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Contribution of intrapulmonary artery Doppler to improve prediction of survival in fetuses with congenital diaphragmatic hernia treated with fetal endoscopic tracheal occlusion

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KEYWORDS: congenital diaphragmatic hernia; intrapulmonary artery; O/E LHR; pulsed Doppler

ABSTRACT

Objective *To evaluate the contribution of intrapulmonary artery Doppler in predicting the survival of fetuses with congenital diaphragmatic hernia (CDH) treated with fetoscopic tracheal occlusion (FETO).*

Methods *A cohort of 41 fetuses (between 24 and 28 weeks of gestation) with CDH was treated with FETO. The observed/expected lung-to-head ratio (O/E-LHR), pulmonary artery pulsatility index (PI), peak early diastolic reversed flow (PEDRF) and peak systolic velocity (PSV) were evaluated before FETO, and their isolated and combined value to predict survival using multiple logistic regression and decision-tree analysis was assessed.*

Results *O/E-LHR and intrapulmonary artery PI and PEDRF were significantly associated with the probability of survival (O/E-LHR* $\geq 26\%$*, OR 14.2; PI* < 1 *Z-score, OR 8.4; and PEDRF* < 3.5 *Z-scores, OR 5.7). Decision-tree analysis showed that O/E-LHR was the best initial predictor of prognosis (O/E-LHR* $\geq 26\%$*, 90% survival; O/E-LHR* $< 26\%$*, 45% survival). For fetuses with an O/E-LHR of* $< 26\%$*, Doppler parameters allowed discrimination of cases with moderate (66–71% survival) and very poor (0% survival) prognosis.*

Conclusion *Intrapulmonary artery Doppler evaluation helps to refine the prediction of survival after FETO in fetuses with severe CDH. Copyright © 2010 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Isolated left congenital diaphragmatic hernia (CDH) complicates about 1 in 5000 live births and is associated with a high mortality rate primarily because of pulmonary hypoplasia and/or hypertension[1–3]. The best predictor of prognosis is the relative size of the lung contralateral to the hernia, measured as the lung-to-head ratio (LHR). Because this parameter changes with gestational age, it can be expressed as a ratio between the observed to the expected mean LHR for that gestational age (O/E-LHR). Combination of the O/E-LHR with the presence of intrathoracic liver herniation allows a relatively accurate prediction of the probability of survival with conventional postnatal treatment[4,5]. Fetuses with an LHR of < 1.0 at 24–28 gestational weeks (corresponding to 27–30% O/E-LHR) and liver herniation present the poorest prognosis, with overall survival rates of $< 16\%$ in multicenter studies[5].

For cases with such a poor prognosis, prenatal therapy with fetal endoscopic tracheal occlusion (FETO) has been proposed to foster lung growth *in utero* and to improve postnatal survival[6–9]. Clinical series have reported overall survival rates of 57.5%, which compare favorably with historical controls managed expectantly[10,11]. However, clinical experience demonstrates that there is a wide individual variability in the response to FETO. The best predictor of survival is the LHR before therapy[12,13]. Thus, for corresponding O/E-LHR values of 10–15%, 16–25% and 26–30%, survival rates have been reported

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to be around 17%, 62% and 78%, respectively[12]. While this information refines individual prognosis in comparison with crude rates, it still leaves considerable uncertainty. The availability of further clinical predictors to refine individual prognosis would be of great help for clinical and patient decisions, and it would contribute to improving our understanding of the variability in the clinical response to FETO.

Doppler evaluation of pulmonary vessels has been suggested as a potential prognostic parameter for the risk of lethal pulmonary hypoplasia in CDH[14–17]. In a previous study we evaluated changes in pulmonary artery Doppler parameters, and their relationship with O/E-LHR, in fetuses with CDH[18]. A significant correlation was observed for the pulsatility index (PI) and the peak early diastolic reversed flow (PEDRF). However, the correlation between lung size and these Doppler indices was relatively weak, which might present an opportunity to combine both parameters to refine clinical prediction. In the present study we evaluated the ability of pulmonary artery Doppler parameters to predict survival in fetuses with CDH treated with FETO, alone or in combination with O/E-LHR.

METHODS

Subjects

A cohort of singleton fetuses with confirmed left isolated CDH and liver herniation, selected for intrauterine therapy with FETO, was followed in the period between October 2006 and February 2009 at the Hospital Clinic, Barcelona, Spain and the University Hospitals Leuven, Leuven, Belgium. Entry criteria for fetal surgery were singleton pregnancies with severe left CDH defined as an O/E-LHR of $< 30\%$ (corresponding to an approximate LHR value of 1.0 at 24 weeks of gestation)[5] and intrathoracic herniation of the liver. Exclusion criteria were (i) other congenital malformations and (ii) chromosomal abnormalities. The protocol was approved by the hospital ethics committee and patients provided written informed consent.

Ultrasound examinations and Doppler measurements

All Doppler measurements and ultrasound examinations were performed by one of three experienced examiners (O.M.A., R.C.M., E.D.) using Siemens Sonoline Antares (Siemens Medical Systems, Malvern, PA, USA) or Voluson 730 Expert (GE Medical Systems, Milwaukee, WI, USA) ultrasound equipment with a 6–2-MHz linear curved-array transducer. All studies were performed before fetal intervention, between 24 and 28 weeks of gestation, as corrected by the first-trimester ultrasound scan[19].

