Chapter 3
Abnormal development of (intra)thoracic anatomy
Developmental, sonographic and clinical aspects

In this chapter, abnormal lung development and thoracic morphology will be discussed with emphasis on pulmonary hypoplasia, hydrothorax, (intra)thoracic structural pathology, and diaphragmatic hernia. Apart from bronchopulmonary sequestration and more recently pulmonary hypoplasia and congenital diaphragmatic hernia, the diagnostic efficacy of colour coded Doppler imaging in the detection and evaluation of intrathoracic abnormalities is so far limited to congenital heart disease\textsuperscript{33,125}.

3.1 Pulmonary hypoplasia

Normal growth and development of the fetal lung requires adequate intrathoracic space, normal fetal breathing movements and an adequate amniotic fluid volume. Disturbances in one or more of these factors may result in pulmonary hypoplasia which has a reported incidence of 1% of all live births\textsuperscript{73}. The histopathological diagnosis of pulmonary hypoplasia can be based upon a reduced lung/body weight ratio and a decreased lung DNA content\textsuperscript{138}, and on low radial alveolar counts\textsuperscript{9}. The severity of pulmonary hypoplasia depends upon the gestational age, the type and severity of the insult, and the duration of the inciting conditions. Causes of fetal pulmonary hypoplasia are renal or non-renal long-term oligohydramnios, pleural effusions, intrathoracic masses (congenital cystic adenomatoid malformation, bronchopulmonary sequestration, bronchogenic cyst, mediastinal teratoma, congenital diaphragmatic hernia), cardiac abnormalities, and neuromuscular and skeletal disorders. Most commonly, pulmonary hypoplasia results from long-term oligohydramnios due to prolonged premature prelabour rupture of the membranes or due to fetal anuria or urinary outflow obstruction. The clinical course of these infants with pulmonary hypoplasia is characterized by an immediate onset of severe respiratory insufficiency after birth, with a small lung capacity and requiring high ventilatory pressures in the absence of obstruction or atelectasis. The radiologic criteria are (i) well-areated lung fields with elevated diaphragms up to the seventh rib, (ii) downward sloping ribs, and (iii) a marked bell-shaped chest\textsuperscript{98}. Overall mortality is high\textsuperscript{16}. 

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Several authors have investigated the usefulness of biometric criteria in the antenatal diagnosis of pulmonary hypoplasia (see paragraph 2.1.3). Unfortunately, apart from the fact that these thoracic measurements can be difficult, they often are only late indicators of hypoplastic lungs. Also, intrathoracic space-occupying masses may compromise lung growth, but still can result in normal thoracic dimensions. In prolonged severe oligohydramnios, contradictory findings have been reported on the association between the presence or absence of fetal breathing movements and lung performance after birth\textsuperscript{16,88}. Also, others have suggested that absence of fetal breathing in prolonged preterm ruptured membranes may be a more important sign of neurological impairment than of retarded pulmonary development\textsuperscript{104}. In 1990, Van Eyck et al. have reported on Doppler evaluation of the fetal ductus arteriosus in the prediction of pulmonary hypoplasia\textsuperscript{134}. They demonstrated that blood flow velocity waveforms obtained from the fetal ductus arteriosus are modulated (i.e., ductal peak systolic velocity is reduced) by fetal breathing activity during normal pregnancies. This was considered a reflection of a decreased pulmonary vascular resistance during lung expansion. In fetuses with pulmonary hypoplasia, they observed a reduced ductal peak systolic flow velocity modulation, which was hypothesized to result from impaired development of the pulmonary vascular bed\textsuperscript{134}. In 1993, fetal upper respiratory tract function was studied in the prediction of diaphragmatic hernia-related pulmonary hypoplasia\textsuperscript{48}. By using conventional and colour Doppler, absence of fetal breathing-related nasal and oropharyngeal flow was suggested as a useful marker for the prediction of pulmonary hypoplasia\textsuperscript{48}. In 1994, the same authors added measurement of the timing components of fetal breathing-related nasal fluid flow velocity\textsuperscript{49}. In non-surviving fetuses with congenital diaphragmatic hernia a significantly longer time of expiration was observed\textsuperscript{49}. Most recently, a new technique for the prenatal detection of pulmonary hypoplasia has been published\textsuperscript{76}. By using combined color coded Doppler and two-dimensional real-time ultrasound in the evaluation of the left fetal pulmonary artery in a fetus with postnatally proven pulmonary hypoplasia, both a change in nature and decreased peak systolic and end-diastolic velocities were observed. The authors suggest that these findings are the result of delayed pulmonary vascular development and raised pulmonary vascular resistance associated with the presence of lung hypoplasia\textsuperscript{76}. Further studies of the fetal pulmonary circulation are needed to substantiate these findings.
3.2 Hydrothorax (chylothorax)

Abnormal collections of fluid in the pleural cavity are detected on ultrasound by the appearance of an anechoic space between compressed lung tissue and the rib cage, and an often displaced mediastinum. Reported incidences vary from one in 10,000 deliveries\textsuperscript{42} to one in 15,000 pregnancies\textsuperscript{78}. Pleural effusions are most commonly of chylous origin, though may also represent one of the several features of fetal hydrops. Differentiation between these two entities is not possible on the basis of gross sonographic appearance of the fluid since both types of effusions appear clear. Also, postnatally lymph is initially clear and colourless and is usually detected by the appearance of chylomicrons in the pleural fluid after oral milk feeding\textsuperscript{102}. Reports have been published on a reliable prenatal diagnosis of chylothorax after invasive testing via thoracentesis by the demonstration of high-density lipoprotein and lymphocyte predominance\textsuperscript{10,85}. More recently however, Eddleman et al.\textsc{(1991)} have emphasized that pleural fluid lymphocyte counts alone are not reliable in establishing the cause of hydrothorax before birth\textsuperscript{42}. Others have used aspirated pleural fluid for rapid prenatal cytogenetic analysis\textsuperscript{141}.

