Fetal Pleural Effusion

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INTRODUCTION

Unlike trace pericardial fluid, which can be seen in normal fetuses, any fluid in the pleural space is abnormal.[1,2] The incidence of fetal pleural effusion is unknown, but has been estimated to occur in 1 in 15,000 pregnancies in tertiary care centers.[2,3,29] The actual incidence of primary fetal hydrothorax may be even higher if one considers that in many cases the condition may remain undiagnosed, it may resolve spontaneously, the fetus may be aborted, or death may occur soon after birth in outlying hospitals before transfer to a tertiary care center.[2]

Fetal hydrothorax, either unilateral or bilateral, is a pleural effusion that may be primary, due to chylous leak, or secondary, in which the effusions are part of a generalized fluid retention associated with immune or non-immune hydrops.[2,4] The management of pleural effusion in the fetus is complicated by the difficulty in distinguishing primary from secondary hydrothorax. Chylothorax is the most common cause of pleural effusion in the newborn. Secondary fetal hydrothorax is far more common in the fetus than in the neonate. Irrespective of the underlying cause, fetal pleural effusions may be potentially responsible of fetal and neonatal death.[3,4] This complication occurs as a consequence of pulmonary hypoplasia due to chronic intrathoracic compression, to hydrops developed from mediastinal shift, cardiac compression, and vena caval obstruction, which diminishes venous return to the heart, resulting in a low-cardiac output state[5] and to the prematurity as a consequence of an excess of amniotic fluid secondary to the esophagic compression. Infants affected by pleural effusions usually present in the neonatal period with severe, and often fatal, respiratory insufficiency. This is either a direct result of pulmonary compression caused by the effusions, or due to pulmonary hypoplasia secondary to chronic intrathoracic compression.[3,29] The overall mortality of neonates with pleural effusion is 25 percent, with a range from 15 percent in infants with isolated hydrothorax to 95 percent in those with gross pleural effusions.[6,7,29] More recently, Longaker *et al* reported that the mortality rate in cases of antenatally diagnosed chylothorax was 53 percent.[2]

Sometimes, it exists an associated maternal morbidity, as in the mirror syndrome characterized by a generalized edema, due to the hydropic placenta that produces vasoactive substances.[8,29]

NATURAL HISTORY

Fetal pleural effusion may occur as a primary abnormality, in which case one conclude that it is a primary condition after excluding other structural abnormalities, chromosomal abnormalities, other causes of hydrops or after evidencing resolution of hydrops after placing a shunt; or as a secondary manifestation of another condition that causes hydrops fetalis.[3,9,10]

Primary pleural effusions are generally chylous in origin, which occurs as a consequence of an accumulation of lymphatic fluid due to atresia, agenesis or fistulas of the lymphatic duct. Aspirated fluid of a chylous effusion in the feeding infant or adult is characteristically "milky" in appearance because of the presence of chylomicrons in the lymph fluid. Aspirates of fetal chylothoraces yield fluid, which is clear and "straw" colored because the lymph fluid does not contain chylomicrons as a consequence of the "fasting" state of the fetus. Cellular analysis of chylous effusion in the fetus typically shows a large number of lymphocytes, and some suggest that > 80 percent lymphocytes in the fluid is pathognomonic for a chylous effusion.[28] Others found the cell count in the aspirated fluid to be less consistent.[10]

Congenital pulmonary lymphangiectasia is another rare cause of primary fetal pleural effusion. This is a congenital pulmonary disease, characterized by a subpleural, interlobar, perivascular or peribronchial lymphatic dilatation. Both incidence and etiology remain understood. Some sporadic and even some infrequent familial cases are reported. Recent advances in neonatal intensive care have modified the ominous prognosis of affected newborns. Those who survive present chronic pulmonary complications[11,12] (Figs 1 and 2).

