Fetal lung and diaphragm malformations

GRZEGORZ H. BREBOROWICZ1, MARIUSZ DUBIEL2, MARIOLA ROPACKA1, MAREK PIETRYGA3

Abstract

Congenital lung abnormalities are relatively rare but very dangerous for the fetus and neonate. This article describes the most common pulmonary complications observed during pregnancy such as congenital cystic adenomatoid malformation, diaphragmatic hernia, bronchopulmonary sequestration, hydrothorax, chylothorax, lung agenesis, pulmonary hypoplasia. The diagnostic methods and available therapy methods are discussed.

Key words: fetal lung, congenital abnormalities, sonography, prenatal diagnosis

Appropriate growth and maturation of the fetal lungs are substantial for the survival of the neonate and it creates the limits of viability. Among others, these processes are regulated by shape and size of the thorax, fetal breathing movements and adequate amniotic fluid volume. Pulmonary abnormalities are rather rare however by changing anatomy of the thorax they can create dangerous complications for the fetus eg. pulmonary hypoplasia. The most common lung abnormalities include: congenital cystic adenomatoid malformation, diaphragmatic hernia, bronchopulmonary sequestration, hydrothorax, chylothorax, lung agenesis, pulmonary hypoplasia, congenital lobar emphysema and congenital high airway obstruction [14].

Originally there were different classifications of the congenital lung abnormalities which based on microscopic criteria, cyst diameter and predominant cell types on histological examination. In 2004 Achiron et al. [1, 3] proposed new classification with five categories based on the lung component involved in pathogenesis, two-dimensional and color Doppler. These categories are as follow:

1) Agenesis of the lung;
2) Normal lung with abnormal vascular supply;
3) Abnormal lung with abnormal vascular supply;
4) Abnormal lung with normal vascular supply;
5) Miscellaneous.

Early and accurate diagnosis of fetal lung abnormalities is very important because it makes possible to reconsider in utero therapy or to prepare immediate postpartum treatment at appropriate perinatal center [2, 17, 20].

Lung development

Pulmonary growth starts very early in pregnancy (∓ 5th weeks) and ends at the first years of childhood. Development of the lungs can be divided in three stages: pseudoglandular, canicular and terminal sac and alveolar stage. The pseudoglandular stage comprise the period between 5th and 17th weeks of gestation. At the beginning of this stage an outgrowth of the ventral wall of the foregut endoderm occurs and the epithelial cells involve the surrounding mesoderm to form proximal structures of the respiratory track. Around 17 weeks of gestation trachea, main bronchi and five lobes are formed. Arterial vascularization, which is formed at that time, derives from the sixth aortic arches. At that period lung looks like a gland.

During canicular stage (17-26 weeks) further development of the distal airways occurs. Definitive primary acini which include respiratory bronchioles, alveolar ducti and rudimentary alveoli are formed. At the end of this stage at the type II pneumocytes surfactant and phospholipids can be detected.

Sacular stage (26-36 weeks) is characterized by acinar tubules dilatation what changes the thickness of the walls and in consequence the area of gas exchange increases. Maturation of pneumocyte is continued.

The last stage, alveolar, starts in the late pregnancy (after 36 weeks) and ends in first years of life. At that stage alveolar formation and final maturation occur. Additionally proliferation of mesenchymal cells and increase of the number of type I and II pneumocytes is observed. It is assumed that the final development and maturation of the human lung end at the early childhood;

1 Department of Perinatology and Gynecology, Poznań University of Medical Sciences, Poznań, Poland
2 Collegium Medicum Nicolaus Copernicus University, Toruń, Poland
3 Department of Obstetrics and Women’s Diseases, Poznań University of Medical Sciences, Poznań, Poland
approximately 80% of alveoli in the adult lung arise postnatally [10].

**Congenital cystic adenomatoid malformation (CCAM)**

CCAM can be characterized as a benign hamartomatous or dysplastic lung tumor with overgrowth of terminal bronchioles and a reduction in the number of alveoli. This tumor is supplied by the pulmonary circulation (arterial) differentiating it from the bronchopulmonary sequestration which is supplied by a systemic artery arising from the abdominal aorta. CCAM is usually unilateral, mostly left sided and usually involves only one lobe of the lung. The perinatal mortality associated with CCAM range from 9% to 49% in different perinatal centers.

CCAM is a rare anomaly of the fetal lung. Its incidence is reported between 1 : 11 000 and 1 : 35 000 live birth. This incidence is underestimated because CCAM may display changes *in utero* and some of them can resolve spontaneously; according to the Kings College London study up to 9% of cases disappeared spontaneously, while in large Canadian observations this disappearance was 56% [5].

