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Congenital Diaphragmatic Hernia

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Abstract

Over the past 20 years, prenatal detection of congenital diaphragmatic hernia (CDH) has improved worldwide, reaching up to 60% in Europe. Pulmonary hypoplasia and persistent pulmonary hypertension are the two main determinants of neonatal mortality and morbidity, so new tools have been focused on their evaluation. Fetal surgery for severe cases requires proper evaluation of the prognosis of fetuses with CDH. It is very important to identify reliable prenatal prognostic factors that can be used worldwide for several reasons: patient counseling is more accurate; the results of pre- and postnatal treatments will be comparable across different institutions; fetuses eligible for fetal surgery will be selected correctly; and a woman expecting a child with a very poor prognosis can prepare herself for the postnatal demise of her baby or, in some countries, opt for termination of pregnancy.

Keywords: congenital diaphragmatic hernia, thoracic anomalies, diaphragm anomalies

1. Introduction

Congenital diaphragmatic hernia (CDH) consists of a defect in variable size in the fetal diaphragm. It occurs more often on the left side and abdominal organs herniate into the thoracic cavity. Most of the time the diagnosis is made during the second trimester fetal morphology ultrasound examination. Diagnosis is based mainly on finding abdominal organs such as stomach, bowel, and liver in the chest cavity or in the presence of a chest mass which pushes the heart toward the lateral thoracic wall.

Although the surgical repair offers excellent results from the technical point of view, the problem with these patients are related to the impaired development of the lungs and their vasculature, therefore, the mortality and morbidity of these babies remain high even after surgery.

2. Spectrum of disease

2.1. Definition

Congenital diaphragmatic hernia (CDH) is defined by the presence of an orifice in the diaphragm that permits the herniation of abdominal contents into the thorax.

2.2. Epidemiology

CDH is a rare condition that occurs in <1–5:10,000 births [1]. The most common anatomic type encountered is the left-sided posterolateral hernia (Bochdalek hernia), including the vast majority of cases 85–90%, while the anterior hernia of Morgagni is rare. A bilateral defect accounts for 15–20% of cases; tissue defect involving most of the hemidiaphragm is called agenesis [2].

2.3. Causes

2.3.1. Environmental causes

No cases of CDH in humans have been unequivocally attributed to teratogenic or environmental exposures. Recently, a potential association with the immunosuppressive drug mycophenylate mofetil has been made, but the mechanism by which this drug could cause diaphragmatic defect is unknown [3].

2.3.2. Heritable causes

About 10% of all individuals with CDH have a chromosome abnormality. The most common abnormalities are trisomy 18 and isochromosome 12p (Pallister-Killian syndrome or PKS), although many additional abnormalities have been reported (**Table 1**). Some of the more common monogenic syndromes in which CDH occurs are listed in (**Tables 2 and 3**) [4].

2.4. Classification

There are six types of CHD (**Figure 1**):

1. Posterolateral defect (Bochdalek hernia) occurs most often on the left side and contains stomach, bowel, and spleen, and if right-sided, contains liver.
2. Parasternal defect (Morgagni hernia), located on anterior retrosternal or parasternal portion of the diaphragm, is rare and more often right-sided or bilateral and usually contains liver or bowel.
3. Other anterior hernias associated with Pentalogy of Cantrell are rare findings but are usually severe, probably derived from septum transversum. These cases are usually associated with Pentalogy of Cantrell (including defects in the midline abdominal wall supraumbilical, lower sternum, diaphragmatic pericardium, and heart).

Chromosome abnormality/locus	Frequency of congenital diaphragmatic hernia	
	Found in this disorder	Attributed to this disorder
Pallister-Killian syndrome/ (isochromosome or tetrasomy 12p)	~30%	? < 5%
Trisomy 13	Rare	Very rare
Trisomy 18	?1–2%	Rare among all CDH; most common chromosome abnormality in prenatally diagnosed CDH
Trisomy 21	Rare (Morgagni hernias > Bochdalek hernias)	Very rare
Del(4)(p16) (Wolf-Hirschhorn syndrome)	Rare	Very rare
+der (22) t(11;22)(q23;q11)	5–10%	Very rare
Del(15)(q26.2)	Unknown (?but possibly majority)	Unknown
Del(1)(q41-q42)	Unknown	Unknown
Del(8)(p23.1)	?30%	Unknown

Table 1. Common chromosome anomalies associated with CDH.

4. Central hernia is rare; the diaphragm defect involves the central tendinous (amuscular) part of the diaphragm. In these cases, the entire rim of diaphragmatic musculature is found to be present.
5. Hiatal hernia, extremely rare, occurs through a congenitally large esophageal orifice.
6. Diaphragmatic eventration is defined as an elevation or abnormal upward displacement of a part or entire normal diaphragm into the chest cavity. This rare type of CDH is caused by the existence of a thinner part of diaphragm which allows the upward displacement of abdominal organs.

For practical reasons regarding the imaging approach and counseling, it was proposed to classify CDH as intrapleural and mediastinal.

Intrapleural hernias occur through defects in the muscular diaphragm, which may result from deficient fusion of the pleuroperitoneal membranes and abdominal wall musculature or absence of the pleuroperitoneal membranes. Intrapleural hernia contents cause compressions on intrathoracic viscera, causing pulmonary hypoplasia and contralateral mediastinal shift. This category includes the traditionally classified Bochdalek hernias.

