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REVIEW ARTICLE

Fetal Lung Surgery

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ABSTRACT

Advances in technology and wide used of obstetric ultrasound have allowed an increase in the antenatal identification of fetal problems, such as fetal lung lesions. Technological advances in transducer and software technology have remarkably improved visualization of structures in the fetus. Additionally, newer understanding of the natural course of several malformations and new methods of *in utero* treatment, the evolution of fetal surgical techniques and anesthesia have made fetal surgery possible and have changed the course of evolution of lung defects before and after birth. Therefore, there is now an increasing demand for an accurate and timely diagnosis, counseling, and planning of appropriate management of the cases whether expectant management or *in utero* therapy at perinatal care centers with timely perinatal transfer.

Keywords: Fetal lung, Intervention, Surgery.

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INTRODUCTION

Fetal examination is an ultrasound evaluation of each system in a systematic manner. The main target of the fetal evaluation is to check whether the fetal anatomy looks normal in appearance and whether it is the diagnosis of abnormality or defects. If something is wrong in which the appearance of the organ does not seem to be normal, the next step is a perinatal care, i.e., an evaluation of targeted system or organs for diagnosis what is questioned. As a part of this examination, fetal thorax can be checked at the axial plan for normal anatomy, also sagittal and coronal plan. Therefore, normal anatomy of thorax has to be known in detail to seek this normal anatomy at the time of fetal examination.

The ossification of the ribs begins at the end of 1st trimester. Lower ribs are the landmarks for the measurement of the abdomen. At the time of measuring abdominal circumference, we can deal to take correct measurements, but at the same time, instantly we can evaluate the other organs, such as thorax. The thoracic transverse diameter, the mean abdominal diameter, and the abdominal circumference measurements are taken virtually at the same level of the fetal body. Measurement of the thoracic length in a long axis of the midline section is done from the superior end of the sternum to the diaphragm.[1]

The fetal thorax extends from the clavicles to the fetal diaphragm. The diaphragm is continuous, thin, and hypoechoic appearance of the boundary of the thorax and the lungs. The thorax is bounded by the sternum anteriorly, the spine posteriorly, and the ribs laterally. The heart is the most prominent structure in the thorax. The lungs are seen to surround the heart. The lungs are homogeneously echogenic and largely isoechoic with other mediastinal structures. The left lung is limited in its extent by the heart. The heart occupies one-third to one-half of the thorax and its location and axis are important to identify and evaluate noncardiac conditions as well. Cardiac and mediastinal shifts have a tremendous effect on the prognosis of a chest lesion. Normally no fluid is seen in normal pleural spaces. The pleural and pericardial space should be evaluated to assess for hydrops, which again, is a prognostic factor in the assessment of a chest mass.

The sternum shows extremely individual variation in its development: The number of sonographically visible ossification centers varies and the first two to three ossification centers appear at 18 to 19 weeks of gestation, a fourth center at 22 to 23 weeks and five ossification centers are usually visible from 29 weeks.[2] The thorax is scanned in a transaxial plane, supplemented by sagittal and coronal planes as needed. The four-chamber view is useful plan to assess chest size and lung status. Color flow Doppler is a valuable adjunct to assess vascular structures and their connections. The heart and bony structures of the thorax are out of scope of this paper.

The thoracic circumference at the level of the heart by the axial section should be roughly similar to the

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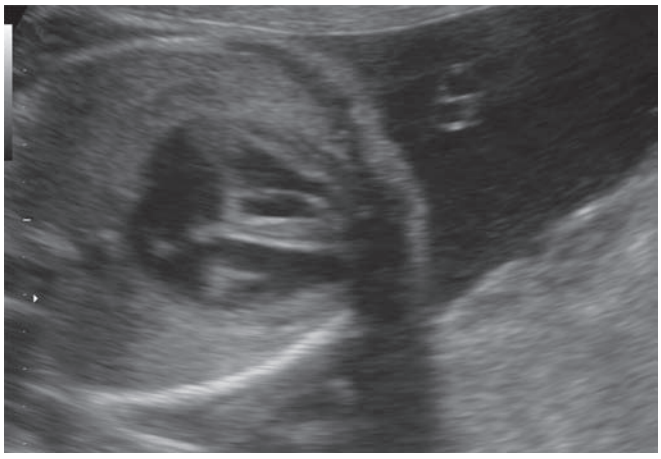


Fig. 1: Axial section of the thorax with only one rib on the screen

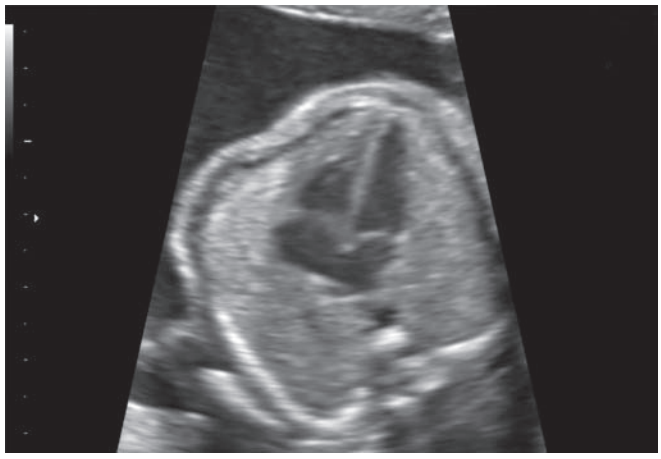


Fig. 2: The apex toward the left side (~45°) with the right ventricle anteromedially and the left ventricle posterolaterally

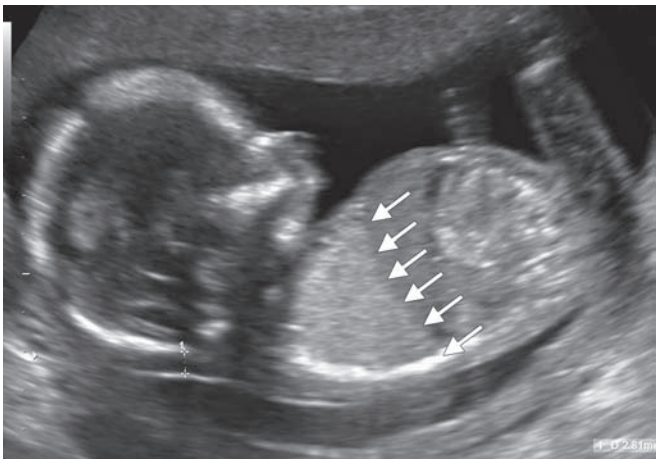


Fig. 3: Demarcation line of the diaphragm (dome shape) with coronal section in 1st trimester

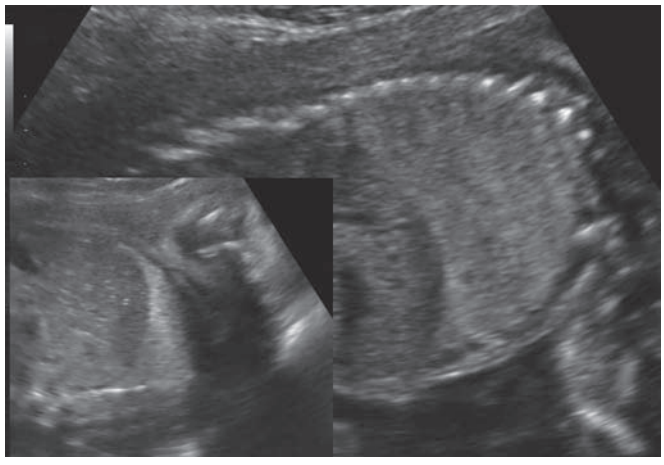


Fig. 4: Dome shape of demarcation line of the diaphragm with coronal section in 2nd trimester

abdominal circumference at the level of umbilical vein (UV). The ribs should enclose about two-thirds of the thorax, which should be almost circular in transverse section. With this section, only one rib should be seen on the screen, otherwise it is not axial or transvers section and may not be possible to see the structures behind the ribs because of heavy shadowing and bad quality of ultrasound insonation (Fig. 1).

The major thoracic contents are the heart, great vessels, thymus, and the lungs. The heart occupies about one-third of the chest and is situated with the apex towards the left side (~45°) with the right ventricle anteromedially and the left ventricle posterolaterally (Fig. 2). The left lung lies just behind the heart and is smaller than the right. Also the continuity of the diaphragm should be checked in sagittal and coronal views, thus confirming that abdominal organs, such as liver and bowels are separated from heart and lungs (Figs 3 and 4).

In a routine fetal examination, abdominal circumference and four-chamber view are the most appropriate and useful scanning plan for evaluation of whole thorax anatomy and pathology. Four-chamber view is not only for fetal heart examination but also for lungs, mediastinum and thymus. As in the four-chamber view for fetal heart examination, apical view which is an anteroposterior scanning plan is most important landmark for a proper routine scanning for the thorax as in any other part of the fetal body (Figs 5 and 6A and B).

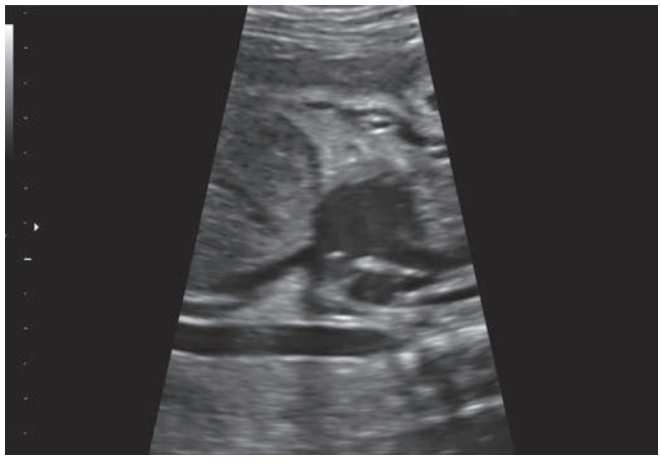
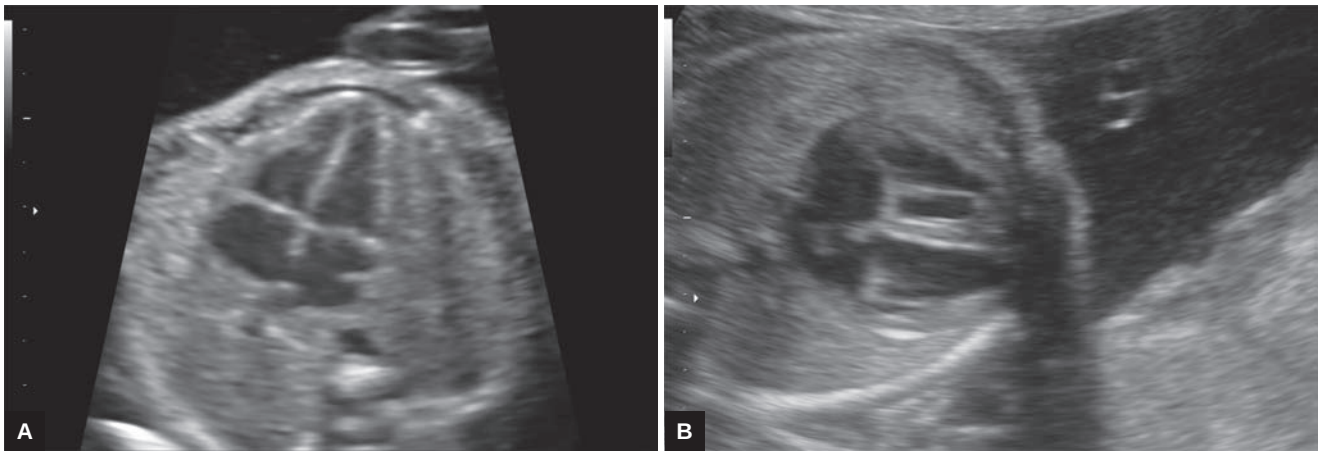


Fig. 5: Diaphragmatic demarcation line at the level of bicaval view of the heart



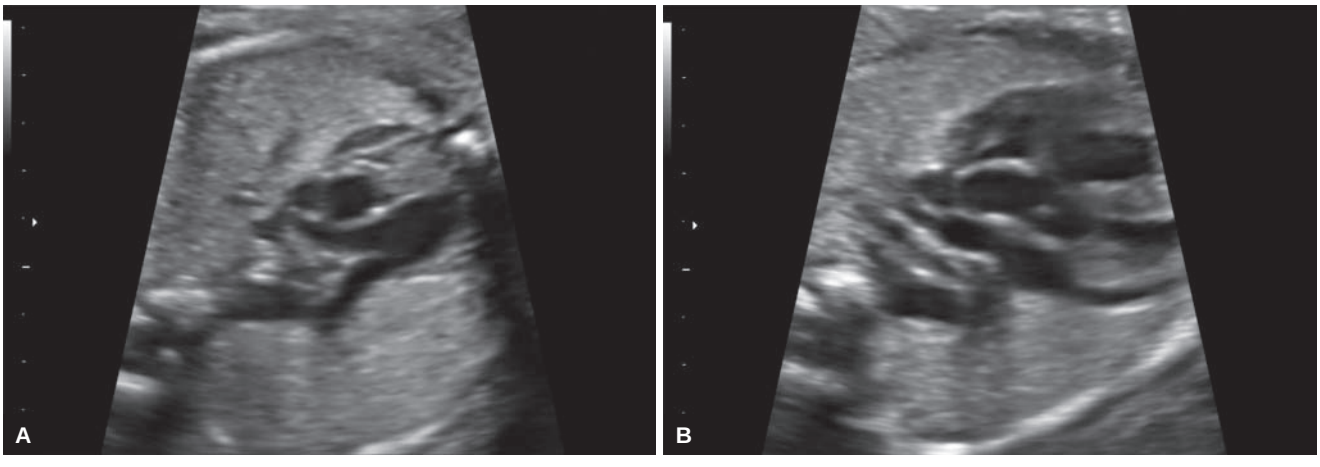
Figs 6A and B: (A) Apical view of the heart and surrounding lungs; and (B) short axis view of the heart and surrounding lungs

FETAL LUNGS

The two lungs can be seen as solid, homogeneous, weakly hyperechoic structures that surround the heart completely (Figs 5 and 6A and B) with a correct transvers section. The heart is mainly located in the left hemithorax, thus the right lung will appear larger than the left one. The pleural cavity is virtual and does not show up; on the contrary, a film of fluid is often seen within the pericardium, especially if insonated with high-frequency transducers. The three-vessel view is a parallel plan to the four-chamber view (Figs 7A and B), but a little bit more cranial that is also for evaluation of thymus. The thymus is just in front of the great arteries at the three-vessel plan. It is easier to recognize from the late 2nd trimester onwards when it starts to undergo significant hypertrophy. Thymus is seen as a well-defined round-shaped solid structure between the great vessels, just behind the sternum, especially if not a high-frequency (>5 MHz) transducer is used. The thymus is located on top of the heart and unlike the lungs, shows movements synchronous with the cardiac cycle.

