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Prenatal diagnosis, imaging, and prognosis in Congenital Diaphragmatic Hernia

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Abstract

Antenatal ultrasound screening identifies more than 60% of Congenital Diaphragmatic Hernia (CDH) cases and provides the opportunity for in utero referral to a tertiary care center for expert assessment and perinatal management. Prenatal assessment of fetuses with CDH has tremendously improved over the past ten years. The outcome may be predicted prenatally by medical imaging and advanced genetic testing. The combination of lung size and liver position determination by ultrasound measurements and MRI are widely accepted methods to stratify fetuses into groups that correlate not only with neonatal mortality but also with morbidity. Notwithstanding this, prediction of persistent pulmonary hypertension of the newborn still needs to be improved.

Word count: 108

Introduction

The prenatal diagnosis of congenital diaphragmatic hernia (CDH) has improved worldwide since the introduction of prenatal screening ultrasound (US) and today, two thirds of cases are detected by the second trimester¹. Ideally, this should lead to referral to a tertiary center given that planning birth of affected fetuses in a center with experience in the perinatal management of CDH, with standardized neonatal management in an optimal neonatal care intensive unit (NICU) and pediatric surgery services, improves outcome^{2,3}. Specialized assessment is also needed to rule out associated anomalies, as in up to 40% of cases CDH is not isolated, and the outcome is codetermined by the severity of associated conditions⁴. Personalized prediction of disease severity and prognosis⁴ by genetic testing and advanced imaging (US and MRI) is mandatory to counsel parents, but also to discuss the potential of antenatal management, such as termination of pregnancy or fetal therapy, which today is available within the framework of clinical trials⁵.

Prenatal assessment

Genetic testing

For exhaustive diagnostic evaluation and accurate counseling, genetic testing should be completed. There is no specific cytogenetic anomaly which has been associated with CDH, but a causative cytogenetic aberration is detected in 2% to 33% of patients^{6,7}. Even if many of the most common chromosomal aberrations can be diagnosed by conventional karyotyping, an additional 6 to 9% have clinically relevant copy number variants identifiable by array comparative genomic hybridization^{6,8}. In a recent study, targeted resequencing has enabled the identification of previously unidentified genetic causes in 10% of archived samples⁹.

Increasingly, more cases are diagnosed in the first trimester and therefore choriovillous sampling (CVS) is then offered. Although array comparative genomic hybridization can be performed on CVS, one has to remember that the mosaic distribution of the supernumerary

isochromosome 12p (Pallister-Killian syndrome) greatly increases the risk of misdiagnosis^{9,10}. Therefore, an amniocentesis with array comparative genomic hybridization on non-cultured cells is recommended¹¹. In case of multiple associated structural anomalies, the search for specific mutations and syndromes is obviously recommended¹².

A more detailed overview on genetic anomalies associated to CDH is included in this edition of the *Seminars* or we refer to the specialized literature^{12,13}.

Prenatal imaging

Accurate prediction of outcome is crucial given the fact that fetuses with the worst prognosis may benefit from prenatal intervention, currently including tracheal occlusion, in the clinical trial setting. Personalized prediction is made based on the isolated nature of the defect, its side, estimation of lung size, and presence and amount of liver herniation, which can also be predicted with stomach position or measured by MRI¹⁴⁻¹⁷ (**Table 1-3**).

Lung size

Measurement of lung size is the most logical and direct approach to assess hypoplasia and subsequently predict neonatal outcome. The lung-to-head ratio (LHR), first described by Metkus et al¹⁵, provides an indirect estimate of the size of the lung contralateral to the hernia, normalized for the head circumference. It is typically measured by 2-dimensional ultrasound at the level of the 4-chamber view (**Figure 1**). The most accurate methods for lung measurement are by tracing the lung contours or by the long axis method¹⁸.

LHR measurement was initially only used in the late second trimester and values under 1.0 were considered predictive of poor outcome. However, the LHR changes over gestation as the lung area grows more rapidly than the head circumference. Correction for gestational age by expressing the LHR of the index case as a function of what is expected in a gestational age matched control (observed/expected LHR or o/e LHR) is therefore used. The formulas

for calculating the o/e LHR are embedded in a freely available web-based calculator ⁵ (www.totaltrial.eu). In left sided CDH (LCDH), when o/e LHR is <25%, hypoplasia is considered severe. The next severity group (25%<o/e LHR<35% irrespective of liver position, or 35%<o/e LHR<45% with liver “up”) is (a bit misleadingly) categorized as “moderate” as survival in that group is limited to 50-60% and survivors have significant morbidity¹⁸.

The o/e LHR has been shown to be an independent predictor of postnatal survival¹⁸ both in LCDH and RCDH, and of some short-term morbidity indicators^{19,20}. The o/e LHR is therefore now widely accepted as a prenatal tool to counsel parents and is used to select patients for fetal therapy, such as the TOTAL (Tracheal Occlusion To Accelerate Lung growth) trials.

