with very early transient suppression of fetal EEG activity, breathing and body movements without induction of hypotension or hypoxia. The significance of the early transient suppression effect is unknown in humans or animals, and the dose, duration or effect of general anaesthesia was not explored. There was no medium-term effect on brain activity or behaviour in all but 1 sheep fetus that developed seizures 18 h after administration of OK-432, and died on day 6. On postmortem histological examination of the brain, a large infarct was observed on both sides of the hippocampi. No other histological changes were found in the surviving fetuses postmortem. It is worth noting that several other invasive procedures were performed on these fetuses during hysterotomy including vascular catheters in the femoral artery, brachial artery, and carotid artery, which would all carry a significant risk of embolic events. In this cohort, there was 1 fetus (case 4) identified to have a cerebral lesion at 28⁺¹ weeks; 3 weeks after OK-432 administration. This lesion most likely represented a frontal horn cyst, but it is difficult to completely exclude an adverse event related to administration of OK-432. This is certainly not a reason alone to abandon treatment with OK-432, but supports the establishment of an international register for use of OK-432 in fetuses with PFHT to monitor treatment success, failure and adverse events.

Limitations of This Study

The main limitation of this study is that it involves a small number of cases treated with OK-432, and there was the potential for selection and treatment bias. The success of treatment with OK-432 in the literature is likely to be

inflated due to publication bias, as evidence by the 100% survival in the two earlier papers compared to the 36% survival in the larger case series. Better estimates of efficacy of OK-432 may be possible with international, multicentre collaboration and registration of treatments with OK-432. Although this is the first study to attempt to quantify the longer-term outcome in fetuses treated with OK-432, the information on the long-term outcome in this study is limited. Interpretation of neurodevelopment outcome in this study through parental questionnaires has several limitations. Furthermore, 4 of the 9 infants screened were 6–12 months of age at the time of screening, where it can be difficult to determine the presence of developmental delay.

Limitations of Treatment with OK-432

A potential limitation of therapy with OK-432 is that some cases of primary hydrothorax appear to be genetic in origin. Familial occurrence in an autosomal recessive inheritance pattern has been observed in four families where chylothorax has affected 2 or more siblings [20, 32]. In our cohort, 1 fetus (case 9) that did not have resolution with OK-432 and had NND had 2 previous siblings affected by PFHT with hydrops; one pregnancy resulting in FDIU at 23 weeks and another resulted in a LB at 32 weeks after in utero treatment with TAS and postnatal

chest tube. Additionally, 2 of the 6 fetuses treated with TAS in the group of 51 fetuses with PFHT were offspring from the same mother. Four possible genes involved in thoracic duct or lymphatic vessel development – VEGFR3, FOXC2, ITGA9 and ITGB – have been implicated in the pathogenesis of chylothorax [33, 34], with up to 30% fetuses with PFHT having mutations in these four loci [22]. The presence of a mutant allele was associated with a poorer response to OK-432 pleurodesis and a worse prognosis. In fetuses where there is a family history, TAS may remain the gold standard for treatment.

Conclusion

Fetal pleural effusion is an uncommon anomaly which can be associated with aneuploidy and a range of other structural malformations or genetic syndromes. Intra-uterine therapy for an apparently primary hydrothorax will be influenced by the expected impact on fetal well-being and GA at presentation. While OK-432 remains an experimental treatment as its safety profile remains to be clarified, this study presents more encouraging human data that OK-432 appears to be a valid treatment option in the setting of PFHT with or without hydrops.

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