Fetal lung lesions are very rare and occur in 1 in 10,000 to 1 in 35,000 pregnancies.[3,4] Most lesions have a good outcome without antenatal intervention despite often impressive appearance in 2nd trimester. Many lesions can regress during pregnancy usually around 28 to 31 weeks of gestation, some disappear completely. Conservative management with weekly examination is commonly the most appropriate approach. In some cases, however, it can progress to more severe conditions because of mass effect or hemodynamic changes. This can lead to pulmonary hypoplasia, progressive cardiac failure, hydrops, and intrauterine demise. Antenatal intervention may be warranted to improve the outcome in those cases.

Fetal echogenic lung malformations are seen and diagnosed on the 2nd trimester ultrasound as a cystic/solid "echogenic" mass in the lungs including congenital cystic adenomatoid malformation (CCAM), bronchopulmonary sequestration (BPS), bronchogenic cyst, lobar emphysema, and segmental bronchial atresia.[5,6] Bronchopulmonary sequestration is a rare malformation with a nonfunctioning mass separated from the bronchial tree, which receives arterial supply directly from



Figs 7A and B: (A) Lungs at the level of three-vessel view and bifurcation of pulmonary artery; and (B) lungs at the level of three-vessel and trachea view-upper part of lung

the aorta.[7-10] The antenatal diagnosis of BPS is based on the identification of feeding vessel from usually aorta, occasionally from other systemic vessels.

The echogenicity of the lungs is usually brighter than the liver which becomes more distinctive by harmonic imaging. The echogenicity of the fetal lungs showed a particular characteristic pattern during the course of pregnancy: It is almost the same as that of the liver at 22 to 23 weeks of gestation, but later on decreased between 23 and 31 weeks and increased again later in pregnancy.[11] These changes of echogenicity are due to saccular and alveolar phases of fetal lung development. It is important to calculate lungs volume to assess lung development in a fetus at risk for pulmonary hypoplasia, such as congenital diaphragmatic hernia (CDH), cystic adenomatoid lung malformation, or hydrothorax.

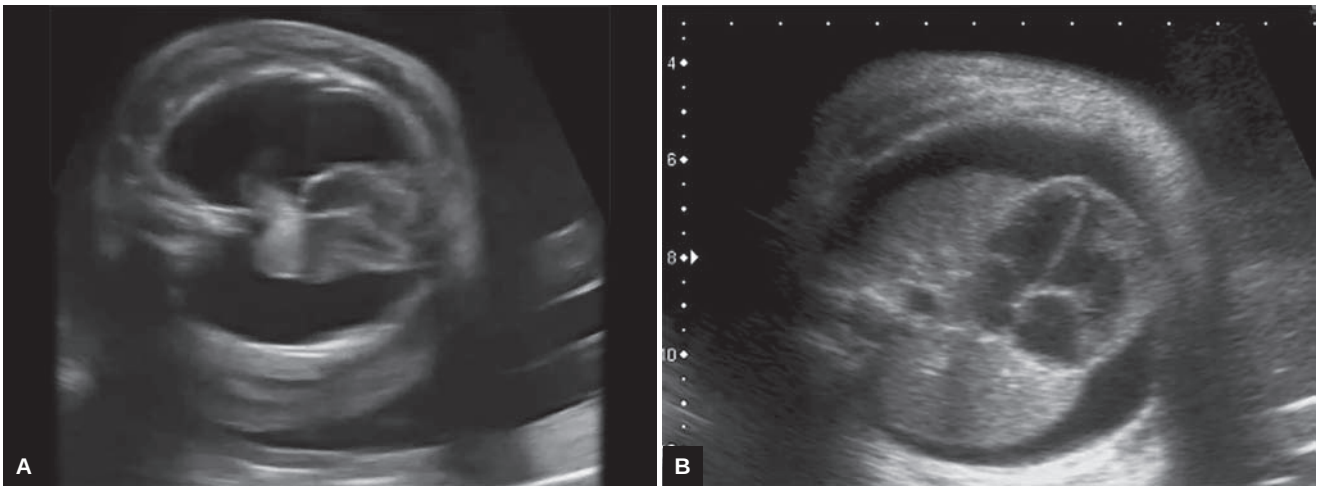
Lung echogenicity does not correlate with lung maturity.[12] Although well studied, lung lengths are not easily reproducible.[13] Thoracic circumference measurement is taken at the level of the four-chamber view without including the soft tissue beyond the ribs.[14,15] The thoracic circumference/abdominal circumference ratio is constant through the late 2nd trimester and in the 3rd trimester and more than 0.80. Three-dimensional (3D) reconstruction techniques are reliable and reproducible for fetal lung volumes.[16-19] During recent years, two-dimensional (2D) and 3D ultrasound assessment of normal and abnormal structure of lungs have been studied extensively.[20,21] The significance of 3D ultrasound volumetry in the antenatal assessment of lung hypoplasia still remains on discussion. The lung volumetry in the antenatal assessment of fetal lung anomalies has been indicated.[22] In diaphragmatic hernia, the delineation of the lung edge is very difficult, especially on the side of the defect. Adequate lung development is essential for fetal viability.[23] Hypoplastic lungs have a reduced lung-to-body weight ratio and histologically demonstrate a reduced number of alveoli.[24] It is rarely unilateral[25,26] and usually secondary to any prolonged severe oligohydramnios,[27-29] with a small bony thorax in skeletal dysplasia, in sizable intrathoracic masses,[30] consequent to neuromuscular dysfunction as in the Pena-Shokeir syndrome,[31] in trisomy 13, 18 and 21, and in conditions with decreased pulmonary artery perfusion.[32]

The pathogenesis of pulmonary hypoplasia can be caused by either inadequate thoracic space for growth, inadequate breathing movements of whatever the cause, inadequate fluid within the lung, and decreased amniotic fluid.

FETAL HYDROTHORAX – HYDROTHORAX

Antenatal diagnosis can be made by an anechoic space surrounding the lungs. Pleural effusions sonographically appear as anechogenic fluid in the thorax. When unilateral and large, the hydrothorax can demonstrate considerable mass effect on the diaphragm, inverting the diaphragm and displacing the heart and mediastinal structures into contralateral hemithorax.[33] If it is bilateral, it shows an ultrasound appearance with two moon-shaped anechoic areas surrounding the mediastinum (Figs 8A and B).

Fetal hydrothorax can be isolated or secondary and its incidence is about 1:10,000 to 15,000 pregnancies.[34] Primary hydrothorax, correctly termed "fetal hydrothorax," is due to lymphatic leakage and can be unilateral or bilateral. Secondary hydrothorax is usually part of a generalized fluid retention in nonimmune hydrops and prognosis depends mainly on the underlying pathology. Secondary hydrothorax is more symmetric in size with little mediastinal shift. If there is septation or solid component within fluid, it should be taken into account as other differential diagnoses.[35-37]



Figs 8A and B: (A) Two moon-shaped anechoic areas surrounding the lungs; and (B) Two moon-shaped anechoic areas surrounding the mediastinum with hydrops

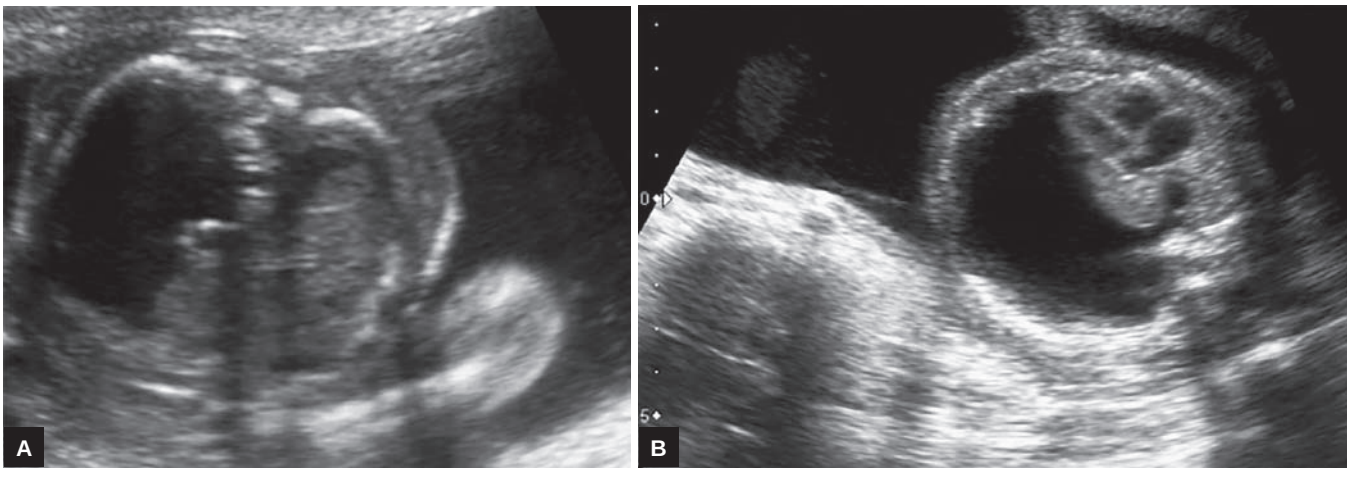
The ultrasound workup should begin with confirmation of the presumed primary and isolated nature of the hydrothorax by excluding out all secondary hydrothorax etiologies. Major congenital abnormality is commonly found in association with hydrops (41% in one series) and also any subtle sign can be a picture of a genetic syndrome.[35,38,39]

Unlike a small amount of pericardial fluid which may be physiological, a fetal pleural fluid collection is always abnormal. Primary hydrothorax may be idiopathic or consequent to thoracic duct malformations.[34] Primary pleural effusions are generally in chylous character, which is the consequence of an accumulation of lymphatic fluid due to atresia, agenesis or fistulas of the lymphatic duct. In the feeding infant or adult, aspirated fluid of a chylous effusion is characteristically milky because of the presence of chylomicrons in the lymph fluid. But aspirate of fetal chylothorax is clear and yellowish in color because of that the lymph fluid does not contain chylomicrons as a consequence of the fasting state of the fetus. Chylous effusion in the fetus contains typically a large number of lymphocytes, and greater than 80% lymphocytes is pathognomonic.[40] Congenital pulmonary lymphangiectasia is another rare cause of isolated fetal hydrothorax. It is a congenital structure characterized by a subpleural, interlobar, perivascular, or peribronchial lymphatic dilatation. On the contrary, fetal hydrothorax is thought to be one of the earliest signs of hydrops fetalis.[38] The causes of fetal hydrothorax with hydrops include cardiac and vascular diseases (50%),[35] chromosomal abnormality (more frequently trisomy 21 and Turner syndrome with the rate of 7 to 10%), anemia and hematological diseases, pulmonary abnormalities, skeletal dysplasia, hepatic or metabolic diseases, and infections.[41] Other major congenital abnormalities, such as CDH, extralobar sequestration, CCAM, thyroid teratoma, or fetal goiter are found in 25 to 40% of fetuses with nonimmune hydrops fetalis.[39] Perinatal mortality is about greater than 90% in hydropic fetuses with hydrothorax if another structural abnormality is identified. Therefore, it is important to make a complete anatomic survey in any hydropic fetus with hydrothorax.

Unilateral fetal hydrothorax (Figs 9A and B) is more sporadical and caused by a congenital malformation of the thoracic duct or the pulmonary lymphatic system.[42] It is usually diagnosed in the 2nd or early 3rd trimester.[43] The prognosis of fetal hydrothorax is difficult to predict with expected perinatal mortality rates between 22 and 53%.[38,44,45] Therefore, counseling on perinatal outcome is very hard for the selection of cases for fetal intervention or early delivery.

