Chest and Lung Malformations

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INTRODUCTION

A remarkable advance can be seen in detection of fetal anomalies in the last decades. This article is a review of chest and lung malformations. Most prenatally diagnosed lung lesions can be managed successfully during the neonatal period. Out of these lesions (e.g. congenital diaphragmatic hernia and cystic adenomatoid malformation, hydrothorax) some have accentuated importance. They are frequent anomalies and after delivery require immediate or/and subsequent special neonatal intensive care. The chest lesions also can be detected prenatally, but the majorities of them are serious malformation with associated malformations or are a part of detrimental syndromes with low survival rate. In some generalized muscular disease the lack of fetal movements turn the attention to lesions.

The improvement of ultrasound technique and experiments gives the possibility of verifying the malformations in early gestational age, on the average 21st to 22nd weeks of gestation. These remaining some weeks provide the opportunity to perform other specific examinations and probes for genetically determined disorders. Among further investigations the fetal cardiologic ultrasound has emphasized role due to the high number—in some type of malformations even up to 40 percent—associated cardiac anomalies. These data help in genetic counseling and in the parent's decision making.

CHEST WALL MALFORMATIONS

The bony abnormalities are rare and are sometimes amenable to operative treatment.[1]

Defects of sternum are sporadic anomalies that usually occur in isolation. Cleft sternums are classified as partial and total. The partial forms can be superior, middle or inferior.[2] In 1985 Hersh *et al* described sternal malformation/vascular dysplasia association which is an association of superior cleft with vascular dysplasia of the craniofacial soft tissues and internal organs, including mucosa of the respiratory and gastrointestinal tracts.[3] The inferior form may be isolated lesion or seen as part of complex anomalies such as pentalogy of Cantrell.[4] The complete sternal cleft in 8 percent associates with cardiac anomalies, especially ectopia cordis.[5,6]

The most common of the sternal defects is the pectus excavatum. It can associate with vertebral anomalies, Pierre Robin and Marfan syndrome, scoliosis and some other connecting tissue lesions. Generally the correction should not be undertaken until several years of age and only in those few children in whom the deformity appears to be progressing.[1]

Several skeletal dysplasias (short-rib polydactyly syndromes, thanatophoric dysplasias, homozygous achondroplasia) are associated with hypoplastic lung and narrow thorax. These disorders may lead to pulmonary hypoplasia, frequent cause of death in these conditions. Another ultrasound finding can be the long and narrow thorax, which can be observed in asphyxiating thorax dysplasia, chondroectodermal dysplasia, metatrophic dysplasia, fibrochondrogenesis, atelosteogenesis, campomelic dysplasia, achondrogenesis and hypophosphatasia.[7] Thoracic dimensions can be assessed by measuring its circumference in the level of the four-chamber view of the heart. The relationship between the gestational age and thoracic circumference and length is summarized in Chitratka *et al* article published in 1987.[8]

A rare condition is the deficiency of the pectoral muscles on one side (Poland syndrome). It may associate with two to four abnormal ribs, hypoplasia of the breast, and vertebral anomalies. After birth breathing may be paradoxic and the cardiac impulse can be easily observed through the soft tissues, but no urgent intervention required in the newborn period.

Other causes of thoracic dysfunction are diseases of the muscles (myasthenia gravis, amytonia congenital, congenital muscular dystrophy), spinal cord or glycogen storage disease.[1] They usually recognized in the context of the associated systemic muscular weakness, fewer fetal movements.

CONGENITAL HYDROTHORAX

Fetal hydrothorax has been estimated to occur in 1:15,000 pregnancies or 1:10,000 births.[9-11] The congenital chylothorax is a special form of primary hydrothorax, defined as the accumulation of lymph in the pleural cavity. The fluid collection may be unilateral or bilateral. Unilateral effusions occur equally on both sides and usually signify a primary etiology. Bilateral effusions occur as a secondary manifestation of any other associated malformation or are signs of fetal hydrops syndrome.[9]

