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Case Report

Tiny Lungs, Big Challenges: Navigating Fetal Pleural Effusion Outcomes, Long Term Follow-up and Implications for Future Pregnancies

***Charu Sharma[1], Shreya Das[1,2], Kalika Dubey[1,3], Dolat Singh Shekhawat[4], Meenakshi Gothwal[1], Shashank Shekhar[1], Pratibha Singh[1], Kuldeep Singh[4].**

[1]Department of Obstetrics &Gynecology, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India. [2]Nil Ratan Sircar Medical College & Hospital, Kolkata, [3] Vyas Hospital, Jodhpur, India, [4] Department of Pediatrics & Medical Genetics, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India.

Abstract

Fetal pleural effusion is a rare condition involving fluid accumulation in the pleural cavity of the fetus. Invasive procedures are required to exclude chromosomal anomalies and infections, as treatment delays can lead to severe fetal complications. We discuss a case where a 30-year-old primigravida presented at 20 weeks gestation with fetal bilateral pleural effusion and mild ascites. At 23 weeks of gestation, thoracocentesis was performed which revealed chylothorax. The pleural effusion resolved spontaneously by 28 weeks. At 36 weeks, severe oligohydramnios prompted an emergency caesarean section. Postnatal genetic testing found two variants of uncertain significance. The baby improved and was discharged on day six, with no complications over 3.5 years of follow-up. The couple's subsequent pregnancy was uncomplicated. We propose a stepwise management protocol emphasising early diagnosis through ultrasound and cytological analysis, followed by thoracocentesis in severe cases. Regular follow-up is essential to monitor fluid dynamics and adjust management as needed.

Keywords: Chylothorax; Lymphatic Malformation; Pleural Effusion; Pleuro-Amniotic Shunt; Thoracocentesis; Whole Exome Sequencing.

***Correspondence:** Dr. Charu Sharma. Department of Obstetrics &Gynecology, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India. **E-mail:** sharma.charu651@gmail.com.

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Introduction

Fetal pleural effusion or hydrothorax is rare, with an estimated incidence of 1 in 10,000 to 1 in 15,000. [1] However, the actual incidence is believed to be higher than this as many cases go undiagnosed due to missed ultrasound screenings, spontaneous resolution, or fetal abortion or death before any investigation can be conducted. [2] Fetal hydrothorax can be unilateral or bilateral and arises from either primary(isolated) or secondary causes, such as structural anomalies, chromosomal abnormalities, or infections.

Chylothorax is the leading cause of primary pleural effusion. [3,4] The presence of milky fluid indicates chylous effusion in infants and adults, as lymphatic fluid contains chylomicrons. However, in fetal chylo thoraces, pleural fluid is typically clear and straw-coloured due to the fetus's fasting state. A high lymphocyte count is often observed in cellular analysis of chylous effusion in fetuses. Studies also suggest that a pleural fluid with white blood cells (WBC) >1000/ml and over 80% lymphocytes indicate chylous effusion. However, other studies have shown that the WBC cell count in aspirated fluid may be inconsistent.[5] Additionally, the pleural fluid triglycerides level >110 mg/dl, pleural fluid cholesterol >1.16 mmol/l or >45 mg/dl, and the ratio of pleural fluid lactate dehydrogenase (LDH) to serum LDH >0.6 U/L suggests an exudate.

Secondary causes of hydrops fetalis encompass a range of conditions, with cardiac and vascular diseases in 50% of cases. Chromosomal abnormalities, particularly trisomy 21 and Turner syndrome, contribute to 7-10% of cases. Other potential etiologies include fetal anaemia and haematological disorders, as well as infections like toxoplasma, rubella, cytomegalovirus, herpes (TORCH), and parvovirus B19. Additionally, causes may involve skeletal dysplasia and abnormalities affecting the placenta or umbilical cord [6], all of which can disrupt normal fetal development and hemodynamics.

Ultrasonography is the primary diagnostic tool for detecting pleural effusion. Prenatal invasive testing on amniotic fluid can yield critical information about the fetal karyotype and possible TORCH infections. Additional assessments include maternal blood group and typing, viral marker screening, and evaluation for antiphospholipid antibodies (APLA) and specific antibodies to rule out immune hydrops. [1,6]

If hydrothorax develops during the first or second trimester of pregnancy, it can cause lung hypoplasia due to the compression effect that inhibits lung growth. This condition may also lead to complications such as mediastinal shift, hydrops, and polyhydramnios, which in turn may result in preterm delivery, neonatal asphyxia, and perinatal death. [7]

In this study, we closely followed the fetus throughout pregnancy, treating pleural effusion by fluid removal and ruling out primary and secondary causes of fetal pleural effusion. The child was monitored until 3.5 years of age, and the mother was followed during her subsequent pregnancy.