Congenital chylothorax probably results from a malformation of or rent in the fetal thoracic duct\textsuperscript{111}. However, although several anomalies have been described\textsuperscript{14,68,132}, often no specific cause can be found at thoracotomy or autopsy, probably due to the small size of the fetal thoracic duct. Hydrothorax as a feature of fetal hydrops is a non-specific finding which can be based on a wide variety of fetal and maternal disorders, including haematological, chromosomal, cardiovascular, renal, pulmonary, gastrointestinal, hepatic and metabolic abnormalities, congenital infection, neoplasms and malformations of the placenta and umbilical cord.

Pleural effusions are often detected because they are associated with polyhydramnios and a therefore large-for-dates uterus which is often the clinical indication for the initial ultrasonography. Polyhydramnios is probably caused by esophageal compression by the pleural fluid collection or production of amniotic fluid by the compressed lung\textsuperscript{102,112}.

The prognosis depends largely on the underlying cause of the effusion and the degree of associated pulmonary hypoplasia\textsuperscript{78}. Favourable prognostic factors are late onset, unilateral effusions (without mediastinal shift or diaphragmatic eversion), spontaneous regression and absence of hydrops\textsuperscript{78}, and absence of polyhydramnios\textsuperscript{44}. However, in a recent meta-analysis of 124 cases of fetal pleural effusions from 38 reports\textsuperscript{36}, polyhydramnios and bilaterality of the pleural effusions were found not to be associated
with a poorer outcome while this was the case for fetal hydrops. Overall mortality was as high as 46% \(^{136}\). After the search for associated malformations and chromosomal anomalies management can vary from simple observation\(^{44,77,103}\), to (repeated) thoracentesis\(^{6-10}\), pleuroamniotic shunting\(^{93,113}\), or pleuromaterinal cutaneous drainage\(^{112}\). As stated in a review by Morin and associates (1994)\(^{92}\) it is however important to realise that, although our understanding of the natural history and pathophysiology of fetal thoracic lesions has improved significantly, still large gaps remain in the current state of knowledge of fetal thoracic lesions. Proof of the efficacy and superiority of invasive therapeutic procedures over conventional obstetrical management await the result of prospective trials, especially given the possibility of spontaneous regression of some lesions\(^{82}\).

3.3 Congenital cystic adenomatoid malformation of the lung

Congenital cystic adenomatoid malformation (CCAM) of the lung is a benign cystic lung mass. Most reported cases are unilateral with no preference of right or left lung\(^{114}\). Prenatal differentiation with other intrathoracic abnormalities such as bronchopulmonary sequestration, bronchogenic cyst, mediastinal teratoma and congenital diaphragmatic hernia may be difficult because the sonographic appearance of these entities may be very similar. Occasionally, fetal lung biopsy has been reported to diagnose CCAM antenatally\(^{96}\). CCAM has been detected prenatally from 16 (microcystic)\(^{31}\) and 19 weeks’ gestation (macrocystic) onwards\(^{39}\). Spontaneous in utero regression in size or resolution has been reported by several authors\(^{21,67,80,114,129}\).

The overall prognosis depends on the size of the space-occupying intrathoracic lesion and on the secondary anatomical and functional distortion through lung compression and through deviation of the mediastinum and heart. In general, fetal hydrops and polyhydramnios suggest a poor fetal outcome\(^{114}\). In appropriately selected cases of fetal cystic adenomatoid malformation associated with hydrops, resection can be considered because this may reverse hydrops and allows sufficient lung growth for survival\(^{5,129}\). Also, serial amniocenteses\(^{84}\) and thoracocenteses\(^{22}\) have been reported as a succesful prenatal treatment of secondary polyhydramnios and fetal hydrops.

In the next subchapter details on our own experience with seven cases of CCAM will be reported.
3.3.1 Prenatal diagnosis of congenital cystic adenomatoid lung malformation: a report of seven cases

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Summary

Six cases of macrocystic and one case of microcystic congenital adenomatoid lung malformation were diagnosed by ultrasound between 20 and 31 weeks of gestation. Combined polyhydramnios and fetal hydrops was present in three cases, polyhydramnios alone in one case, and isolated fetal hydrops also in one case. In the remaining two cases, both polyhydramnios and fetal hydrops were absent. Fetal outcome was poor, i.e., two terminations of pregnancy, three early neonatal deaths, and two survivors.

Introduction

Congenital cystic adenomatoid malformation (CCAM) is a rare pulmonary anomaly, usually restricted to one lung. It may present itself in association with other abnormal clinical findings such as polyhydramnios, fetal hydrops, and hypoplasia of the contralateral lung.

The objective of this paper is to discuss our experiences with seven cases of CCAM with emphasis on reasons for referral, ultrasound and amniotic fluid findings, fetal outcome, and post-mortem pathology.

Case reports

Case 1

A 25-year-old woman, gravida 3, para 0, spontaneous abortion 2, was scanned locally because of a large-for-dates uterus. Polyhydramnios and fetal hydrops were diagnosed and the woman was subsequently referred to our centre for an anomaly scan at 23 weeks of gestation. A large homogeneous echogenic mass filled the entire fetal thorax with a marked shift of the heart towards the anterior thoracic wall (Figure 1). There was a two-vessel cord and the presence of fetal hydrops and polyhydramnios was confirmed.
Figure 1.  Longitudinal scan of a fetus with bilateral microcystic CCAM of the lungs (arrows) at 23 weeks of gestation. A=abdomen; Th=thorax; B=urinary bladder; S=stomach

The amniotic fluid alpha-fetoprotein (AFP) level was 11.5 μg/ml (normal <5 μg/ml) and the fetal karyotype was normal 46,XY. The parents opted for termination of pregnancy which was carried out by means of Nalador® (sulprostone). Post-mortem examination showed a microcystic CCAM of both lungs without other congenital anomalies.