There are few classifications of CCAM. Kwitken et al. [11] introduced classification based on microscopic criteria such as: proliferation of polyploid glandular epithelium, proliferation of smooth muscle and elastic tissue in cyst walls, absence of cartilage, absence of inflammation and normal arterial and venous connections. Another classification was proposed by Stocker et al. [23] which depends on cyst diameter and predominant cell types in histological examination. The weak part of this classification is a fact that prenatally we cannot do histological analysis. Adzick et al. [4] defined two types of CCAM based on gross anatomy and ultrasound. The macrocystic group contains single or multiple cysts \( \geq 5 \text{ mm} \) diameter, while the tumors from microcystic group are more solid and have cysts \(< 5 \text{ mm} \) diameter. So far this classification has become the gold standard of *in utero* CCAM diagnosis and prognosis.

Up to the end of XXth century CCAM was considered as a very serious complications for the fetus and newborn. At that time, it was frequently considered as an indication for termination of pregnancy.

Currently with new ultrasound facilities and therapeutic procedures our understanding of CCAM completely changed. Now we know that some of them regress spontaneously *in utero* and other can be treated *in utero* or after delivery. The main fetal adverse features include hydrops, polyhydramnion, mediastinal shift and fetal death. Neonates with CCAM mostly present tachypnoea, increased work of breathing, hypoxemia, carbon dioxide retention, poor feeding or overt respiratory failure requiring invasive or non-invasive ventilatory support [12].

![Fig. 1. 24 weeks of gestation – diamniotic dichorionic twins – abnormalities in right lung of one cotwin – macrocystic type of CCAM](image1)

![Fig. 2. Congenital cystic adenomatoid malformation](image2)

![Fig. 3. Newborn – CCAM before and after operation (mediastimum and heart shifted to the left; after operation reposition of the heart)](image3)
In the management of CCAM the most important is early diagnosis. The time of the surgery depends on the size of the tumor and the condition of the child. All infants with symptomatic CCAM require surgery. Fetal intervention depends on gestational age, the size of the lesion, condition of the pregnant woman and condition of the fetus (e.g. hydrops of the fetus). The therapy available during pregnancy include thoracoamniotic shunting, open maternal-fetal therapy at the third trimester or as EXIT (ex-utero intrapartum treatment) delivery. The survival rate associated with these type of these therapies are 75%, 50% and 89% respectively.

**Bronchopulmonary sequestration**

Bronchopulmonary sequestration (in Latin – seques-tra means separate, remove) represents a non-functional bronchopulmonary tissue that is separate from the tracheobronchial tree. It receives arterial blood from systemic circulation, abdominal or thoracic part of the aorta. It is the main difference that helps in differential diagnosis with CCAM (Table 1)[11]. It is very rare complication which is often diagnosed as CCAM. BPS and CCAM have malignant potential. Fetal therapy can be used only in cases with large lesions which compress healthy structures of the lungs or other organs.

<table>
<thead>
<tr>
<th>Table 1. Differences between CCAm and BPS [12]</th>
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<td><strong>Incidence</strong></td>
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<td><strong>Vascular supply</strong></td>
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<td><strong>Laterality</strong></td>
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<td><strong>Sex</strong></td>
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<td><strong>Tracheobronchial communication</strong></td>
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BPS can have intra or extra lobar character depending on whether the mass is within or outside of a normal lung lobe. Extralobar BPS is completely covered with pleura; some of these lesions are below the diaphragm. Depending on the size of the lesion polyhydramnion, mediastinal shift, pleural effusions and hydrops can be detected. Large lesions may compres residual tissue increasing the risk of pulmonary hypoplasia [8].

Intrauterine interventions include thoracocentesis, thoracoamniotic shunt, laser ablatio or injection of sclerosing agent into the feeding artery. Interventions during pregnancy are rare, unless pleural effusions or hydrops develops. Surgical management of BPS in neonates involves lobectomy or nonanatomical segmentectomy. Lobectomy is suggested for intra lobar sequestrations because of risks of incomplete resection. The vascular supply may be difficult to identify increasing the risk of bleeding.

The prognosis for BPS depends on the degree of pulmonary hypoplasia. Extra lobe sequestration seems to have improved outcomes over intra lobe sequestration because of decreased risk of pulmonary hypoplasia. Fetal survival up to term is high (95%); neonatal survival is lower. Prognosis for the fetuses which do not manifest hydrops is better.

**Congenital diaphragmatic hernia**

Congenital diaphragmatic hernia (CDH) refers to a developmental defect of the formation of the diaphragm. It is characterized by incomplete formation of this structure or eventration of a portion of the diaphragm that is thinned as a result of incomplete muscularization. Very often CDH is connected with other genetic anomalies. The incidence of CDH is approximately one in 3000 birth [18].