Case Presentation

This case was reported during the COVID-19 pandemic and followed up through 2024. A 30-year-old primigravida presented at 20 weeks gestation with the anomaly scan report that revealed bilateral mild pleural effusion (left >right) and mild ascites with no gross structural abnormality. There was no evidence of fetal skin oedema, tricuspid regurgitation, or pericardial effusion, and the middle cerebral artery peak systolic velocity (MCA-PSV) was within normal limits.

Maternal physical examination showed tachycardia and moderate pallor. Per abdominal examination indicated the fundal height of the uterus corresponding to 20 weeks gestation. Lab results revealed B+ blood type and moderate anaemia. Further investigations identified the mother as having sickle cell trait (SCT), while her spouse tested normal for SCT via high-performance liquid chromatography (HPLC).
The rest of the routine investigations were within normal limits. The couple was counselled on fetal pleural effusion, including its causes both genetic and acquired, associated anomalies, and the possible risks and treatment options. A third-generation pedigree was drawn. The couple has a non-consanguineous marriage and is unaware of any inherited disorders in the family.

Amniocentesis was performed to rule out genetic causes and TORCH infections for pleural effusion. Chromosomal microarray (CMA) and TORCH polymerase chain reaction (PCR) analyses of the amniotic fluid were normal. A follow-up ultrasound at 23 weeks revealed an increase in pleural effusion size, resulting in left lung collapse, mediastinal shift, and minimal ascites (Fig. 1a and b). Thoracocentesis was performed to treat the pleural effusion, and 20 ml of straw-colored fluid was aspirated (Fig. 1c and d).

