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Prenatal diagnosis and risk stratification of congenital diaphragmatic hernia

Nimrah Abbasi,[1] Sami Backley,[2] Greg Ryan,[1] Anthony Johnson [2]

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[1]Ontario Fetal Centre & Fetal Medicine Unit, Department of Obstetrics & Gynaecology, Mount Sinai Hospital PLM, University of Toronto, Toronto, Ontario, Canada
[2]Division of Fetal Intervention, Department of Obstetrics, Gynceology and Reproductive Sciences, The University of Texas Health Science Center at Houston, Houston, Texas, USA

Correspondence to
Dr Anthony Johnson; anthony.johnson@uth.tmc.edu

ABSTRACT

Congenital diaphragmatic hernia (CDH) is a rare heterogenous disorder with varying degrees of severity. Infant survival rates in high-income countries are approaching 80% in isolated CDH; however, over 50% will have long-term morbidities. Advanced antenatal imaging, including ultrasound and magnetic resonance imaging, has made it possible to prognosticate severity of CDH and to stratify risk when counseling expectant parents. Risk stratification can also better prepare healthcare teams to enable optimal neonatal management, and provide options for fetal intervention or, where legally permitted, pregnancy termination. Factors that may affect the immediate and long-term prognosis for CDH include prenatal diagnosis, gestational age at detection and delivery, side of the defect, presence of additional structural or genetic abnormalities, defect size, estimation of fetal lung volume, the extent of visceral herniation, and the delivery center's experience in caring for neonates with CDH. Optimizing the outcome for families and infants begins with an early prenatal diagnosis followed by referral to a diverse and inclusive multidisciplinary center with CDH expertise. Prediction of disease severity is supported by accurate fetal imaging and comprehensive genetic testing, and allows the care team to provide realistic outcome expectations during the counseling of expectant parents of all racial and ethnic backgrounds.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a rare disorder with an estimated prevalence of 2.3–2.6 per 10 000 births.[1 2] In countries with established tertiary treatment centers, 70%–80% of children born with isolated CDH survive. CDH is not a single clinical entity, but a heterogenous disorder with highly variable outcomes ranging from perinatal death to mild, if any, respiratory issues. Most (85%) diaphragmatic defects are left-sided, 13% are right-sided, and 2% are bilateral.[2] Reported mortality rates for CDH vary, with survival rates of ≥90% when only liveborn infants are considered compared with 30%–40% when prenatally diagnosed cases are included.[3–6] The latter figure accounts for the 'hidden mortality' associated with CDH, which includes fetal and early neonatal deaths as well as pregnancies that are terminated.[7]

Rates of neonatal death are higher in those affected by multiple congenital anomalies and syndromes than those with isolated CDH (45% *vs.* 29%).[7–9] With contemporary antenatal ultrasound (US) screening, 60%–70% of CDH cases are now detected antenatally, enabling early referral to experienced multidisciplinary centers which counsel families, optimize peripartum and neonatal care, and in recent years, provide an opportunity for fetal intervention in the most severe cases.[10]

Advanced antenatal imaging has made it possible to prognosticate severity of CDH and to stratify risk when counseling expectant parents. Risk stratification can also better prepare healthcare teams to enable optimal neonatal management, and provide options for fetal intervention or, where legally permitted, pregnancy termination.[10 11] Factors that may affect the immediate and long-term prognosis for CDH include prenatal diagnosis[4]; gestational age (GA) at detection[12]; laterality[13]; presence of additional structural or genetic abnormalities[14 15]; defect size,[16] which is indirectly assessed by US and magnetic resonance imaging (MRI) estimation of fetal lung volumes[17] and the extent of visceral herniation[18]; GA at delivery[19 20]; and the delivery center's experience in caring for neonates affected by CDH.[21]

This review aims to highlight the components of prenatal diagnosis that may play a role in risk stratification in pregnancies complicated by CDH.