Pleural effusion is thought to be one of the earliest signs of hydrops fetalis.[2,13] The causes of pleural effusions with hydrops

Fig. 1: Pleural effusion secondary to pulmonary lymphangiectasia. Macroscopic appearance of pulmonary edema and subpleural lymphatic ectasia that gives a fine reticular aspect to the visceral pleural surface

Fig. 3: MAQ . Oblique section of the fetal thorax. The pulmonary mass is responsible for the mediastinal shift that develops hydrops fetalis. It constitutes a poor prognostic sign. Ascites (*)

include those of immune hydrops fetalis and non-immune hydrops fetalis: cardiac and vascular diseases (50%),[14] chromosomal abnormality (more frequently trisomy 21 and Turner syndrome 7 to 10%),[3] anemia and hematological diseases, pulmonary or digestive abnormalities, hepatic or metabolic diseases, infections (including TORCH, parvovirus B_{19}, skeletal dysplasia and placental or funicular abnormalities. Other major congenital abnormalities are found in 25 to 40 percent of fetuses with non-immune hydrops fetalis: congenital diaphragmatic hernia, extralobar sequestration, congenital adenomatoid pulmonary disease, thyroid teratoma or congenital fetal goiter.[29] And perinatal mortality is > 90 percent in hydropic fetuses with pleural effusion if another structural abnormality is identified. This underscores the necessity for a complete anatomic survey in any hydropic fetus with hydrothorax. The risk of chromosomal
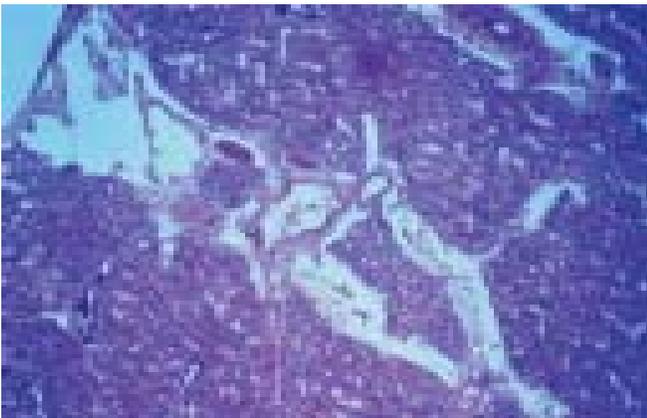
abnormality is also increased in association with non-immune hydrops fetalis or isolated fetal pleural effusion (6 to 10%). While the underlying cause of a secondary fetal pleural effusion may be evident from detailed sonographic examination and karyotype analysis, in many instances the etiology remains obscure even after a postmortem examination[3] (Figs 3 to 16).

The prognosis associated with a fetal hydrothorax is determined by many features that are observed with sonography, by this way the cause can sometimes be established and also generalized hydrops may be excluded. The assessment should begin with confirmation of the presumed

Fig. 2: Lymphangiectasia affects not only subpleural lymphatic vessels but those located in the interlobar spaces and those adjacent to the vascular vessels

Fig. 4: A 20 weeks male fetus with an hydropic aspect, distended abdomen

Fig. 5: After the incision at post-mortem autopsy a mass that shifts the mediastinum and collapses fetal heart and left lung with a central right hepatic lobule is exposed
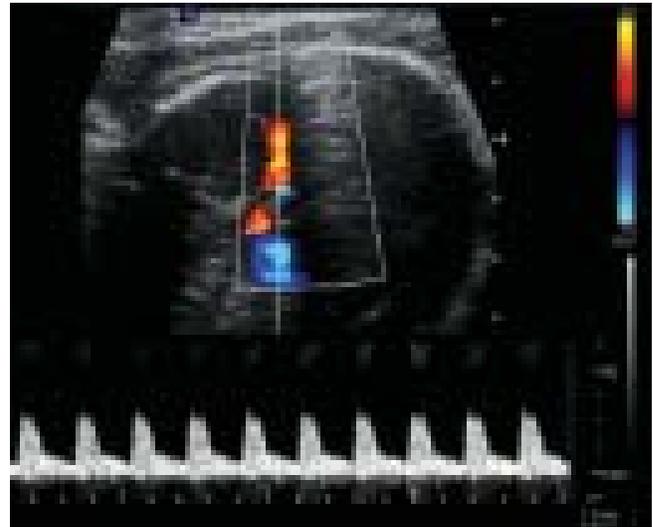

Fig. 7: Hydrops. During diagnostic evaluation a meticulous US must be performed in order to detect fetal or placental malformations and to exclude fetal anemia by Doppler study of the peak systolic velocity of the middle cerebral artery

Fig. 6: MAQ II. Hyperrefringent mass with median size cysts occupying all the right lung and collapsing the contralateral one. Evident cardiac shift (*)

primary and isolated nature of the hydrothorax by ruling out all secondary hydrothorax etiologies and any associated malformation. The maternal assessment serves as a starting point and should include a review of past obstetrical and medical history, along with a current pregnancy evaluation. Maternal serologies should be verified for all known congenital infections (toxoplasmosis, rubeola, CMV, parvovirus B_{19}, adenovirus, syphilis, herpes). Other laboratory tests may be performed