Mediastinal hernias can be classified into two types: retrosternal and central. Retrosternal hernias are categorized as Morgagni hernias, although a true Morgagni hernia is only a small anatomic located in the space between the sternal and costal heads of the diaphragm. True Morgagni hernia is considered to be a subtype of retrosternal mediastinal hernias, with larger

Syndrome	Frequency of CDH in this disorder	Mode of inheritance	Gene
Cornelia de Lange syndrome	?up to 5%	AD	<i>NIPBL</i>
			<i>SMC3</i>
Craniofrontonasal syndrome	Unknown	XL	<i>SMC1A</i>
			<i>EFNB1</i>
Denys-Drash syndrome	Rare	XL (but males less severely affected than females)	<i>WT1</i>
Donnai-Barrow syndrome	Rare	AD	<i>WT1</i>
Donnai-Barrow syndrome	~70%	AR	<i>LRP2</i>
Fryns syndrome	>80% (but ascertainment may be biased)	AR	Unknown (possible etiologic heterogeneity)
Matthew-Wood syndrome	~50%	AR	<i>STRA6</i>
Spondylocostal dysostosis (SCDO)	Rare	AR	<i>DLL3</i>
	Rare		<i>MESP2</i>
	Rare		<i>LFNG</i>
	Rare		<i>HES7</i>
Simpson-Golabi-Behmel syndrome	Rare	XL	<i>GPC3</i>

Table 2. Selected syndromes in which CDH is a feature.

ventral hernias which are defects in the central tendon stemming from septum transversum impaired development. Hiatal hernias, as their name shows, develop more through the esophageal hiatus and do not involve the central tendon. Differentiating ventral mediastinal hernias from intrapleural hernias is important because the intrapleural hernias, usually, do not lead to pulmonary hypoplasia, which is the major complication of CHD [5] (**Table 4**).

2.5. Embriology

The diaphragm starts to develop at approximately 4 weeks of gestation. It develops from several structures. The anterior central tendon develops from an infolding of the ventral body wall: the septum transversum. Another infolding on the posterolateral sides establishes the pleuroperitoneal membranes. Closure of the pleuroperitoneal canals occurs when the septum transversum fuses to the structures surrounding the esophagus, the esophageal mesentery, and connects to the pleuroperitoneal membranes. Closure of the pleuroperitoneal canals normally occurs around the eighth week of gestation in humans. The right side of the diaphragm closes before the left side [6].

The central portion and possibly anterior regions are thought to develop from the septum transversum, which is initially fused to the liver during development and becomes the unmuscularized central tendon of the diaphragm [7].

The posterolateral section, the place where Bochdalek hernia occurs, develops from the pleuroperitoneal folds (PPFs), which are triangular structures derived from mesoderm that form in

Syndrome	Gene (locus)
Apert syndrome	<i>FGFR2</i>
Beckwith-Wiedemann syndrome	Dysregulation of imprinted genes on 11p15.5
CHARGE syndrome	<i>CHD7</i>
C (trigonocephaly) syndrome	<i>CD96</i>
Coffin-Siris syndrome	Unknown
Czeizel-Lozonci syndrome	Unknown
Gershoni-Baruch syndrome	Unknown
Goltz syndrome (focal dermal hypoplasia)	<i>PORCN</i>
Kabuki syndrome	Unknown
Marfan syndrome	<i>FBN1</i>
Mathieu syndrome	Unknown
Meacham syndrome	<i>WT1</i>
Microphthalmia with linear skin lesions syndrome	<i>HCCS</i>
PAGOD syndrome	Unknown
Pentalogy of Cantrell	Unknown
Poland anomaly	Unknown
Swyer syndrome	Unknown
Thoraco-abdominal schisis	Unknown

Table 3. Syndromes in which CDH is less frequently a feature.

the thorax in the early development of the diaphragm. These PPFs are part of the diaphragmatic connective tissue. The membranous diaphragm is later muscularized by migrating muscle precursor cells to the PPF from the cervical somites. This phenomenon happens before these cells proliferate, differentiate, and migrate onto the membranous diaphragm [8, 9]. The hypothesis is that a Bochdalek hernia occurs if the PPFs do not fuse with the septum transversum and the dorsal mesentery of the esophagus by the 10th week of gestation [4].

The lung originates as an outpouch of the ventral wall of the posterior end of the laryngotracheal tube and divides into two bronchial buds at 3–4 weeks of gestation [10]. As the two buds elongate, the primitive tubular foregut tube begins to pinch into two tubes, namely, the dorsal esophagus and the ventral trachea [11]. Further outgrowth of the lung-buds produces the secondary bronchi. In humans, the right lung has three lobes, whereas, the left lung is composed of two lobes. The branching of the primary bronchial buds are monopodial. Every secondary bronchus then undergoes progressive dichotomous branching as each branch bifurcates repeatedly. Reproducible branching in humans is completed at 16 generations in 16 weeks of gestation [12]. The last seven generations of airway are completed during the last part of gestation. Alveolization starts after 28–30 weeks in humans and is completed in postnatal period [13]. Reid [14] presented this process in her laws of development of the human lung:

- 1. The bronchial tree is completed by the 16th gestational weeks.
- 2. Alveoli, developed after birth, increase in number until 8 years of age and in size until the chest wall finishes growing.
- 3. Blood vessels are remodeled and increase, as new alveoli form, probably until the chest growth is complete.