PRENATAL DETECTION

In high-income countries, the incorporation of US into routine obstetric care has significantly increased the rates of prenatal detection of CDH from 15% to over 60%,[22 23] which is likely a contributing factor to enhanced postnatal survival.[24]

GA at diagnosis is a likely determinant of CDH mortality. Previous studies have reported prenatal diagnosis prior to 25 weeks as being indicative of a poor prognosis.[25 26] Other reports have not found GA at diagnosis

to be a significant predictor of perinatal outcome,[27 28] however those studies were small and treated GA as a categorical, rather than continuous variable. In an analysis of 377 cases of prenatally diagnosed isolated left and right CDH, mortality rates at 28 days and at 6 months of age differed significantly based on the trimester in which the diagnosis was made. At 28 days of life, mortality rates for CDH detected in the first, second, and third trimesters were 61%, 39%, and 10% ($p<0.001$), respectively and this difference was maintained at 6 months of age. Earlier GA at detection also correlated with higher rates of respiratory morbidity and a greater need for patch repair.[29]

The impact of CDH laterality on outcome remains controversial. Increasing evidence suggests that right-sided CDH (RCDH) is not simply a variant of left-sided CDH (LCDH) with a similar response to treatment.[13 30] Several reports have suggested a worse prognosis for RCDH,[31 32] while others have found no difference or even better outcomes in RCDH compared with LCDH.[33] Higher perinatal morbidity may be partly related to later GA at diagnosis and to a larger defect. In the absence of intrathoracic herniation of the stomach, and due to the sonographic similarity of the fetal liver and lung, RCDH goes undetected more often than LCDH.[4 34] RCDH usually have larger defects than LCDH, with nearly all cases having liver herniation. When corrected for defect size and liver herniation, RCDH does not appear to have a higher mortality than LCDH.[34 35]

MALFORMATIONS ASSOCIATED WITH CONGENITAL DIAPHRAGMATIC HERNIA

Additional structural and/or genetic anomalies may be seen in 25%–60% of CDH cases,[14 36] which can substantially influence perinatal outcome.[5 37] The most frequently associated anomalies involve the cardiovascular system, followed by urogenital, limb, orofacial, and gastrointestinal malformations.[15 38] Accumulation of fluid in different body cavities may also be seen in CDH (e.g., pleural or pericardial effusions, skin edema), but these do not appear to affect survival.[39] Intrathoracic herniation of the stomach, seen more often in LCDH, may result in kinking of the distal esophagus, which can compromise fetal swallowing, resulting in polyhydramnios. Although a risk factor for prematurity, earlier studies have not consistently found polyhydramnios to be associated with perinatal outcome in LCDH.[40–43]

All fetuses with prenatally diagnosed CDH should undergo a detailed anatomical survey and echocardiogram, with referral to a tertiary care fetal medicine center that has expertise in CDH.[3 44] Differences in predicting CDH severity and detecting additional anomalies occur frequently between referring centers and fetal surgery centers.[6] Of note, 'isolated' CDH can only truly be ascertained after birth, as additional anomalies may be detected in up to 4% of cases postnatally.[11]

GENETICS

A detectable genetic etiology will be found in 30%–57% of CDH cases with multiple anomalies (i.e., complex/syndromic cases). Routine chromosomal analysis in CDH can detect a chromosomal abnormality in up to 10% of cases, most commonly trisomy 18 and isochromosome 12p (Pallister-Killian syndrome) in addition to trisomies 13 and 21. Commonly associated syndromes also include Cornelia de Lange syndrome, Donnai-Barrow syndrome, Fryn's syndrome, Denys-Drash syndrome, craniofrontonasal syndrome, Beckwith-Wiedemann syndrome, CHARGE syndrome, Simpson-Golabi-Behmel syndrome, and Wolf- Hirschhorn syndrome.[45 46] Chromosomal microarray (CMA) with targeted next-generation sequencing can detect pathological and likely pathological variants, which occur in 9%–13% of suspected 'isolated' CDH cases.[47] The expanded use of single gene testing, gene panels, exome sequencing, and family trio whole exome sequencing (WES) has been shown to identify a genetic etiology in over 30% of non-isolated, prenatally detected CDH cases.[48] WES can be concurrent or sequential with trio (parental) testing preferred over fetal-only testing, due to the high rate of de novo sequence variants in both complex and isolated CDH.[47] Postnatally, whole genomic sequencing (WGS) has been used as second-line or third-line testing when prior testing has been negative. Recent reports have found that WGS provides incrementally more accurate and likely more cost-effective genetic information in fetuses with structural malformations, including CDH, and may replace CMA and karyotyping as first-line for prenatal diagnosis.[49 50] Until then, comprehensive genetic evaluation should include CMA, with consideration of WES where available, as part of prenatal risk assessment.[51 52]

Once structural and genetic abnormalities have been excluded, the neonatal prognosis in 'isolated' CDH is based primarily on estimation of the severity of pulmonary hypoplasia (PH), pulmonary hypertension (pHTN), and cardiac dysfunction, the triad of factors that determine the severity of CDH.[17 31] In the sections that follow, we will discuss each factor and the prenatal imaging modalities and metrics that are currently used to quantify them.