Irrespective of the underlying cause, fetal hydrothorax is potentially responsible for fetal and neonatal death due to pulmonary hypoplasia caused by chronic intrathoracic compression;[41,46] due to hydrops caused by mediastinal shift, cardiac compression, and vena caval obstruction with low cardiac output;[47] and also due to the prematurity as a consequence of polyhydramnios caused by esophagus compression (mediastinal shift) and/or low amniotic fluid uptake of the lungs. Infants affected by fetal hydrothorax present usually severe respiratory problem and insufficiency. Sometimes, it can be seen as an associated maternal morbidity, as in the mirror syndrome characterized by a generalized edema, due to the hydropic placenta that produces vasoactive substances.[48]

For prognostic features, several investigators reported outcomes of fetuses with antenatally diagnosed hydrothorax. Longaker et al reported that the mortality rate in cases of antenatally diagnosed fetal chylothorax was 53%.[34] Aubard et al reported[38] that overall mortality was 39% in their series, similar to other reports.[44] Adverse



Figs 9A and B: (A) Bilateral hydrothorax with one side very severe form; and (B) unilateral hydrothorax pushing the mediastinum contralaterally just before shunting procedure

prognostic indicators included bilaterally, presence of hydrops, absence of spontaneous resolution and premature delivery. Polyhydramnios has also prognostic significance because the uterine overdistention can increase the risk of preterm delivery. Even without hydrops, large pleural effusions can cause pulmonary hypoplasia due to compression. The time of onset, size, and duration of the pleural effusion influence the development of pulmonary hypoplasia. The most common cause of neonatal mortality with fetal hydrothorax is respiratory insufficiency due to pulmonary hypoplasia.[33,49]

Whatever the underlying etiology, infants affected by hydrothorax usually present a severe respiratory insufficiency in the neonatal period. This is because of direct result of pulmonary compression caused by the effusions or due to pulmonary hypoplasia secondary to chronic intrathoracic compression. The overall neonatal mortality with hydrothorax increases from low rate in infants with isolated hydrothorax to very high rate in cases with gross hydrops.[42]

There are several options in the management of fetuses with isolated hydrothorax, which are depending on gestational age, severity of effusion, evidence of progression, hydrops, polyhydramnios, or mediastinal shift. The outcome of fetal hydrothorax is significantly worsened by prematurity (less than 32 weeks of gestation), the presence of hydrops, and lack of fetal therapy.

Management of fetal hydrothorax is controversial because some are not significantly compromised, whereas some others can progress to hydrops and die *in utero* or at birth from pulmonary hypoplasia. The first step in case of fetal hydrothorax is to determine whether it is primary or secondary. Primary or isolated fetal hydrothorax is a diagnosis with exclusion of hydrops and congenital infections (parvovirus B19, cytomegalovirus, toxoplasmosis, rubella, syphilis, herpes), Rh-antibody to rule out immune hydrops, and Doppler evaluation of the peak systolic velocity in the middle cerebral artery (MCA) to exclude fetal anemia. Fetal anemia will usually be together with ascites before a hydrothorax appears. Fetal karyotype should be done because aneuploidy (mainly trisomy 21 and 45, X0) has been reported in 6 to 17% of fetuses with hydrothorax, the vast majority of which are hydropic.[50]

The hydrothorax are associated with structural fetal malformations in about 25% of cases, therefore this association highlights the importance of meticulous ultrasound and echocardiographic evaluations. Differential diagnosis for secondary hydrothorax due to CCAM, BPS, or CDH should be evaluated. Congenital heart disease is observed in up to 50% of cases of antenatally diagnosed hydrothorax. Large pleural effusions with shift of the mediastinum and cardiac compression may limit the evaluation of cardiac anatomy. After thoracentesis or shunting procedure, fetal echocardiography is necessary for a complete workup.[51]

The clinical course of fetal pleural effusions is unpredictable.[38] The natural history of fetal pleural effusion is significantly different from chylothorax in the newborn and has a much poorer prognosis. The mortality rate for chylothorax in the newborn is at most 15%, but the mortality rate for fetal pleural effusion is much higher at 53%.[38] If it is secondary hydrothorax with hydrops, the reported mortality rate of may be as high as 95%.

The major concern in a fetus with a primary hydrothorax is potentially the development of hydrops and pulmonary hypoplasia. Spontaneous resolution or regression has been reported to occur in 9 to 22% of primary fetal hydrothorax.[45] But it is not possible to predict accurately which effusions will be resolved or progressed based on finding of a single ultrasound examination.

The fetus with a pleural effusion is at significant risk for polyhydramnios and preterm delivery. Most authors recommend a close 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 polyhydramnios. The goals of fetal therapy are the prevention of compression and allowing normal lung development, prevention or reversal of hydropic changes and hydramnios, and avoiding fetal death and preterm delivery.

Fetal therapy is preferable over preterm birth of a very sick child. Therefore, fetal interventions should be seriously considered up to 37 weeks' gestation. The shunting procedure for hydrothorax up to 37 weeks' gestation has been proposed by Toronto group.[42] Successful intervention can reduce hydrops and therefore maturation of the lungs and other organs can be possible which makes postnatal surgery much less risky.

When the hydrothorax is small, isolated, and well tolerated, expectant management with frequent follow-up may be most beneficial because of the possibility of spontaneous resolution. If the fetal pleural effusion is very large or increases by gestational age, then a fetal intervention is needed. Fetal intervention for pleural effusion can include a single and serial thoracentesis (less effective) or thoracoamniotic shunting to allow the drainage of fetal fluid into the amniotic fluid.

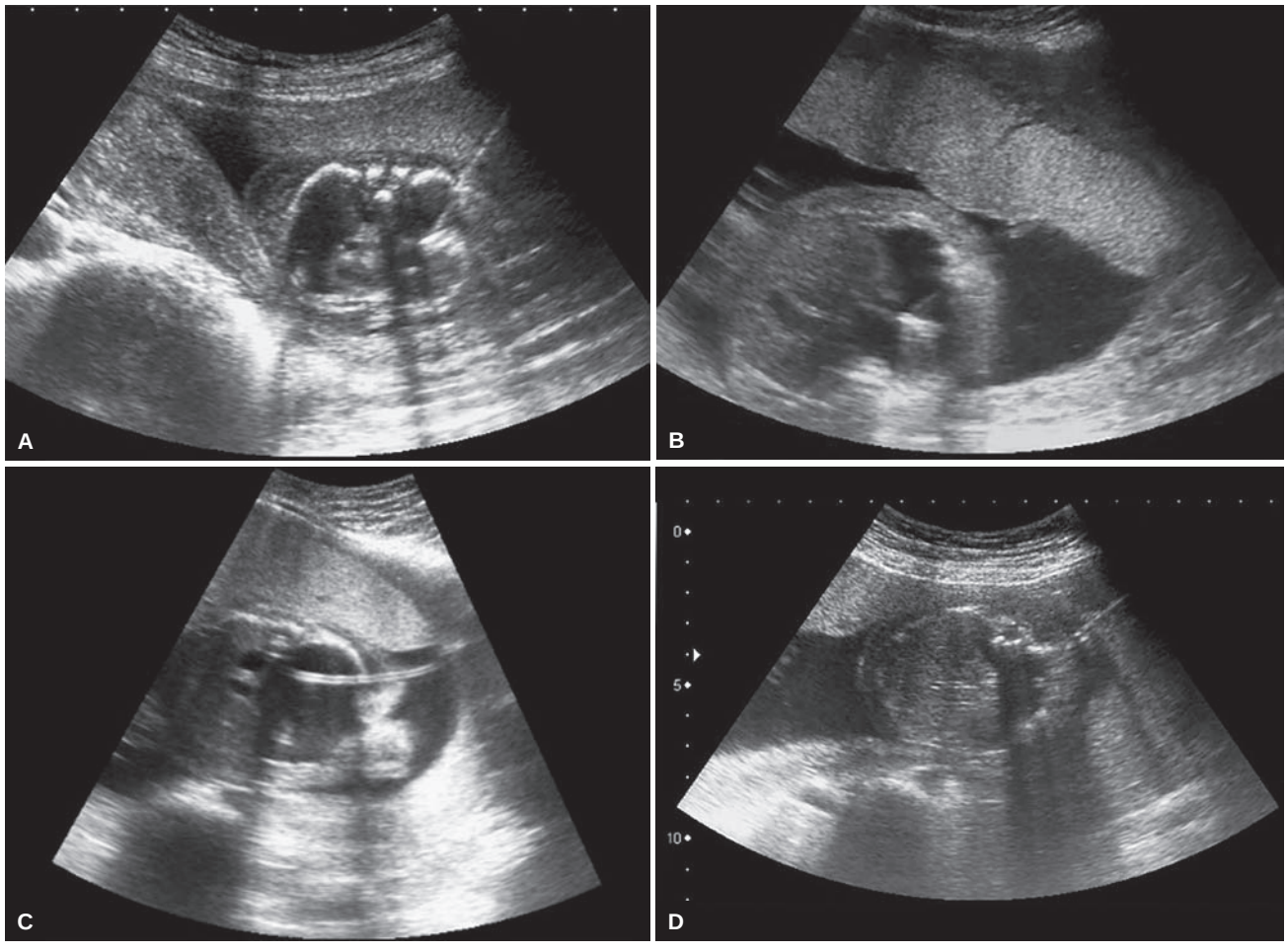
Thoracentesis as a treatment for fetal hydrothorax was proposed for the first time by Petres et al in 1982.[52] It is a diagnostic procedure to obtain pleural fluid for cell count, culture and to establish whether the effusion is chylous. Additionally and importantly, ultrasound evaluation should be done again after decompression because undiagnosed cardiac abnormality or other intrathoracic lesion may become apparent which cannot be seen easily due to compressed organs and anatomy.

There are some reports of thoracentesis for fetal hydrothorax which can be resolved with good outcome.[37] In one study, Aubard et al[38] reported that 16 of 29 (55%) fetuses treated by thoracentesis had good outcomes and the rest have had poor results with repeated thoracentesis because of quick reaccumulation and neonatal death due to respiratory failure. Thoracentesis may be extremely useful before delivery or for temporary stabilization, but this treatment alone is often not effective earlier in gestation because of the rapid accumulation in most (76%) of cases.

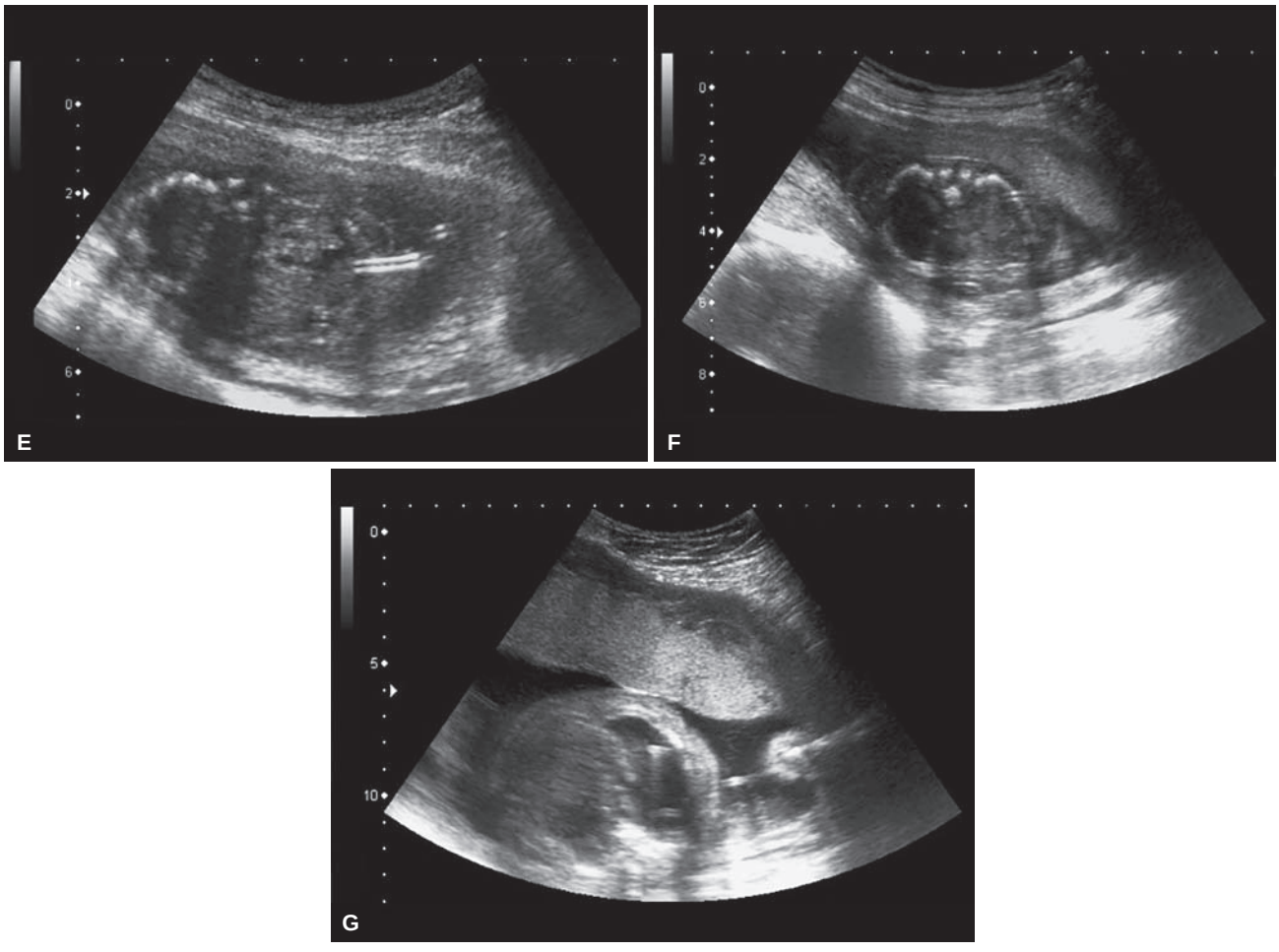
When hydrothorax reaccumulates after the initial thoracentesis, and with the development of mediastinal shift or fetal hydrops, a thoracoamniotic shunt should be done which was first proposed by Seeds and Bowes in 1986.[53] The most commonly used technique for thoracoamniotic shunting is described by Rodeck et al.[54] This technique has been successfully used in the treatment of isolated hydrothorax and in some cases secondary to pulmonary sequestration or cystic adenomatoid malformation with hydrothorax.[55]

As an intervention for thoracoamniotic shunting, a trocar with cannula is introduced into the fetal thorax preferably at 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 then the internal loop is deployed into the cavity by an introducer or pusher. As the trocar and introducer are removed from the wall of fetal thorax into amniotic cavity, the external end of the catheter is left in the amniotic cavity. With this intervention, hydrothorax is decompressed and allows the fetal lungs to expand and grow properly. As a consequence of decompression, a pressure on the venous system is reduced, thereby increasing venous return to the heart and improving heart failure, if present (Figs 10A to G and 11A to H).