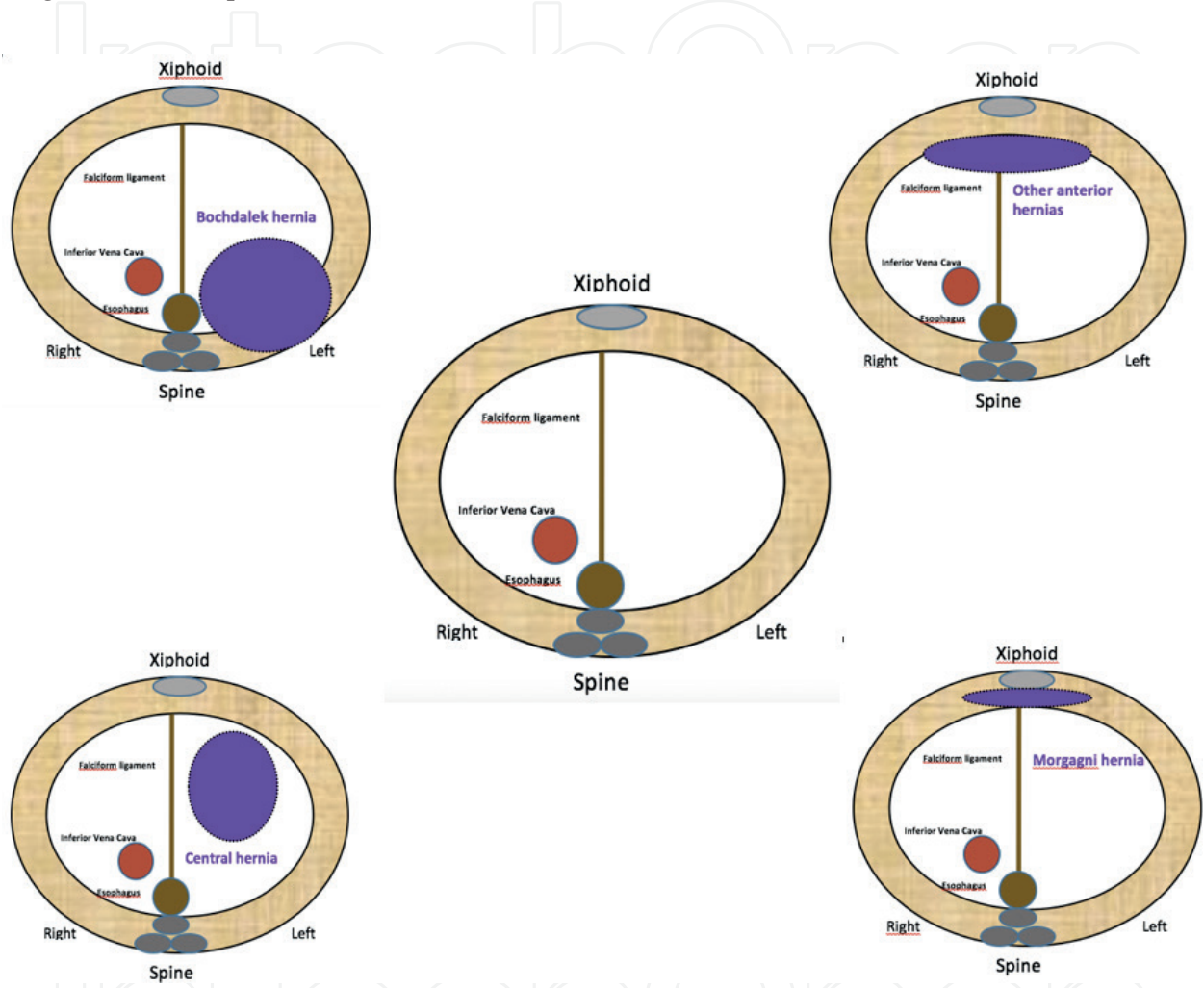


Figure 1. Types of congenital diaphragmatic hernia.

Hernia type	Location	Contents	Associated findings
Intrapleural	Lateral, usually left-sided	Stomach, bowel, spleen, variable-sized portions of the liver	Pulmonary hypoplasia
Mediastinal			
Ventral	Anterior and central	Liver, bowel	Pericardial effusion, pentalogy of Cantrell
Morgagni	Anteromedial, small, typically isolated	Liver, bowel	No pericardial communication
Hiatal	Posterior and central	Stomach, sometimes other organs	Congenital short esophagus

Table 4. Texas Children’s Fetal Center classification of CDH.

2.6. Pathogenesis

The pathogenesis of CDH is poorly understood. The diaphragmatic defect is caused by delayed or impaired separation of the two compartments: thoracic and abdominal. This is due to closure of embryonic pleuroperitoneal canals influenced by the growth of the post-hepatic mesenchymal plate and of the pleuroperitoneal folds [15, 16]. In CDH, respiratory failure at birth is the result of pulmonary hypoplasia (PH), reduced airway branching, and surfactant deficiency. Extensive muscularization of the pulmonary vessels may result in persistent pulmonary hypertension (PPH) of the newborn. Historically, PH was believed to be the result of compression of the lungs by the herniating intrathoracic abdominal organs. However, our understanding of abnormal pulmonary development in relation to CDH has significantly improved and we know that pulmonary development is already affected prior to development of the diaphragmatic hernia, implicating that the lungs are primarily disturbed in their development before mechanical compression can happen [17, 18].

2.7. Associated anomalies

The most common associated anomalies are cardiovascular in 40–60% of live-born infants and in 95% of fetal demise; therefore, a detailed ultrasound examination must be performed in every case diagnosed with CDH [19] (Table 5).

2.8. Ultrasound diagnosis

Ultrasound evaluation of the thorax can be carried out easily until 25–26 weeks of gestation; after this period, the increased mineralization of the ribs limits the display of intrathoracic organs, especially for coronal or sagittal views. A number of thoracic anomalies evolve; they can appear only in the third trimester or they can regress before birth. Therefore, if an initial assessment of the thorax can be performed as early as at the 12th week of gestation, in order to follow up abnormal cases, late third-trimester scans may be needed.

Scanning planes: the most important view for the assessment of intrathoracic anatomy is the classic *four chamber view* of the fetal heart. In this plane, most thoracic viscera can be visualized, including the ribs, the sternum, and the cutaneous outline. The *midsagittal* and *parasagittal views* allow display of the diaphragm as a hypoechoic line below the lungs and the heart and above the liver and the stomach. The diaphragm shows a curved outline, convex toward the thorax.

Cardiovascular	VSD, ASD, tetralogy of fallot, hypoplastic left heart syndrome
Gastrointestinal abnormalities	Meckel diverticulum, anal atresia
Central nervous system	Neural tube defects, hydrocephalus, agenesis of corpus callosum
Limb abnormalities	Absence defects, polydactyly, syndactyly
Genitourinary abnormalities	Cryptorhydia, absent testes, ectopic kidney, horseshoe kidney
Eye abnormalities	Microphthalmia and anophthalmia

Table 5. Associated anomalies.