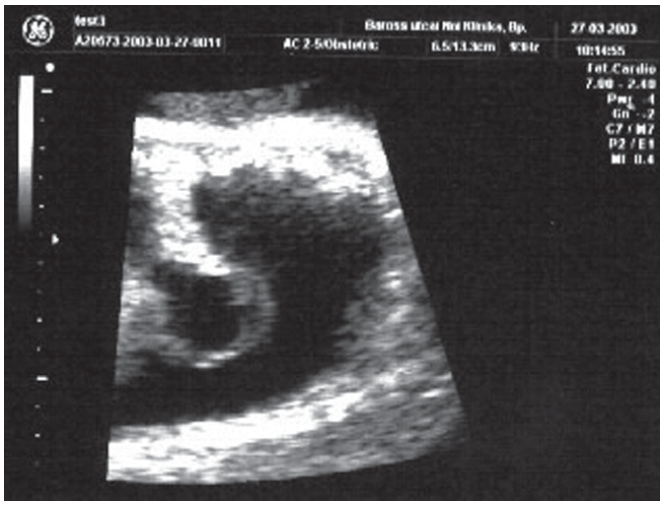

Fig. 1: Small diaphragmatic hernia—the herniation of peritoneum into the chest, caused hydrothorax

The ultrasound enables the differentiation between hydrothorax and hydrops syndrome. The chylothrorax can be diagnosed by cytological and biochemical analysis of the fluid. Congenital chylothorax occurs more common in males and on the right side.[12]

The exact mechanism of development of pleural fluid collection is unclear. The primary fetal pleural effusion is thought to be vena cava obstruction, reducing venous return and causing cardiac compression, resulting in low output cardiac failure.[10] The fluid accumulation through compression lead to pulmonary hypoplasia especially early in onset forms.

Fetal pleural effusions may be associated with pulmonary malformations such as pulmonary sequestration, cystic adenomatoid malformation or congenital heart defects (Fig. 1). Congenital infections by adenovirus, parvovirus B19, cytomegalovirus or others should be excluded and in some cases other markers of infection can be found on ultrasound. Pleural fluid may be also associated with chromosomal anomalies (trisomy 21, monosomy X), thus cytogenic investigation should be performed as part of the check-up.[9-11]

Prenatal management is variable, depends on the natural history of the effusion. Small, temporary, isolated volumes may be tolerated, but serial ultrasound scans required. In cases of large volume of hydrothorax therapeutic intervention via thoracocentesis or thoracoamniotic shunt is warranted. In bilateral hydrothorax cases single-needle thoracocentesis may be useful prior to delivery or as a temporizing maneuver. Usually it is preferred as the first step, because the spontaneous resolution of the effusion. It may identify the etiology of the fluid collection and will help in the parental counseling. Shunting may be useful if the fetus is less than 32 weeks of gestation, but in 26 percent of cases complications (clogging, fetal death, and migration) may occur.[9] In the vast majority of cases the procedure was carried out in the second trimester, but in some cases it was performed around the 20th week of gestation to prevent the development of fetal hydrops and pulmonary hypoplasia.[10]

As mentioned before the natural history is variable thus there are different data about the mortality. If it left untreated the overall mortality has been reported to be 35 to 53 percent. Spontaneous regression has been reported to occur in 9 to 22 percent, with 100 percent survival. The progression to hydrops may result 76 percent mortality compared in 25 percent mortality in non-hydropic fetuses.[9,11]

CONGENITAL DIAPHRAGMATIC HERNIA

The prevalence of congenital diaphragmatic hernia is variable in different publications. It is usually reported 1 per 2000 to 5000 live births.[13-22] Approximately 85 percent of defects are left-sided, 13 percent right-sided, and 2 percent are bilateral.[23,24]