PREDICTION OF PULMONARY HYPOPLASIA

Ultrasound

Metkus *et al.* first described the sonographic prediction of PH by obtaining the area of the lung contralateral to the diaphragmatic defect and the fetal head circumference, to determine the lung-to-head ratio (LHR), with severe hypoplasia defined as an LHR of <1.[26] Subsequently, in a study of normal lung growth in 650 fetuses, Peralta *et al.*, demonstrated a fourfold increase in lung size compared with head circumference with advancing GA.[53] To account for this exponential growth in normal fetal lung volume, the observed-to-expected LHR (o/e LHR) was subsequently introduced by Jani *et al.*, which is

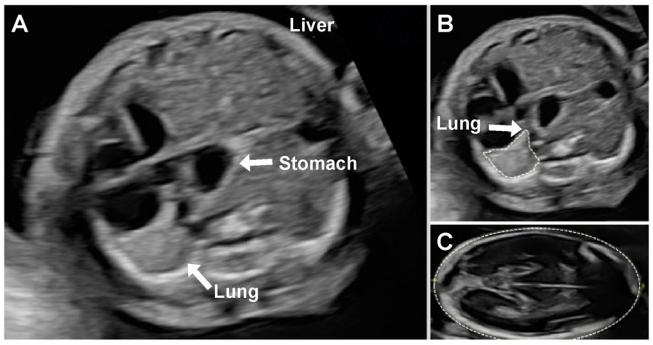

Figure 1 (A) Prenatal ultrasound image of left congenital diaphragmatic hernia with intrathoracic stomach and liver herniation on axial view. (B) Lung area obtained by trace method for determination of the lung-to-head ratio. (C) Head circumference, which is measured in the standard biparietal view. These measurements are typically acquired at 24–32 weeks' gestation.[32 61 62]

independent of GA and expresses the observed LHR as a percentage of the expected mean LHR for a given GA.[32]

Systematic reviews and meta-analyses have found that a threshold o/e LHR of <25% is associated with a postnatal mortality OR of 11.98 (95% CI 4.64 to 30.89) and mortality >70%.[54 55] In practice, severe hypoplasia in LCDH is defined as an o/e LHR of ≤25%; moderate hypoplasia as an o/e LHR of 25%–34.9% or 35%–44.9% with liver herniation, with postnatal survival rates of approximately 40%–60%, and mild hypoplasia as an o/e LHR of >45% or an o/e LHR of 35%–45% in the absence of liver herniation, with postnatal survival approaching 65%–90%.[32 56] Severe hypoplasia in RCDH is predicted by an o/e LHR <50%.[31] A reduced o/e LHR is also associated with significant neonatal morbidity, including greater use of extracorporeal lifet support (ECLS), need for prosthetic patch repair, prolonged duration of assisted ventilation, need for supplemental oxygen at 28 days, and incidence of feeding problems.[57 58]

Although o/e LHR has become the most commonly used screening tool for outcome prediction, it should be noted that variability in lung area measurement methods, experience, and the specific formula used influence the accuracy of o/e LHR for prognosticating outcomes in CDH.[59 60] The preferred method for measuring lung area involves tracing of the lung perimeters (figure 1), as this is more reproducible than other methods, including both the longest and anterior-posterior diameter methods, which can overestimate lung area by 45% and 35%, respectively.[61] Moreover, the calculator used for the Tracheal Occlusion for To Acclerate Lung grow (TOTAL) trial should be used to determine o/e LHR, to ensure that consistent reference standards for determination of expected lung areas are used. As there is a significant learning curve for reliably measuring o/e LHR,[62] it is recommended that this assessment be performed in experienced centers, where its predictive value may be better compared with smaller, less experienced centers.[59]