Three larger series were reported by Nicolaides and Azar (n = 35), Mussat et al (n = 18) and Aubard et al (n = 80).[38,41,56] These series suggest that shunting procedure has the most dramatic effect on survival even among fetuses with the sign of hydrops. In the series of Aubard et al, only 10% of hydropic fetuses survived after



Figs 10A to D: (A) Shunting procedure for fetal hydrothorax under ultrasound guidance with trocar in the pleural cavity; (B) shunting procedure for fetal hydrothorax under ultrasound guidance, one pigtail end of the catheter just at tip of the trocar; (C) shunting procedure for fetal hydrothorax under ultrasound guidance, one pigtail in the pleural cavity and other pigtail in the amniotic cavity; (D) Shunting procedure for fetal hydrothorax under ultrasound guidance, trocar with catheter just coming out from fetal thorax. *(Continued)*



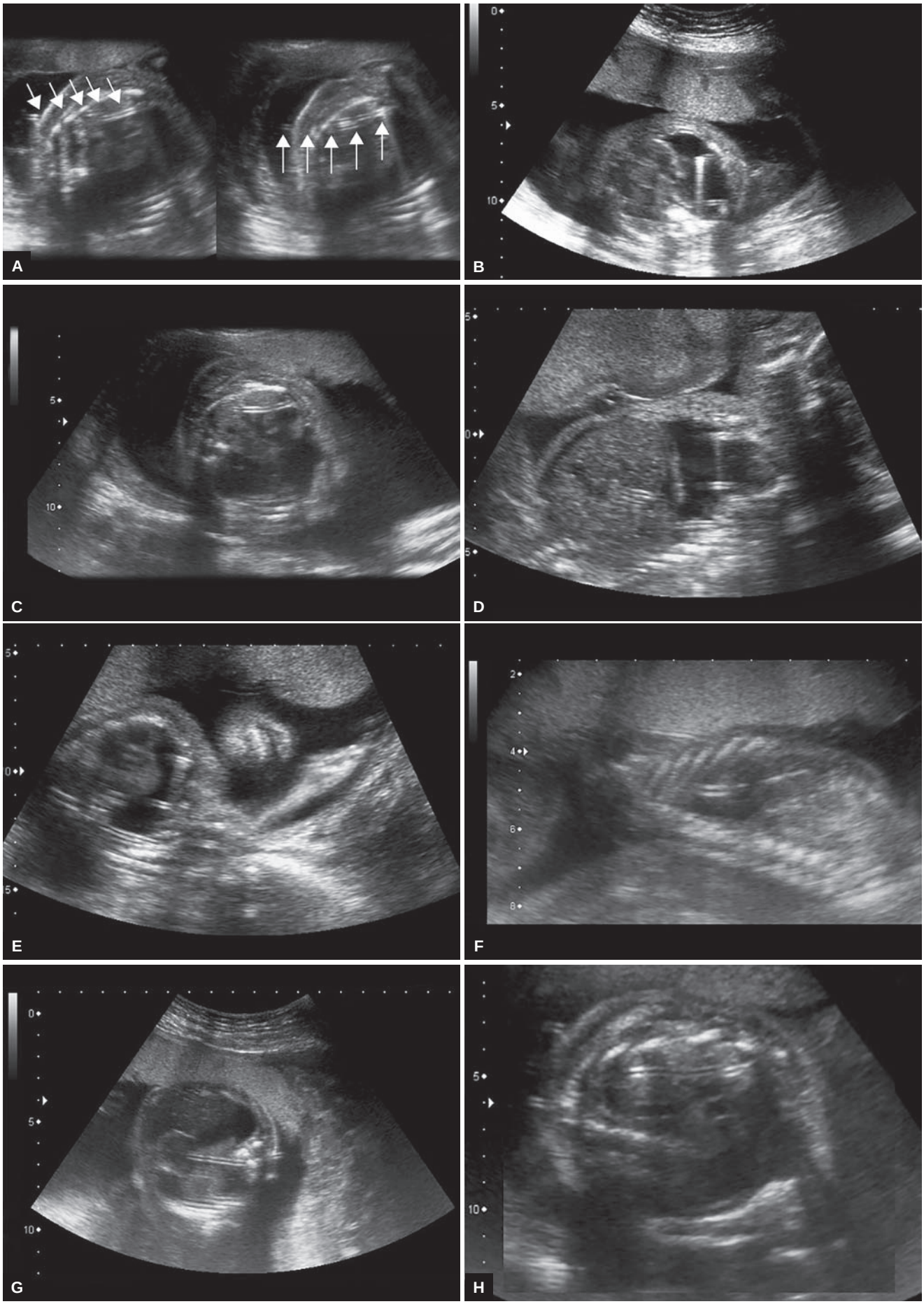
Figs 10E to G: (E) Shunting procedure for fetal hydrothorax under ultrasound guidance, disappearance of the hydrothorax just after shunting; (F) shunting procedure for fetal hydrothorax under ultrasound guidance, shunting catheter passing through the wall of thorax; and (G) shunting procedure for fetal hydrothorax under ultrasound guidance, both pigtail end of catheter seen

thoracentesis alone, whereas 67% of hydropic fetuses survived after thoracoamniotic shunting. In the series of Nicolaides and Azar and Rodeck et al, they reported similar survival rate ranging between 50 and 75% after thoracoamniotic shunt.[41,54] Also one should bear in mind that shunt failures were reported in 26% of cases.[57-59]

The risks of thoracentesis and thoracoamniotic shunting to mother and fetus have been minimal and quite far from the potential benefits. Some complications have been reported for either fetal thoracentesis and thoracoamniotic shunts. In the series of Smith et al,[60] 23 cases of shunting, one case ended in a fatal fetal hemorrhage at the time of shunt insertion at 23rd week and one neonatal death following the procedure related to abruption at 30th week of gestation. Displacement of the catheter has been a not uncommon problem. It has been found in the intra-amniotic cavity, maternal peritoneal cavity, neonatal subcutaneous tissue, and the intrathoracic cavity.[58] Acute maternal compromise has occurred due to amniotic fluid leakage into the maternal peritoneal cavity.[61] It should be recognized that these procedures have the potential for infection, bleeding, premature rupture of membranes, preterm labor, and fetal injury. After delivery, the catheter should be clamped immediately, otherwise it can result in temporary neonatal compromise. There is no evidence that fetuses that had a successful intervention suffer after delivery from any chronic respiratory disease. Thompson et al[62] described a series of 17 survivors after a successful intervention; all of them had a normal pulmonary development and an adequate lungs function. Of course, the prognosis after shunting is determined by the underlying cause of the hydrothorax.

LUNG MASSES

Lung masses cannot be all delineated with ultrasound in the 18 to 20 weeks although embryologically they do exist.[63,64] They may result in unilateral or bilateral hypoplasia of the lungs. Prognosis depends on the size of the lesion, heart and mediastinal displacements, presence of hydrops, associated structural anomalies, underlying chromosomal abnormalities, associated polyhydramnios on preterm premature rupture of membranes, and prematurity.[65-67] Common chest masses include CDH and CCAMs, isolated hydrothorax, and BPS. Other lung



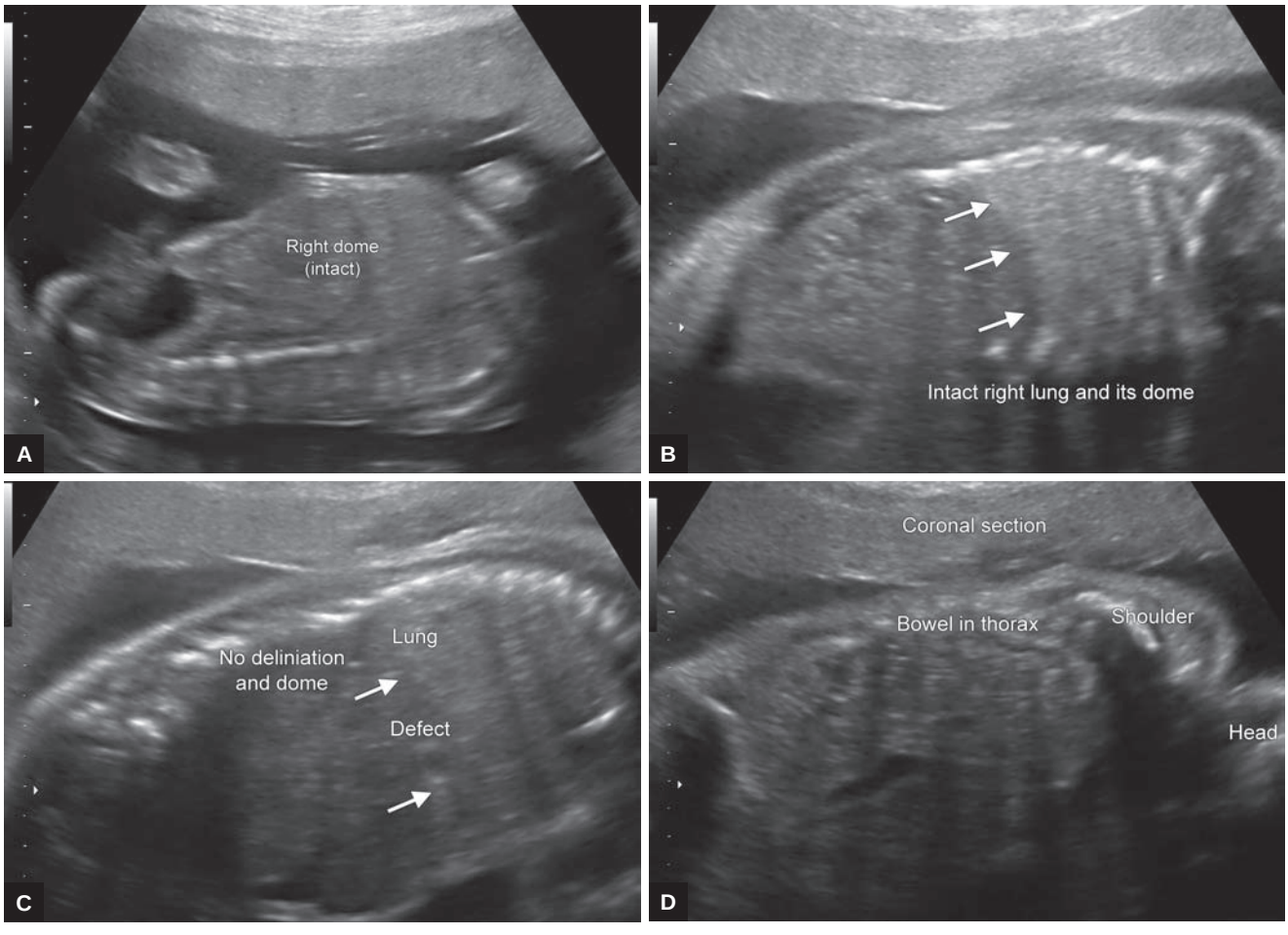
Figs 11A to H: Shunt catheter in the fetus after procedure

lesions include congenital lobar emphysema (CLE), bronchial atresia, bronchogenic cysts, neuroenteric cysts, BPS, and mediastinal masses.