Case 2

A 32-year-old woman, gravida 3, para 2, was scanned locally because of a large-for-dates uterus at 25 weeks. She was subsequently referred to our centre because of suspected diaphragmatic hernia. Instead, a macrocystic fetal left lung (Figure 2) with some mediastinal shift to the right was documented. There was polyhydramnios, but no fetal hydrops. Amniocentesis revealed a normal 46, XY male karyotype and amniotic fluid AFP level (<5 μg/ml). The pregnancy progressed uneventfully. Spontaneous labour at 38 weeks resulted in the vaginal delivery of a male infant who was intubated immediately and ventilated with 100 per cent oxygen. A chest X-ray showed a multi-septated CCAM on the left side of the chest and the mediastinal shift to the right. There was aeration of the right lung. The same day, left-sided partial pneumonectomy was performed and the infant has subsequently done well. Histological examination confirmed the diagnosis of macrocystic CCAM.
Case 3

A 38-year-old primigravida was scanned locally because of a large-for-dates uterus at 28 weeks. A lung tumour was suspected. At our centre, a macrocystic left lung with a mediastinal shift to the right as well as fetal hydrops and polyhydramnios was seen. There were no additional structural defects. Because of the advanced maternal age, amniocentesis had been performed at 16 weeks. The fetal karyotype was 46,XY, and the amniotic fluid AFP level was <5 μg/ml (normal). No structural fetal anomalies were noted at that time. The abnormal ultrasound findings remained fairly constant during the remainder of the pregnancy. An emergency Caesarian section was performed at 35 weeks because of fetal compromise. The infant died 20 minutes after delivery from respiratory insufficiency despite intubation and 100 per cent oxygen ventilation. Post-mortem examination confirmed macrocystic CCAM of the upper segment of the left lung and a pneumothorax. The remainder of the left lung and the right lung revealed no abnormalities. No additional anomalies were seen.

Case 4

A 33-year-old woman, gravida 4, para 3, was scanned elsewhere because of a large-for-dates uterus at 25 weeks. She was referred to our centre because of suspected intra-abdominal cystic structures and an enlarged amniotic fluid compartment. A large
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Macro cystic left lung with a mediastinal shift to the right and downwards displacement of the diaphragm were found. There was also ascites and polyhydramnios. Amniotic fluid AFP level was 6.5 μg/ml (normal <5 μg/ml), the fetal karyotype was normal 46,XY. Premature labour occurred at 29 weeks, resulting in the vaginal delivery of a male infant who died 13 minutes later due to severe respiratory insufficiency. Post-mortem examination confirmed macrocystic CCAM of the left lung and a hypoplastic contralateral lung. There were no other malformations.

Case 5

A 30-year-old primigravida was seen locally for a routine scan. A fetal diaphragmatic hernia was suspected because of intrathoracic cysts. Following referral to our centre, a macrocystic left lung with a marked mediastinal shift to the right and compression of the right lung were established at 20 weeks. There was no fetal hydrops or polyhydramnios. The amniotic fluid AFP was 7.5 μg/ml (normal <5 μg/ml), the fetal karyotype was normal 46,XY. The parents opted for termination of pregnancy, which was carried out using Nalador® (sulprostone) one week later. Post-mortem examination confirmed macrocystic CCAM of the left lung with a small contralateral lung; no other malformations were encountered.

Case 6

A 26-year-old woman, gravida 3, para 2, was referred for a scan elsewhere at 25 weeks because of a large-for-dates uterus. A multicystic structure of the left lung was suspected. Amniocentesis revealed a normal female karyotype and AFP level (4.2 μg/ml). Later in the pregnancy, the woman was referred to our centre for a detailed anomaly scan. A macrocystic left lung with a mediastinal shift to the right was diagnosed at 31 weeks. There was no polyhydramnios or fetal hydrops, although both had been seen during earlier scans at 25, 27 and 29 weeks. The pregnancy progressed uneventfully. Spontaneous delivery occurred at 38 weeks, resulting in the vaginal delivery of a female infant who was immediately intubated and ventilated with 100 per cent oxygen.

After three days left-sided partial pneumonectomy was performed; the right lung was normal. Histological examination confirmed the diagnosis of macrocystic CCAM. At 6 weeks of age, hydrocephaly was diagnosed, resulting in the placement of a ventriculo-peritoneal shunt. The infant has subsequently done well.
Case 7

A 32-year-old woman, gravida 2, para 1, was referred to our unit at 25 weeks. A scan had been performed elsewhere because of a large-for-gestational-age uterus and fetal hydrops was suspected. Besides a large amount of ascites and extensive skin edema, a macrocystic right lung was seen which extended into the left hemithorax. On the left side, only a rim of lung tissue could be observed. There was a decreased amniotic fluid compartment. On amniocentesis, a normal female karyotype and a raised AFP level of 19.5 μg/ml (normal <5 μg/ml) were found. Labour was induced at 31 weeks because of severe pre-eclampsia. The female infant died two hours after delivery because of respiratory insufficiency. Post-mortem examination confirmed macrocystic CCAM of the right lung and a hypoplastic left lung.

Discussion

CCAM of the lung is a hamartoma characterized by overgrowth of the terminal bronchioles at the expense of the saccular spaces. The exact mechanism causing CCAM is not known, although an arrest in the connecting mechanism between the ectodermal component (conducting airways) and the mesenchymal, i.e., respiratory component with subsequent overgrowth of the terminal bronchioles at the beginning of the sixth week of gestation has been attributed to the development of CCAM101,126.

The clinical presentation of CCAM may vary from perinatal death to respiratory problems in childhood. In this study, CCAM was separated into two groups based on sonographic and gross anatomical findings4, i.e., macrocystic tumours containing single or multiple fluid-filled cysts at least 5 mm in diameter and microcystic tumours which are more solid with cysts less than 5 mm in diameter. In accordance with the literature, most of our cases of CCAM were unilateral (six out of seven cases)82,101. Bilateral CCAM (case 1) was only seen once. The earliest diagnosis of CCAM was made at 20 weeks of gestation.

In six out of seven cases, a large-for-dates uterus was the reason for performing a fetal scan elsewhere. Polyhydramnios, whether or not combined with fetal hydrops, was a principal finding in five instances. These pathological entities usually develop relatively late in pregnancy, i.e., during the second half of gestation, which explains the late referrals to our centre. Polyhydramnios may be due to decreased fetal swallowing of amniotic fluid as a result of oesophageal compression by the lung mass41 or to increased fetal lung fluid production by the abnormal lung tissue74.
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Fetal hydrops may result from vena cava obstruction\textsuperscript{59}. Polyhydramnios may occur without fetal hydrops, as shown in case 2. On the other hand, there may be simultaneous resolution of polyhydramnios and fetal hydrops, as observed in case 6. Polyhydramnios has been reported to disappear following spontaneous resolution of CCAM\textsuperscript{119}. In case 6, surrounding fetal organ growth in the presence of an unchanging CCAM may have led to the fore-mentioned normalization of amniotic fluid volume.