Axial four-chamber view: the following structures should be checked: the two lungs appear as solid, homogeneous; weakly hyperechogenic that almost completely surrounds the heart, right larger than left lung; thoracic aorta behind the left atrium; the heart oriented toward the left; the ribs and overlaying cutaneous tissue; and posterior, the spine (**Figure 2**).

Three-vessel view: allows visualization of the thymus and its relationship with the great vessels and appears as a well-defined roundish solid structure interposed between the great vessels and the sternum. It is weakly hypoechogenic in comparison with the surrounding lungs. In front of the spine and behind the three vessels, the trachea, and, with some difficulty, the esophagus can be seen (**Figure 3**).

Midsagittal view: does not give significant information regarding the lungs because it is occupied mainly by the heart.

Right parasagittal view: the diaphragmatic hypoechogenic layer can be seen below the right lung.

Left parasagittal view: the diaphragmatic hypoechogenic layer can be seen below the left lung and the heart and allows to demonstrate that the stomach is located below the diaphragm.

The ultrasound diagnosis of CDH is, in general, indirect: the abnormal intrathoracic position of the stomach and/or the other migrated viscera and the displacement of the heart and the mediastinum is detected (**Figure 4**).

Left posterolateral CDH: in the *four-chamber view*, the stomach is in the left hemithorax or in the mediastinum (**Figure 5**).

Frequently, a few small bowel loops can be visualized near the stomach, while the heart and the mediastinum are pushed contralaterally. Much more rarely, the spleen and/or the left liver lobe may migrate as well. In few cases, only some ileal loops and/or the left hepatic



Figure 2. Four chamber view.

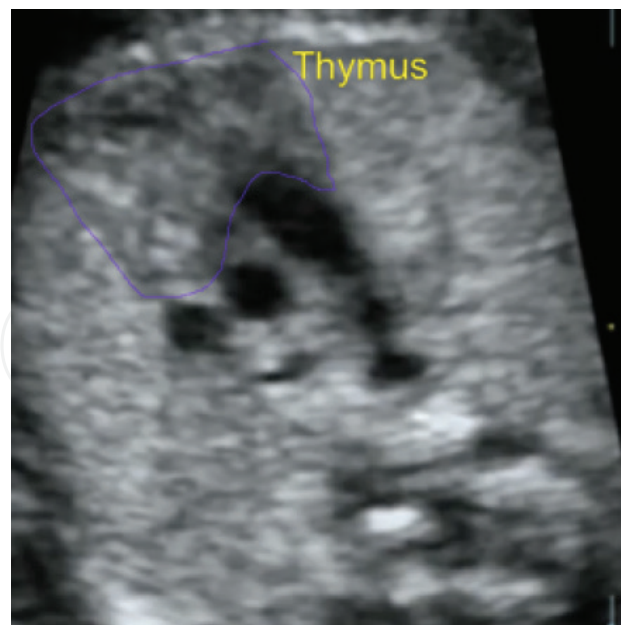


Figure 3. Three-vessel view. Note the thymus slightly hypoechoic than lungs.

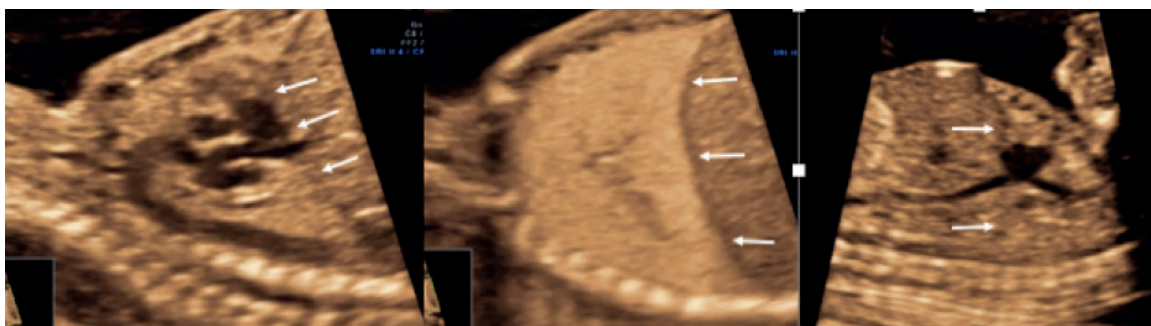


Figure 4. Sagittal view. Note the different echogenicity between lungs and abdominal viscera. Diaphragm appears as a hypoechoic thin line.

lobe migrate into the thorax; therefore, the diagnosis is based only on dextrocardia and the unusual inhomogeneous appearance of the left hemithorax (**Figure 6**).

Kinking of the sinus venosus is a reliable sign in case of herniated left liver lobe; the bowing of the umbilical segment of the portal vein (portal sinuses) to the left of the midline and coursing of portal vessels to the lateral segment of the left hepatic lobe toward or above the diaphragm is considered the best predictor for liver herniation [20] (**Figure 7**).

It must be kept in mind that even though the diaphragmatic defect occurs in the first trimester, the visceral herniation is variable in time, from early second trimester to the first hour of life.

The sagittal views allow to detect some additional features that help confirm the diagnosis; the evidence of intrathoracic viscera on the four-chamber view is the basic requirement for a correct diagnosis of CDH.

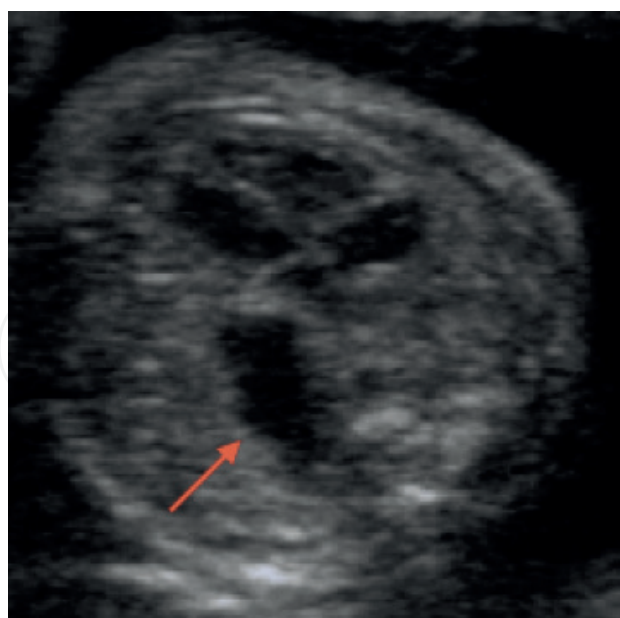


Figure 5. Left congenital diaphragmatic hernia. The stomach is in the left hemithorax and the heart is displaced to the right.