The cause of development is poorly understood even today. One theory in that malformation of the diaphragm is linked to abnormal development of the adjacent lung. Another theory is that diaphragm malformation is the result of abnormal muscle innervations by the phrenic nerve. The third theory is that improper myotube formation, which can be either decreased in number or maldistributed, causes the congenital diaphragmatic hernia. The pressure of intra-abdominal viscera on this thinned-out and weakened diaphragmatic muscle causes rupture of the diaphragm and leads to herniation. The currently most popular theory is the impaired closure of the pleuroperitoneal canal at the eighth to tenth weeks of gestation.[14,24-26] Allan and Greer demonstrated in animal model that the defect in diaphragm development results from failure of the pleuroperitoneal fold to form properly at a significantly earlier stage of embryogenesis than previously was anticipated. The factors that contribute the defective development of the pleuroperitoneal fold are unexplored. Increased cell death in the cervical somites was reported to one reason.[27] Animal model data led to the hypothesis stating that the amuscular mesenchymal component of the pleuroperitoneal fold is defective and does not provide a full foundation for the formation of the diaphragmatic musculature.[28] These findings can resolve the disturbance of development of diaphragm, but not give explanation for several associated malformations. In the 1940s Anderson *et al* observed, that the vitamin-A deficiency augment the incidence of CDH.[29] Several data strongly imply that the retinoid system is candidates for involvement in the CDH, in the pulmonary hypoplasia and in the cardiac anomalies.[15,30,31] Major's clinical study showed that mothers and their infants with CDH had lower plasma retinol levels compared with the levels in mothers and healthy infants.[32] There is increasing evidence that the long arm of chromosome 15 (15q24-26) plays crucial role in the development of diaphragm and some associated malformations. This region encodes for the cellular retinoic acid binding protein-1 (CRABP1).[13,15,33-35]

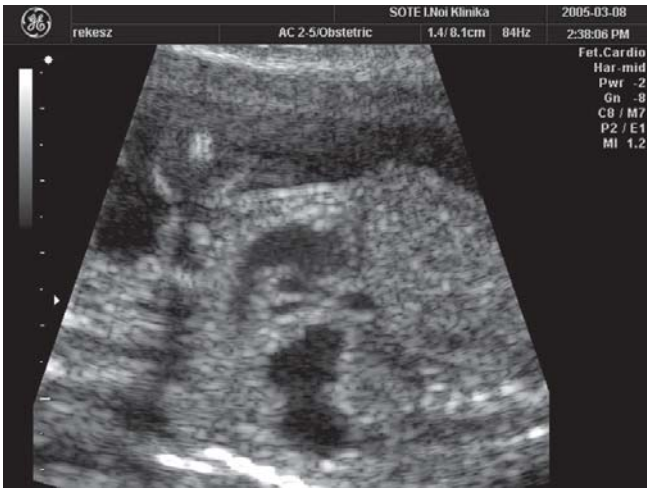

Fig. 2: Congenital diaphragmatic hernia—the posterior part of the diaphragm is absent, stomach is visible behind the heart

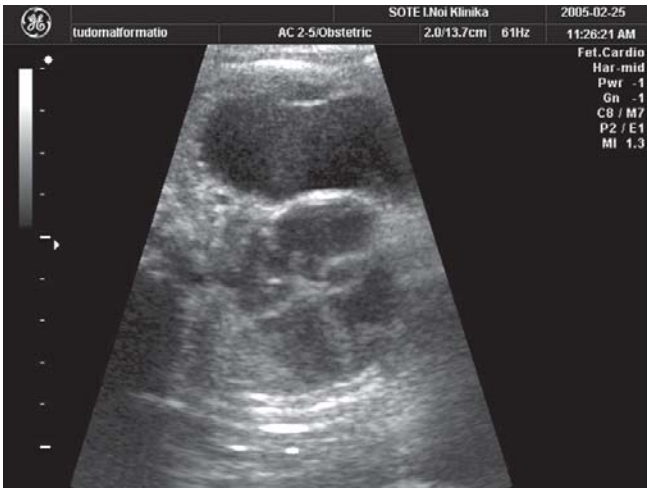

Fig. 3: A large bronchogenic cyst in the right thoracic region dislocating the heart

The congenital diaphragmatic hernia may also cause poor development of the vascular bed with the result being pulmonary hypertension. As the molecular genetic background of the condition developed it was established that impaired expression of proteins such as VEGF (vascular endothelial growth factor), FGF (fibroblast growth factor) and SHH (sonic hedgehog) plays an important role. FGF10 is essential in pulmonary development from the beginning. FGF7 regulates the branching process of the bronchi while VEGF influences the normal development of the canalicular phase of pulmonary development.[21,36-38] In the lung of congenital diaphragmatic hernia cases Solari *et al* has been observed an increased glucocorticoid receptor expression.[39] In diaphragmatic hernia cases not only morphologic, but biochemical lung immaturity, lower concentration of desaturated phosphatidylcholine (DSPC) and SP-A, was observed.[40]

