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Review

Novel non-surgical prenatal approaches to treating congenital diaphragmatic hernia

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SUMMARY

This review focuses on the emerging field of non-surgical in-utero therapies in the management of fetal pulmonary hypoplasia and pulmonary hypertension associated with congenital diaphragmatic hernia (CDH). These experimental approaches include pharmacologic as well as stem-cell-based strategies. Current barriers of non-surgical therapies toward clinical translation are emphasized. As the severity of CDH will likely influence the efficacy of any in-utero therapy, the current status of prenatal imaging and the role of novel biomarkers, especially those related to fetal inflammation, are also reviewed.

1. Introduction

Despite improvements in perinatal care, there is still significant morbidity and mortality in infants with congenital diaphragmatic hernia (CDH) [1]. Based on data from the CDH Study Group, the survival rate of CDH has remained stable at ~70% over the past decade [1]. Among survivors, the pulmonary morbidity associated with this disease can be quite significant, as validated by the spawning of multidisciplinary clinics involving surgeons, pulmonologists, and other specialists at major children's hospitals across the USA.

Pulmonary hypoplasia and perhaps more importantly, pulmonary hypertension, are the major aberrations associated with poor outcomes in CDH. Numerous fetal surgical interventions have been attempted in an effort to alter the natural history of lung development in these infants. For more than a decade, minimally invasive (fetoscopic) tracheal occlusion has been shown to augment fetal lung growth prenatally in experimental animal models [2] and in human clinical trials [3]. However, the procedure is limited by the steep learning curve, device availability for effective occlusion and release, and pregnancy complications such as premature delivery [3]. Moreover, the precise effect of tracheal occlusion on pulmonary vascular development is poorly defined, and not all fetuses with CDH, such as those with severe congenital heart disease, are eligible for the procedure. Thus, antenatal non-surgical approaches to promote lung growth continue to be appealing options for the prevention and treatment of pulmonary hypoplasia and pulmonary hypertension before birth.

2. Prenatal pulmonary hypoplasia and pulmonary hypertension

Since the severity of lung hypoplasia will likely influence the efficacy of non-surgical in-utero therapy, an accurate prenatal assessment of the degree of pulmonary hypoplasia and pulmonary hypertension is essential. Fetal imaging by ultrasound, magnetic resonance imaging (MRI), and echocardiography has been studied in CDH, and parameters have been identified for risk stratification of these fetuses (Box 1).

2.1. Ultrasound and MRI

Ultrasound parameters have been explored to estimate the degree of pulmonary hypoplasia including two-dimensional measurements such as lung-to-head ratio (LHR), three-dimensional measurements such as total fetal lung volume or contralateral lung volume, and the position of the liver and stomach [4,5]. The oldest and most widely used measurement is the LHR, with values <1 associated with a higher risk of death, need for ECMO, and pulmonary hypertension at one month, whereas values >1.4 are associated with more favorable outcomes [6]. Whereas the LHR must be measured between 22 and 26 weeks of gestation, the observed-to-expected LHR (O/E LHR) is not dependent on gestational age, and

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Box 1
Prenatal markers used for stratification of congenital diaphragmatic hernia severity.

Ultrasound
Lung to head ratio
O/E lung to head ratio
O/E contralateral fetal lung volume
O/E total fetal lung volume
Fetal lung volume to fetal weight ratio
Liver herniation
Stomach position
MRI
Fetal lung volume to fetal body volume ratio
% predicted lung volume
O/E total fetal lung volume
O/E right lung volume
% liver herniation
Liver to thoracic volume ratio
Combined ultrasound and MRI
Right lung volume (MRI) to body weight (ultrasound) ratio
Echocardiography/Doppler ultrasound
Pulmonary artery diameter
Modified McGoon index
Cardiac axis (measure of mediastinal shift)
No. of pulmonary artery divisions
O/E contralateral pulmonary artery diameter
O/E main pulmonary artery diameter
Contralateral vascularization index
Amniotic fluid
Lamellar body count
Cord blood
Inflammatory mediators and growth factors
O/E, observed to expected; MRI, magnetic resonance imaging.