Figure 6. Left CDH. Herniation of left liver lobe and bowel loops. The heart is displaced to the right hemithorax.

Right-sided CDH: the diagnosis is difficult because the main feature, the intrathoracic displacement of the stomach, is absent because the defect is on the other side of the diaphragm. There are several indirect signs that lead to diagnosis. One is the leftward rotation of the heart with increase of the cardiac axis (**Figure 8**) and the upward displacement of the right hepatic lobe into the right hemithorax. This sign is best observed using color Doppler to identify the suprahepatic veins in the thorax because of the similar echogenicity of the lung and liver. Right-sided intrapleural hernias are less common, always contain liver, and may contain variable amounts of bowel and stomach. Rarely, intrapleural hernias may be bilateral; these tend to be associated with severe pulmonary hypoplasia. The midline position of the heart, the lack of

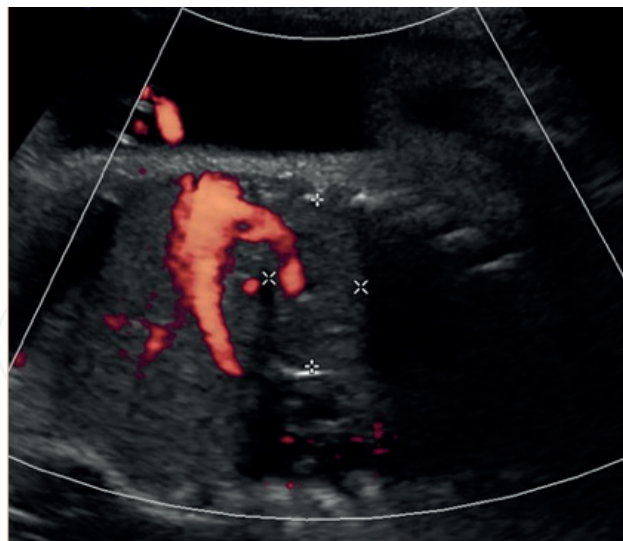


Figure 7. Portal vessels extending into the thorax. Left liver lobe (markers).



Figure 8. Leftward rotation of the heart with increase of the cardiac axis and upward displacement of the right hepatic lobe into the right hemithorax.

cardiomediastinal shift in cases of suspected intrapleural hernia should raise suspicion for the presence of bilateral intrapleural hernias.

Anterior and central CDH: the ventral type appears anteriorly because of the central tendons' defect. The central tendon of the diaphragm on his upper surface and the pericardium are

communicating, if there is a defect at this site a pericardial effusion may develop. Ventral hernias may push the heart posteriorly but do not tend to cause pulmonary hypoplasia (Figure 9).

The smaller Morgagni hernia, usually is an isolated anterior defect and given its small size and location does not cause compression of thoracic organs. Morgagni hernias do not communicate with the pericardial space; therefore, this feature is a key element in differentiation from mediastinal hernias (Table 6).

Hiatal CDH: on ultrasound examination, it may appear as a hypoechogenic image behind the fetal heart in the posterior mediastinum, anterior to the vertebral body in continuity with a small fetal stomach located in the abdominal cavity just below the diaphragm in a median position. Parasagittal sonographic sections of the fetal thorax show an intact diaphragm on both sides. During the examination, stomach peristalsis may be visualized or the up and down movements of the stomach into the fetal thorax [21, 22]. The absence of liver in a hiatal hernia should help distinguish it from a right-sided intrapleural hernia.

The diagnosis of diaphragmatic hernia is rare during the first trimester. Early diagnosis has been associated with poor prognosis and the presence of additional defects [23, 24]. A diagnosis of CDH is suggestive if a displacement of the fetal heart in association with an intrathoracic mass having the appearance of the liver or stomach is detected.

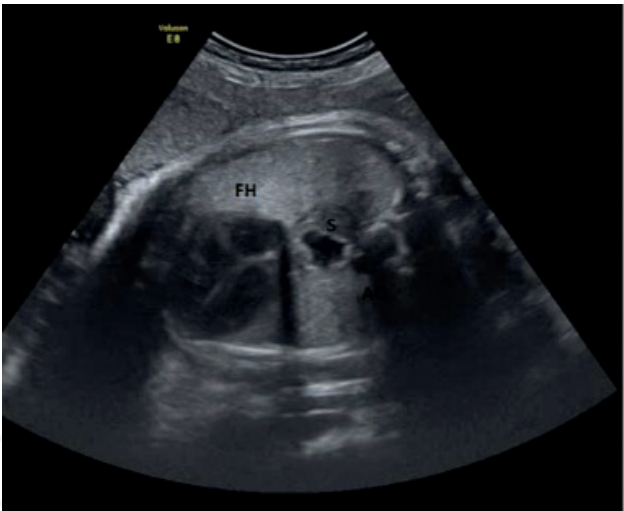


Figure 9. Transverse view of the fetal thorax with an anechogenic mass behind the heart; FH—fetal heart; Ao—aorta; S—stomach.

-
- Thoracic mass with mediastinal shift.
 - Left-sided CHD: stomach is in thorax seen in *four-chamber view*, almost half of the cases have liver herniation.
 - Right-sided CHD: almost always have liver herniation which is difficult to see; diagnosis is suspected in case of left mediastinal shift and Doppler reveals abnormal course of hepatic vessels.
 - Polyhydramnios secondary to esophageal compression.
-

Table 6. Key sonographic features.