Fig. 8: Hydrops fetalis of infectious etiology. Distended abdomen as a consequence of an important congestive hepatomegaly

(complete blood cell count, blood type and antibody screen). In cases in which an hemoglobinopathy is suspected an hemoglobin electrophoresis is performed and if there is a concern
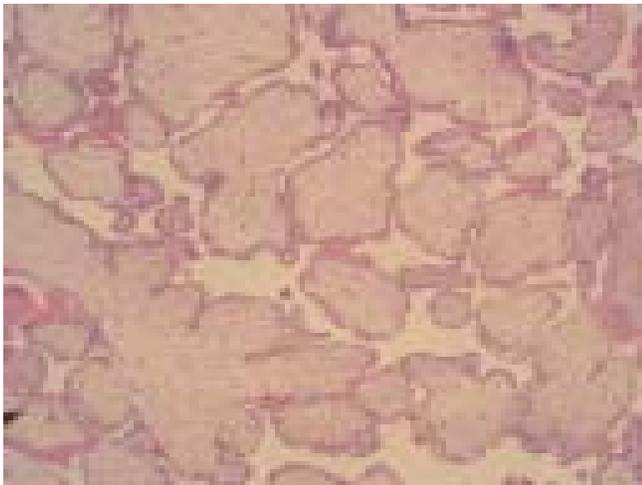
Fig. 9: Placental microscopic aspect of a parvovirus B19 congenital infection. Generalized edema of chorionic villous
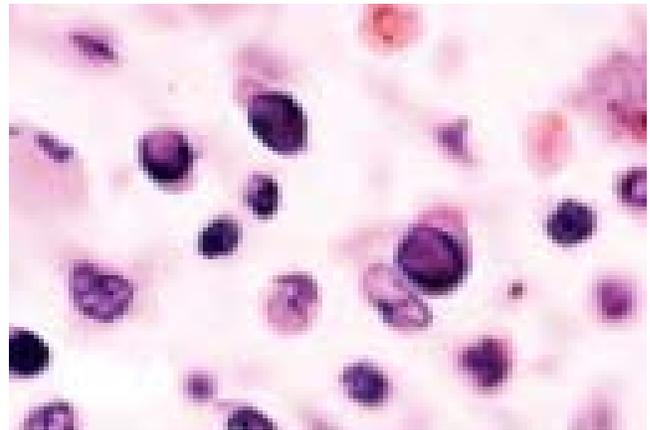

Fig. 11: Placental microscopic aspect of a parvovirus B19 congenital infection. Intrahemopoyetic inclusions typically found in parvovirus infection
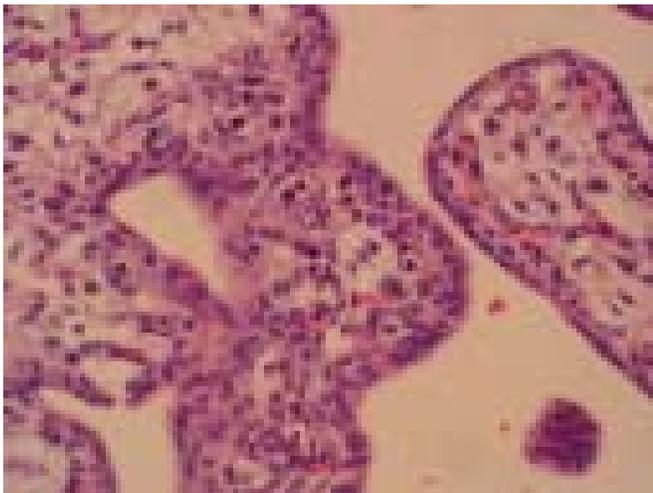