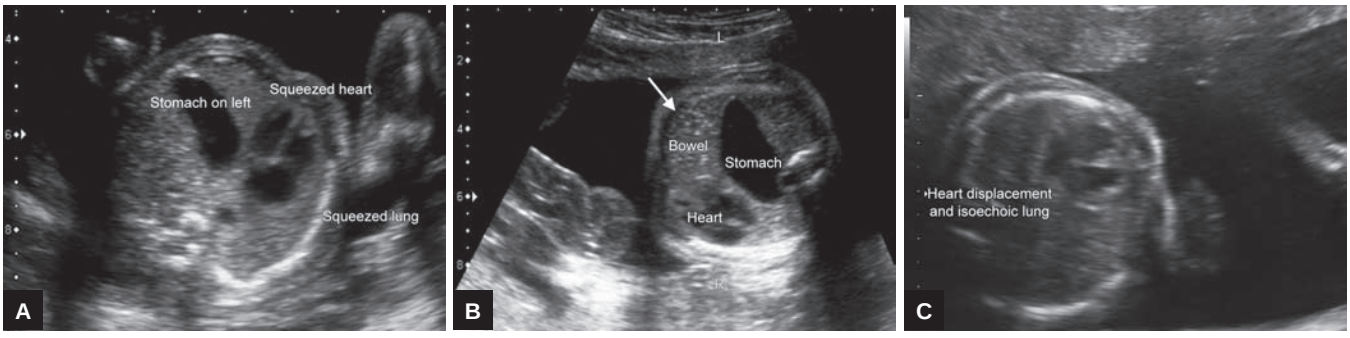
Diaphragmatic Hernia

The diaphragm is a borderline between the thorax and the abdominal cavity. Sonographically, the diaphragm appears as a thin, dark, hypoechoic, arched line. Continuity of this thin and darker line is actually a kind of demarcation between abdominal and thoracic contents. If this line is interrupted or cannot be seen clearly, then diaphragmatic hernia should be questioned. The costodiaphragmatic recess is most commonly located at the level of the 9th rib. The function of the diaphragm has been studied extensively by ultrasound as diaphragmatic movements start as early as 9 to 10 weeks. Hiccups can be seen first, followed by breathing movements at 10th week of gestation.[68,69] Diaphragmatic hernia is herniation of the abdominal contents into the chest through a defect in the diaphragm. The defect in diaphragm exists from the 10th week of gestation, but the herniation of the gut into the chest in about 50% of the cases may not occur before the 22 to 24 weeks of gestation. Increased nuchal translucency (NT) could be a marker also for diaphragmatic hernia in the 1st trimester which are bad prognostic cases.[70] The incidence of diaphragmatic hernia at birth is one-half, 500 to 4,000.[71]

Congenital diaphragmatic hernia is more common on the left side but can also be seen right-sided or bilateral. Failure of fusion of the pleuroperitoneal membranes results in a herniation of abdominal contents into the thorax when the gut returns to the abdomen by 11th week of gestational age. The disorder is progressive and the organs that are herniated in the thorax include the stomach, liver, spleen, small bowel, and colon. Left-sided CDH usually involves the stomach (Figs 12A to D and 13A to C). Right-sided CDH involves herniation of the liver. The herniation may be small, isoechoic, and intermittent[72] and therefore can be unrecognized. Four out of five fetuses die in the neonatal period usually because of pulmonary hypoplasia and pulmonary hypertension. Newborns have feeding problems, gastroesophageal reflux, chronic lung disease, and neurodevelopmental delays.[72,73] Sonographic signs include a low abdominal perimeter, failure to visualize the fetal stomach in the fetal abdomen, visualization of the herniated viscera in



Figs 12A to D: Coronal view of a left diaphragmatic hernia with the help of dome shape of demarcation line and isoechoic ultrasound appearance in early second trimester



Figs 13A to C: Axial section of left diaphragmatic hernia with stomach in the thorax

the thorax, cardiomediastinal shift, hydrothorax, and hydrops.

There may also be failure to delineate the diaphragm in its entire extent. Right-sided hernias are difficult to identify because of isoechoic lung and therefore in a suspected case it should be evaluated by color Doppler whether the portal vein is located in the thorax. Although identification of the liver is not critical, it has a major impact on the prognosis.[74,75] This is because the ductus venosus and UV often get kinked or compromised after surgical repair and thereby contributing to morbidity and often mortality. Sometimes the gallbladder may be seen in the CDH. If bowel segments are not fluid-filled as common in the 2nd trimester, they may appear as a nonspecific chest mass. A peristalsis can be seen in the 3rd trimester at the time of real-time scanning.

Bilateral CDH may be difficult to detect because of no cardiomediastinal shift. Ascites within a herniation may be mistaken as a hydrothorax. Not all fetuses with a CDH have a poor prognosis.[76-78] Prognosis depends on stage of gestational age especially if it is less than 24 weeks.

There are three types of hernias:[79]

1. *Bochdalek hernia*: Posterolateral defect which accounts for about 90% of cases found in the neonatal period. It is usually on the left side in 80% of cases, on the right side in 15% and bilateral in approximately 5%. The most common herniated contents of a left-sided hernia are stomach, bowel, and spleen. If it is right-sided the usual intrathoracic organs are liver and gallbladder.
2. *Morgagni hernia*: Parasternal defect which accounts for 1 to 2% of cases and is usually on the right side or bilateral and liver in the thorax.
3. *Central hernia*: It occurs in 5% of cases and is more commonly on the right side.

Prenatal diagnosis by ultrasound is based on demonstration of abdominal organs in the thorax, heart displacement, and polyhydramnios. On longitudinal follow-up, a defect in the posterior part of the diaphragm may be seen, the most common Bochdalek type. Mediastinal shift and displacement of the heart can be seen and also fluid-filled structures of stomach or bowels within the thoracic cavity. In the right-sided CDH, the right lobe of the liver usually herniates into the chest, which is with mediastinal shift to the left and/or cardiac compression. A right-sided CDH can be more difficult to diagnose because echogenicity of the lung and liver tissue is almost similar, but the trick is mediastinal shift or hydrothorax. Doppler of the UV and hepatic vessels may be helpful in diagnosis. Polyhydramnios is a common additional finding and is due to either esophageal compression or reduced absorption of fluid by the hypoplastic lungs and rarely seen before 24 weeks' gestation.

The incidence of aneuploidy was reported in overall 14% of pregnancies, particularly trisomy 13 and 18 (West Midlands Congenital Malformation Register, 2003).[80] In the case of normal karyotype, it is important to take a three-generation family tree for about consanguinity. Some of very rare autosomal recessive conditions are commonly found in parental consanguinity with a recurrence of anomalies. Comprehensive anatomy scanning including fetal echocardiography is essential to detect other structural anomalies because at least 33% of cases will have other anomalies including cardiac defects.[81] When the karyotype is normal, the syndromes discussed below should be considered. Storing fetal DNA or fetal tissue is very important for future genetic analysis, and a postmortem examination should be discussed with the patient for a complete diagnosis and the definition of recurrence risk.

Syndromes associated with diaphragmatic hernia are as follows:

- *Pallister-Killian syndrome (tetrasomy 12p)*: Polyhydramnios, rhizomelic limb shortening, abnormal facial profile with prominent philtrum, fetal somatic overgrowth in addition to those findings are variable and even absent in some cases. Pallister-Killian syndrome is a mosaicism for an isochromosome of 12p, which is an extra two short arms of chromosome-12. Therefore, the fetus has four copies of 12p in some cell lines. In a case of a highly suspicion of Pallister-Killian syndrome, the amniocentesis should be done for correct diagnosis because the cytogenetic

abnormality may not be detected in either chorionic villi or fetal blood.[82]

- Fryns syndrome is a rare autosomal recessive disorder of multiple congenital abnormalities, but incidence is about 4% of fetuses in CDH cases with normal chromosomes. Main criteria for diagnosis include CDH, hypoplasia of distal limb and nail, and abnormal facies.[83] Cataracts may be detected later in gestation. Intrauterine growth restriction (IUGR) and an increased nuchal fold together with CDH are the cases to be suspected for Fryns syndrome. Prognosis is very poor and 86% with an early lethal outcome. This is a difficult diagnosis in a fetus in the absence of history for a previously affected child or parental consanguinity, therefore, it is important to have genetic consultation when a diaphragmatic hernia is found together with other anomalies and normal karyotype.
- *Simpson-Golabi-Behmel syndrome*: It is an X-linked recessive disorder due to mutations in glypican 3 (Xq26). There is overlap with the features of Pallister-Killian syndrome and Beckwith-Wiedemann syndrome (BWS) with overgrowth of somatic organs antenatally and postnatally. The birthweight and birth head circumference of affected males are usually both more than 97th percentile. Cardiac defects and gastrointestinal malformations and polydactyly can be found with elevated maternal alpha-fetoprotein (AFP). Unless there are life-threatening malformations, i.e., not a lethal condition with most male fetuses with learning difficulties and overgrowth later in life. As in the case of BWS, males require screening for Wilms tumor (WT1). There may be a family history of X-linked development problems and carrier mothers may have distinctive facial features for which a genetic consultation can be useful for definitive diagnosis antenatally.[84]
- Cornelia de Lange syndrome is a rare sporadic syndrome with a birth incidence of about 1 in 50,000 and caused by new mutations in nipped-B-like protein (NIPBL).[85] The fetus has IUGR (usually apparent in the 3rd trimester), with upper limb anomalies, such as short forearms with small hands and tapering fingers to oligodactyly, and severe limb reduction defects. The features are more typical with brachycephaly, depressed nasal bridge, long philtrum, and micrognathia. Maternal serum pregnancy associated plasma protein-A is significantly reduced in Cornelia de Lange syndrome.
- Wilms tumor related conditions [Wilms associated genital anomalies retardation (WAGR), del 11p13 WT1 aniridia, Frasier syndrome, Meacham syndrome, Denys-Drash syndrome]: Predisposition to WT1 and male pseudohermaphroditism together with other external and internal genital anomalies are clinical features. A 46, XY karyotype in a phenotypic female with a diaphragmatic hernia would suggest one of these conditions. Denys-Drash, Frasier and Meacham syndromes are all caused by mutations in WT1, but WAGR is a microdeletion syndrome requiring specific fluorescence *in situ* hybridization (FISH) analysis.[86]
- Donnai-Barrow syndrome is caused by mutations in the gene LRP2[87] and a rare condition with corpus callosum agenesis, sensory-neural deafness and developmental delay, dysmorphic facies with hypertelorism, and CDH.

About 50% of fetuses have an isolated diaphragmatic defect and in the rest associated anomalies, such as chromosomal abnormality usually trisomy 18, as well as a major defect, including congenital heart disease, exomphalos, renal anomalies, brain anomalies and spinal abnormalities, Fryns, Goldenhar, Beckwith-Wiedemann, Cornelia De Lange, Apert's, and lethal pterygium.[88,89]

The primary determinant of survival is the presence of pulmonary hypoplasia and pulmonary hypertension in neonates with isolated diaphragmatic hernia. The mortality is very high despite optimal postnatal management and the introduction of extracorporeal membrane oxygenation (ECMO). Antenatal prediction of pulmonary hypoplasia is more difficult and is the most important part in counseling parents for selecting those cases that may benefit from fetal surgery.

Four-chamber view is the important section not only for fetal heart examination but also for other organs in the thorax. The contralateral lung with the longest axis is measured, multiplied by the longest measurement perpendicular to and is divided by the head circumference for calculating the lung-to-head ratio (LHR) (Fig. 14).[90] Recent research shows that in isolated CDH, fetal lung volume measurement by 3D ultrasound may be a potential predictor for pulmonary hypoplasia and postnatal outcome.[91] When the liver is intrathoracic, in isolated cases of CDH, prognosis is poor.[92,93]

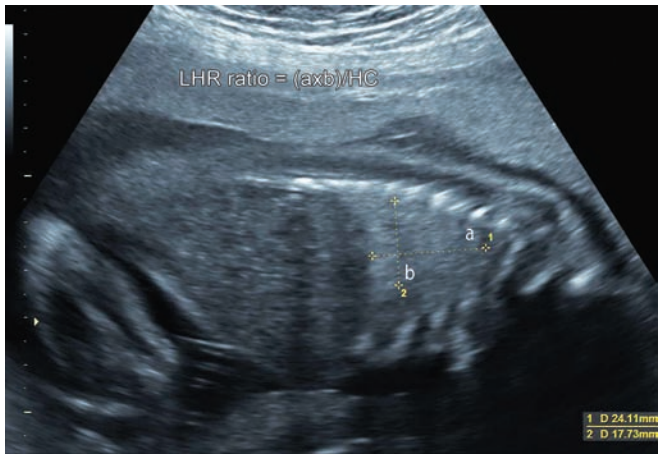


Fig. 14: Parasagittal view of the contralateral intact lung for lung to head circumference ratio

Fetal surgery can be a reasonable approach in the treatment of CDH.[94] The aim of surgery is to prevent lung hypoplasia. Although fetal surgery initially involved reduction of the hernia by open repair *in utero*, current practice involves ballooning of the trachea. Tracheal occlusion (TO) results in increased lung volume and accelerated lung maturity.

The first step of perinatal management is a nondirective counseling which is depending on accurate differential diagnosis. Counseling is best performed by a multidisciplinary team which has extensive experience with CDH and usually includes perinatal expert, geneticist, pediatric surgeon, and neonatologist. The family should be informed about the severity of this anomaly and the prognosis in fetal and neonatal life including severe neurologic, pulmonary and gastrointestinal morbidity, impact on quality of life, and death. This is very important for decision-making with respect to options of termination or fetal surgery as an experimental intervention.

Optimal perinatal management is a well-coordinated multidisciplinary team approach for optimal outcomes. The fetuses with known CDH should be delivered at tertiary centers, preferably with ECMO. Delivering and transporting the baby with CDH is not advisable and hazardous which can cause pulmonary vasospasm with unfavorable condition. Neonatal transport of cases with CDH is associated with poorer survival, comparing to cases delivered at a tertiary center.[95,96] We do suggest a planned vaginal delivery (unless there are obstetric indications for cesarean section) with induction of labor at around 38 weeks of gestation and vaginal delivery is beneficial for lung function. This planned delivery gives more comfortable time to the team for optimal preparation. Failure to progress or sign of fetal compromise is indication for quick cesarean delivery as perinatal hypoxia and acidosis can also induce pulmonary vasospasm.