The basis of prenatal diagnosis is the obstetrical ultrasound screening (Fig. 2). The prognosis considered to be unfavorable if the liver is in the hemithorax, the lung/head ratio is smaller than 1.4, there is polyhydramnios, the abdominal circumference is smaller than 5th percentile, the gestational age at the time of diagnosis is smaller than 25th week of gestation, and if the stomach is positioned posterior. There are some new approaches to assess the lung volume, e.g. measuring the diameter of pulmonary artery and measuring the lung volume with 3D ultrasound and MRI.[41,42]

The diagnostic evaluations should be completed with fetal echocardiography and fetal karyotype determination to research and detect additional abnormalities (Fig. 3).[43]

Generally the associated malformation rate is given around 20 to 50 percent.[19,22,23,44-48] Bollmann *et al* mentioned 72.7 percent incidence rate of their 33 patients, where the malformations were detected with the prenatal ultrasound.[51]

Among the associated malformations cardiovascular malformations are generally mentioned at first. Stege *et al* 38.7 percent, Dott *et al* and Tonks *et al* 16 percent and Borys *et al* 23.1 percent incidence rate published.[22,46,50,52] In our cases it occurred in 43.7 percent. Bedoyan *et al* found similar high (51.6%) rate.[49]

The rate of central nervous system anomalies are reported around 20 to 22 percent.[19,22] In other communications the incidence rate is mentioned 10 to 15 percent.[46,49] The craniofacial anomalies and skeletal anomalies are generally mentioned nearly in the same rate, among 15 to 25 percent. The gastrointestinal malformations incidence rate is a bit lower, 7 to 11 percent. Observing only the abdominal wall closure defects Bedoyan *et al* found 1.6 percent, Garne *et al* 13 percent incidence rate.[19,46,50]

Chromosomal anomaly was observed in 5 to 30 percent of cases.[51-53] Often trisomy 18 was observed, but several other genetic disorders (trisomy 13, trisomy 21, Fryns syndrome, Brachmann-de Lange syndrome, Goldenhar syndrome, Fraser syndrome, Beckwith-Wiedemann syndrome) may associate.[16,19,22,24,46,48]

In general 50 to 60 percent of diaphragmatic hernia cases are diagnosed before the 24th gestational week, but often the abnormal thoracic situation of abdominal organs becomes obvious only in the third trimester. Garne *et al* on the basis of data collected from 20 centers of 12 European countries the highest rate of diagnosis found on the 20 to 22nd gestational weeks and on the forepart of the third trimester.[18,19]

Despite improvements in neonatal intensive therapy and pediatric surgery it is a life-threatening anomaly with a significant mortality rate. Beside associated anomalies the pulmonary hypoplasia is the major determinant of survival.

In the background of the pulmonary hypertension Kobayashi *et al* reported that the serum adhesion molecule levels strongly correlate with severity pulmonary hypertension.[54] They conclude that the up-regulated expression of adhesion molecules on the endothelium of pulmonary vasculature and high circulating levels of adhesion molecules in congenital diaphragmatic hernia patients with persistent pulmonary hypertension suggest the adhesion molecules may play a role in the development of persistent pulmonary hypertension in diaphragmatic hernia cases. Measurement of circulating adhesion molecules may be a new useful method for determining disease severity and may be of value for monitoring the progression. It may have therapeutic implications as well because agent that block or prevent adhesion molecule expression could, theoretically, reduce vascular endothelial damage.

The question is which form of ventilation will be useful for these babies. Regardless of whether conventional ventilation or HFOV is used to achieve "gentle ventilation" as Wung *et al* suggested in 1995, good survival may be achieved with this method. The aim is to avoid hyperventilation and barotrauma as a significant cause of mortality and morbidity.[18,55,56]

Another interesting question is the administration of exogen surfactant. As we previously mentioned it is proven that surfactant level is low, but the capability to produce it is intact.[40] In recent publications opinions are divided about routine administration of exogen surfactant. Exogen surfactant in term infants with congenital diaphragmatic hernia showed no benefit, however, surfactant may be of benefit in the preterm infants because they may have intrinsic lung immaturity even without diaphragmatic hernia.[18,57,58]