Additional methods of assessing lung volume have been proposed, including lung-thorax (L/T) ratio,[62–64] three-dimensional (3D) US,[65] quantitative lung index (QLI),[66] and mediastinal shift angle (MSA).[67] The L/T ratio is independent of GA and has a linear correlation with the o/e LHR, such that an o/e LHR threshold of <25% is comparable to an L/T ratio cut-off of <0.08.[63 64] A systematic review and meta-analysis of the five studies of L/T ratio found a predictive OR of mortality of 10.28 (95% CI 3.38 to 31.31).[55 63 64] The ratio has been used primarily in Japan and has yet to be validated in other countries as a predictor of perinatal outcome in prenatally diagnosed CDH. The use of 3D US to predict total fetal lung volume has proven to be inadequate in obtaining ipsilateral lung measurements in >40% of cases.[17 65] Further studies are needed to evaluate the clinical accuracy of L/T ratio, QLI, and MSA as prognostic indicators in CDH.[66 67] We recommend that o/e LHR be used in counselling as it is the most widely studied and validated US predictor of postnatal CDH outcomes.

Liver position: up or down

In addition to reduced o/e LHR, intrathoracic liver herniation (ILH) is a well-established predictor of perinatal mortality in LCDH.[28 54 68] In a systematic review and meta-analysis of 20 studies including >700 fetuses with CDH, survival was significantly lower in fetuses when liver herniation was documented by either US or MRI (45.4% *vs.* 73.9% p<0.005).[68] US assessment of the degree of ILH is feasible, however reproducibility of accurate measurements is limited due to the similar echogenicity of lung and liver.[28] ILH by US has been primarily reported as a binary variable, 'up' (intrathoracic) or 'down' (intra-abdominal). Intrathoracic stomach herniation (ISH) indirectly approximates ILH,[69 70] which, as a screening tool, can serve as a surrogate for quantifying ILH in LCDH, with progressive ISH displacement being associated with more ILH.[71 72] There is a linear association between the degree of ISH and mortality, ECLS use, need for prolonged mechanical ventilation, and respiratory support.[68 73–76] ILH in RCDH has not been shown to be predictive of outcome, as liver herniation is present in essentially all such cases.

Quantitative liver herniation

When compared with dichotomous reporting of liver herniation as 'up' or 'down' in LCDH, quantifying the percentage of liver herniation (%LH) (figure 2) or liver/thoracic volume ratio (LiTR) by MRI has proven superior in predicting survival and need for ECLS.[73] When MRI and US parameters were compared, the best combination of measurements for prediction of mortality were observed-to-expected total fetal lung volume (o/e TFLV), discussed below, with %LH.[74] Furthermore, MRI parameters (including o/e TFLV and %LH) were found to have greater sensitivity and specificity for the prediction of mortality when compared with US-derived parameters (including LHR and o/e LHR).[77]

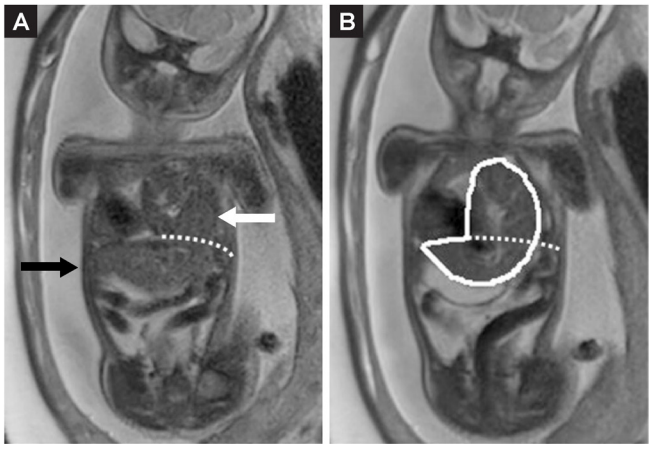

Figure 2 Percentage of liver herniation is defined as the volume of liver herniating into the thoracic cavity (white arrow) divided by the total liver volume.[74]

A %LH >21% is associated with higher mortality and a greater need for ECLS, with an accuracy of 87% and 79%, respectively. LiTR >14% is associated with greater mortality and ECLS use, with an accuracy of 85% and 72%, respectively.[73] Chronic lung disease is strongly predicted by %LH (OR=10.96, 95% CI 2.5 to 48.9, p=0.002) and, when combined with o/e TFLV, %LH predicts mortality or need for ECLS better than all other MRI and US parameters.[74 77–79]