In the delivery room, immediate intubation as first-line procedure is crucial because of that a bag-masking leads to gastric and abdominal distension and, therefore, compression of the lung is avoided. Because any delay in obtaining a quick airway can cause the acidosis and hypoxia and consequently increases the risk of pulmonary hypertension. A nasogastric tube is placed in the stomach and an umbilical artery line for monitoring of blood gases and blood pressure and also a UV catheter for administration of fluids and medications are correct management. In cases of liver herniated CDH, another venous access should be obtained because the UV catheter does not work through the ductus venosus. Blood pressure support includes the use of isotonic fluids and inotropic agents, such as dopamine at 50 mm Hg to minimize any right to left shunting. Surfactant therapy has been proposed for treating infants with CDH,[97] but the CDH Registry did not find an improvement in outcomes.[98] Surgical repair is delayed to maximize resolution of pulmonary vascular reactivity.

Most pregnancies with isolated CDH will carry to term with the exception of an incidence of stillbirth about 3 to 8%.[99,100] Expectant management is one of the standard of care with ultrasound surveillance for fetal complications. Some of fetuses with severe CDH will develop polyhydramnios, i.e., related to herniation of the stomach into the chest with kinking of the gastroesophageal junction and therefore increasing the risk of preterm labor. In these cases, prognosis is more severe because of prematurity plus pulmonary immaturity and severe pulmonary hypoplasia is often lethal.

Congenital diaphragmatic hernia was one of the first anomalies for prenatal intervention. Despite great effort, effectiveness and success rate of fetal surgery for CDH is still highly controversial. The rationale for fetal surgery is to prevent or reverse pulmonary hypoplasia and restore adequate lung growth for survival.[30,101] The initial fetal surgery was a patch closure of the diaphragmatic defect with abdominal silo with an open fetal surgery. Also fetuses with herniation of the left lobe of the liver could not be solved by this way because of that reduction of the herniated liver led to kinking of the UV which compromised the blood flow.

More recently, fetal TO has been used as a treatment modality for CDH. It has been shown that the dynamics of fetal lung fluid affect lung growth. Under normal circumstances, lung liquid volume and intratracheal pressure are maintained at constant values by fetal laryngeal mechanisms. Disruption of this normal fluid dynamics has an effect on lung growth. In case of CDH, this fluid dynamics could not be happened because of compressed lungs. Tracheal occlusion can reverse the high impedance to flow in the fetal pulmonary circulation and normalizes its physiological response in the sheep model of CDH,[102] and the vascular changes can be reversed.[103] Although TO might offer a relatively simple approach to accelerate lung growth in human fetuses with CDH, but further experimental studies in the sheep model also demonstrated that TO had a detrimental effect on lung maturation because of disappearance of type II pneumocytes,[104,105] however other studies demonstrated that released TO at an interval prior to delivery could induce type II pneumocytes and significant lung growth.[105-108] Although lung function was not restored to normal level because of abnormally thick wall making in a limited gas exchange.[109]

With that experimental data, clinical trials were initiated at the University of California, San Francisco (UCSF).[110] The technique evolved from an open fetal surgery to a fetoscopic surgery with uncontrolled case

series which showed an improvement in survival of severe CDH with fetoscopic surgery.[111] At the same period of time, another nonrandomized, prospective trial was performed at the Children's Hospital of Philadelphia (CHOP) utilizing the open technique to assure complete TO.[112] Tracheal occlusion resulted with a 33% survival but the survivors had significant neurologic and pulmonary morbidity. In another trial, which was a single center controlled, randomized trial at UCSF, it was demonstrated that there is no benefit in the TO group due to the unexpected enhanced survival in the control group.[113]

A minimally invasive approach to TO in the sheep model utilizing a deployable balloon technology placed via a single small trocar has been studied by investigators in Europe.[114,115] Later on the Eurofetus study group in a multicenter clinical trial reported the results of using only TO[116] and then release of occlusion.[117,118] Overall outcomes in 210 fetoscopic tracheal occlusion (FETO) interventions increased survival from 24 to 49% in severe cases with left-sided CDH and from 0 to 35% in right-sided CDH when compared to expectantly managed cases.[119] But the results were still not very successful as expected but subsequent reports have demonstrated better than expected short-term morbidity in survivors of FETO compared to cohort of expectantly managed cases.[119-122]

On a randomized controlled study, the fetal endoscopic TO *vs* postnatal management of severe isolated CDH has been compared for the survival improvements. In this study, FETO improves infant survival in isolated severe CDH. The risk of prematurity and preterm premature rupture of membranes was high, despite the use of small-diameter fetoscopes with a high incidence of prematurity (50.0%), extreme prematurity (15.0%) and preterm premature rupture of the membranes (35.0%). Infant survival to 6 months was 10% in FETO group and 4.8% in controls, and severe pulmonary arterial hypertension is 50% in FETO group and 85.7% in controls.[123]

In fetuses with isolated CDH, prognosis depends on lung size. Lung size can be reliably measured by the LHR, which should be expressed observed/expected (O/E) ratio for that gestational age. Fetuses with an O/E LHR more than 45% have a good prognosis and less than 25% have worse prognosis with expectant management and therefore are candidates for fetal therapy.

Fetoscopic TO results in expansion of the fetal lungs and healthy survival in 50% of cases. Survival for these cases depends on lung size before surgery. However, the fetal intervention carries an inherent risk for rupture of amniotic membrane, and hence a higher chance of early preterm delivery.

Tracheal occlusion with and release of tracheal balloon would appear to be the most promising fetal therapy to date (healthy survival in 50% of cases), the application of this therapy still needs more improvement and development because of high-risk for amniorrhexis and higher chance of early preterm delivery. This therapy should be performed in perinatal centers with appropriate CDH patient volume, experience for fetoscopic and *ex utero* intrapartum treatment (EXIT) procedure. In addition, timing and duration of TO for optimal results have not been answered.

In CDH cases, delivery by cesarean section has not been confirmed any advantage of the operative delivery. Currently there is no recommendation to deliver fetuses with CDH by cesarean section. In a recent study, survival was significantly higher for deliveries occurring later than 40 weeks of gestation than for those occurring at 38 to 40 weeks.[124]

Long-term follow-up of CDH is another issue that has to be taken into account. The postnatal survival rate at tertiary centers has improved to rates of 70 to 92%.[125-129] This is a result of shifting from early surgical intervention to intensive preoperative supportive care. However, these data represent the survival rate of cases of CDH that were full-term infants born or transferred to tertiary care centers with available skilled team and access to advanced technology (e.g., ECMO). Also these survival rates do not account for the cases of CDH that are stillborn, died outside a tertiary center, or fetal loss due to spontaneous or medical abortion.

The increase in CDH survival over the past two decades (with or without prenatal intervention) has shifted the focus to improving survivor morbidity. At the same time, CDH survivors have been shown in several reports to have a high incidence of respiratory, nutritional, musculoskeletal, neurological, and gastrointestinal morbidities.[130-134]

At a tertiary center with large volume of severe CDH patients, patch repair of the diaphragm was necessary in the majority of patients. In a recent retrospective review of 198 consecutive patients between 1999 and 2010, 99 cases (54%) required a Dual Mesh Gore-Tex patch with 75% survival. Recurrence rates in the surviving (75 patch) patients were similar to (74 cases) primary repair patients at 5.4 and 4% respectively.[135] In cases complicated by recent bacteremia, infection, or recurrence with infection, a transversalis/internal oblique muscle flap or a reversed latissimus dorsi flap has been used with success as previously described.[136-139]

Bronchogenic Cysts

These cysts can be seen as a consequence of abnormal foregut budding and show variable echogenicity and

progress. The left upper lobe is the most frequent site. They may be mediastinal or peripheral and often associated with foregut malformations and hemivertebrae. These cysts do not require specific obstetric management. Their importance is being one of the differential diagnoses of a fetal lung mass.[137] Usually it is an echogenic lesion representing fluid-filled lung below the stenosis.

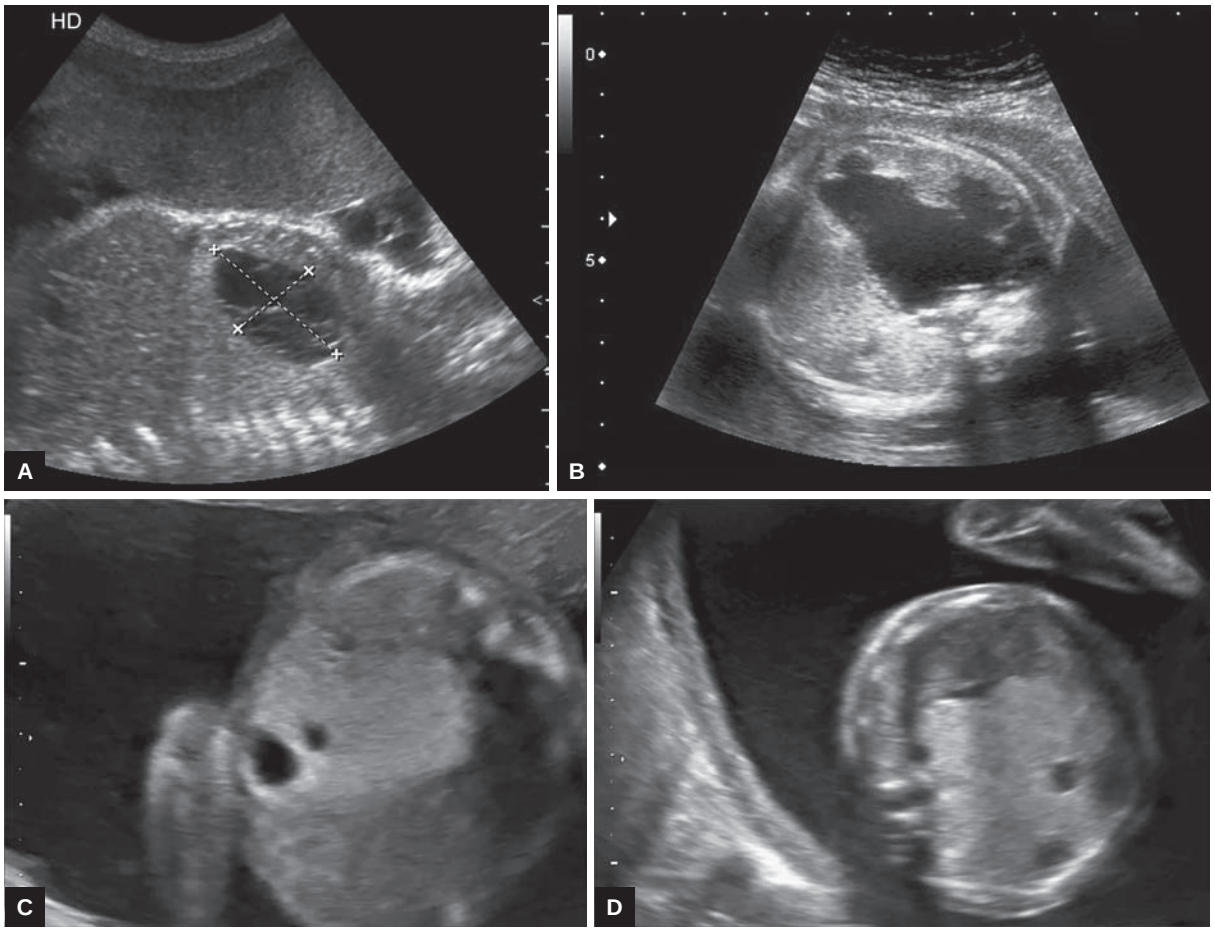
Congenital Cystic Adenomatoid Malformation

Congenital cystic adenomatoid malformation is a developmental lung abnormality characterized by a cystic mass of pulmonary parenchyma with the proliferation of terminal bronchioles and a failure of normal alveoli.[138] CCAMs occur as a result of failure of induction of mesenchyme by bronchiolar epithelium. The lesion is characterized by focal abnormal proliferation of bronchiolar like air spaces and absence of alveoli.[140] CCAM is usually unilateral and sometimes may be associated with sequestration in the same lung.