The survival rate of congenital diaphragmatic hernia is generally mentioned around 45 to 60 percent.[22,48] Some authors mention 19 percent, while in other publications, 92 percent.[17,59,60] If the diagnosis was performed before the 25th gestational week, British authors published a 42 percent survival rate, while the French result was 38 percent.[17,61] In an English group data 70 percent of diaphragmatic hernia cases associated with other malformations was terminated.[22]

CONGENITAL LUNG MALFORMATIONS

Congenital lung anomalies are easily detected during routine prenatal ultrasound examination. Two main categories have been reported: bronchopulmonary sequestration and congenital adenomatoid malformation. Both of them have a solid or cystic sonographic appearance. They differ in their arterial supply. In cases of bronchopulmonary sequestration the artery arises from the abdominal aorta, while in cases of adenomatoid malformation the blood supply arises from the pulmonary circulation. This distinction would be very simple, but it seems that about 50 percent of these anomalies are hybrid forms.[62] In 1987 Clements and Warner propose unifying theory that encompasses a cause for all the major bronchopulmonary malformations. This depends on the relative growth and development of the pulmonary tree and pulmonary vessels. The early bronchial buds are supplied by capillaries from the primitive systemic circulation, but as the lung grows these vessels regress and the pulmonary artery supply becomes dominant. Interruption of this process at different times and sites during the development would determine the exact development of the affected lung tissue and final blood supply resulting in pulmonary sequestration, cystic adenomatoid malformation or a mixture of the two lesions.[63]

On this occasion Achiron *et al* in 2004 proposed a new classification of the fetal lung anomalies. They divided the cases in five types of dysplasia such as agenesis of the lung, normal lung with abnormal blood supply, abnormal lung with normal or abnormal blood supply and miscellaneous form.[62] In the next part some essential data are detailed of these anomalies.

Cystic Adenomatoid Malformation

Congenital cystic adenomatoid malformation is a hamartoma of the lung that is usually unilateral and involves only one lobe of the lung. More than 80 percent of fetal thoracic lesions are adenomatoid malformations.[43] The estimated incidence is 1: 25,000 to 35,000.

The etiology of adenomatoid malformation is unknown. It probably results from a cessation of bronchomaturation and concomitant overgrowth of mesenchymal elements, which probably occur about the 5th and 6th weeks of gestation.[64,65] One of the potential genes of influence for this development disorder is HOXB5.[66] The disruption of FGF7-dependent (fibroblast growth factor-7) interactions between epithelium and mesenchyma may be involved in the pathogenesis of congenital cystic adenomatoid malformation. In cases that grew rapidly, progressed to hydrops and required *in utero* resection showed increased platelet derived growth factor (PDGF-B) gene expression and PDGF-BB protein production was observed in transgenic mice.[67,68]

Several classification exist. The histopathologic classification of Stocker *et al* needs careful use.[69] Adzick *et al* redefined adenomatoid malformation based on gross anatomy and ultrasound characteristics.[70] Microcystic lesions (< 5 mm in diameter) appear more dense (Fig. 4), solid and bulky and have worse prognosis than macrocystic forms (Fig. 5). The diagnosis by ultrasound can be made as early as 12th weeks gestation. Typically a mediastinal shift is found.[9] Hubbard *et al* demonstrated the accuracy of prenatal magnetic resonance imaging (MRI) for diagnosing and characterizing congenital pulmonary lesions. It is useful for defining tissue and anatomic effects of large and atypical chest masses.[71]

The natural history is variable. Some large lesions decrease in size and even disappear before birth, whereas other remain stable, grow without adverse effects or grow and compress the

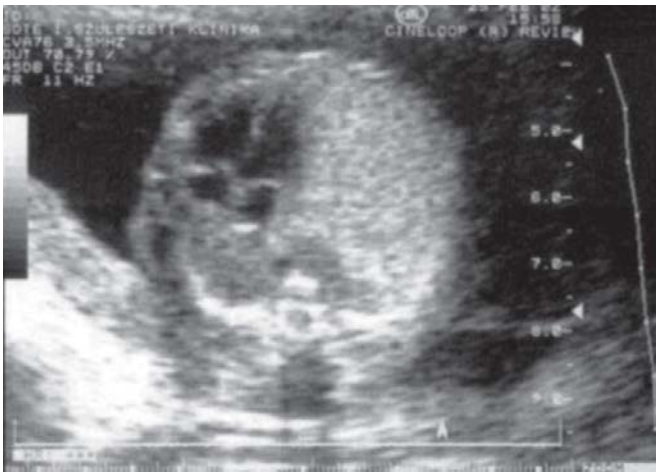

Fig. 4: Left-sided congenital cystic adenomatoid malformation (type III), microcystic form, a homogenous hyperechoic mass dislocating the heart