The reason for referral to our centre was suspected lung pathology in two instances (cases 3 and 6) and diaphragmatic hernia, also in two cases (cases 2 and 5). Twice, patients were referred because of fetal hydrops (cases 1 and 7) and in one instance intra-abdominal pathological cysts were suspected (case 4). Multiple cystic areas in the fetal thorax are consistent with either diaphragmatic hernia or macrocystic CCAM. The former anomaly should be ruled out by the presence of normal fetal upper abdominal anatomy and the absence of any bowel in the chest. Other anomalies presenting as a thoracic mass are pulmonary sequestrations\textsuperscript{116}, bronchogenic cysts\textsuperscript{66}, and mediastinal teratoma\textsuperscript{52}. Extrapulmonary structural defects were limited to a two-vessel cord in case 1, which is in agreement with several other reports\textsuperscript{1,140}, but at variance with a study by Stocker et al.(1977), who observed associated anomalies in 26 per cent\textsuperscript{126}. Since in case 6 hydrocephaly developed six weeks after delivery, this was not considered a congenital anomaly.

Obstetric management was limited to termination of pregnancy (cases 1 and 5). In both instances, pregnancy duration was below 24 weeks, which is the legal upper limit for pregnancy termination in The Netherlands.

CCAM was macrocystic in six out of seven cases. Earlier reports suggest that fetuses with either microcystic or macrocystic CCAM which are not hydropic, have a good chance of survival\textsuperscript{4}. Fetal hydrops was absent in cases 2, 5 and 6. Excluding case 5, which was terminated, the remaining two cases resulted in two neonatal survivals.

In utero surgical decompression or removal of CCAM has been suggested to improve survival\textsuperscript{97}. Thoracentesis was offered in case 3 but was refused by the parents. Needle aspiration was contemplated, but not carried out for reasons of limited accessibility of the affected lung due to the fetal position in case 4 and suspected severe contralateral lung hypoplasia in case 7. We support the view that needle aspiration or pleuro-amniotic shunting of these macrocystic tumors should be considered with the objective of reducing or preventing fetal hydrops and the risk of lung hypoplasia.

Fetal lamb studies have demonstrated compensatory lung growth following partial pneumonectomy\textsuperscript{58}. Recently, Harrison et al.(1990) described two cases of in utero
resection of CCAM resulting in one case dying from severe hydrops after premature delivery and in the other case, in the delivery of a healthy female infant at 30 weeks of gestation\textsuperscript{59}. Further animal studies and better assessment of the risks of fetal surgical intervention may ultimately improve fetal outcome in CCAM.

It can be concluded that although CCAM does not always lead to polyhydramnios and fetal hydrops, these findings are often the way that such cases present prenatally and should therefore indicate a careful ultrasonographic inspection of the fetal lungs. When polyhydramnios and fetal hydrops are found in association with intrathoracic cystic abnormalities, CCAM should be suspected.

Although resolution of fetal hydrops has been observed, it appears to be an important sign of poor outcome. The prognosis also depends on the extent to which one or both lungs are affected and whether the remaining lung is hypoplastic.

3.4 Bronchopulmonary sequestration

Bronchopulmonary sequestration is a congenital pulmonary anomaly in which a portion of the bronchopulmonary parenchyma is separated from the normal lung which does not communicate with an airway and receives its blood supply from the systemic circulation. It most often occurs in the lower lobes and is considered to result from development of anomalous vascular connections during embryogenesis\textsuperscript{70} and either originates from a separate outpouching of the foregut, or is a segment of the developing lung that has lost its connection with the rest of the tracheobronchial tree. Bronchopulmonary sequestrations are uncommon with an overall incidence of 0.15-6.4 per cent of all congenital pulmonary malformations\textsuperscript{120}, or an estimated incidence of one in 15,000 pregnancies\textsuperscript{78}. Depending on the timing of the separation, i.e., before or after the formation of the pleura, the sequestration will be intralobar (i.e., adjacent to the normal lung and surrounded by the same visceral pleura) or extralobar (i.e., covered by its own visceral pleura)\textsuperscript{118}.

Associated anomalies are more common and severe in extralobar (60 per cent) than in intralobar (10 per cent) sequestration including predominantly diaphragmatic hernia, other foregut and cardiac anomalies\textsuperscript{120}. Also an association with fetal hydrops has been reported, due to the anomalous blood supply to the sequestered lung, leading to left-to-right shunting with secondary cardiac failure\textsuperscript{131}.

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Bronchopulmonary sequestration typically appears as a well-defined, homogeneous hyperechogenic mass in the lower thorax or upper abdomen which may be isolated or associated with polyhydramnios, mediastinal shift, pleural effusion or fetal hydrops\textsuperscript{39,75} and which needs to be differentiated from microcystic adenomatoid malformation of the lung\textsuperscript{131}. Occasionally, cystic components are present which may closely resemble macrocystic adenomatoid malformation, diaphragmatic hernia or a bronchogenic cyst\textsuperscript{120}. The most characteristic sign of bronchopulmonary sequestration seems to be the visualization of its anomalous arterial supply with colour Doppler\textsuperscript{64,80}.

The prognosis of bronchopulmonary sequestration is thought to depend on the associated anomalies, the presence of fetal hydrops or pulmonary hypoplasia and is generally poorer for extrapulmonary sequestration based upon the higher incidence of serious associated anomalies\textsuperscript{120}. In two recent reviews of antenatally diagnosed bronchopulmonary sequestrations\textsuperscript{39,75}, the authors emphasize the often unpredictable outcome of bronchopulmonary sequestration during the course of pregnancy as even in the presence of mediastinal shift, pleural effusion, fetal hydrops and polyhydramnios outcome can be favourable, i.e., through spontaneous regression or after in-utero catheter drainage\textsuperscript{45}. However, as in isolated hydrothorax, the definitive place of pleuro-amniotic shunting remains to be determined\textsuperscript{12,75}. Infants with this pulmonary anomaly may be symptom free, though usually present with recurrent infections, respiratory distress\textsuperscript{79} or secondary heart failure from left-to-right shunting\textsuperscript{23,72}. Treatment consists of surgical resection though will not always be required\textsuperscript{15}.