Other 2D ultrasound methods to assess lung size, such as the lung to thorax ratio²¹ and the quantitative lung index ²² have also been proposed, but they are less validated hence not discussed here. Lung volume estimated by 3-dimensional US also correlates with neonatal outcome, yet is not better than O/E-LHR, and volume estimation may be difficult on the ipsilateral side ^{23,24}.

Liver position evaluation: direct and indirect methods

In addition to measuring the o/e LHR, the severity of CDH is estimated based on the binary variable, hence, either “up” (in the thorax) or “down” (confined to the abdomen) liver position^{25,26}. In left sided cases, this factor is an independent predictor next to lung size (as o/e LHR) according to some studies^{14,25}. However, in right-sided CDH, the liver is nearly always herniating through the defect, hence it has no predictive value²⁷.

Werneck-Britto et al.²⁸ described the liver-to-thoracic area ratio (US-LiTR) by 2D US, measured on the standard 4-chamber view and demonstrated a predictive accuracy for neonatal outcome. As the echogenicity of the liver is very similar to that of the lung, it can be

difficult to assess the liver position or its extent into the thorax and therefore it is more easily evaluated prenatally by MRI. Cannie et al proposed to measure the ratio of the volume of liver to that of the total chest (liver-to-thoracic volume ratio, LiTR), whereas Lazar et al. calculated the percentage of liver that is into the fetal chest (MRI-% Liver herniation) ^{29,30}. The amount of liver into the chest seems to be a predictive marker of postnatal survival in CDH ²⁹⁻³².

However, it is far easier to determine the stomach position rather than quantify liver herniation, as the stomach is anechoic, whereas liver echogenicity is close to or identical to that of the lung ³³. Stomach position was suggested as an indirect method to estimate severity of the disease and a prognostic indicator previously in 1992³⁴. Kitano et al,¹⁶ proposed a simple stomach grading correlated to the degree of herniation (in 4 steps) on coronal sections of the thorax using MRI. He demonstrated there is a relationship between stomach position and intrathoracic liver position. More recently, we introduced a 4-step grading system using the standard 4-chamber views on US, hence facilitating its reproducibility, and correlated this with the proportion of intrathoracic liver LiTR determined by MRI in left-sided CDH (**Figure 2**)³⁵. In that series, the position of the stomach correlated well with postnatal outcome, independent from the o/e LHR¹⁷.

Most prenatal management centers use a combination of the position of the liver and the o/e LHR to stratify patients into different groups with increasing degree of pulmonary hypoplasia and corresponding risk of mortality. Lung size and liver herniation can also predict short term neonatal morbidity in terms of assisted ventilation, need for supplemental oxygen, need for patch repair and time to full enteral feeding³⁶⁻³⁸. These factors, in some studies, also correlated with persistent pulmonary hypertension of the newborn^{37,39}.

Hernia sac

A particular anatomical form of CDH is when a hernia sac, formed by a peritoneal layer covering the digestive organs herniated in the thorax, is present. A number of studies have focused on the association between the presence of a hernia sac in CDH and morbidity and mortality⁴⁰⁻⁴⁵. The percentage of CDH cases with a hernia sac ranges between 14.2%⁴² and 25.7%⁴⁰. Several authors report a better survival rate for CDH-neonates with a hernia sac, but difference in morbidity is still controversial⁴⁰⁻⁴⁵.

Zamora et al described 3 prenatal signs revealed by MRI: (1) meniscus of lung posterior or apical to the hernia contents, (2) encapsulated appearance of hernia contents, and (3) presence of pleural fluid outlining a sac from above⁴¹. They found that these MRI signs were correlated very specifically with the presence of a hernia sac. However, Bouchghoul et al, evaluated those signs retrospectively by ultrasound; the positive predictive value of the 3 signs was low, but the negative predictive value was high⁴⁴.

The efficiency of these prenatal signs is currently not sufficient to allow their use in prenatal counselling. Further prospective studies are necessary to evaluate those prenatal ultrasound signs of hernia sac in CDH.

Imaging for associated structural anomalies

The prevalence of associated structural anomalies ranges widely in different studies, being higher where stillbirths or cases undergoing termination of pregnancy are included^{46,47}.

A wide spectrum of structural anomalies associated with CDH has been reported in the literature. Cardiovascular defects are the most common anomalies associated with CDH and are found in about one third of all CDH patients and in 15% of non-syndromic cases.

Therefore, all patients with CDH should undergo high-quality fetal echocardiography.

Finally, intrafetal fluid effusions are a relatively common ultrasound finding in CDH fetuses, observed in up to 5% and 29% of left- and right-sided CDH cases, respectively. One series did not observe a correlation with poorer outcome⁴⁸.

CDH-associated pulmonary hypertension (CDH-PH)

Neonatal death in CDH infants is a consequence of pulmonary hypoplasia, but also of CDH-PH⁴⁹. CDH-PH is believed to have a morphological and functional basis. Smaller and fewer pulmonary arteries lead to increased pulmonary vascular resistance along with increased vasoconstriction.