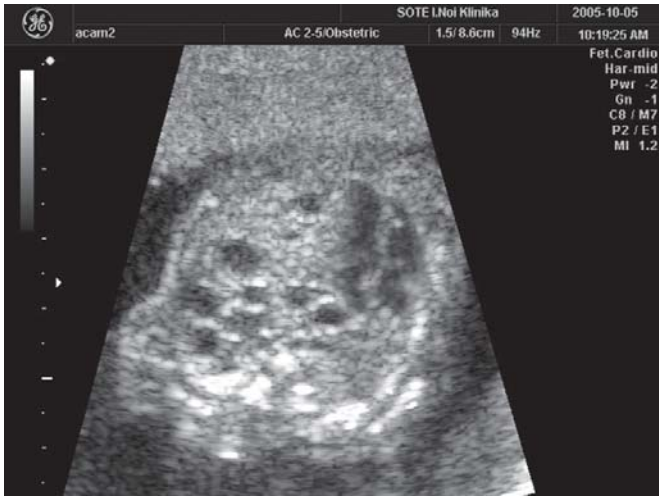

Fig. 5: Left-sided thoracic mass dislocating the heart—congenital cystic adenomatoid malformation (type II). No sign of decompensation

adjacent tissues and organs, producing hydrops syndrome.[43] In about 6 percent of cases progression, and in 6 to 43 percent decrease or disappearance was observed. Suspected resolution *in utero*, however, does not necessarily imply complete resolution of primary pathology. Usually significant abnormalities are shown to persist thus the postnatal imaging, computer tomography scans is essential.[9,72,73]

The development of an ultrasound-derived congenital adenomatoid malformation volume and head circumference ratio (CVR) has allowed a gestational age corrected volume ratio to be used prognostically when adenomatoid malformation lesions are identified. In "high-risk" cases, when CVR greater than 1.6 or lesion with significant macrocystic component, lesions being

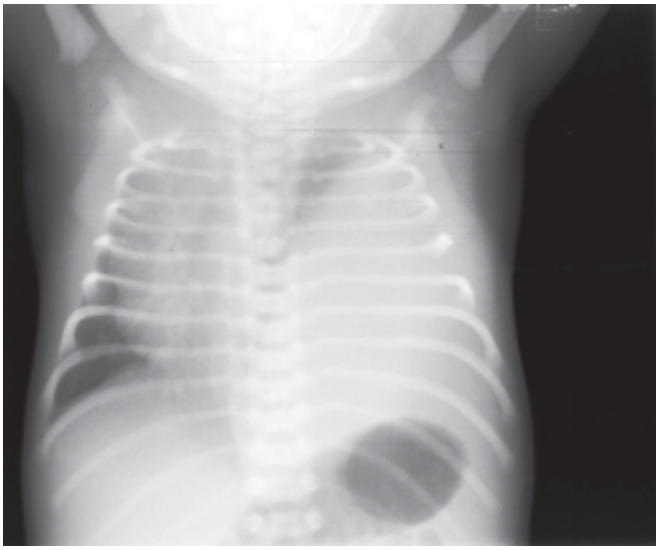

Fig. 6: Postnatal X-ray picture—left-sided mass dislocating the heart—congenital cystic adenomatoid malformation (surgical and histological diagnosis)

followed two-three times per week. Smaller lung lesions (CVR < 1.2) may be followed on a weekly basis.[74] Other ultrasound features such as cardiac function, mediastinal shift, amniotic fluid volume, placental thickness and Doppler flow pattern of umbilical artery and ductus venosus should assess regularly. There is no known association of adenomatoid malformation with chromosome abnormalities, but some additional abnormalities in cardiovascular, renal and gastrointestinal systems are observed.[43,68]