It was reported in a prospective study on 78,000 pregnancies at first trimester screening for chromosomal abnormalities by nuchal translucency thickness, 19 chromosomally normal fetuses with diagnosis of congenital diaphragmatic hernia. Only one of them was diagnosed in the first trimester; diagnosis was based on the visualization of the stomach in the thorax. In about one-third of the cases of diaphragmatic hernia, they found increased nuchal translucency. In the majority of the infants (83%) who died in the neonatal period due to pulmonary hypoplasia, nuchal translucency was increased, while the respective percentage for the survivors was 22%. The authors hypothesized that the accumulated nuchal fluid may be caused by venous congestion determined by intrathoracic compression due to early herniation of the abdominal organs [25].

The compression of herniated organs on esophagus or gastric outlet obstruction causes polyhydramnios which may become visible later in pregnancy. Another cause of polyhydramnios in cases with CDH is esophageal atresia with tracheoesophageal fistula, which may be very difficult to diagnose because the visualization of the proximal esophageal pouch is dependent on its being distended by swallowed amniotic fluid.

2.9. Differential diagnosis

Bronchogenic cysts (foregut duplication) contain several components of the bronchi, including respiratory epithelia, mucous glands, and cartilage and may occur anywhere along the length of the trachea or esophagus [26]. Most are diagnosed incidentally or if large enough, can compress the esophagus and/or trachea.

Congenital cystic adenomatoid malformation (CCAM): a developmental abnormality of the lung resulting from abnormal cell proliferation and decreased programmed cell death of lung tissue. Type I CCAM is most common and is distinguished by relatively large cysts and mucin production.

Cystic teratomas are benign tumors most often found in the anterior mediastinum. They consist of several differentiated cell types derived from endoderm, ectoderm, and/or mesoderm [27, 28].

Neurogenic tumors are the most common lesion found in the posterior mediastinum. They are likely to be of neural crest origin; the majority is benign: neurilemoma, neurofibroma, ganglioneuroma, pheochromocytoma, and neuroblastoma.

Pulmonary agenesis refers to partial or complete absence of lung tissue that is caused by failure of lung bud development.

Pulmonary sequestration results from primitive lung tissue that is not connected to the tracheobronchial tree. Sequestration may be intrapulmonary, occurring within the pleura of the normal lung or extrapulmonary, occurring outside the normal lung within its own pleural sac.

2.10. Prognostic indicators

The best validated measurement is contralateral lung area assessed by 2D ultrasound through the so-called lung area/head circumference ratio (LHR) [29]. Different methods for measuring were described but the most reproducible and accurate method involves tracing the lung contours.

Normal lung area develops four times more than the head circumference between week 12 and 32; therefore, the LHR needs to be adjusted according to gestational age. The effect of gestational age on LHR can be minimized by expressing the observed LHR as a ratio to the expected mean LHR for that gestational age.

2.10.1. *The lung area to head circumference ratio*

The lung-to-head circumference ratio (LHR) is a sonographic measure proposed to identify fetuses with congenital diaphragmatic hernia (CDH) that have a poor prognosis. The lung area contralateral to the CDH is measured at the level of *four-chamber view* by manual tracing of the lung which appears to be the most reproducible way of measuring the lung area [30]. The product is divided by the head circumference (HC) to obtain the LHR.

The lung area to head circumference ratio (LHR) = lung area/head circumference.

2.10.2. *Observed/expected lung-to-head ratio*

The observed LHR may be expressed as a percentage of the expected mean for gestational age as the observed/expected lung-to-head ratio O/E LHR [31, 32].

$$\text{O/E LHR} = (\text{observed LHR} / \text{expected LHR}) \times 100$$

There has been proposed a four-step stratification of fetuses based on their observed/expected (O/E) LHR wherein it was also taken into account their liver position.

- Fetuses with an O/E LHR <15% have extreme pulmonary hypoplasia and there are no survivors reported.
- Fetuses with an O/E LHR between 15 and 25% have severe pulmonary hypoplasia and survival prediction is about 20%, those with the liver down having better prognosis than those with liver up in the thorax.
- Fetuses with an O/E LHR between 26 and 35% and those with an O/E LHR between 36 and 45% but with the liver up have moderate hypoplasia. They have an expected survival rate between 30 and 60%, which depends on the lung size.
- Fetuses with an O/E LHR between 36 and 45% with the liver down and those with an O/E LHR > 45% have mild hypoplasia and have better prognosis, >75% survival rate [33, 34] (**Table 7**).

-
- Prenatal prediction of postnatal outcome in CDH patients is based on ultrasound measurement of contralateral lung size and magnetic resonance total lung volumetry.
 - The ratio of observed to predicted lung/head ratio is the most validated predictor for postnatal outcome; the liver position is also predictive.
 - Fetal tracheal occlusion has been shown safe and feasible by minimally invasive means.
-

Table 7. Key points.

2.10.3. *Fetal lung volumes*

On fetal MR imaging there are several methods described for estimation of fetal pulmonary hypoplasia. All of these methods include the measuring of total fetal lung volume (TFLV). MR volumetry is considered the most accurate method for measuring ipsilateral lung and, therefore, for best estimation of fetal lung volumes, compared to three-dimensional ultrasound [35].

2.10.4. *Fetal intervention*

Because CDH is an anomaly with poor prognosis that can be identified in the prenatal period, it is justified to perform an intervention which improves lung function. Di Fiore and Wilson studied the concept of triggering lung growth by tracheal occlusion [36]. This was observed in an experiment of nature occurring in fetuses with congenital high airway obstruction syndrome (CHAOS), who display impressive lung growth. Through pregnancy, fetal lungs secrete fluid during their development, which creates a positive pressure under the glottis. Fluid secretion of the lung and a cyclical pressure change are essential for development and growth of the lung [37]. Fluid secretion increases the pressure in airways but during fetal breathing movements, the pressure gradient is normalized as glottis opens. This phenomenon creates cyclical periods of tissue stretch, which are important for an optimal balance between growth and differentiation [38]. Intrauterine tracheal occlusion acts like a closed glottis trapping the fluid causing subsequently increased tissue stretch, which triggers lung growth. The tracheal occlusion decreases the number of type II alveolocytes and lowers surfactant expression in occluded lungs [39–42]. This unwanted effect may be improved by either removing the tracheal occlusion before birth and/or by antenatal steroid administration [43, 44]. Experimentally, in-utero reversal of occlusion (clinically translated as a plug-unplug sequence) achieved morphologically better lung maturation [45].