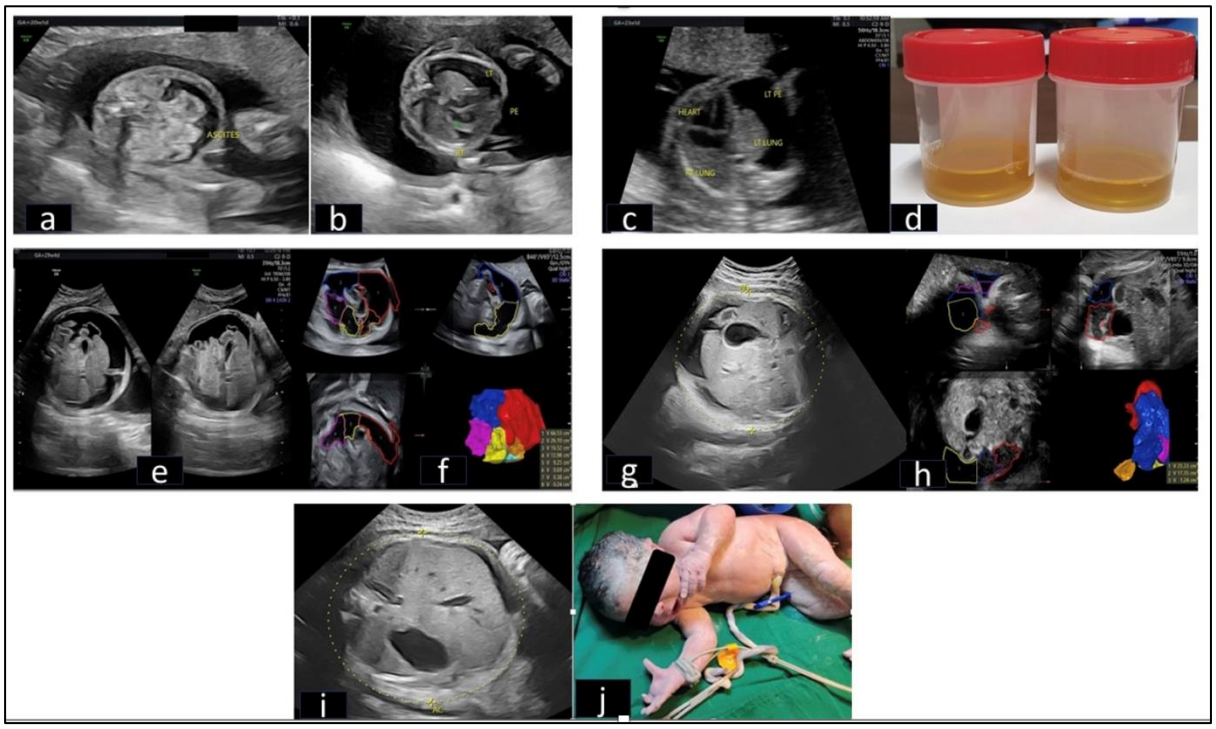

Figure 1*: Ultrasonography findings at different gestational ages (a) Mild fetal ascites and (b) mild bilateral fetal pleural effusion (left>right) at 20 weeks of gestation. (c) Transverse section of the fetal thorax showing severe pleural effusion at 23 weeks and a right shift of the heart. Left lung compressed by the effusion. Antenatal thoracocentesis is performed to facilitate lung development. (d) Straw-coloured chylous pleural fluid after thoracocentesis. (e) Transverse section of the abdomen showing gross fetal ascites at 29+5 weeks. (f) The volume of Fetal ascites on 3D ultrasonography is ~132 ccs. (g) Transverse section of the abdomen showing mild ascites and no pleural effusion at 32 weeks gestation (h) Volume of Fetal ascites on 3D ultrasonography ~40 ccs. (i) Transverse section of the abdomen showing minimal residual ascites and no pleural effusion at 35.5 weeks gestation (j) Newborn at 36 weeks with no gross abnormality and APGAR 8/9 at 1 and 5 minutes.*

The cytologic analysis of the pleural fluid revealed lymphocytic effusion and elevated triglyceride levels, consistent with chylothorax. Details are given in **Table 1.**

Table 1: Cytologic analysis of fetal pleural fluid

Parameters	Value	Reference range
WBC (cells/µl)	4.560 x10^3 (4560 cells/cumm), lymphocytes-99%	Fewer than 1000 WBCs per cumm. Lymphocytes; 2-30%
Protein (g/dl)	2.06	< 2% (1-2 g/dL)
Glucose (mg/dl)	100	Glucose content like that of plasma
Albumin (g/dl)	1.60	1-2
LDH (U/litre)	92	>2/3rd of the upper limit of serum LDH indicative of exudate. *
Total cholesterol (mmol/l)	14	<1.16 (If more than 1.16 mmol/l or 45 mg/dl-indicative of exudate)
Triglyceride (mmol/litre; mg/dl)	7; 126	>110 mg/dl

*RBC-red blood cells, WBC-white blood cells, LDH-lactate dehydrogenase (*A pleural fluid/serum LDH ratio greater than 0.6 suggests exudate)*

The couple was counselled for thoracocentesis. After undergoing thoracocentesis at 23 weeks, the fetus did not experience any complications. On ultrasonography at 25 weeks, there was persistent gross pleural effusion on the left side, along with significant ascites and skin oedema. The MCA-PSV was 0.84 multiples of the median (MoM), which is considered normal. The patient required urgent shunting and was referred to a higher medical facility. However, due to travel restrictions related to the coronavirus disease (COVID-19), she could not reach the referral centre in time. Surprisingly, during this delay, the pleural effusion resolved spontaneously by 28 weeks, and the shunting procedure was no longer required.

During her next visit at 29+5 weeks, it was found that the fetus had only mild pleural effusion along with gross ascites with a volume of 132 cc **(Fig. 1e and f).** The mother was advised for regular follow-up every two weeks, and at 32 weeks, moderate ascites was observed, measuring 40 cc, while no pleural effusion was present (Figure 1g and h).

At 36 weeks, the fetus had minimal residual fetal ascites and no pleural effusion with MCA-PSV 1.09 MoM with severe oligohydramnios. (Fig. 1i) As a result, an emergency cesarean section was performed. A girl weighing 2576 grams was delivered, exhibiting mild breathing difficulties. **(Fig. 1j)**

Postnatally, the whole exome sequencing was performed, encompassing a comprehensive panel of genes known to cause lymphatic disorders and rasopathy syndromes. No pathogenic variants were detected in either panel. However, two variants of uncertain significance (c.1178G>A and c.386T>C), suggestive of autosomal dominant lymphatic disorders, were noted **(Table 2).** Sanger sequencing confirmed that these variants were also present in the father in heterozygous form.