Magnetic resonance imaging

Over the past decade, MRI has become complementary to US for antenatal prognostication of CDH in most referral centers. MRI allows for more accurate imaging of most fetal structures than US because of its superior tissue contrast, wider field of view, and image quality that is independent of maternal body habitus, fetal position, or abnormalities of amniotic fluid. MRI provides a more reliable measurement of lung area, especially on the ipsilateral side, for assessing the TFLV, that is, the sum of both lung volumes (figure 3). The methodologies, techniques, and formulae used to assess fetal lung volume on MRI vary.[80] MRI can assess fetal lung volume with TFLV, o/e TFLV, or per cent predicted lung volume (PPLV).[81–83] Systematic reviews and meta-analyses have found that o/e TFLV performs well in predicting perinatal mortality, with area under the curve (AUC) of 0.8.[54] An o/e TFLV threshold of <25% for predicting perinatal mortality has an OR of 11.14 (95% CI 5.19 to 23.89).[54 82] The optimal window for MRI in the prenatal risk assessment of CDH is generally prior to 30 weeks of gestation, with the ideal timing falling between 25 and 28 weeks' gestation, especially if there is the option for fetal intervention.[83–85] The value of serial MRI remains unclear. Some studies have suggested that MRI should be repeated >30 weeks due to the finding of progressive reduction in lung volumes with advancing GA.[86 87] Others have found no difference in the predictive value of MRI when comparing early (<28 weeks) and late (>32 weeks) gestational ages.[88]

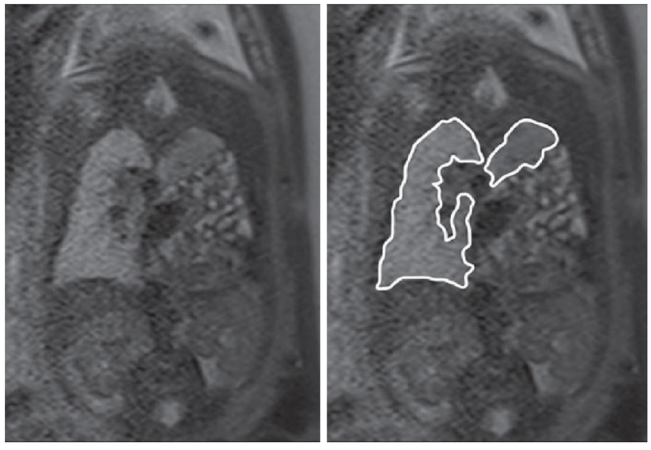

Figure 3 Total fetal lung volume is defined as the sum of both lung volumes measured by MRI (as traced in this image).[82–85]

PPLV is the sum of the right and left lung volumes divided by the predicted lung volume, multiplied by 100. A PPLV <15% is associated with a greater use of ECLS, longer hospital length of stay, and a 60% mortality rate.[80 82 86] PPLV decreases throughout pregnancy in fetuses with CDH.[82] A meta-analysis found that PPLV effectively predicted mortality (overall effect 3.95, p<0.001), but was less discriminatory than o/e TFLV. While not all studies have agreement, a growing body of evidence indicates that o/e TFLV is a better discriminator of survival than PPLV and predictor of respiratory morbidity up to 2 years of age.[31 81 83 89 90] Ruano *et al.* reported a good association between o/e TFLV and PPLV in predicting mortality with no statistical difference between the techniques; however, o/e TFLV combined with %LH was found to be the most accurate in predicting mortality and need for ECLS.[74]

Right-sided versus left-sided CDH

Compared with LCDH, the threshold for the prediction of severe PH using o/e LHR (on US) is higher but inconsistent between reports, which may reflect the comparatively small numbers of cases. The initial reports from the Eurofetus antenatal CDH registry found that survival with an o/e LHR ≤45% was 17% (3/18), compared with 69% (18/26) in cases with an o/e LHR >45%.[91] A recent European report involving 86 expectantly managed RCDH cases further affirmed that the o/e LHR threshold for predicting mortality is higher in RCDH versus LCDH. With an AUC of 0.77 (95% CI 0.64 to 0.89), the best cut-off for mortality prediction was an o/e LHR >50% (sensitivity 78%, specificity 72%).[31] In a single US center study of 24 cases of prenatally detected RCDH with an overall survival of 60%, o/e LHR, o/e TFLV, and liver herniation were not predictive of outcome.[90] Similarly, a recent report from the CDH study group (CDHSG) did not identify an o/e LHR threshold that was predictive of survival in RCDH, but did find that ECLS use was more common in neonates with a fetal o/e LHR <45% (60%) *vs.* fetal o/e LHR ≥45% (29%; p=0.0027).[33] ILH has not