3.5 Bronchogenic cyst

Bronchogenic cysts are cystic structures lined by bronchial epithelium which result from abnormal budding from the foregut. Their wall usually contains cartilage, smooth muscle and mucous glands\textsuperscript{70}. When they remain attached to the primitive tracheobronchial tree early in development they are usually found more centrally within the thorax (along the trachea, in the mediastinum or within the pulmonary parenchyma) whereas later development may result in lesions more peripherally and even outside the lung (into vertebrae or below the diaphragm) when contact with their origin is lost\textsuperscript{110,115}.

Their sonographic appearance consists of a small, well-defined, unilocular hypoechogenic intrathoracic cystic lesion without associated mediastinal shift, polyhydramnios or hydropic changes.
Symptoms depend on their strategic localization. Although they may cause recurrent respiratory infections, airway obstruction, and rarely dysphagia\textsuperscript{100,127} or even hemodynamic deterioration\textsuperscript{50}, bronchogenic cysts usually are coincidental radiographic findings during childhood\textsuperscript{43} or in later life\textsuperscript{50}. In general, most authors recommend surgical excision to confirm the diagnosis, relieve symptoms, and to minimize possible complications\textsuperscript{100,127}. Although only occasional reports on the prenatal diagnosis of bronchogenic cysts have been published\textsuperscript{7,86,142}, they should be included in the differential diagnosis of an intrathoracic cystic mass.

### 3.6 Mediastinal teratoma

Teratomas are the most common congenital neoplasm with a reported incidence of 1:20,000 to 1 : 40,000 livebirths and most frequently found in the sacrococcygeal region\textsuperscript{130}. They are formed from omnipotent embryonic germ cells with ectodermal, mesodermal and endodermal derivatives.

Congenital mediastinal teratomas are rare and may cause non-immune fetal hydrops\textsuperscript{137} and eventually stillbirth\textsuperscript{51} by direct compression of the heart and major blood vessels. Postnatally, respiratory distress by compression of the lungs and airways may occur\textsuperscript{121}.

Their sonographic appearance is diverse, in keeping with the wide variety of tissues contained. Although only few reports on the prenatal detection of mediastinal teratomas have been published\textsuperscript{51,137}, they should be included in the differential diagnosis of (cystic) intrathoracic masses. Treatment consists of surgical extirpation to alleviate symptoms and to prevent malignant degeneration\textsuperscript{50,89}.

### 3.7 Congenital diaphragmatic hernia

The diaphragm is a dome-shaped musculotendinous septum between the thoracic and abdominal cavity and consists of a central aponeurotic segment and a peripheral muscular part. The embryologic development ends around the eighth week of conception and consists of the fusion of four different components\textsuperscript{34,91}, i.e., ventrally from the septum transversum (mesoderm), which fuses with the pleuropitoneal membranes, with the dorsal foregut mesentery and laterally with muscular components of the thoracic wall.
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The last areas to close are the posterolaterally situated foramina (Bochdalek) which are closed by the pleuroperitoneal membranes. The diaphragm allows passage of organs, vessels and nerves from the thoracic into the abdominal cavity.

The normal fetal diaphragm can be discretely observed as a smooth hypoechoic line between the fetal lungs and the liver or spleen. Congenital diaphragmatic hernia (CDH) is characterized by protrusion of abdominal viscera into the thoracic cavity through a diaphragmatic defect. As a result of this, lung development may be impaired and may even result in lung hypoplasia. Either delayed fusion of the four diaphragmatic components or a primary diaphragmatic defect with secondary migration of abdominal organs into the thoracic cavity is hypothesized to cause this defect. Almost all of hernias occur through the posterolaterally located Bochdalek foramina which characteristically involves the left side (75 per cent). Foramen of Morgagni hernias occur in the anteromedial retrosternal part of the diaphragm as a result of maldevelopment of the septum transversum.

Controversial reports have been published on the role of surfactant deficiency in the pathophysiology of CDH in human. Based on amniotic fluid phospholipid data, Sullivan et al. (1994) found no surfactant deficiency, whereas Moya and co-workers (1995) established decreased surfactant components in amniotic fluid in pregnancies complicated by CDH. In a recent study comparing bronchoalveolar lavage in CDH patients and in infants without CDH, no significant differences in concentrations of the surfactant components were found. It was therefore concluded that a primary surfactant deficiency is an unlikely phenomenon in infants with CDH and possibly does not determine the clinical course in these patients.

Eventration of the diaphragm is characterized by herniated viscera which are covered by a sac composed of abdominal peritoneal layers and components of the congenitally weak diaphragm. Although this anomaly is not a hernia in the strict sense, it may have the same dramatic effects on fetal lung development as true diaphragmatic hernias.

Associated structural or chromosomal abnormalities have been found in more than half of cases of congenital diaphragmatic hernia.

The typical sonographic findings of diaphragmatic hernia are mediastinal shift caused by the herniated viscera and the visualization of abdominal organs in the thoracic cavity. Polyhydramnios which is thought to result from gastrointestinal obstruction, is common and is frequently the indication for the initial ultrasound. The differential diagnosis of CDH includes cystic adenomatoid malformation of the lung, bronchogenic...
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cysts and bronchopulmonary sequestration.

