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Fetal imaging and therapy for CDH—Current status

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ABSTRACT

In congenital diaphragmatic hernia (CDH), herniation of the abdominal organs into the fetal chest causes pulmonary hypoplasia and pulmonary hypertension, the main causes of neonatal mortality. As antenatal ultrasound screening improves, the risk of postnatal death can now be better predicted, allowing for the identification of fetuses that might most benefit from a prenatal intervention. Fetoscopic tracheal occlusion is being evaluated in a large international randomized controlled trial. We present the antenatal imaging approaches that can help identify fetuses that might benefit from antenatal therapy, and review the evolution of fetal surgery for CDH to date.

Background

Congenital diaphragmatic hernia (CDH) occurs in 1 in 2000–5000 live births.[1] Herniation of abdominal organs into the fetal chest leads to pulmonary hypoplasia and pulmonary hypertension (due to exaggerated muscularization of the pulmonary vasculature),[2] which are the main causes of morbidity and mortality. For isolated CDH, current survival rates fluctuate around 70%,[3] whereas older studies reported survival rates as low as 40%.[4]

As antenatal ultrasound (US) imaging improves, more CDH cases are diagnosed before birth, and the risk of postnatal death can now be predicted prenatally for individual fetuses. This allows the identification of fetuses that are likely to have a particularly poor postnatal outcome and that might benefit from a prenatal intervention.

We review the antenatal imaging strategies that can be employed, and discuss how fetuses can be appropriately selected for antenatal therapy.

Patient selection for fetal surgery

As any fetal intervention carries a risk of preterm premature rupture of the membranes (PPROM) and preterm birth, most studies have only assessed these interventions in fetuses with a very poor prognosis, as any potential benefits might not outweigh the risks in less severe cases of CDH, which would have a better long-term outcome. A number of parameters have been evaluated to try and predict the prognosis in fetuses with CDH.

Liver herniation

Liver herniation can be assessed antenatally, both by US and magnetic resonance imaging (MRI). Various meta-analyses have shown liver herniation to be a predictor of neonatal mortality.[5,6] Although herniation is usually categorized on US as being either "liver up" or "down," several investigators have tried to quantify the degree of herniation using MRI.[7,8] Victoria et al.[9] investigated the "%HL" as the ratio of hepatic volume above the diaphragm to total liver volume. Ruano et al.[10] showed that intra-thoracic liver herniation quantified by %HL (with a threshold of 21%) performed well in predicting neonatal mortality (AUC = 0.912, accuracy 77%), while liver intra-thoracic ratio (LiTR), the ratio of herniated liver volume to total thoracic volume (using a threshold of 14%) also performed well in predicting neonatal mortality (AUC = 0.72, accuracy 77%). Cannie et al.[8] showed an additive value of LiTR, when combined with MRI estimation of lung volume, in predicting neonatal mortality.

(Absolute) lung-to-head ratio (LHR) and observed to expected LHR (o/e LHR)

The most common, and best validated, US method for estimating lung size is the LHR, defined as the area of the lung, contralateral to the diaphragmatic defect, measured at the level of the four chamber view, divided by the head circumference (HC) (Figure). Historically, the sonographic LHR as described by Metkus et al.[11] has been used to assess fetal lung volume, using thresholds of 0.6 (for extreme lung hypoplasia), 1.0 (for severe hypoplasia), or 1.4 (for moderate to mild hypoplasia) to predict neonatal outcome.[6,11–17] A number of meta-analyses have shown that a LHR threshold of < 1.0 (when measured at approximately 24 weeks' gestation) was a good predictor of neonatal mortality in isolated CDH.[6,18]

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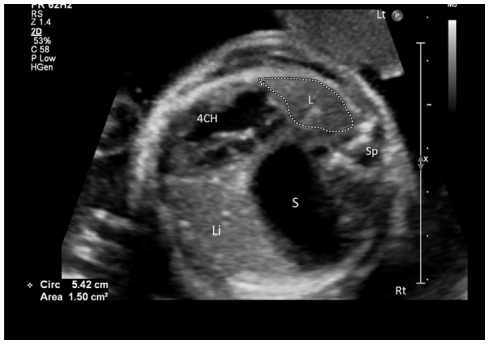

Fig. Lung-to-head ratio. 4CH, 4 chamber view of the heart; L, lung; Li, liver; Lt, left; Rt, right; S, stomach; Sp, spine.