Fig. 10: Placental microscopic aspect of a parvovirus B19 congenital infection. Microscopic aspect of a chorionic villous showing numerous erythroblasts circulating in fetal capillaries
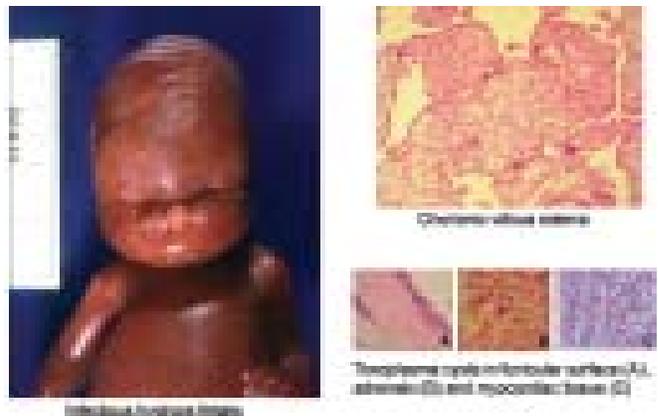

Fig. 12: Congenital toxoplasmosis infection

about a maternal fetal transfusion a Kleihauer-Betke test is recommended. Fetal karyotype must always be confirmed, as most authors agree that there is a 6 to 10 percent associated chromosomal anomalies. A detailed ultrasound examination is recommended because major congenital abnormalities are commonly found in association with hydrops (41% in one series)[1] and also any subtle sign that may suggest a genetic syndrome must be individualized.[13,14,29]

An detailed echocardiographic examination is also performed to identify any structural or rythmogenic abnormality that can explain fetal pleural effusion. A careful sonographic inspection should be made to detect subtle signs of hydrops, hydramnios and placental or umbilical cords associated anomalies.

SONOGRAPHIC FINDINGS

Although the earliest gestational age at which prenatal diagnosis has been made sonographically is 17 weeks, the vast majority of cases are not diagnosed until third trimester.[2]

Sonographically, pleural effusions appear as anechogenic fluid collections in the fetal chest and diaphragmatic contour. When unilateral and large, the hydrothorax can demonstrate considerable mass effect on the diaphragm, fattening or inverting it and displacing the heart and mediastinal structures into contralateral hemithorax. The latter are usually primary fetal pleural effusions.[26] Secondary hydrothoraces tend to be more symmetric in size with little mediastinal shift. The presence of septations or solid components within the intrathoracic fluid collection suggests alternative diagnoses.[2,14,15,26] Fetal

Fig. 13: Metabolic cause of hydrops fetalis

Fig. 14: Metabolic hydrops fetalis. Wolman's disease. Transverse section of fetal adrenal gland showing an increased size and yellow aspect as a consequence of lipid storage

hydrothorax has been reported in association with congenital diaphragmatic hernia, congenital cystic adenomatoid malformation of the lung and bronchopulmonary sequestration, but it can usually be differentiated from simple hydrothorax by its more echogenic appearance.[2]
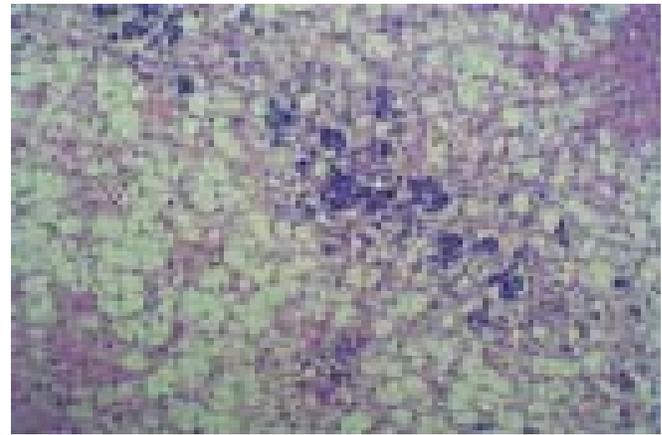

Fig. 15: Wolman's disease: Adrenal glands histological section that shows an adipous degeneration of the cortex surrounding medullar neuroblasts and granular calcifications (*)

Fig. 16: Mucolipidosis: vacuolization of syncytiotrophoblast cells

Fetal pleural effusion may be the first sign of non- immune hydrops, and a careful sonographic inspection should be made to detect signs of hydrops fetalis. Congenital heart disease is observed in up to 50 percent of cases of antenatally diagnosed hydrothoraces.[29] Large pleural effusions with shift of the mediastinum and cardiac compression may limit delineation of cardiac anatomy on fetal echocardiography. Evacuation of these effusions by fetal thoracocentesis will shift the heart to de midline and may facilitate an imaging of the heart (Figs 17 to 26).

In up to 70 percent of cases hydramnios is associated with fetal hydrothorax[2,3,10] as a consequence of interference with fetal swallowing due to mediastinal shift.