3. Conclusions

As prenatal detection of fetal CDH improved in recent years, it is important to use standardized prognosis markers around the world. Currently, available markers are not 100% accurately predictive of outcome and their use is much less accurate in the presence of chromosomal anomalies or other malformations. This shows the fact that all fetuses diagnosed with CDH should undergo an ultrasound examination by a well-trained sonographer, as well as fetal echocardiography.

Conflict of interest

No conflict of interest to declare.

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References

- [1] Gallot D, Boda C, Ughetto S, Perthus I, Robert-Gnansia E, Francannet C, Laurichesse-Delmas H, Jani J, Coste K, Deprest J, et al. Prenatal detection and outcome of congenital diaphragmatic hernia: A French registry-based study. *Ultrasound in Obstetrics & Gynecology*. 2007;**29**:276-283
- [2] Tudorache S, Chiuțu LC, Iliescu DG, Georgescu R, Stoica GA, Simionescu CE, Georgescu EF, Nemeș RN. Prenatal diagnosis and perinatal outcome in congenital diaphragmatic hernia. Single tertiary center report. *Romanian Journal of Morphology and Embryology*. 2014;**55**(3):823-833
- [3] Parisi MA, Zayed H, Slavotinek AM, Rutledge JC. Congenital diaphragmatic hernia and microtia in a newborn with mycophenolate mofetil (MMF) exposure: Phenocopy for Fryns syndrome or broad spectrum of teratogenic effects? *American Journal of Medical Genetics: Part A*. 2009;**149A**:1237-1240
- [4] Pober BR, Russell MK, Ackerman KG. Congenital diaphragmatic hernia overview. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. *Gene Reviews*. Seattle (WA): University of Washington, Seattle; 1993-2017
- [5] Mehollin-Ray AR, Cassady CI, Cass DL, Olutoye O. Fetal MR imaging of congenital diaphragmatic hernia. *Radiographics*. 2012;**32**:1067-1084
- [6] Moore KL. *The Developing Human: Clinically Oriented Embryology*. 3rd ed. Philadelphia: WB Saunders; 1982
- [7] Yuan W, Rao Y, Babiuk RP, Greer JJ, Wu JY, Ornitz DM. A genetic model for a central (septum transversum) congenital diaphragmatic hernia in mice lacking Slit3. *Proceedings of the National Academy of Sciences of the United States of America*. 2003;**100**:5217-5222
- [8] Birchmeier C, Brohmann H. Genes that control the development of migrating muscle precursor cells. *Current Opinion in Cell Biology*. 2000;**12**:725-730
- [9] Babiuk RP, Zhang W, Clugston R, Allan DW, Greer JJ. Embryological origins and development of the rat diaphragm. *The Journal of Comparative Neurology*. 2003;**455**:477-487
- [10] Hopper AF, Hart NH. *Foundations of Animal Development*. Oxford: Oxford University Press; 1985

- [11] Spooner BS, Wessels NK. Mammalian lung development: Interactions in primordium formation and bronchial morphogenesis. *The Journal of Experimental Zoology*. 1970;**175**:445-454
- [12] Boyden EA. Development of the human lung. In: Brennenman J, editor. *Practice of Pediatrics*. Hagerstown, PA: Harper & Row; 1972
- [13] Keijzer R, Puri P. Congenital diaphragmatic hernia. *Seminars in Pediatric Surgery*. 2010;**19**:180-185
- [14] Reid L. The embryology of the lung. In: de Reuck AVS, Porter R, editors. *Ciba Foundation Symposium*. London: J. & A. Churchill Ltd; 1967. pp. 109-130
- [15] Kluth D, Keijzer R, Hertl M, Tibboel D. Embryology of congenital diaphragmatic hernia. *Seminars in Pediatric Surgery*. 1996;**5**:224-233
- [16] Greer JJ, Allan DW, Babiuk RP, Lemke RP. Recent advances in understanding the pathogenesis of nitrofen-induced congenital diaphragmatic hernia. *Pediatric Pulmonology*. 2000;**29**:394-399
- [17] Jesudason EC, Connell MG, Fernig DG, et al. Early lung malformations in congenital diaphragmatic hernia. *Journal of Pediatric Surgery*. 2000;**35**:124-127, discussion: 128
- [18] Keijzer R, Liu J, Deimling J, et al. Dual-hit hypothesis explains pulmonary hypoplasia in the nitrofen model of congenital diaphragmatic hernia. *The American Journal of Pathology*. 2000;**156**:1299-1306
- [19] Puri P, Gorman F. Lethal nonpulmonary anomalies associated with congenital diaphragmatic hernia: Implications for early intrauterine surgery. *Journal of Pediatric Surgery*. 1984;**19**(1):29-32
- [20] Bootstaylor BS, Filly RA, Harrison MR, Adzick NS. Prenatal sonographic predictors of liver herniation in congenital diaphragmatic hernia. *Journal of Ultrasound in Medicine*. 1995;**14**:515-552
- [21] Ruano R, Benachi A, Aubry MC, Bernard JP, Hameury F, Nihoul-Fekete C, Dumez Y. Prenatal sonographic diagnosis of congenital hiatal hernia. *Prenatal Diagnosis*. 2004;**24**(1):26-30
- [22] Di Francesco S, Matteo Lanna M, Napolitano M, et al. A case of ultrasound diagnosis of fetal hiatal hernia in late third trimester of pregnancy. *Case Reports in Obstetrics and Gynecology*. 2015;**2015**. Article ID 194090, 3 pages. DOI: 10.1155/2015/194090
- [23] Garne E, Quataert P, de Vigan C. Congenital diaphragmatic hernia: A European population-based study of epidemiology, prenatal diagnosis and mortality. *Prenatal and Neonatal Medicine*. 1999;**4**:441-447
- [24] Garne E, Haeusler M, Barisic I, Gjergja R, Stoll C, Clementi M, the Euroscan Study Group. Congenital diaphragmatic hernia: Evaluation of prenatal diagnosis in 20 European regions. *Ultrasound in Obstetrics & Gynecology*. 2002;**19**:329-333