Although fetal volume estimation is now feasible by 2D-ultrasound, 3D-ultrasound or MRI determinations, their use for the prediction of the occurrence and severity of CDH-PH is still part of research programs. This represents a weak point of prenatal prognostic assessment.

The logical approach to assess lung vascularization is by direct measurement, which has been attempted by a variety of techniques^{23,50–56}. These measurements are not easily reproducible, and their added predictive value remains to be proven as shown in a recent meta-analysis⁵⁷. However, prediction of CDH-PH would be desirable, as it correlates with mortality and long-term morbidity⁵⁸.

Magnetic Resonance Imaging (MRI)

Fetal MRI is widely used in the assessment of fetal lung disorders including CDH and is currently the reference technique for fetal lung volume estimation^{59,60}. MRI, with shorter acquisition times, is not limited by maternal habitus, fetal position, or amniotic fluid volume¹⁴ and allows for accurate and reliable measurement of both lungs⁶¹. Analogous to the o/e-LHR, absolute bilateral volumes are converted to a percentage of what is expected in a normal fetus (observed-to-expected total fetal lung volume; o/e-TFLV)⁵⁹ (**Figure 3**).

Volumetry can also be used to quantify liver and stomach herniation. The degree of volumetric intrathoracic liver herniation has been shown to better predict postnatal survival than the dichotomous assessment of either presence or absence of the liver into the chest^{29,30,62,63}. However, due to its wider availability, ultrasound remains in many centres the modality on which decisions regarding prenatal management are based.

Right-sided congenital diaphragmatic hernia

Right-sided diaphragmatic hernia accounts for 13-17% of all CDH cases. Right CDH (RCDH) is considered to be overall more severe than left CDH, but this is still debated⁶⁴⁻⁶⁷.

Jani et al.¹⁸ and De Koninck et al.²⁷ documented an overall survival of 44% to 53% respectively. In those studies, the o/e LHR correlated with survival, yet the cut off for severe hypoplasia apparently is higher; when O/E LHR is <45%, survival rate was extremely low. Additionally, liver herniation is not discriminative in RCDH, as it is nearly always present^{27,64}. Schaible et al.⁶⁵ reported that right CDH carries a higher risk of long-term morbidity, especially chronic lung disease. Given the rarity of RCDH it will be difficult to get sufficient data to develop a side specific prediction algorithm for RCDH. Right and Left CDH data must not be pooled in clinical studies as the prognostic evaluation and probably the physiopathology could be different between the two diseases.

Future or emerging methods of diagnosis

Further emerging methods of diagnosis are needed in order to better evaluate CDH-PH. As mentioned before evaluation of distal lung vascularization could be the ideal technique. Diffusion MRI has been used as well as quantitative analysis of fetal pulmonary vasculature²³. Unfortunately, the external validation by other teams has never been published, and therefore is not been considered as been reproducible. Those techniques are also time-consuming preventing them to be used in regular clinical setting.

As defect size has been considered as the only real reliable post-natal marker of morbidity^{68,69}, a recent paper has focused on the possibility of evaluating the exact size of the defect by prenatal MRI⁷⁰. Prayer et al. has measured surface areas of the intact diaphragm and of the defect to calculate defect-diaphragmatic ratio⁷⁰. It seems that this ratio correlates with the need for patch at surgery and that MRI-based 3D reconstruction allows location, classification and quantification of the defect.

Conclusion

Today, prediction of neonatal outcome and morbidity is possible based on prenatal imaging. Prenatal sonographic assessment remains heterogenous and should improve, especially in the era of prenatal treatment because not all CDH fetuses will be eligible to receive prenatal investigational intervention (FETO, sildenafil, etc)⁷¹. Efforts must continue to improve the quality and consistency of prenatal diagnosis and evaluation, in both right and left CDH. Moreover, survivors require multidisciplinary follow-up, and research linking antenatal markers for CDH-PH with long-term morbidity is still needed.

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Tables

Table 1. Imaging options and measurements allowing an exhaustive assessment of CDH. LHR: Lung to Head Ratio; TFLV: Total fetal Lung Volume; LiTR: Liver into Thorax Ratio

US	MRI
LHR o/e ¹⁸	TFLV o/e ¹⁴
Liver position	LiTR ²⁹
Stomach grading ¹⁷	Stomach grading ³¹
	3D defect's size ⁷⁰

Table 2. Prognosis of Left CDH with liver UP correlates with LHR observed/expected measured at US evaluation

Left CDH, liver UP	LHR o/e	Survival
Very Severe	<15%	<5%
Severe	16-25%	20-30%
Moderate	26-45%	40-60%
Mild	>45%	95%

Table 3. Prognosis of Left CDH depending on liver position and TFLV (Total Fetal Lung Volume) by MRI.

	TFLV o/e	Survival	
		Liver UP	Liver DOWN
Very Severe	<15%	12%	40%
Severe	16-25%	40%	85%
Moderate	26-45%	65%	85%
Mild	>45%	75%	85%