The prognosis associated with a fetal hydrothorax is influenced by many features that can be observed by sonography. One of the most important contributions of
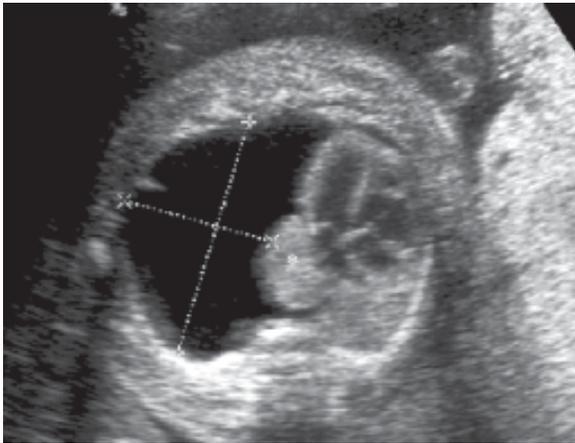
Fig. 17: Severe left pleural effusion (as shown). Transversal section of the fetal thorax showing right shift of the heart. Left lung compressed by the effusion (*)

Fig. 20: Bilateral severe pleural effusion. Coronal section of the trunk. Heart (*). No signs of ascites

Fig. 18: Severe pleural effusion in a term fetus. Longitudinal section of the thorax. Antenatal thoracocentesis is performed in order to facilitate newborn reanimation

Fig. 21: Hydrops. Axial section of fetal thorax showing bilateral hydrothorax (*) and evident subcutaneous edema (white arrow)

Fig. 19: Bilateral pleural effusion. Axial section of the thorax. Both lungs appear collapsed(*) at both sides of the heart

Fig. 22: Atelectasia and pulmonary hypoplasia secondary to bilateral pleural effusion

Fig. 23: Hydrops. Transversal section of fetal vault showing evident subcutaneous edema (white arrow)

Fig. 24: Hydrops. Severe ascites (*), pleural effusion (+) subcutaneous edema (white arrow)
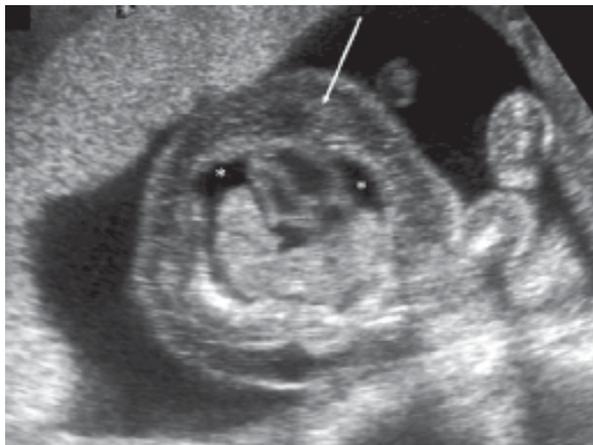

Fig. 25: Hydrops. Axial section of fetal thorax showing bilateral hydrothorax (*) and evident subcutaneous edema (white arrow)

sonography is determining whether the hydrothorax is a primary or secondary abnormality.

Sonographic features suggestive of primary fetal pleural effusion include the following:

- The hydrothorax is unilateral, or bilateral, very asymmetric
- The unilateral hydrothorax occurs as an isolated finding (no other abnormalities)

Fig. 26: A 22 weeks of gestation fetus with generalized hydropic aspect. Subcutaneous edema and abdominal distention secondary to ascites
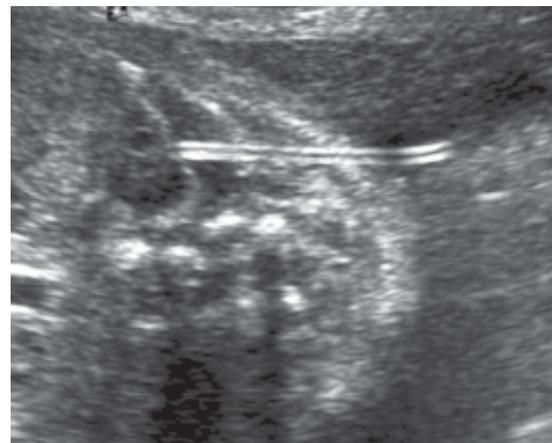

Fig. 27: MAQ II. Placement of a catheter in one of the cysts connecting with the amniotic cavity

- There is considerable mediastinal shift implying mass effect from the hydrothorax If there are other serous effusions (i.e. ascites), the pleural fluid is disproportionately large compared with other effusions.