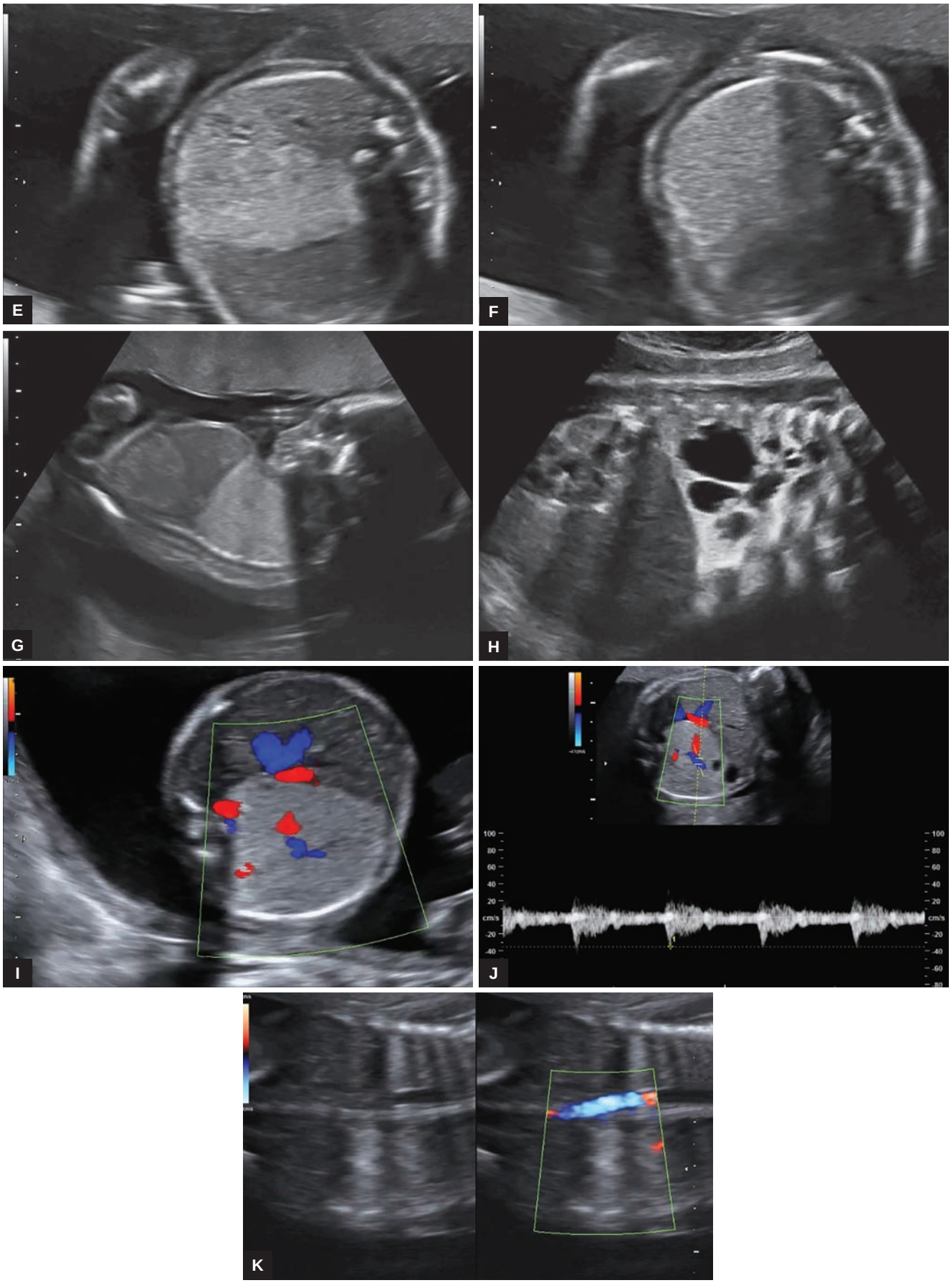
The prevalence of CCAM is about 0.13:1,000 in the 2nd trimester of pregnancy and 0.09:1,000 at birth.[141] This difference is due to fetal lost and spontaneous resolution in 15 to 45% of the cases.[142]

Diagnosis depends on the demonstration of a mass in the thorax. This may be macrocystic (cysts 2–10 mm), microcystic (cysts 0.3–0.5 mm) or mixed.[63,64] These may cause a cardiomediastinal shift, ipsilateral and contralateral lung compression, pulmonary hypoplasia, and finally hydrops. We have to bear in mind that the lesion may regress spontaneously.[143]

By definition, CCAMs have been classified into three major types.[141,142,144,145] Type I, macrocystic, which accounts for 50 to 70%, contain one or more large cysts more than 2 cm with ciliated pseudostratified columnar epithelium. CCAM type I, macrocystic variant can be single or multiple and is anechoic cystic structure, located in one hemithorax, almost always unilateral and heart displaced contralaterally (Figs 15A to K). Type II presents with several cysts, each 0.5 to 2 cm in size and is considered a mixture of the previously described types. Type III is microcystic-solid type and the most rare type, consists of several noncystic masses less than 0.5 cm with cuboidal epithelium. It is homogeneously highly hyperechoic pulmonary mass, almost always involves one lobe only, the volume of the mass does not allow the remaining intact lobe(s) to be displayed on ultrasound. If large enough, the mediastinum shifts toward the contralateral hemithorax.



Figs 15A to D: Type I and III congenital cystic adenomatoid malformation with different type *(Continued)*



Figs 15E to K: Type I and III congenital cystic adenomatoid malformation with different type

Several prognostic factors have been described in patients with CCAM, including the type of CCAM (type III has the worst prognosis with 58% survival rate *vs* type I with 74% survival) and polyhydramnios and hydrops.[65] The mortality rate for cases with type III CCAM with hydrops before 30 weeks was reported from 66 to 100%.[142,146]

A large CCAM may lead to pulmonary hypoplasia due to compressing effect.[147] Microcystic lesions are more likely to cause pulmonary hypoplasia and hydrops. The arterial supply of CCAM is via pulmonary artery and drainage into a pulmonary vein. Treatment of the lesion consists of expectant management, monitoring for hydrops or premature/term delivery followed by lobectomy if necessary.[65] Referral to a tertiary care center is important because emergency thoracic surgery is often necessary. Recurrence is rare in later pregnancies.

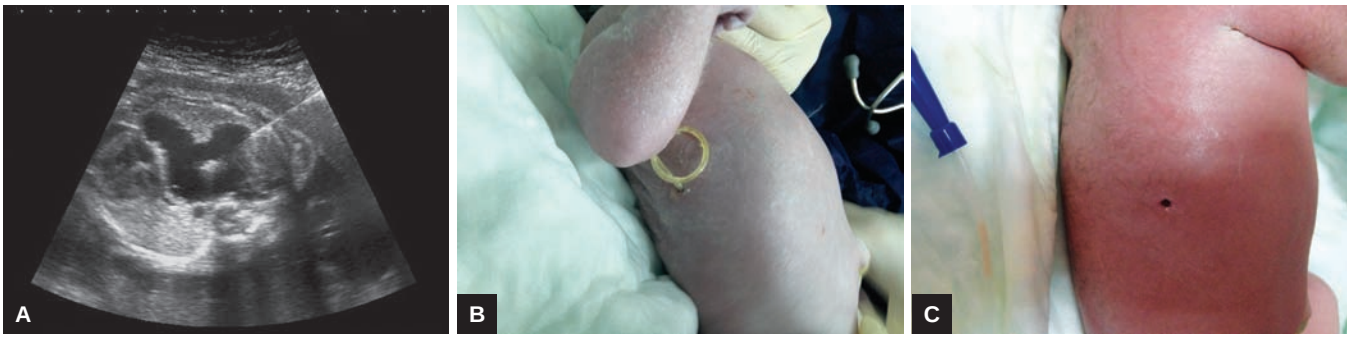
The CCAM usually arises from a single pulmonary lobe, and multilobar or bilateral lung involvement is quite rare. The CCAM is usually unpredictable in its growth potential between 18 and 26 weeks of gestation. The natural history of CCAM is quite variable, in severity extending from as a rapidly growing intrathoracic mass with resulting in nonimmune hydrops and *in utero* demise or spontaneously regress and "disappear" during the 3rd trimester. About 40% of CCAMs will progress to hydrops. Those cases are almost uniformly fatal without fetal surgery while some of them will regress and even may disappear completely.[148] The mechanism leading to spontaneous regression is not clear. The rates of spontaneous regression of CCAM vary from 15 to 65%.[67,149] The largest published series demonstrated sonographic evidence of regression in 76 of 154 CCAMs (49%).[6]

Serial ultrasonographic evaluation is important to follow fetal lung lesions for its growing pattern and the early occurrence of fetal hydrops. For the prediction of fetal hydrops, a prognostic tool using sonographic measurement of the CCAM volume was developed. The CCAM volume ratio (CVR) is calculated with dividing the CCAM volume (length × width × height × 0.52) by head circumference. A greater ratio more than 1.6 is predictive of increased (75%) risk of the development of fetal hydrops.[138]

The fastest growth in the CVR appears to be occurred between 20 and 25 weeks reaching to its peak at 25 weeks of gestational age.[138] There is a plateau in CCAM growth beginning at 25 weeks' gestation with a decrease in the CVR after 25 weeks of gestational age. If the mass causes mediastinal shift or cardiac displacement, this should be an indication for fetal surgery before going to hydrops. If there is a significant shift of the mediastinum, the heart and its function should be evaluated. Additionally, amniotic fluid volume, umbilical artery Doppler flow patterns, ductus venosus Doppler flow patterns, and placental thickness are important parameters.

Unilateral lesions are usually associated with the shift of the mediastinum into the contralateral side. In bilateral disease, the heart can be severely compressed and is usually associated with ascites due to venocaval obstruction or cardiac compression. In about 85% of cases, CCAM is unilateral. During the 3rd trimester, polyhydramnios may develop, which is likely to be due to decreased fetal swallowing, the consequence of esophageal compression by the mass.

The majority of fetuses with CCAM have a decreased size in the 3rd trimester and undergo normal vaginal delivery with postnatal resection at 5 to 8 weeks of life (no respiratory symptoms at birth; resection of lesion due to risks of infections, pneumothorax, and malignant degeneration), but some fetuses require more extensive evaluation and treatment *in utero* (Figs 16A to C). The literature recently has been systematically reviewed trying to determine the result of fetal surgery on perinatal survival in fetuses with congenital cystic lung lesions and no randomized studies were found. However, in cases accompanied by fetal hydrops, a significantly higher chance of survival in treated cases was reported.[150] On the contrary, studies of large CCAMs that were treated by fetal surgery have shown a higher rate of cellular proliferation and lower rate of apoptosis comparing to normal fetal lung at the same gestational age.[144,151]



Figs 16A to C: Shunting procedure for congenital cystic adenomatoid malformation type I and picture after delivery

Good prognosis has been shown with about half of cases that were allowed to continue resulting in spontaneous regression.[3,4] In the majority of cases with antenatal resolution, postnatal investigation with chest X-ray, computed tomography (CT) and magnetic resonance imaging (MRI) will demonstrate residual lung disease.

According to existing literature, the prognosis for a fetus with a lung lesion is generally favorable. Fetal hydrops is an important prognostic factor. Fetuses that develop hydrops are candidates for fetal surgery. Several centers advised that hydropic fetuses at or after 32 weeks' gestation can best be delivered, with or without an EXIT procedure, with reasonable chances of survival. Fetal interventions due to their inherent risks of rupture of amniotic membrane, preterm birth and other complications may be restricted to hydropic fetuses below 32 weeks' gestation. However, a severely hydropic neonate born with a large lung tumor could be very hard to resuscitate, and therefore this situation is also more high-risk approach. Because of that, we do advice fetal surgery up to 36 weeks of gestation for better outcome (not just for fetal outcome, also for neonatal outcome).

Open fetal surgical resection was originally suggested in case of poor prognosis for hydropic fetuses with large cystic lung lesions.[152,153] Subsequently, it has become clear that these fetuses can be successfully treated with the minimal invasive approach of thoracoamniotic shunting. Insertion of such a catheter in a large cyst of a CCAM has been successful, first reported by Nicolaides et al.[154] Several case reports and small series reported the results of this technique in hydropic and nonhydropic fetuses with CCAM or BPS.

In Dommergues study, only fetuses with significant polyhydramnios were shunted, with a survival rate of 33%; two newborns died postnatally after unsuccessful shunting.[67] In another study in which the indication for shunting was the presence of a large cyst, survival in three shunted nonhydropic cases was 100%.[63] Shunting procedure is usually offered only in more severe cases, i.e., those with polyhydramnios, large lesions or severe mediastinal shift.[155] Wilson reported their series of CCAM with a total of 23 pregnancies that have undergone fetal surgery. There was no difference in the CCAM location with 11 right-sided and 12 left-sided lesions. Fetal hydrops was present in 18 fetuses and polyhydramnios in 11 pregnancies with 9 fetuses having both hydrops and polyhydramnios. The gestational age at evaluation, shunt placement, and delivery was 21.4, 22.3, and 36.3 weeks respectively. The mean interval of shunt to delivery was 11.8 weeks. The evaluation before shunt showed that the mean CCAM volume was 70.8 cc (of 19.6–263 cc) and the mean CVR was 2.4. Following thoracoamniotic shunting, the mean CCAM volume decreased to 22.7 cc and the mean CVR to 0.7. Overall reduction in volume and CCAM ratio was approximately 70%. The perinatal outcome for these 23 shunted fetuses was 22 live born and 1 intrauterine death, but there were 5 subsequent neonatal deaths. Overall survival was 74% (17/23). Evaluations of the perinatal mortality showed that the gestational age at shunting was similar for both the surviving and nonsurviving neonates. The main difference between the two outcomes was the shunt to delivery interval, survivors with 76.8 days compared to nonsurvivors with 19.7 days.

A systematic review concluded an improved survival rate of 62% in treated hydropic fetuses *vs* 3% in those untreated.[150] Controversy about the role of thoracoamniotic shunting in nonhydropic fetuses remains as a discussed issue. It may be difficult to predict the evolution of a macrocystic lung lesion and timing of development of hydrops. Also, there are no randomized studies comparing treatment *vs* nontreatment in nonhydropic fetuses.

In a recent review, the result of thoracoamniotic shunting in type I CCAM has been reported in 68 cases by Witlox et al[156] including 44 hydropic fetuses. Within the hydropic fetuses 89% were live-born and nine infants died in the neonatal period. Overall perinatal survival in this group was thus 68%. With the nonhydropic fetuses (n = 24) all were live-born. Three infants died in the neonatal period due to pulmonary hypoplasia. Overall survival was, therefore, 87.5%. Therefore, the shunting procedure is preferable before going to hydrops in appropriate case, such as mediastinal or cardiac shift with a large cystic CCAM.