values less than ~20% correlate with death [5]. The position of the liver and stomach has also been used to stratify patients with CDH [4]. Liver herniation into the thoracic cavity increases the risk of death almost 7-fold, and stomach herniation, which can be graded based on the thoracic component, results in a 2.5-fold higher risk of death with increasing degrees of intrathoracic content [4]. Several authors have developed stratification systems based on ultrasound parameters that correlate with outcomes [4,5].

Volumetric measurements of the lung, liver, and thoracic cavity obtained with MRI have been assessed to stratify patients with CDH. The more widely used parameters are observed-to-expected total fetal lung volume (O/E TLV), percent predicted lung volumes (PPLV), and percent liver herniation, which have been found to correlate with survival, need for ECMO, and development of chronic lung disease [7–9]. A cut-off of 21% for liver herniation results in a sensitivity and specificity of 72% and 79%, respectively for predicting survival [8]. MRI and ultrasound measurements have been compared to one another [10]. In a study examining the ultrasound parameters LHR and O/E LHR, and MRI parameters O/E TLV and percent liver herniation, MRI parameters had better sensitivity and specificity for predicting survival at clinically used cut-off values than ultrasound [10].

2.2. Echocardiography

Although the degree of pulmonary hypoplasia is often correlated with the severity of pulmonary hypertension, there can be discordance with implications on postnatal lung function and clinical outcomes. Moreover, some novel pharmacologic agents specifically target the pulmonary vasculature but likely have little effect on pulmonary parenchymal growth. In an effort to more accurately quantify the degree of pulmonary hypertension, echocardiogram with Doppler ultrasound of the pulmonary vasculature have been studied antenally. Enumeration of the pulmonary artery divisions is one method used to assess pulmonary vascularization. Patients with fewer than three divisions identified have a 14-fold higher risk of death than those with more pulmonary artery divisions [11]. The size of the pulmonary arteries has been evaluated as a surrogate for pulmonary hypoplasia. The modified McGoon index, which is the combined diameter of the hilar pulmonary arteries indexed to the descending aorta, has also been found to predict mortality with a sensitivity of 85% and specificity of 100% when $\leq$1.3 [12]. The observed-to-expected contralateral and main pulmonary artery diameters were found to be predictive of survival and pulmonary hypertension, as well as the contralateral vascularization index which is a measure of the pulmonary vascularization [5].

2.3. Practice points

- LHR is the most widely used ultrasonographic measure to stratify fetuses with CDH and values <1 associated with a higher risk of death, need for ECMO, and pulmonary hypertension at one month.
- MRI parameters have better sensitivity and specificity for predicting survival at clinically used cut-off values than ultrasound, though are more costly.
- Echocardiographic measurements of the pulmonary vasculature, such as the modified McGoon index, have a high sensitivity and specificity for predicting death in fetuses with CDH.

2.4. Novel biomarkers

Several biomarkers have been investigated to further stratify the severity of CDH. In one study examining amniotic fluid at birth, pulmonary maturity, as measured by the lamellar body count, was found to be higher in infants that survived compared to those who died [13]. The MacKenzie laboratory recently reported that the fetal inflammatory milieu of CDH patients differs from those without CDH at birth, and these factors correlate with the severity of pulmonary hypertension seen at two weeks of age [14]. Fetuses with CDH have increased levels of growth factors, including epidermal growth factor and platelet-derived growth factor-AA (PDGF-AA), and proinflammatory cytokines including interleukin (IL)-1α, IL-3, macrophage inflammatory protein-1β, monocyte chemoattractant protein-3, and interferon-α2 [14]. Inflammatory mediators are increased in patients with pulmonary hypertension, which may