These observations are oriented to aid the examiner in recognizing a primary hydrothorax because hydrops caused by a chylothorax is one of the most treatable causes of non- immune hydrops fetalis.[16,17]

PROGNOSIS

Overall, the clinical course of fetal pleural effusions is unpredictable.[13] This fact difficult both management and parental counseling.

The natural history of fetal pleural effusion is significantly different from chylothorax in the newborn and carries a much poorer prognosis. The mortality rate for chylothorax in the newborn is at most 15 percent, but the mortality rate for prenatally diagnosed fetal pleural effusion is 53 percent.[2] The reported mortality rate in cases of secondary hydrothorax with associated hydrops may be as high as 95 percent.

The major concern in a fetus with a large primary hydrothorax is the potential development of hydrops and pulmonary hypoplasia.

Spontaneous resolution or regression has been reported to occur in 9 to 22 percent of primary fetal hydrothoraces, even in cases of large[1,7,9,15,23] and has been associated with nearly 100 percent of survival.[15] Unfortunately, it is not possible to predict accurately which effusions will resolve or progress based on finding of a single ultrasound examination. One can nevertheless try to define the characteristics of fetal pleural effusion cases which spontaneously resolve: diagnosis is generally made early in second trimester (67%), they are more often unilateral (65%), they are not associated with hydramnios (69%), there is not hydrops (90%). If regression is possible, worsening is, however more frequently reported in the literature.[13] Spontaneous resolution of fetal hydrothorax has occurred in approximately 5 to 10 percent of cases.[2,3,10,23] Because of the possibility of spontaneous resolution, a period of observation and follow-up is warranted in all cases. In some cases the fetal pleural effusion remains stable a satisfactory postnatal treatment may be undertaken.[2,16]

To better define prognostic features, several investigators reported outcomes of fetuses with antenatal diagnosed hydrothoraces. Aubard *et al* summarized the information reported in 35 untreated fetuses. Overall mortality was 39 percent in this series, similar to 35 to 50 percent mortality reported by other authors.[1,2] Adverse prognostic indicators included bilaterality, presence of hydrops, absence of spontaneous resolution and premature delivery.[13]

Of all the poor prognostic indicators, hydrops is probably the most important. The development of hydrops in a fetus with primary fetal hydrothorax is a poor prognostic sign, with a mortality rate of 52 percent.[2] It is thought that hydrops develops from mediastinal shift, cardiac compression, and vena caval obstruction, which diminishes venous return to the heart, resulting in low- cardiac- output state.[5]

The mortality rate associated with primary fetal pleural effusion is still significantly better than the 95 to 98 percent mortality rate observed in secondary fetal pleural effusion.[1,2] In the report of Longaker *et al* of 32 fetuses with hydrothorax, the absence of hydrops was associated with 100 percent survival. The best outcomes are reported with unilateral effusions and no more anomalies.

In cases of fetal hydrothorax diagnosed prior to 33 weeks, the survival rate was only 43 percent, versus 80 percent if it was diagnosed before that gestational age. Similarly, a gestational age of less than 35 weeks at delivery had a survival rate of only 30 percent, versus 79 percent if delivered after 35 weeks.[2]

Hydramnios has no independent prognostic significance, except that it results in uterine overdistention, predisposing to preterm labor and delivery.[17,30]

Even in the absence of hydrops, large pleural effusions can cause pulmonary hypoplasia due to compression. It is likely that time of onset, size, and duration of the pleural effusion probably influence the development of pulmonary hypoplasia. The most common cause of neonatal death in a fetus diagnosed with hydrothorax is respiratory insufficiency due to pulmonary hypoplasia.[17,30]

MANAGEMENT OF PREGNANCY

Fetal pleural effusion is frequently associated with extrathoracic anomalies**.** The risk of an abnormal karyotype in fetal hydrothoraces is small, but significant (up to 7% in most series). Prenatal karyotyping is recommended, especially if fetal intervention is considered. The incidence of Down's syndrome in fetal pleural effusion is 4.9 percent.[1] Because the incidence of associated congenital heart disease may be as high as 5 percent most authors agree in recommending to perform a meticulous fetal echocardiography. As previously mentioned sometimes it is not until the effusion's evacuation that a congenital heart disease is detected.