Table 1 Prenatal imaging parameter thresholds for prediction of mortality in expectantly managed cases of CDH

Prenatal marker	Cut-off	Mortality (%)
o/e LHR (on US)		
LCDH[54 55 120]	<25%	50–70
RCDH[31]	<50%	80
L/T ratio on US[63]	<0.08%	53
o/e TLFV (on MRI)[55]	<25% <35%	75–100 30–75
PPLV (on MRI)[80 82 86]	<15%	60–87
Liver herniation on MRI[73 74]	>21%	20–52.4
Combined (on MRI)		
o/e TFLV with liver herniation[121]	<35% with liver 'up'	75
o/e TFLV %LH[78]	<32% and >21%	52
Stomach herniation (on US)[122]	Grade 3/ Retrocardiac	61
GA at delivery[19 20]	<32 weeks	52–68

GA, gestational age; LCDH, left-sided congenital diaphragmatic hernia; LH, liver herniation; L/T, lung-thorax; L/T ratio, lung to thorax; o/e LHR, observed-to-expected lung-to-head ratio; PPLV, per cent predicted lung volume; RCDH, right-sided CDH; TFLV, total fetal lung volume; US, ultrasound.

been found to be a predictive parameter prenatally in RCDH, since liver herniation is present in essentially all cases.

The reported thresholds for prediction of mortality of the various prenatal US and MRI parameters are listed in table 1.

PREDICTION OF PULMONARY HYPERTENSION

Given the importance of pHTN in determining postnatal outcome, there has been interest in determining whether its severity could be predicted prenatally using a variety of fetal pulmonary artery vascular Doppler measurements.[42 92–96]

Pulmonary vascular index of the contralateral lung determined by 3D power Doppler has been reported to be significantly lower in fetal CDH cases that end with perinatal death or severe pHTN, however, these findings have not been reproducible. [92] Measurement of the proximal main, right and left pulmonary artery diameters were found to be predictive of perinatal death but not postnatal pHTN.[93] Spectral Doppler intrapulmonary artery (IPA) indices, specifically pulsatility index (PI) and peak early diastolic reversed flow have been shown to be predictive of survival and neonatal morbidity in fetuses with severe CDH that undergo fetal tracheal occlusion.[94 95] A multicenter retrospective report found that IPA Doppler in combination with o/e LHR was predictive of neonatal outcome in mild and moderate LCDH. Increased IPA PI was associated with an increased risk of mortality, pHTN, and the need for oxygen supplementation at discharge, with an OR of 3.96 (95% CI 1.62 to 9.70); 2.20 (95% CI 1.01 to 4.59); and 1.90 (95% CI 1.10 to 3.40), respectively. When combined with o/e LHR, the AUC was 0.917 for the prediction of pHTN.[96] A recent meta-analysis by Russo *et al.* found that Doppler and US assessment of pulmonary vascular indices for the prediction of pHTN has yet to be proven beyond small single-center series, with variability in technique and gestational timing of measurement as well as inconsistent findings. Further work is needed to derive and validate fetal vascular Doppler measurements as potential antenatal predictors of pHTN.[57]

CARDIAC PARAMETERS

Fetuses with CDH are at risk of developmental cardiac chamber abnormalities, particularly left ventricular hypoplasia, with resultant right and left ventricular dysfunction after birth. There is growing evidence that cardiac dysfunction is a major contributor to the pathophysiology of CDH. It is unclear whether the morphological cardiac changes are part of the primary embryological disorder or whether they are secondary to redistributed cardiac flow in utero and/or cardiac compression from visceral herniation. Postnatal ventricular disproportion and ventricular dysfunction have been associated with increased mortality and an increased need for ECLS,[97 98] however, there is not a consistent relationship between fetal cardiac dimensions and outcome. Some studies have found an association between pHTN severity with fetal echocardiographic evidence of right ventricular enlargement and left ventricular hypoplasia, which are both predictors of overall prognosis and outcome,[99–101] while others have not replicated this correlation.[102 103] Further research is needed to determine which fetal cardiac parameters may be beneficial in predicting neonatal outcome in prenatally diagnosed CDH.