- [25] Sebire NJ, Snijders RJM, Davenport M, Greenough A, Nicolaides KH. Fetal nuchal translucency thickness at 10-14 weeks of gestation and congenital diaphragmatic hernia. *Obstetrics and Gynecology*. 1997;**90**:943-947
- [26] Knudtson J, Grewal H. Thoracoscopic excision of a paraesophageal bronchogenic cyst in a child. *JSLs*. 2004;**8**:179-182
- [27] Jagers J, Balsara K. Mediastinal masses in children. *Seminars in Thoracic and Cardiovascular Surgery*. 2004;**16**:201-208
- [28] Ionescu C, Haradja H, Gheorghiu D, Vladescu T, Pacu I, Dimitriu M. Prenatal ultrasound diagnosis of cervical teratoma. *Gineco.ro*. 2011;**7**(23):25-27
- [29] Metkus AP, Filly RA, Stringer MD, Harrison MR, Adzick NS. Sonographic predictors of survival in fetal diaphragmatic hernia. *Journal of Pediatric Surgery*. 1996;**31**:148-151
- [30] Peralta CFA, Cavoretto P, Csapo B, Vandecruys H, Nicolaides KH. Assessment of lung area in normal fetuses at 12-32 weeks. *Ultrasound in Obstetrics & Gynecology*. 2005;**26**:718-724
- [31] Jani J, Nicolaides KH, Keller RL, Benachi A, Peralta CFA, Favre R, Moreno O, Tibboel D, Lipitz S, Eggink A, Vaast P, Allegaert K, Harrison M, Deprest J. Observed to expected lung area to head circumference ratio in the prediction of survival in fetuses with isolated diaphragmatic hernia. *Ultrasound in Obstetrics & Gynecology*. 2007;**30**:67-71
- [32] Jani JC, Peralta CFA, Nicolaides KH. Lung-to-head ratio: A need to unify the technique. *Ultrasound in Obstetrics & Gynecology*. 2012;**39**:2-6
- [33] Deprest JA, Flemmer AW, Gratacos E, Nicolaides K. Antenatal prediction of lung volume and in-utero treatment by fetal endoscopic tracheal occlusion in severe isolated congenital diaphragmatic hernia. *Seminars in Fetal & Neonatal Medicine*. 2009;**14**:8-13
- [34] Ionescu C, Gheorghiu D, Pacu I, Sardescu G, Ionescu V. Prognosticul fetal în hernia diafragmatică congenitală sîngă. *Obstetrica si Ginecologia*. 2009;**LVII**(3):183
- [35] Jani JC, Cannie M, Peralta CFA, Deprest JA, Nicolaides KH, Dymarkowski S. Lung volumes in fetuses with congenital diaphragmatic hernia: Comparison of 3D US and MR imaging assessments. *Radiology*. 2007;**244**(2):575-582
- [36] DiFiore JW, Fauza DO, Slavin R, Peters CA, Fackler JC, Wilson JM. Experimental fetal tracheal ligation reverses the structural and physiological effects of pulmonary hypoplasia in congenital diaphragmatic hernia. *Journal of Pediatric Surgery*. 1994;**29**:248-256
- [37] Moessinger AC, Harding R, Adamson TM, Singh M, Kiu GT. Role of lung fluid volume in growth and maturation of the fetal sheep lung. *The Journal of Clinical Investigation*. 1990;**86**:1270-1277
- [38] Nelson SM, Hajivassiliou CA, Haddock G, et al. Rescue of the hypoplastic lung by prenatal cyclical strain. *American Journal of Respiratory and Critical Care Medicine*. 2005;**171**:1395-1402

- [39] Probyn ME, Wallace MJ, Hooper SB. Effect of increased lung expansion on lung growth and development near midgestation in fetal sheep. *Pediatric Research*. 2000;**47**:806-812
- [40] Luks FI, Roggin KK, Wild YK, et al. Effect of lung fluid composition on type II cellular activity after tracheal occlusion in the fetal lamb. *Journal of Pediatric Surgery*. 2001;**36**:196-201
- [41] De Paepe ME, Papadakis K, Johnson BD, Luks FI. Fate of the type II pneumocyte following tracheal occlusion in utero: A time-course study in fetal sheep. *Virchows Archiv*. 1998;**432**:7-16
- [42] O'Toole SJ, Sharma A, Karamanoukian HL, Holm B, Azizkhan RG, Glick PL. Tracheal ligation does not correct the surfactant deficiency associated with congenital diaphragmatic hernia. *Journal of Pediatric Surgery*. 1996;**31**:546-550
- [43] Bratu I, Flageole H, Laberge JM, et al. Surfactant levels after reversible tracheal occlusion and prenatal steroids in experimental diaphragmatic hernia. *Journal of Pediatric Surgery*. 2001;**36**:122-127
- [44] Davey MG, Danzer E, Schwarz U, Adzick NS, Flake AW, Hedrick HL. Prenatal glucocorticoids and exogenous surfactant therapy improve respiratory function in lambs with severe diaphragmatic hernia following fetal tracheal occlusion. *Pediatric Research*. 2006;**60**(2):131-135
- [45] Flageole H, Evrard VA, Piedboeuf B, Laberge JM, Lerut TE, Deprest JA. The plug-unplug sequence: An important step to achieve type II pneumocyte maturation in the fetal lamb model. *Journal of Pediatric Surgery*. 1998;**33**:299-303