CDH is classified in three groups: Bochdalek hernia, Morgani and other anterior hernia, and central hernia.
Bochdalek hernia is a posterolateral defect in the diaphragm. It is often accompanied by herniation of the stomach, intestines, liver and/or spleen into the chest cavity. The most serious complications of this hernia type is the absence of the hemidiaphragm. Morgani hernia is an anterior retrosternal or parasternal hernia that can result in the herniation of the liver or intestines. Central hernia is a rare defect involving the central tendinous portion of the diaphragm.

CDH is characterized by high morbidity and mortality rate; mortality ranges from 20% to 60%. According to the meta-analysis performed by Stege et al. [22] approximately one-quarter of all prenatally diagnosed cases of hernia were electively terminated, 3% spontaneously miscarried and 3% were stillborn; 31% of the liveborn died within the 24 hours of life. Among the survivors the morbidity is high. Most of the complications are observed in pulmonary, gastrointestinal and musculoskeletal systems. The neurologic development of these infants is often abnormal.

Therapy of CDH can be performed in utero or postnatally. Prenatal therapy is very important in the case of severely affected fetuses. Leaving them without any help end in intrauterine death. Discovery that laryngeal obstruction in animals lead to lung distension from retained fluid opened new chapter in the therapy of CDH. Currently in few centers high risk fetuses may receive in the second trimester tracheal occlusion by fetal endoscopic balloon placement. This procedure is performed only in fetuses without chromosome abnormalities. So far we don’t have any randomized clinical trial, but clinical observations indicate that survival rates in high risk fetuses increased.

After delivery there are two phases of therapy which start immediately after delivery. The first phase starts with attempts to stabilize respiratory and cardiovascular systems. Secondly surgical diaphragmatic repair is performed.

Lung agenesis

Pulmonary agenesis is a rare congenital anomaly resulting from embryological defects (1 per 15 000 pregnancies). It is characterized by the complete absence of lung tissue. Frequently it is associated with skeletal, cardiovascular and other anomalies (up to 50%). Unilateral right lung agenesis appear to carry a worse prognosis due to more frequent additional congenital anomalies [13].

Cardiomiastinal shift may often be the first clue suggesting the possibility of unilateral agenesis. The keys to the diagnosis of bilateral pulmonary agenesis during prenatal sonography include the absence of the right and left branches of pulmonary artery and the inability to locate the pulmonary vein orifices in the left atrium [25].

Prenatal diagnosis of pulmonary agenesis is challenging because of the potential difficulty in distinguishing this anomaly from others. Most frequent differential diagnosis of this condition include a congenital diaphragmatic hernia, a congenital cystic adenomatoic malformation and pulmonary sequestration. Other, less frequent diagnoses include: isolated dextrocardia, dextroposition, emphysema, mediastinal teratoma and neuroblastoma.

The absence of lung tissue is though to allow the diaphragm and abdominal organs to be displaced cephalad. Such displacement can mimic a right or left-sided congenital diaphragmatic hernia during prenatal sonographic evaluation.

Right and left lungs seem to be affected in the same proportion, but prenatally the diagnosis of right lung agenesis is 5 times more frequent (greater mediastinal shift and the higher incidence of other associated abnormalities) [15].

The etiology of this anomaly is unknown. No familial tendency has been recognized. However, it is assumed that viral agents, dietary deficiency of vitamin A during pregnancy can be implicated.

Correct prenatal diagnosis provides information to the pediatricians which can further reduce the mortality, morbidity and improve prognosis. In the last decades the prognosis improved significantly due to the advances in neonatal care.

Pulmonary hypoplasia

Pulmonary hypoplasia (PH) is a developmental abnormality of the lung. The diagnosis of PH is based on measurement of the lung-to-body weight ratio (LBWR), which by definition is a postmortem finding. After adjusting LBWR for gestational age a diagnosis of PH is suspected when LBWR < 0.012 at gestational age of ≥28 weeks and < 0.015 at < 28 weeks. Prediction of PH in utero has been attempted on the basis of lung size measurements related to fetal body size using 2- and 3-dimensional ultrasound or magnetic resonance. Assuming abnormal pulmonary vascularization in some studies Doppler analysis has been applied. It is assumed that the most accurate prediction of PH will be achieved by combining clinical, biometrical and Doppler parameters.

There are different classifications of HP. In one of them PH is categorized in three groups:
• agenesis in which there is complete absence of lung tissue;
• aplasia with rudimentary bronchus without lung tissue;
• hypoplasia with normal pulmonary tissue that is under developed [24].