The fetus with a pleural effusion is at significant risk for the development of hydramnios and preterm delivery. Most authors recommend a careful follow- up, with ultrasound examination every 1 to 2 weeks for early detection of signs consistent with tension hydrothorax, such as mediastinal shift, diaphragmatic eversion, development of hydrops, and hydramnios.

The fetus affected by an hydrothorax is also at significant risk for pulmonary hypoplasia and respiratory distress following delivery. It seems convenient that fetuses with large pleural effusion be delivered in a tertiary-care center. Prenatal consultations with a pediatric surgeon, neonatologist, geneticist, and pediatric cardiologist may be indicated.

The presence of hydrothorax does not influence the mode of delivery. Cesarean delivery should be reserved for obstetrical indications.

FETAL INTERVENTION

The goals of antenatal therapy, as described by Weber and Philipson[1] are:
• Prevention of lung compression, allowing normal development
• Prevention or reversal of hydropic changes and hydramnios, avoiding fetal death and preterm delivery
• Improved postnatal respiratory function.

The primary goal of any intervention is to avoid progression of an otherwise frequently fatal disease. Then it is crucial to select fetuses that could be candidates for intrauterine therapy.

There are several options in the management of fetuses with isolated hydrothorax; the options depend on gestational age, severity of effusion, evidence of progression, and the presence or absence of hydrops, hydramnios or mediastinal shift. The outcome of fetal pleural effusion is significantly worsened by prematurity (less than 32 weeks of gestation), the presence of hydrops and lack of prenatal therapy.[1] Therefore occurrence of fetal pleural effusion at less than 32 weeks of gestation should be treated prenatally for the majority of authors.

When the hydrothorax is small, isolated, and well tolerated, frequent surveillance may be most prudent because of the possibility of spontaneous resolution. If the fetal pleural effusion is very large or increases over time with signs of fetal decompensation (i.e. hydrops), a fetal intervention may be needed.

Prenatal therapy for pleural effusion can include a single thoracocentesis, serial thoracocentesis or catheter placement to drain fetal fluid into the amniotic fluid. Thoracocentesis is considered the initial procedure of choice because it can provide cytologic and biochemical diagnostic information as well as a relief of intrathoracic compression (Flow chart 1).

Thoracocentesis

Thoracocentesis was proposed for the first time as a treatment of fetal hydrothorax by Petres *et al* in 1982. [27]

It is a diagnostic maneuver to obtain pleural fluid for cell count, differential, and culture and to establish whether the effusion is chylous. Additionally, the diagnosis of an underlying cardiac abnormality or other intrathoracic lesion may become apparent only after effective decompression and return of the mediastinum to its normal position. It may be useful in the prenatal diagnosis of pulmonary hypoplasia because in such cases the lungs often fail to expand after the procedure.

It may also be done in the immediate prepartum period to help improve the neonatal respiratory status.

Clinical outcomes after fetal thoracocentesis alone are variable. There are several reports of thoracocentesis for fetal pleural effusion, performed with either complete resolution or a good outcome despite reaccumulation.[16,18,19,31] In their summary, Aubard *et al* reported that 16 of 29 (55%) fetuses treated by thoracocentesis had good outcomes. Others have had disappointing results with repeated thoracocentesis for fetal hydrothorax because of rapid accumulation of the effusion and neonatal death from respiratory insufficiency.[1-3] Thoracocentesis cannot adequately decompress the fetal chest to allow pulmonary expansion and prevent pulmonary hypoplasia.[2]

Thoracocentesis may be extremely useful before delivery or for temporary stabilization of the fetus, but this treatment alone is often not effective earlier in gestation owing to the rapid accumulation of fluid in most (76%) of cases.[13]

However, if the effusion reaccumulates, thoracoamniotic shunting is felt to be less traumatic than repeated aspiration.[35]

Pleuroamniotic Shunting

When the pleural fluid reaccumulates rapidly after the initial tap, and if the condition worsens with the development of fetal hydrops, a thoracoamniotic shunt should be considered for permanent *in utero* drainage. This may be especially useful in fetus < 32 weeks of gestational age because of the higher risk of preterm delivery.