RISK STRATIFICATION

Models based on known risk factors for CDH have been developed by various groups, including the CDHSG, the Canadian Neonatal Network, and the Japanese CDH study group for risk stratification of severity to predict neonatal mortality and morbidity.[104–106] Combining prenatal and postnatal markers have been shown to be predictive of long-term outcomes,[107] however, all of these systems depend on early neonatal assessment. To enable feasible antenatal counseling, to prepare healthcare teams for delivery and neonatal care, and to evaluate candidacy for fetal intervention, strategies for the accurate prenatal assessment of CDH severity are needed.[108]

Combining prognostic parameters may improve prenatal risk stratification. A review of 81 cases of isolated CDH that had undergone MRI and US reported that the combination of o/e TFLV and %LH best predicted neonatal mortality and the need for ECLS.[74] Subsequently,

that center proposed a classification of severity based on a combination of these imaging parameters at different thresholds. Mild disease was predicted by an o/e TFLV >32% and %LH <21%. Moderate disease was predicted by either TFLV >32% with %LH >21% or TFLV <32% with %LH <21%. Severe CDH was predicted by TFLV <32% and %LH >21%.[74 109]

Other investigators have reported better prediction of neonatal survival and long-term morbidity by combining multiple prenatal imaging parameters. A proposed risk stratification system based on a retrospective multicenter analysis of an isolated CDH cohort, combined US markers of L/T ratio (threshold <0.08) and ILH (threshold >1/3) to predict neonatal mortality at 90 days of age: OR=9.34 (95% CI 1.92 to 70.2, p=0.011) and 8.28 (95% CI 2.33 to 33.3, p=0.002), respectively. Stratifying cases into 'low' (neither threshold is met), 'moderate' (one threshold is met), and 'high risk' (both thresholds are met) yielded mortality rates of 0%, 20%, and 65%, respectively, with ECLS use in 2.1%, 14.3%, and 40% of neonates, respectively.[41]

An alternative prenatal risk stratification model has been proposed that uses calculated ORs from five US parameters that have been reported to be associated with poor outcomes.[110] The prenatal risk factors with weighted scores include: o/e LHR <25% (+1), intrathoracic herniation of either the liver (where it occupies one-third of the thoracic space) (+1) and/or stomach (+1), RCDH (+2), and presence of other severe malformations (cardiac, central nervous system, or ventral wall defects) (+3). Exclusion criteria include: chromosome abnormalities, bilateral CDH, and cases treated with fetal endoluminal tracheal occlusion (FETO). Adverse neonatal outcomes were defined as death within 90 days or hospitalization >180 days. The latter served as a surrogate to integrate the morbidities associated with prolonged hospitalization. Adverse outcome was scaled as 'low', (0–2 points), 'intermediate' (3–5 points), or 'high' (6–8 points).[110] All cases were treated aggressively (ie, without intentional palliation) following delivery. The model's prognostic performance was better than that of any single predictor; the C-statistic (ability of the model to rank patients from high to low risk) for derivation and validation datasets was 0.83 and 0.80, respectively. Observed rates of adverse outcome in predicted low, intermediate, and high-risk groups were 12%, 56%, and 100%, respectively, in the derivation dataset and 17%, 46%, and 100%, respectively, in the validation dataset (p<0.001).[110] As with each of the proposed predictive models, further prospective studies are needed to validate them.

While there is general agreement on the imaging parameters and their respective thresholds for predicting severity of CDH, an important determinant of predictive accuracy is the effectiveness of postnatal care and the potential contribution of non-standardization to observed outcome differences between centers.[111] This was highlighted recently in a response to publication of a 15% (6/40) survival rate in the expectantly managed 'severe' arm of the TOTAL trial.[10] In comparison, using the same o/e LHR threshold for severity, the North American Fetal Therapy Network (NAFTNet) FETO Consortium cohort study reported a survival rate of 58% (25/43) in expectantly managed severe cases.[112] Acknowledging that the NAFTNet cohort was non-randomized, there are other potential explanations for the disparity in outcomes between the two 'severe' cohorts. In the NAFTNet study, prenatal care, delivery, and neonatal management for all patients (FETO and expectantly managed cases) were provided in 10 FETO centers with CDH expertise.[112] In contrast, the care for patients in the severe arm of the TOTAL trial was distributed across 10 FETO and 26 delivery/neonatal centers.[10] Additionally, there were postnatal differences in care between NAFTNet and TOTAL trial centers in terms of ECLS use (52% *vs.* 29%) and rates of non-repair (47% *vs.* 63%).[10 112] Systematic review and meta-analysis have shown that institutional integration of prenatal and postnatal care results in better survival rates in prenatally diagnosed severe CDH.[113] Furthermore, aggressive surgical management, with higher rates of surgical repair, has been shown to improve risk-adjusted mortality rates.[114]