Table 2: Whole Exome Sequencing of the baby after birth

Gene & Transcript	Variant	Location	Zygosity	Disorder (OMIM)	Inheritance	Classification
FLT4 NM_182925.5	c.1178G>A (p.Ser393Asn)	Exon 9	Heterozygous	Lymphatic Malformation 1	AD	VOUS
GRIP1 NM_021150.4	c.386T>C (p.Val129Ala)	Exon 4	Heterozygous	Fraser Syndrome 3	AD	VOUS

AD; Autosomal Dominant, OMIM; Online Mendelian Inheritance in Men, VOUS; Variant of Uncertain Significance

To rule out the possibility of inborn errors of metabolism, tandem mass spectrometry and time-resolved fluoroimmunoassay were performed, yielding normal results. Fortunately, the baby's health improved, and she was discharged from the hospital on the sixth day after birth. The baby was monitored by a neonatologist for six days, during which her health improved. The baby is under follow-up, and medical records indicate no serious complications in the last 3.5 years. The couple planned their next pregnancy, which was delivered to our centre only, with no similar complications observed.

Discussion

Congenital hydrothorax is a condition that can be diagnosed prenatally through sonographic examination. This condition is characterized by a fluid-filled mass in the fetal chest that exerts pressure on the lungs. It may be associated with polyhydramnios. Fetal hydro thoraces, either unilateral or bilateral, may occur in isolation or with other intrathoracic structural abnormalities that hinder lymphatic drainage, primary lymphatic disorders or infections, and aneuploidies like Turner syndrome and Trisomy 21, or lung tumours. In the case presented, fetal infections, chromosomal disorders, and structural malformations were ruled out, indicating that the most likely cause could be a genetic mutation or a single gene disorder. This may include conditions such as Noonan Syndrome (Rasopathies), rarer syndromes like Gorham-Stout Syndrome, missense mutations in the integrin α9β1, yellow nail syndrome, etc.

In the absence of any genetic pathology, the outcome depends on gestational age at presentation, the severity of effusion, progression or not, and the presence or absence of hydrops. Much literature suggests that pleural effusion at less than 32 weeks of gestation should be treated prenatally if feasible for optimal outcomes.

The management strategy for fetal pleural effusion is based on symptom management.[8] We followed the same protocol as described in Figure 2. Prenatal therapy for pleural effusion can include a single thoracocentesis, serial thoracocentesis, or thoracic-amniotic shunt. Thoracocentesis is the initial procedure of choice because it can provide cytologic and biochemical diagnostic information and relieve intrathoracic compression. [9] However, it may need to be repeated if the effusion increases. In cases where the effusion worsens, thoraco-amniotic shunting is the preferred treatment option. In such cases, the placement of thoraco-amniotic shunts can help restore normal intrathoracic anatomy, resulting in the resolution of associated hydrops and polyhydramnios. [10] An alternative to shunting is pleurodesis, where a sclerosant substance is injected into the pleural cavity. [11].