PH may be regarded as primary (idiopathic) or secondary. In primary the causative factor is difficult to be established, whereas secondary is frequently associated with adverse intrauterine influences that cause fetal lung compression; it may be intrathoracic or extrathoracic. Among extrathoracic causes there are neuromuscular disorders, central nervous system malformations and severe oligohydramnion due to renal agenesis, obstructive uropathy or amniotic fluid leakage [6]. Intrathoracic causes of PH are thoracic masses (e.g. congenital diaphragmatic hernia), pleural effusions, significant cardiomyopathy, thoracic wall hypoplasia and absence of breathing movements.

Pulmonary hypoplasia coincides frequently with other congenital anomalies such as anencephaly, diaphragmatic hernia, cardiac abnormalities, deformation of thoracic spine, urinary and renal anomalies and pleural effusions.

Early diagnosis of PH and definition of its cause influence significantly the prognosis. PH due to congenital diaphragmatic hernia can be prevented by prenatal diagnosis and fetoscopic trachea occlusion. In the situation of preterm premature rupture of membranes resulting in severe oligohydramnion, stimulation of fetal lung maturation using glucocorticosteroids with earlier ending the pregnancy (when neonate has chance to survive – today at least 24 weeks of gestation) improves the prognosis.

Congenital lobar emphysema

Congenital lobar emphysema (CLE) is characterized by over inflation of pulmonary lobe. It is a rare complication (between 1 in 70 000 to 1 in 90 000 live births) diagnosed most commonly in the left upper lobe or the right middle lobe. Patients typically present with respiratory distress, most commonly in the neonatal period, and usually within first 6 months of life [7].

Etiology of CLE is unknown. It is assumed that the pathophysiological mechanism of this anomaly consists of disruption of bronchopulmonary development due to abnormal interaction between embryonic endodermal and mesodermal components of the lung, resulting in progressive lobar hyperinflation.

Most cases are idiopathic (50% of cases). In the remaining group several mechanisms are postulated:
• air trapping in the emphysematous lobes;
• endobronchial obstruction from extensive mucosal proliferation and infolding;
• extrinsic compression of the bronchi from aberrant cardiopulmonary vasculature;
• diffuse bronchial abnormalities that maybe related to infection [16].

The main fetal sonographic features of CLE include a bright echogenic lung with or without cystic lesions, a mediastinal shift and associated cardiovascular anomalies [19]. In utero sonographic appearance is thought to be caused by entrapment of lung fluids in the pulmonary lobes. Often CLE, CCAM and pulmonary sequestration are described as a single clinical group. Prenatal diagnosis of CLE is rarely reported in the literature.

Usually, the management of CLE is resection of the affected lobe, but in asymptomatic or mildly asymptomatic patients conservative approach is warranted.

Fig. 5. Congenital lobar emphysema of the left lung

Congenital high airway obstruction (CHAOS)

Congenital high airway obstruction syndrome is a very rare fetal malformation caused by obstruction of fetal airway because of laryngeal or tracheal atresia, subglottic stenosis, laryngeal cyst or laryngeal web. The prenatal diagnosis is inferred from secondary changes such as enlarged, hyperechogenic lungs, ascites and/or hycrops, flattened or everted diaphragms, dilated distal airways and mediastinal compression. There are only few cases of long-term survival described in literature. Our group presented the case of fetus with such secondary changes diagnosed during routine ultrasound evaluation in 20 weeks’ gestation [9]. There were no other abnor-
malities and the karyotype was normal. In 26 weeks' gestation fetal hydrops appeared and subsequent polyhydramnios occurred in 28 weeks' gestation. The patient was planned for EXIT procedure during labor in experienced in CHAOS cases center. In 29 weeks' gestation the premature rupture of membranes and regular uterine contractions occurred and we've performed cesarean section. A multidisciplinary team of neonatologists, laryngologists and pediatric surgeons made their efforts to save the newborn, but there was complete laryngeal atresia and tracheal agenesis and immediate tracheostomy was impossible. The most important about CHAOS are early diagnosis, detailed fetal assessment and an adequate postnatal intervention for establishing fetal airways.

**Fig. 6. Congenital high airway obstruction (CHAOS)**

**Conclusions**

Congenital lung malformations are rare. Prenatal evaluation of each lung should be performed and in the case of any abnormality the patient should be consulted. Early diagnosis in utero of lung abnormalities increases the chance for the child. For adequate correction (therapy) the pregnant woman should be referred to a center with adequate experience and facilities for the treatment of such fetus/child. Prognosis depends on the type of congenital abnormality, condition of the fetus/mother and facilities offered by perinatal center.

**References**


Grzegorz H. Bręborowicz
Department of Perinatology and Gynecology
Poznań University of Medical Sciences
60-535 Poznań, Polna 33, Poland
e-mail: gbrebor@wp.pl