Therefore, interpretation of the prediction of CDH severity by prenatal diagnosis should also take into consideration peri-operative and surgical management protocols and their degree of standardization.

ANTENATAL COUNSELING

Following the initial diagnosis of CDH, families begin a long emotional journey of dealing with an unknown and the subsequent trajectory is characterized by clinical parameters that may not be available at the first evaluation. Thus, avoidance of speculation on severity and outcome should be avoided with prompt referral to a CDH specialist center to minimize stress and the uncertainty burdening the expectant parents. The treatment center should have expertise in prenatal imaging modalities, including obstetric US, fetal echocardiography, and fetal MRI. In both isolated and non-isolated CDH, patients should be offered comprehensive genetic evaluation. Sufficient and thorough information is crucial to guide families in making informed decisions. Families should be provided with an understanding of the fetal condition, neonatal risks, and immediate and long-term outcomes. This should include center-specific outcomes, as each center has its own unique practices and experiences. The integration of a racially and ethnically diverse prenatal and postnatal team in both counseling and care results in a multidisciplinary care model that has been proven to improve survival outcomes and the overall satisfaction of these families with the experience of care.[113 115] CDH centers of excellence include a unique infrastructure with collaboration between fetal medicine, maternal medicine, pediatric surgery, neonatology, pediatric subspecialists, and nursing.[116]

The need for care coordinators, social workers, and access to psychosocial support should also be part of the standard of care in CDH and other complex prenatal diagnosis.[117] While most neonates do not benefit from ECLS, prenatally detected severe CDH cases show a significant survival benefit with ELCS use. Additionally, center experience and high case volume play a major role in improving outcomes.[118 119] If ECLS is not available at the planned birthing site of a high-risk CDH fetus, then transfer to a delivery center that can offer ECLS must be initiated. Risks and benefits of FETO should be included in the counseling and management options when discussing tailored treatment plans with families. If antenatal intervention is not provided at the treatment center, referral to a level III fetal center should be a consideration in cases which meet criteria.[116] Critical to antenatal counseling is the availability of center-specific outcomes. These require multidisciplinary and long-term surveillance of patients with CDH and transparency in reporting. Multidisciplinary clinics should include pediatric surgery, pulmonary medicine, gastroenterology, nutrition, and developmental specialists to address the long-term sequelae of CDH beyond the delivery unit.[113] Parents may choose to pursue expectant management, fetal therapy, pregnancy termination, active neonatal care, or palliation. Respecting parental preferences through unconditional acceptance of their choices and needs is the duty of the treatment center, regardless of the management approach selected.[113 116]

CONCLUSION

Prenatal risk stratification goes hand-in-hand with postnatal management of CDH. Despite improvements in prenatal detection and prognostication of CDH disease severity via fetal imaging and genetic testing, uncertainty remains regarding the accuracy of mortality predictions and the severity of morbidity in survivors. Optimizing the prenatal care of a fetal CDH pregnancy begins with an early diagnosis, followed by referral to a CDH center experienced in both fetal imaging and advanced genetic diagnosis to allow families to be counselled accurately and comprehensively. Although US alone supports accurate prenatal diagnosis, the current standard of prenatal CDH care includes fetal MRI assessments of lung volume and liver herniation as a means of refining the accuracy of prenatal prediction.

Although existing clinical practice guidelines for CDH management include recommendations for standardized prenatal diagnosis, there is a need for international consensus on imaging modalities and thresholds for risk stratification. Additionally, there should be a commitment to validate these thresholds through outcome measurement in high-volume CDH centers of excellence that offer standardized care.

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ORCID iD

Anthony Johnson http://orcid.org/0000-0002-4450-1275

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