The prognosis of in utero diagnosed diaphragmatic hernia is poor\(^2,37\) and largely depends on the associated structural and chromosomal anomalies, and on the degree of secondary pulmonary hypoplasia\(^53\). In 1993, using conventional and colour Doppler, fetal upper respiratory tract function was studied in a small series of five cases of antenatally diagnosed CDH\(^48\). It was suggested that absence of fetal breathing-related nasal and oropharyngeal flow might be a useful marker for the prediction of pulmonary hypoplasia\(^48\). From the same center it was subsequently reported that also a significant longer time of expiratory was measured in fetuses with CDH and a poor postnatal outcome compared to survivors and unaffected controls\(^49\). Although polyhydramnios\(^90\) and an intrathoracic stomach\(^24\) have been recommended as clinically useful sonographic markers for a poor fetal outcome, their value is disputed by others\(^46,53,83,87\). Survival, however, seems likely if the liver is not herniated into the thorax and/or the contralateral lung is large\(^55,87\). In a prospective study of the natural history and outcome for fetuses with isolated congenital diaphragmatic hernia diagnosed prior to 24 weeks gestation, perinatal mortality was as high as 58 per cent despite optimal postnatal care, including improved respiratory support, delayed surgery and extracorporeal membrane oxygenation (ECMO)\(^62\). More recently, from the same ECMO center an overall survival rate of 65% has been reported, including both early and late diagnosed diaphragmatic hernias\(^87\). In a retrospective series of prenatally and postnatally diagnosed cases of CDH survival was 58 per cent\(^27\). In our own series overall mortality was 69 per cent when multiple anomalies were excluded\(^83\)(chapter 3.7.1). ECMO has been introduced in The Netherlands in the early Nineties\(^133\) and is found to be a valuable addition in the management of high-risk CDH infants\(^8\). Although most centers report a relatively low morbidity of ECMO, a greater number of neurodevelopmental, respiratory, and feeding abnormalities during the first year of life have been encountered in the CDH population\(^13\).

Open fetal surgery for CDH has been suggested as a strategy for salvaging selected fetuses at high risk for pulmonary hypoplasia\(^90\). The results of these techniques, however, have been disappointing as hysterotomy induces premature labour and as reduction of the herniated liver from the thorax into the fetal abdomen is associated with fetal death\(^46\). This seems to be related to the fact that the liver does not simply rotate up into the chest through a diaphragmatic defect, but more likely develops in the chest, with its abnormal vascular anatomy accordingly\(^81\). Now that colour Doppler ultrasonography allows visualization of the aberrant vascularization of the herniated liver\(^123\), these fetuses should be excluded from complete in-utero repair\(^5,17\). Newer in-utero techniques include
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blocking the trachea\textsuperscript{63}, the creation of an artificial gastroschisis\textsuperscript{90,105}, and induction of graft tolerance for postnatal lung transplantation\textsuperscript{25,46}.

In the next subchapter our experiences with the prenatal diagnosis of fetal diaphragmatic hernia is described. Subchapter 3.7.2 deals with the possible role of colour coded Doppler ultrasound in the evaluation of CDH.

3.7.1 Prenatal diagnosis of congenital diaphragmatic hernia: a retrospective analysis of 28 cases


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Summary

In a retrospective analysis of 28 cases of fetal diaphragmatic hernia, overall mortality was 86 per cent, but fell to 70 per cent when multiple anomalies were excluded. Congenital heart disease constituted the majority of associated anomalies. The incidence of an abnormal karyotype was 10.5 per cent, but rose to 20 per cent when only fetuses with multiple anomalies were included. Polyhydramnios, which occurred in 75 per cent, was a poor predictor of fetal outcome. The same applied to the intrathoracic position of the fetal stomach. In all four survivors, diaphragmatic hernia was diagnosed beyond 32 weeks of gestation.

Introduction

The prenatal diagnosis of congenital diaphragmatic hernia is now well established\textsuperscript{26}. Perinatal mortality is, however, high; overall mortality rates of 75 per cent and higher have been reported\textsuperscript{3}. It is mainly the degree and time of lung compression resulting in pulmonary insufficiency which will determine the neonatal outcome, although the presence of polyhydramnios and associated anomalies has also been reported to contribute to the poor survival rate\textsuperscript{40}.

Minimum incidence figures for congenital diaphragmatic hernia vary between 1 in 2400 and 1 in 5000 live-births, with a true incidence including stillborns of approximately 1 in 2200 births\textsuperscript{57,107}.
In this paper, we review the impact of associated anomalies, polyhydramnios, intrathoracic herniation of abdominal contents, gestational age at diagnosis, and mode of delivery on the perinatal outcome in 28 cases of fetal congenital diaphragmatic hernia seen in our unit over a 7-year period.

Patients and methods

Over a 7-year period (1986-1993), fetal congenital diaphragmatic hernia (CDH) was diagnosed at a mean gestational age of 31 weeks (range 19-36 weeks) in 28 women referred to our unit for further assessment mainly because of polyhydramnios or suspected CDH at routine ultrasound examination in the referring hospital (Table I). The mean maternal age was 30 years (range 22-38 years).

Each fetus was subjected to a complete anomaly scan with a Toshiba SSA 270 curved linear array system. The diagnosis of CDH was made from a sagittal and a transverse sonographic cross-section of the fetal trunk at the thoraco-abdominal level establishing an interruption of the continuity of the diaphragm whether or not in combination with herniation of intra-abdominal contents and displacement of the heart to the opposite side. Polyhydramnios was defined as a large fluid pocket of 10 cm or more.

Additional fetal karyotyping was offered to 27 out of 28 women by means of amniocentesis or cordocentesis. In the remaining case, karyotyping was carried out postnatally. Decisions on obstetric management were based on structural ultrasound findings and fetal karyotype.