Use of this technique to drain primary fetal hydrothoraces was first proposed by Seeds and Bowes in 1986.[32] Presently, the most commonly used technique for pleuroamniotic shunting is that described by Rodeck *et al*.[33] This technique has been successfully used in the treatment of isolated hydro- or chylothorax and more rarely in cases of pleural effusion secondary to congenital lung abnormalities such as pulmonary sequestration or cystic adenomatoid malformation.[34]

To accomplish thoracoamniotic shunting, a metal trocar with cannula is introduced through the maternal abdominal wall and uterus into the fetal thorax as close as possible to the midaxillary line of the fetus. Once the trocar has been introduced into the thorax, a double pigtail catheter is passed through the trocar, and the "internal" loop is deployed into the thorax with an introducer rod. As the trocar and introducer are removed, the "external" end of the catheter is left in the amniotic space. Situated in this way, the catheter creates a permanent communication between the pleural space and the amniotic cavity.

The mechanism by which shunting benefits the fetus is by allowing the pleural fluid to decompress to the pressure of the amniotic fluid. This allows the lungs to expand, potentially reducing the risks of pulmonary hypoplasia, and also reduces pressure on the venous system, increasing venous return to the heart and improving coexisting heart failure. However there are no randomized trials of its use, nor are there data from animal

Flow chart 1: Algorithm for the management of pleural effusions. TS = thoracocentesis, TSA= thoracoamniotic shunting, TOP= termination of pregnancy

models confirming these mechanisms of action in cases of fetal pleural effusion.[35]

This has been accomplished in many fetuses; two larger series were reported by Nicolaides and Azar (n = 35) and Mussat *et al* (n = 18). Aubard *et al* summarized 80 reports of thoracoamniotic shunting in fetuses with bilateral or unilateral pleural effusions. This series suggests that shunting has the most dramatic effect on survival among fetuses already showing signs of hydrops.[13] In the series of Aubard *et al*, only 10 percent of hydropic fetuses survived after thoracocentesis alone, whereas 67 percent of hydropic fetuses survived after thoracoamniotic shunting. Other series reported similar survival rate ranging between 50 and 75 percent after in uterus pleuroamniotic shunting.[3,33] Shunt failures were reported in 26 percent of cases.[13,20,21,25]

The risks of thoracocentesis and shunt placement to mother and fetus have been minimal and far outweighed by the potential benefits. Few complications have been reported for either fetal thoracocentesis and thoracoamniotic shunts. In the series of (Smith *et al)* 23 cases of shunting, one ended in a fatal fetal hemorrhage at the time of shunt insertion at 23rd week and one in a neonatal death following the procedure-related abruption at 30th week of gestation.[35] Migration of the catheter has been a consistent problem. It has been found in the intra-amniotic cavity, maternal peritoneal cavity, neonatal subcutaneous tissue and the neonatal intrathoracic cavity.[21] Drainage of amniotic fluid into the fetal pleural cavity has been reported.[33] Acute maternal compromise has occurred due to amniotic fluid leakage into the maternal peritoneal cavity.[36] It should be recognized that these procedures have the potential for infection, bleeding, premature rupture of membranes, preterm labor and injury to the fetus.[2] Procedure risks may be increased by maternal obesity, hydramnios or fetal position. After delivery, delay in clamping of the catheter can result in temporary neonatal compromise.

The prognosis after shunting is determined by the underlying cause of the effusion. There is no evidence that fetuses that had a successful intervention suffer later from any chronic respiratory disease. Thompson *et al* described a series of 17 survivors after a successful intervention, all of them had a normal pulmonary development and an adequate functional capacity[22,24,25] (Figs 18 to 29).

CONCLUSION

Published studies emphasize on the fact of the vast heterogeneity of fetal hydrothorax etiology. A careful sonographic evaluation is then mandatory.

The clinical course of primary fetal hydrothorax is highly variable, ranging from complete resolution with good outcome to progression to hydrops fetalis and perinatal death.

Fig. 28: Left pleural effusion. Pleuroamniotic shunting (pig tail). One of the ends is within the amniotic cavity (*) the other (**) in the pleural cavity. It allows to drain the effusion, decompress the lung and prevent pulmonary hypoplasia

Fig. 29: Thoracoamniotic shunt

The more accurate targeting of therapeutic approaches to particular cases may allow us to significantly ameliorate the somber overall prognosis of this condition, and make infant survival without sequelae more feasible.

This condition is rare in prenatal medicine but it does nevertheless warrant special attention.

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