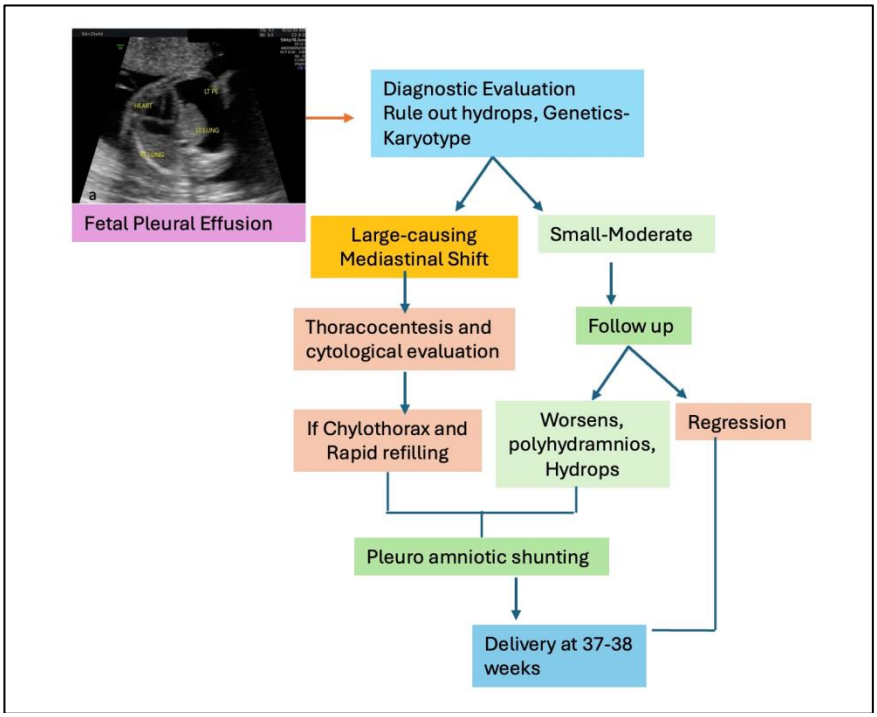

Figure 2: Stage-based management of fetal pleural effusion

Recent studies have reported survival rates of around 60% for patients treated with thoracoamniotic shunting, approximately 50% for those treated with thoracocentesis, and 35% to about 60% for those receiving conservative management. Hidaka et al. performed thoracocentesis in a fetus with bilateral isolated pleural effusion at 20 weeks POG, achieving complete resolution with a single procedure and uneventful outcomes. [9].

In our case, we performed thoracocentesis and cytological analysis of the fluid, confirming it to be chylothorax. Fortunately, the effusion resolved before proceeding for Pleuro- amniotic shunt. Post-natally. Tandem mass spectrometry and Time-Resolved Flouroimmunoassay screening for inborn errors of metabolism was negative. However, whole exome sequencing revealed the presence of variants of uncertain significance, as mentioned above. Post-test genetic counselling was conducted, and parents were offered Sanger sequencing for the same variants identified in the fetus. The baby is being followed in the paediatric department and is doing well in the second year of life.

The survival rates for cases of fetal pleural effusion treated with thoracocentesis range from 50% to 60%. Better outcomes are reported when treatment occurs before the onset of hydrops. For instance, in this case, early thoracocentesis performed at 23 weeks of gestation prevented the progression to hydrops. This finding aligns with Wada et al., who reported a survival rate of 97.8% for cases managed prior to the development of hydrops, compared to 58% for hydrothorax cases with hydrops. [12] Additionally, Aubard et al. reported a 75% survival rate in cases of primary hydrothorax without hydrops and only 24% when hydrops was present. [13] Similarly, Rustico et al. observed survival rates of 73% in primary pleural effusion cases and 25% in those with hydrops. [1]

A study by Lee CJ et al. found that among 29 cases with a prenatal diagnosis at 34 weeks or earlier, infants who received prenatal therapy had a significantly higher survival rate than those who did not (76.9% vs. 11%, respectively; $p = 0.008$). [14] A recent systematic review of cases with isolated fetal pleural effusion also concludes that these cases have a favourable outcome with a survival rate of 87.3% amongst the continuing pregnancies, and only a small number (1.1%) progress to hydrops. [15]

The fetus with a pleural effusion is at significant risk for developing hydramnios and preterm delivery. But in our case, she developed oligohydramnios, which is a contradictory finding.

Jelin et al. performed exome sequencing on six cases affected by pleural effusions. A pathogenic variant was identified in one case (16.7%), while four cases had variants of uncertain significance (VOUS). [16] In our case also, two VOUS were detected for Fraser syndrome 3 and lymphatic malformation 1. Fraser Syndrome is a genetic disorder inherited in an autosomal recessive pattern. It is caused by mutations in the GRIP1 (NM 021150.4) gene and is characterized by certain physical features such as syndactyly, cryptophthalmos, and abnormalities of the respiratory and urogenital tract. However, these features did not match the phenotype of the baby in our case.

Lymphatic malformation 1 (OMIM# 153100) is a group of autosomal dominant disorders caused by mutations in the FLT4 (NM_182925.5) gene. This condition is associated with non-immune hydrops. Further analysis using Sanger sequencing revealed that the identified FLT4 and GRIP1 variants were inherited from the father in a heterozygous state. Functional assays suggested that these variants may impact lymphatic development, indicating a potential contributory role in the condition. This underscores the importance of parental segregation studies for determining the clinical significance of variants of uncertain significance (VOUS) in similar cases.

Conclusions

Based on our findings, we propose a stepwise management protocol emphasising early diagnosis through ultrasound and cytological analysis, followed by thoracocentesis in severe cases. Regular follow-up is essential to monitor fluid dynamics and adjust management as needed. This approach aligns with guidelines from recent systematic reviews.

Treating pleural effusion during pregnancy can save lives by alleviating symptoms, promoting lung development, and improving fetal outcomes. It is crucial to implement a stepwise treatment plan to ensure successful results. Additionally, genetic counselling is essential in these cases to help determine whether to pursue prenatal testing in future pregnancies. Exome sequencing can be helpful when the underlying cause is not diagnosed.

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