A number of factors may affect the accuracy of LHR measurement, including technique and operator experience. Peralta et al. noted that multiplying two perpendicular lung diameters, as originally described by Metkus, may systematically overestimate the LHR. They proposed a more reproducible method of measuring lung area, by tracing the lung contour.[19]

Using cumulative sum analysis to monitor learning curves and competence over time, Cruz-Martinez suggested that approximately 70 US examinations would be required to establish competence in measuring LHR. They suggested that differences in operator competence might be one of the contributors to the variability noted amongst LHR prediction and CDH outcome studies.[20]

As LHR increases with gestation, crude LHR measurements were not found to be comparable at different gestational ages (e.g., whereas a LHR of 1.0 is normal at 16 weeks, it would predict severe lung hypoplasia at 32 weeks' gestation). Therefore, to compensate for the effect of gestational age, the observed LHR was normalized by dividing it by the expected value for that gestation.[21] The observed/expected or "o/e LHR" does not change significantly with gestational age and thus allows comparison at different stages of pregnancy. An o/e LHR of 25% is equivalent to an "absolute" LHR threshold of 1.0 at 24–26 weeks.[21] A recent meta-analysis and review showed a statistically significant difference between o/e LHR of CDH survivors versus non-survivors, suggesting that o/e LHR was a good predictor of neonatal mortality. The best test performance for o/e LHR was when it was measured using a trace method (AUC = 0.85).[6] This review also found that survival with an o/e LHR < 25% ranged from 12.5% to 30%, while survival ranged from 65% to 88% for fetuses with o/e LHR > 35%.

Another, less validated method of normalizing LHR for gestational age is the quantitative lung index (QLI), as there was some concern that even the o/e LHR could vary somewhat with gestation. Quintero et al. argues that LHR is dependent on gestational age, because lung measurement is an area (2nd order polynomial), whereas HC is linear (1st order polynomial). It is, therefore, hypothesized that since the LHR is a division of 2 polynomials of different order, lung area will increase faster than HC. The QLI (contralateral lung area/(HC/10)^2 attempts to overcome this deficiency in LHR, and was found to remain relatively stable at a QLI value of ~1.0, between 16 and 32 weeks' gestation.[22] Lung hypoplasia (≤ 1st percentile) is defined as a QLI 0.6.[22] Ruano et al.[23] found that US QLI, US o/e LHR, and MRI o/e total fetal lung volume (TFLV) were all predictive of neonatal mortality (p < 0.001, AUC: 0.79–0.82), but QLI had the lowest accuracy of the three parameters (71%).

Three-dimensional lung measurements (3D US and MRI TFLV)

Several studies have evaluated the ability of 3D US to predict neonatal mortality in CDH. Most have shown that 3D US has some prognostic value in prenatally diagnosed CDH. Multiple authors have shown that 3D US can reliably measure lung volume (LV), particularly that of the contralateral lung.[24–27] When compared to other imaging modalities, 3D US performed fairly well in predicting neonatal mortality,[26,28] but factors such as rotational angles[26] and operator experience[29] may affect the accuracy of LV assessment. Ruano et al. reported that a threshold of 0.35 for o/e 3D LV best predicted neonatal mortality.

Pulmonary artery parameters

Some authors have evaluated the predictive ability of fetal pulmonary artery (PA) parameters in CDH, based on the concept that intrapulmonary circulation is altered in fetuses that develop pulmonary hypoplasia. Several studies have shown that small pulmonary artery diameters[30] and increased resistance on Doppler US correlate with postnatal mortality, however, these were not superior to LHR in predicting survival.[31] Cruz-Martinez[32] suggested that Doppler indices, when combined with LHR, allowed discrimination between fetuses with good versus poor prognosis, after fetal tracheal occlusion (FETO).

Other Doppler parameters, including fractional moving blood volume (FMBV) and hyperoxygenation tests (pulmonary artery Doppler response to maternal hyperoxia) have been investigated as predictors of neonatal mortality. FMBV is a quantitative method that expresses the percentage of power Doppler signals and colored pixels (i.e., moving blood) in a well-defined region. An increase in FMBV of 30%, in combination with an increase in LHR, was significantly predicted survival after FETO.[33] Conversely, hyperoxygenation[30,34–36] has shown contradictory results in predicting neonatal outcome, with one study[37] showing positive, but another showing negative results.[38]

Stomach position

Stomach position (as an indicator of liver herniation)[39] was found in some studies to be predictive of neonatal outcome.[40] Different quantification methods have been used to assess its prognostic ability. Most have reported that the quantity (and location) of stomach in the chest was predictive of neonatal outcome. A summary of relevant studies, with their classifications, shown in Table 1.

MRI

MRI has some potential advantages over US in imaging fetal lung tissue. Since the lung is primarily composed of water, on T2

Table 1
Stomach herniation and grading systems.

Study	Grading of stomach herniation
Basta et al.[41]	Anterior left chest (fetal stomach contacting the anterior chest wall) Mid-to-posterior left chest (fetal stomach not contacting the anterior left chest wall) Retrocardiac (a portion of the stomach located posterior to the left cardiac atrium)
Cordier et al.[40]	Grade 1: 94% survival Grade 2: 96% survival Grade 3: 66% survival Grade 4:12% survival
Kitano et al.[42]	Grade 0 Grade 1 OR: 6.3 (0.8–52.1) Grade 2 OR: 13.3 (1.4–127.6) Grade 3 OR: 95.0 (9.7–928.3)