The indication for antenatal intervention is controversial; thought a range of options is available. Macrocystic disease may be aspirated, shunted with thoracoamniotic shunt or excised using fetal surgical techniques. Microcystic lesions may be excised or fulgurated using percutaneous applied laser therapy.[75] Intrauterine surgery, however, has failed to improve survival rate, compared to non-interventional management.[76] Hydrops, placentomegaly, polyhydramnios progressive growth and severe mediastinal shift and everted diaphragm are the prognostic indicators of the unfavorable prognosis.[43]

The postnatal surgical management of completely asymptomatic patients is controversial (Fig. 6). Some author even in asymptomatic cases recommend resection, because congenital cystic lung lesions may potentially act as a predisposing agent for oncogenesis, while other perform the surgical excision in symptomatic cases which have failed medical treatment.[65,73]

In conclusion the prognosis is favorable in fetuses without hydrops and with isolated, unilateral congenital adenomatoid malformation. Serial ultrasound scans proposed to assess the natural history.

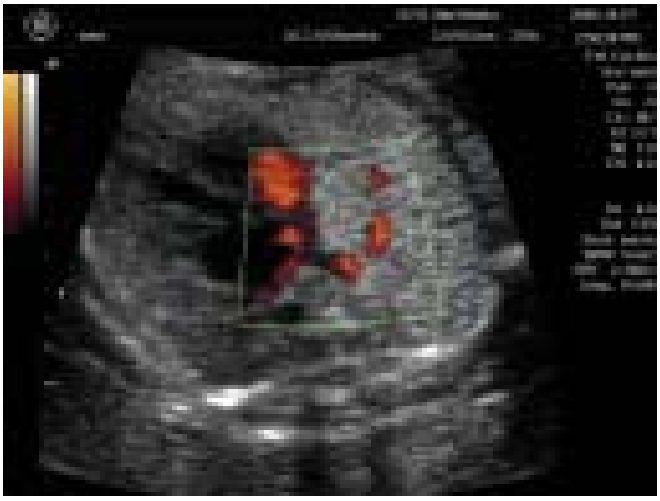

Fig. 7: Left-sided hyperechoic mass in the lower left lobe of the lung—a great vessel is visible in it, what is typical for a sequestration

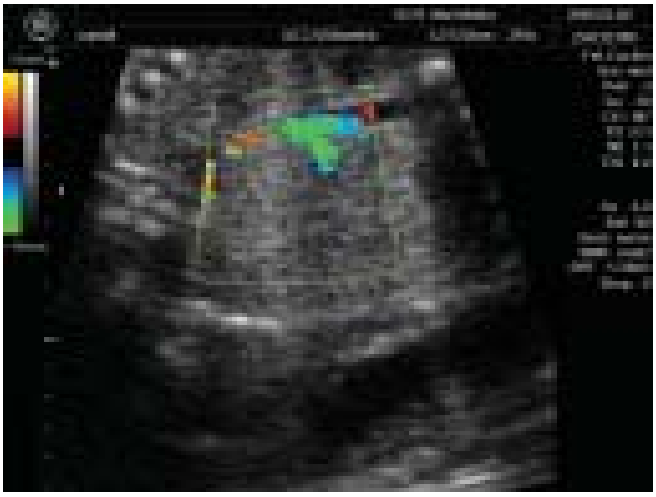

Fig. 8: A great vessel originated from the systemic circulation is visible in a sequestrum

Bronchopulmonary Sequestration

Congenital pulmonary sequestration is characterized by a segment of nonfunctioning lung parenchyma that does not communicate with the tracheobronchial tree, with anomalous systemic artery blood supply (Fig. 7). The venous drainage may be pulmonary or systemic. The systemic drainage may be into the inferior vena cava (Fig. 8), the azygous vein or the portal vein. In case of pulmonary venous return large left-to-right shunt and congestive heart failure may be. They are classified according to the correlation of the visceral pleura and the normal lung tissue. In intralobar pulmonary sequestration cases the common pleura shared by sequestered and normal lung and in extralobar pulmonary sequestration cases sequestered lung has its own visceral pleura. They are mainly