In microcystic lesions (CCAM type II or CCAM type III), cysts are too small for drainage. In these cases, open fetal surgery has been performed but with very high complications. When a systemic feeding vessel is found, which is very easy after technological advancement, percutaneous laser coagulation or injection of a sclerosing agent can be successful. Percutaneous ablation of a microcystic CCAM in a hydropic case using laser has been described. In all cases a laser fiber was passed through the lumen of an 18G-needle and then to coagulate the feeding vessels. In the last case, resolution of hydrops was described but further outcome was not reported.[157] In another case[158] the fetus died prenatally. In one case[159] the fetus died 4 days after birth. Bermudez reported on three cases of CCAM with fetal hydrops and treated with percutaneous insertion of a sclerosing agent directly into the CCAM.[160] In cases where hydrops was resolved all fetuses were born alive. One neonate died after 10 days because of nosocomial sepsis.

Resolution of a large CCAM after steroid therapy given for lung maturation was first described by Higby

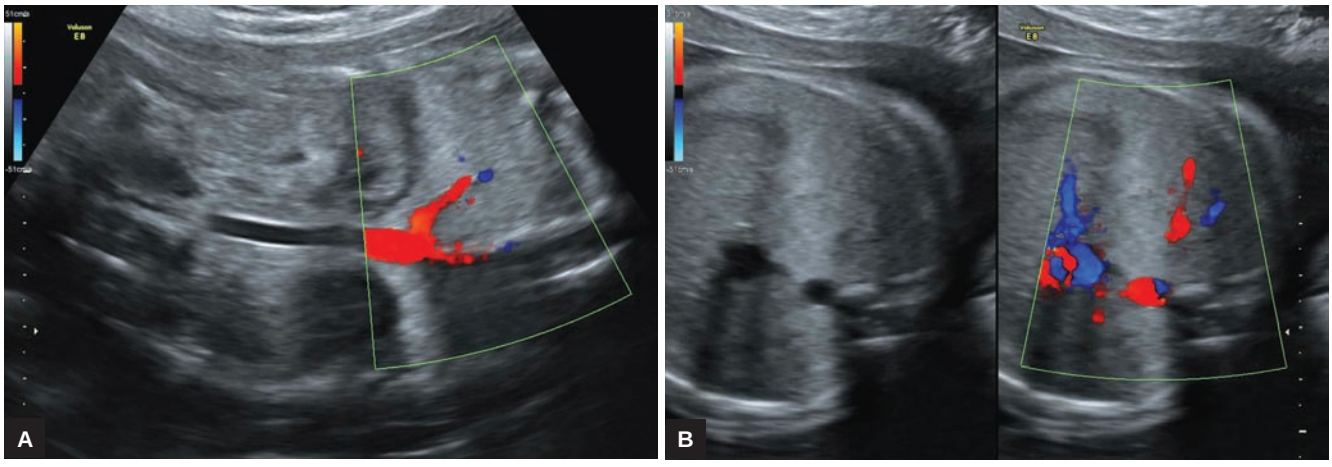
et al.[161] Tsao et al[162] reported that there were three fetuses with large, solid fetal lung lesions with the result of unexpected resolution of hydrops shortly after injection with betamethasone to the mother for lung. They postulated that steroids could have a beneficial effect on large CCAMs. After that, several others have observed the same results, after giving the standard dose of two times 12 mg betamethasone, 24 hours apart. Later series reported a more variable response on maternal betamethasone treatment. Morris et al[163] treated 15 high-risk fetuses (macro- and microcystic CCAM with fetal hydrops and/or CVR > 1.8). They found resolution of hydrops in only 54% of cases and a survival rate of 53%. Curran et al[164] treated 13 fetuses with microcystic CCAM and hydrops and/or CVR more than 1.6. They found resolution of hydrops in 78% cases described as high-risk cases, with a survival rate of 85%. In the meantime, current evidence suggests that in large CCAMs with hydrops, steroids therapy appears to be a reasonably first-line therapy, also because of the virtual absence of maternal side-effects. But there was a case report from Hong Kong in which a fetus with a large CCAM and hydrops was resolved after steroids but followed by sudden and unexplained fetal demise at 34 weeks' gestation.[165] Whether steroids should also be used in CCAMs without hydrops is more questionable, as the prognosis without intervention is generally good and spontaneous regression can be often occurred.

LUNG/PULMONARY SEQUESTRATION

Also known as pulmonary sequestration and accessory lung, the sequestration is a congenital malformation consisting of lung parenchyma which is separated from normal lung and does not communicate with the normal tracheobronchial tree. If it happens prior to closure of the pleura there is no separate pleural and called intralobar sequestrations. After closure of the pleura, it is called as extralobar sequestrations with its own pleura. Typical sonographic appearance is a lobar or triangular echogenic lesion in the base of lung and usually left side. Color Doppler shows an atypical arterial blood supply from the descending aorta and occasionally from the intercostal, celiac, or splenic arteries (Figs 17A and B). Intralobar sequestrations drain into pulmonary veins and extralobar sequestrations usually into a systemic vein, occasionally the azygos, hemiazygos, or inferior vena cava. Extralobar sequestrations may be thoracic or extrathoracic.[166-168] It is highly hyperechoic same as CCAM-III. Differential diagnosis relies on the identification of the feeding vessels with power or color Doppler originating from the descending aorta in the pulmonary sequestration. As with CCAM, pulmonary sequestration is virtually always unilateral usually on the left side and it involves the left lower lobe in 90% of cases.

Pulmonary sequestration seems to be a roughly triangular shape, with the apex pointing toward the mediastinum. Pulmonary sequestrations are occasionally associated with other thoracic and foregut anomalies such a CDH, CCAMs, bronchogenic cysts, neuroenteric cysts, and also including congenital heart disease, renal anomalies, and hydrocephalus. They can show ipsilateral hydrothorax. There is a variable mediastinal shift and hydrops. Several sequestrations regress spontaneously. No specific features indicate which sequestrations are likely to resolve. Persistent sequestrations may stabilize or may need surgical resection (postnatal).

Differential diagnosis between BPS and CCAM may not all the time be possible at antenatal ultrasound examination. Extralobar sequestration with an atypical systemic feeding vessel and associated pleural effusion can be easily diagnosed with BPS and not associated with microcystic CCAM. This distinction is of utmost importance when prenatal intervention is considered. If there is no severe pleural effusion and mediastinal shift, BPS has a high chance of spontaneous regression and therefore has a favorable prognosis.[169-171]



Figs 17A and B: Pulmonary sequestration lung tissue with its feeding vessels coming from aorta

Extrapulmonary anomalies are found in about 60% of cases with extralobar sequestration and 10% of those with intralobar sequestration. Intralobar sequestration typically affects the lower lobes. In extralobar sequestration, it is most commonly located between the lower lobe and diaphragm but it can also be found below the diaphragm in the abdomen. Ultrasonically, the abnormal lung appears as an echogenic intrathoracic or intra-abdominal mass. In about 50% of cases there is an associated hydrothorax. Polyhydramnios is also an associated finding.

The most common echogenic microcystic fetal lung lesions for differential diagnosis are type III microcystic congenital cystic adenomatoid malformation (mCCAM), bronchopulmonary sequestration (BPS) or both. The differential diagnosis should be made for CDH and, rarely, mediastinal teratoma, neuroblastoma, and mesoblastic nephroma.

In some cases, pulmonary sequestration is associated with hydrops. In these cases, a single tap or the placement of a thoracoamniotic shunt can be considered because that may resolve the hydrops due to venous compression. Minimally invasive ultrasound-guided interventions for pulmonary sequestration include thoracoamniotic shunting with associated hydrothorax as well as occlusion of the vascular supply to the lung mass, either by vascular injection of a sclerosing agent, laser ablation, or radiofrequency ablation. Still the optimal fetal therapeutic strategy remains controversial.

Interruption of blood flow in the feeding vessel of BPS has been described using pure alcohol in one case, polidocanol in three cases and N-butyl-2-cyanoacrylate in one case. The sclerosing agent was injected directly into the feeding vessel of BPS in all cases.[160,172,173] Hydrops resolved in all cases after treatment modality. But one child, treated with polidocanol sclerotherapy died in the neonatal period from operative complications after resection of the remaining lesion.

Interruption of blood flow in the feeding vessel of a BPS by intrafetal laser has been described as a treatment modality in hydropic fetuses with BPS. Successful ultrasound-guided laser coagulation of the feeding vessel of BPS using laser through a 18G-needle was described by Oepkes et al[174] and Witlox et al.[175] In both cases, hydrops have been dissolved after laser surgery and the fetuses survived uneventfully. Rammos et al[176] described resolution of hydrops in two fetuses with BPS treated with laser surgery. But in both these cases the feeding vessel remained open after laser treatment. One fetus had thoracoamniotic shunting for residual hydrothorax. The other child needed a thorax shunt after birth. The lesions in both cases were resected and in one child respiratory distress was noted after birth.

A preliminary result and a literature review by Ruano on ultrasound-guided intrafetal laser ablation of the abnormal systemic blood supply of BPS have been reported.[177,178] This technique might be more effective than drainage of pleural effusion as it targets the tumor rather than its symptoms. Laser therapy can also reduce the need for postnatal surgery; in cases treated only with drainage of the fetal hydrothorax, postnatal surgery was necessary to resect the tumor in five out of six live-born cases, whereas, in cases treated with antenatal occlusion of the feeding vessel, postnatal surgery was necessary in only one out of five cases.

More recently, Mallmann et al[179] reported a series of BPS of 41 cases with and without hydrothorax. The cases of BPS without hydrothorax were treated with expectant management and there was partial or complete regression in 65% of those cases. Those cases were born alive and half of them required sequestrectomy. In other 12 cases of BPS with hydrothorax, all had fetal surgery in which seven of them had shunting with no complete regression in this group and one was died *in utero*. Other five cases with hydrothorax had laser ablation of feeding vessel. In all cases in this group there was complete regression and were delivered at term and one neonate required sequestrectomy. Complete regression of the lesion was also more frequent in the laser group compared to cases without intervention. They concluded that in the absence of pleural effusion, the likelihood of spontaneous regression of BPS is high and the prognosis is therefore favorable. In cases with massive pleural effusion, treatment by laser ablation of the feeding vessel seems to be more effective than pleuroamniotic shunting with fewer complications. It might also reduce the need for postnatal surgery.

Congenital High Airways Obstruction

Laryngeal/tracheal atresia are rare congenital anomalies which are associated with demise soon after birth, unless treated antenatally. These arise as consequence of either subglottic laryngeal atresia, tracheal stenosis or atresia, or tracheal webs or cysts and are also known as congenital high airways obstruction (CHAOS). Pathologically, failure of efflux of fluid from the fetal lung results in exaggerated lung development. Ultrasound features include symmetric enlargement of both lungs with squeezed and anterior displacement of the heart and reduced cardiac angle (sometimes to zero) by high intrathoracic pressure.[180,181] The lungs are homogeneously echogenic, often similar to autosomal recessive infantile polycystic kidneys, since the underlying lesion consists of numerous fluid-filled spaces. The diaphragm is flat or inverted and cutaneous edema is common as is hydrops. Polyhydramnios is seen consequent to esophageal compression. The distal trachea and bronchi may be identified as tubular bulging fluid-filled structures in the mediastinum. The risk of chromosomal abnormality is extremely low, but extremely high-risk for

Fraser syndrome with extremely unfavorable outcome (laryngeal atresia, cleft lip/palate, congenital heart disease, microphthalmia, syndactyly, external ear anomalies, and bilateral renal agenesis, genital abnormalities with fused labia and enlarged clitoris).[182] Fraser syndrome shows autosomal recessive inheritance caused by mutation in the *FRAS1* gene or in the *FREM2* gene. Postnatal therapy is the only available option to manage the fetus with laryngeal atresia is the EXIT procedure.

We can conclude that in the majority of pregnancies where the fetus is diagnosed with an isolated lung lesion, the parents can be reassured that the outcome is likely favorable. In the absence of hydrops, even large lesions can be treated expectantly with weekly or bi-weekly monitoring. Also selection of an appropriate site for delivery is another important point which is crucial for better outcome. If there is a growing pattern of the pathology by gestational age, especially with a mediastinal shift and displacement of the heart, there is indication for fetal surgery. In mCCAMs with hydrops, a course of steroids may be beneficial less than 32 weeks of gestational age. Although promising, more evidence is needed to establish its role. Minimally invasive fetal interventions, such as thoracoamniotic shunting of fetal hydrothorax and large cysts, or occlusion of the feeding artery of microcystic-CCAM or pulmonary sequestrations should be taken into account in appropriate cases. Therefore, those cases should be taken care of in a fetal or perinatal center where this surgery is performed because it is not so easy and possible sometimes to predict the prognosis for expectant or interventional management.

The fetal procedures at our center is performed under local maternal anesthesia with skin infiltration with 1% lidocaine and fetal anesthesia by injecting fentanyl (15 mg/kg) and paralysis with pancuronium (200 µg/kg) as an intramuscular injection under ultrasound guidance. An 18-G needle was placed percutaneously into the fetal lung lesion toward the abnormal "feeding vessel" (as identified using color flow Doppler), and the tip of the laser fiber (400 mm) is positioned almost in contact with the vessel (vascular ablation) (Fig. 1) in BPS or CCAM cases. If it is not possible to identify the feeding vessel, such as in fetuses with "microcystic" CCAM, the tip of the needle with the laser fiber is inserted in the middle of the fetal lung lesion (interstitial ablation) (Fig. 2). In our center, a diode laser is used, with its power setting varying from 30 to 40 W, with 2.0-second pulses at 0.5-second intervals.

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