### Table 1

<table>
<thead>
<tr>
<th>Referral diagnosis</th>
<th>No. of women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected fetal diaphragmatic hernia</td>
<td>8</td>
</tr>
<tr>
<td>Polyhydramnios</td>
<td>8</td>
</tr>
<tr>
<td>Combined fetal diaphragmatic hernia and polyhydramnios</td>
<td>3</td>
</tr>
<tr>
<td>Cystic structure in fetal thorax</td>
<td>3</td>
</tr>
<tr>
<td>Combined cystic structure in fetal thorax and polyhydramnios</td>
<td>1</td>
</tr>
<tr>
<td>Miscellaneous: fetal hydrops, previous infant with congenital heart disease, IUGR, discrepancy fetal BPD/femur length, routine fetal scan</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
</tr>
</tbody>
</table>
Table II  
Associated anomalies and karyotype in 15 fetuses with diaphragmatic hernia

<table>
<thead>
<tr>
<th>Types of associated anomalies</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ASD, hydrops; polyhydramnios</td>
<td>46,XY</td>
</tr>
<tr>
<td>2. Abnormal hand/foot position; polyhydramnios</td>
<td>46,XY</td>
</tr>
<tr>
<td>3. Hypotelorism, retrognathia, cleft palate, webbed neck*, polyhydramnios</td>
<td>46,XX</td>
</tr>
<tr>
<td>4. VSD; oligohydramnios</td>
<td>47,XX,+21</td>
</tr>
<tr>
<td>5. AVSD, hypoplastic left heart, hypotelorism, abnormal hand/foot position; polyhydramnios</td>
<td>47,XY,+18</td>
</tr>
<tr>
<td>6. Pulmonary artery stenosis, microphthalmia*, micrognathia, cleft palate, horse-shoe kidney*; polyhydramnios</td>
<td>46,XY</td>
</tr>
<tr>
<td>7. VSD, intestinal malrotation*, abnormal hand/foot position; polyhydramnios</td>
<td>46,XX</td>
</tr>
<tr>
<td>8. VSD, ASD, hypoplastic left heart, unilateral multicystic kidney, anal atresia*, rocker-bottom feet; polyhydramnios (Fryns’ syndrome)</td>
<td>46,XY</td>
</tr>
<tr>
<td>9. VSD, unilateral hydronephrosis, cleft palate; polyhydramnios</td>
<td>46,XY</td>
</tr>
<tr>
<td>10. VSD, bilateral cystic kidneys; oligohydramnios</td>
<td>46,XX</td>
</tr>
<tr>
<td>11. Unilateral cystic kidney, webbed neck*, low ear implant*; polyhydramnios</td>
<td>46,XY + abn.marker chromosome</td>
</tr>
<tr>
<td>12. Hypoplastic left heart, aortic stenosis; polyhydramnios</td>
<td>46,XY</td>
</tr>
<tr>
<td>13. Preauricular appendix*; polyhydramnios</td>
<td>46,XY</td>
</tr>
<tr>
<td>14. Unilateral cystic kidney; normal amniotic fluid volume</td>
<td>46,XX</td>
</tr>
<tr>
<td>15. Microcephaly; oligohydramnios</td>
<td>46,XX</td>
</tr>
</tbody>
</table>

* Anomaly diagnosed postnatally
VSD = Ventricular septal defect; ASD = atrial septal defect; AVSD = atrioventricular septal defect.
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The outcome of each pregnancy was documented. Evidence of associated anomalies at the time of ultrasonographic examination was noted. In all cases, the diagnosis of CDH was confirmed either clinically or at autopsy.

Results

CDH as a single anomaly was present in 13 (46 per cent) cases and associated with one or more anomalies in 15 (54 per cent) cases. The nature of these associated anomalies, the presence of polyhydramnios or oligohydramnios, and the fetal karyotype are given in Table II. CDH was left-sided in 25 cases and right-sided in the remaining three cases.

Polyhydramnios was present in 21 cases (75 per cent); oligohydramnios was diagnosed in three cases; and the amniotic fluid volume was normal in the remaining four cases. The overall mortality was 86 per cent. When CDH was the only anomaly, the incidence of polyhydramnios was 84 per cent (11/13) and the mortality was 70 per cent (9/13); in the presence of multiple anomalies, the percentages were 67 per cent (10/15) and 100 per cent (15/15), respectively.

Of the associated anomalies, congenital heart disease was established in eight out of 15 cases (53 per cent) and congenital urinary tract defects in six out of 15 cases (40 per cent).

An abnormal karyotype occurred in three cases, all of which were associated with multiple anomalies. Two were established prenatally (trisomy 18 and extra marker chromosome) and one postnatally (trisomy 21).

Intrathoracic herniation of the stomach (n=19) was associated with a mortality rate of 84 per cent (16/19), and intra-abdominal position of the stomach (n=19) was associated with a mortality rate of 79 per cent (4/5). Vaginal delivery took place in 22 cases and Caesarean section in six cases, the latter having no advantage in terms of survival.

Elective termination of pregnancy was carried out in two cases because of trisomy 18 or fetal hydrops. There were three intrauterine deaths and 19 neonatal deaths, of which 14 occurred before corrective surgery and five after corrective surgery. Cardiorespiratory insufficiency was the main cause of death during the neonatal period. All four cases that survived displayed a single anomaly (CDH) and polyhydramnios, and were diagnosed after 32 weeks of gestation.
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Discussion

In this study, over half of the fetuses were referred for an anomaly scan for reasons other than suspected diaphragmatic hernia. It is therefore not surprising that this series shows a high association with other structural anomalies. It also emphasizes the different spectrum of disease in the fetus compared with the postnatal period\(^7\).

The overall mortality rate was 86 per cent, which is similar to the rate reported elsewhere \(^3,96\). When only single anomalies (CDH) were considered, the mortality rate fell to 69 per cent. Congenital heart disease constituted the majority of associated pathology. The association of congenital heart disease with congenital diaphragmatic hernia has been reported by others\(^54,122\). A hypoplastic left heart was observed in three out of eight cases with congenital heart disease. In all three cases, there was a left-sided diaphragmatic hernia with the stomach in an intrathoracic position. Sharland et al. (1992) suggested that in the presence of a left-sided diaphragmatic hernia, left heart underdevelopment may be the result of a combination of increased left atrial pressure reducing normal right-to-left atrial blood flow and decreased pulmonary venous flow as a result of lung hypoplasia\(^122\).

There were three fetuses with an abnormal karyotype. This represents an overall incidence of 10.5 per cent, which rose to 20 per cent when only fetuses with multiple anomalies were included. Different series have demonstrated different incidences in abnormal karyotype, varying between 3.6 per cent\(^122\) and 21 per cent\(^11\). Whereas this may be subject to specific referral patterns, it emphasizes the need for karyotyping, in particular when multiple anomalies are present.