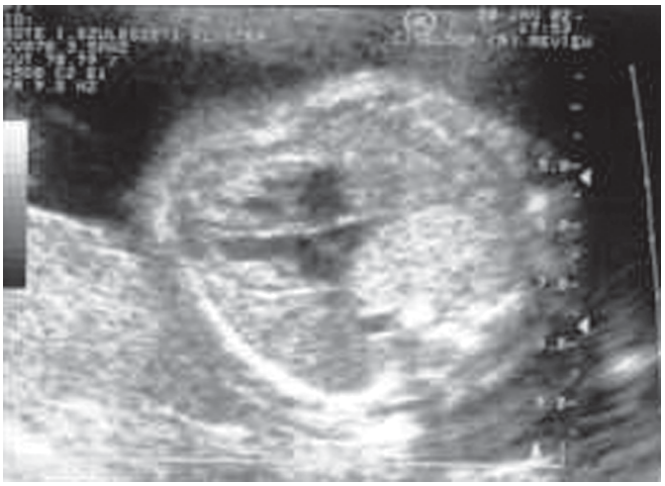

Fig. 9: Small hyperechoic mass in the chest, the dislocation is mild, the prognosis is favorable

supradiaphragmatic but can be infradiaphragmatic. The malformation is slightly more common in males and on the left side.[43,77,78]

Bronchopulmonary sequestration is cause by the branching of an accessory diverticulum of the foregut, caudal from the branching of the normal lung bud.[21]

The prenatal diagnosis is usually based on identification of echodense, homogenous or microcystic mass in the lower chest or upper abdomen with systemic feeding artery from the aorta. Distinguish pulmonary sequestration (Fig. 9) from congenital cystic adenomatoid malformation would be interest in order to the counseling parents and the planning of the postnatal management. Ruano *et al* suggest that 3D power Doppler ultrasound can be used to differentiate accurately fetal lung malformations, because the tortuous feeding vessel may be missed by 2D analysis.[78]

Beyond the adenomatoid malformation foregut malformation, tracheo-oesophageal fistula, oesophageal duplication or diverticulum, neurenteric cysts, skeletal deformities, congenital heart disease, congenital diaphragmatic hernia, renal and cerebral abnormalities may associate to sequestration. In some cases hydrops fetalis, hydrothorax, placentomegaly, polyhydramnion may be observed, in which cases the prognosis is poor, and stillbirth or neonatal death is common.[43,77]

The lesion due to the occlusion of the feeding vessel may disappear spontaneously during the third trimester of pregnancy. The postnatal management (Fig. 10) may include the open lobectomy or the embolization of the abnormal feeding vessel by angiography.[78-80]

CONCLUSION

The improvement of technical facilities and experiments give the possibility to verifying large number of malformations before

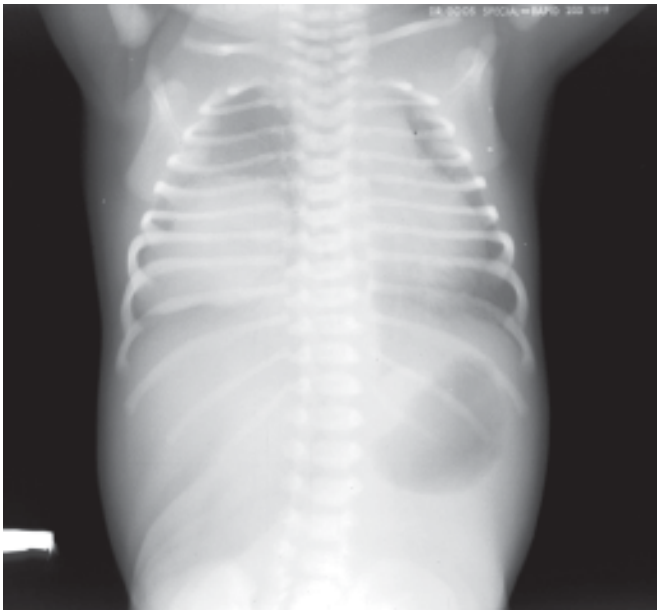

Fig. 10: Postnatal X-ray picture—right-sided terime above the diaphragm—sequestrum (surgical and histological diagnosis)

24th week of gestation. The evolution and natural history of chest and congenital lung anomalies are increasingly understood. In some cases the high rate of associated malformations, the cardiovascular disturbances, the developing hydrothorax or hydrops fetalis indicate the close prenatal control. The accurate prenatal ultrasound diagnosis completed with fetal echocardiography and in certain cases chromosomal analysis may provide appropriate background for correct estimation of prognosis, genetic counseling and planning the postnatal management.

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