Polyhydramnios, which was present in 75 per cent of the cases, has been associated with poor fetal outcome\(^60\). This could not be confirmed in the present study, since all four pregnancies resulting in postnatal survival displayed polyhydramnios.

Similarly, the intra-thoracic position of the fetal stomach as a predictor of poor fetal outcome\(^29\) could not be confirmed. Both intra-thoracic and intra-abdominal positions of the stomach resulted in a mortality rate of approximately 80 per cent.

Late intrauterine detection of congenital diaphragmatic hernia seems to be associated with a better perinatal outcome. In the group of fetuses seen before 32 weeks of gestation (n=14), the overall mortality rate was 100 per cent, whereas after 32 weeks of gestation (n=14) it was 71 per cent.

Improvement of fetal outcome has been attempted both prenatally and postnatally. The main cause of perinatal death in the presence of congenital diaphragmatic hernia is pulmonary hypoplasia\(^60\). Optimal obstetric management will therefore depend on the early
detection of this lung condition. In utero treatment has been successful in some instances\textsuperscript{60}, whereas postnataally the introduction of extracorporeal membrane oxygenation may improve the chance of survival. Indirect estimation of the fetal lung mass through measurement of the fetal thoracic area or circumference\textsuperscript{99} has been only moderately helpful in predicting lung hypoplasia. Doppler flow velocity measurements in the fetal ductus arteriosus are modulated by fetal breathing movements. No such breathing-related modulation seems to occur in cases of lung hypoplasia\textsuperscript{124}. Although this appears to be a promising method for the early detection of lung hypoplasia, the Doppler recording technique is rather time-consuming. Since pulmonary vascular resistance will be raised in cases of lung hypoplasia\textsuperscript{139}, it may be useful to study the pulmonary circulation directly using the colour-coded Doppler technique.

It can be concluded that fetal congenital diaphragmatic hernia is associated with a high mortality. Fetal outcome is better if multiple anomalies are excluded. Polyhydramnios and the intra-thoracic position of the stomach are poor predictors of fetal outcome. Particularly in the presence of multiple anomalies, fetal karyotyping should be performed. Proper counselling should be offered to parents in a multidisciplinary setting which includes the obstetrician, pediatric surgeon, neonatologist, and clinical geneticist.

### 3.7.2 Colour coded Doppler ultrasound and diaphragmatic hernia

Data on the role of colour Doppler imaging in the prenatal detection of congenital diaphragmatic hernia (CDH) originate from a study funded by the "Ontwikkelingsgeneeskunde" Committee of the Dutch Sickness Benefit Council (Ziekenfondsraad) during the period 1990-1993 (OG 89-023); see chapter 4.4. During that period a total of eight cases of postnatally confirmed diaphragmatic hernia was studied. Pregnancy duration varied between 23 and 35 weeks (median 28 weeks). Colour coded Doppler ultrasound did not contribute to the diagnosis. However, diaphragmatic hernia may be associated with displacement of the heart depending on the severity of the diaphragmatic hernia. Diaphragmatic hernia and cardiac anomalies may occur in combination. In these cases conventional real-time ultrasound hardly allows any information on cardiac structure and function which would be of importance since in seven out of eight cases of diaphragmatic hernia there was a marked displacement of the heart. As opposed to conventional real-time ultrasound, colour coded Doppler provided additional information on cardiac structure and function with emphasis on the outflow
tract anatomy (ascending aorta, pulmonary artery, ductus venosus) and atrioventricular outflow tract velocities. This despite the presence of polyhydramnios (largest amniotic fluid pool > 10 cm) in five cases. There were no cardiac anomalies. In one case, colour coded Doppler identified a renal artery, thus establishing the presence of an intrathoracic kidney. Eventually, there was one case of intrauterine demise. Four infants died in the neonatal period, predominantly as a result of pulmonary hypoplasia. Of the three surviving infants, the prenatal diagnosis of diaphragmatic hernia was made after 32 weeks in every instance. Recently, also others reported on the use of colour Doppler ultrasonography in a case of a left-sided diaphragmatic hernia. Colour and pulsed Doppler evaluation documented an intrathoracic umbilical vein and ductus venosus and respective waveforms, confirming extensive herniation of the left hepatic lobe.

3.8 Fetal thoracic wall abnormalities

Fetal thoracic wall defects are encountered in cases of ectopia cordis and thoracopagus conjoined twins. Also in the rare pentalogy of Cantrell and Poland’s syndrome, rib cage abnormalities have been reported.

Normal fetal lung growth requires appropriate growth of the thoracic cage. Therefore, a small but otherwise morphologically normal thoracic cage frequently results in pulmonary hypoplasia. A small thorax most commonly occurs in the setting of prolonged oligohydramnios related to bilateral renal agenesis or rupture of the membranes. Morphologic abnormalities of the thoracic cage, secondary to skeletal dysplasia or chromosomal anomaly, may also result in a small thorax and pulmonary hypoplasia with subsequent asphyxiating thoracic dysplasia and resulting compression of the lungs and heart. Although osteogenesis imperfecta type IIa is known for its rib fractures with sharp concave deformity of the thoracic cage, the configuration and size of the thoracic cage usually are not as distinctive as other features in defining the specific type of skeletal dysplasia antenatally.

Thickening of the soft tissue of the chest wall may be a physiological variant in case of hypertrophy of breast tissue, probably as a result of stimulation by maternal hormones, though can also be caused by cutaneous edema in cases of fetal hydrops. Although rare, several causes for focal enlargement of the fetal chest wall have been described. A hamartoma may arise within a rib and extend into the fetal thorax and more recently, a prenatal diagnosis of a chest wall hamartoma and sternal cleft has been
reported\textsuperscript{117}. Occasionally, a cystic hygroma may extend onto the fetal chest wall\textsuperscript{71,108}, or large cutaneous hemangiomata in case of the Klippel-Trenaunay-Weber syndrome\textsuperscript{65}. Other infrequent causes include transthoracic herniation of the fetal lung through an intercostal space\textsuperscript{19}, a melanoma or neuroblastoma\textsuperscript{38}. As with other fetal tumours, secondary hydrops may develop as a result from high-output cardiac failure\textsuperscript{125}.
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