The lung contralateral to the side of the hernia was evaluated in a cross-sectional view of the fetal thorax at the level of the cardiac four-chamber view. The LHR was estimated using the two major perpendicular diameters of the lung, as previously described by Metkus *et al.*[20]. The expected LHR value was calculated using normal reference ranges, according to gestational age, as $-3.4802 + (0.3995 \times GA) - (0.0048 \times GA^2)$[5]. The observed LHR was compared with the expected LHR in order to calculate the O/E-LHR, and this was expressed as a percentage.

Using color directional pulsed Doppler, the proximal branch of the intrapulmonary artery in the lung contralateral to the side of hernia was located. Spectral Doppler was applied and the characteristic pulmonary blood flow waveform was identified as previously described by Laudy *et al.*[21,22] and Moreno *et al.*[18]. The Doppler sample volume (2 mm) was located close to the emerging most proximal branch of the intrapulmonary artery (Figure 1), with an angle of insonation as close as possible to 0. A high-pass wall filter of 70 Hz was used to record slow flow movements and to avoid sound artifacts. Doppler recordings, including three to five good-quality similar waveforms, were used for analysis. All studies were performed in the absence of fetal corporal or respiratory movements and, if required, with voluntary maternal suspended breathing. Mechanical and thermal indices were maintained below 1. The waveform analysis included (a) PI, (b) PEDRF and (c) peak systolic velocity (PSV). All values were converted into *Z*-scores according to previously reported normal ranges[18]. Only the first examination before FETO was included in the analysis.

Fetoscopic tracheal occlusion and postnatal care

FETO was performed under combined spinal-epidural anesthesia and fetal analgesia, as previously described[23,24]. Briefly, a 1.2-mm endoscope within a 3.0-mm sheath (Karl Stortz, Tüttlingen, Germany) was introduced into the trachea to position a detachable balloon between the carina and the vocal cords. Ultrasound examination to confirm the endotracheal presence of the inflated balloon and to monitor the lung growth by means of the LHR value was performed every week. Whenever preterm delivery was anticipated, a course of corticosteroids (betamethasone) was administered and active tocolysis was attempted, unless contraindicated. The balloon was removed either prenatally, by fetoscopy or ultrasound-guided puncture, or by tracheoscopy at the time of delivery using an *ex utero* intrapartum technique (EXIT)[25]. Postnatal therapy included interventions ranging from ventilator support to endotracheal intubation and mechanical ventilation, the use of high-frequency ventilation, inhaled nitric oxide for refractory pulmonary hypertension, extracorporeal membrane oxygenation and surgical repair. All fetuses were followed up until delivery and survivors were followed up until 3 months of age. In non-survivors, histological examination of the lung was performed to confirm the diagnosis of pulmonary hypoplasia, defined as a lung/body weight ratio of < 0.012 after 28 weeks of gestation[26].

Statistical analysis

The Student's *t*-test and Pearson's chi-square test were used to compare quantitative and qualitative data,

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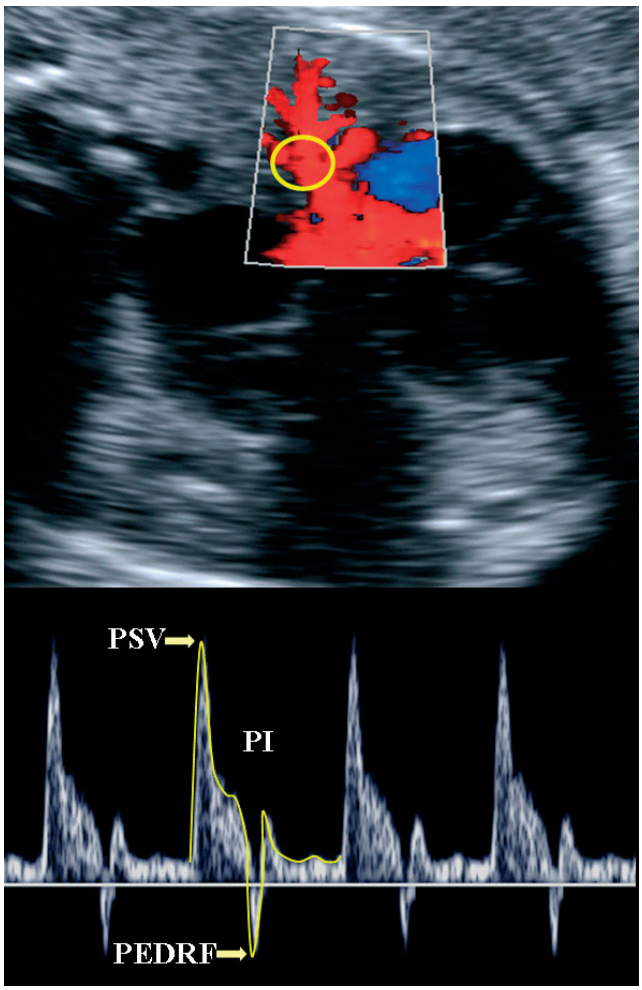

Figure 1 Pulsed Doppler image from the proximal branch of the intrapulmonary artery in the lung contralateral to the hernia. PEDRF, peak early diastolic reversed flow; PI, pulsatility index; PSV, peak systolic velocity.

respectively. The association between pulsed Doppler parameters, O/E-LHR and survival was adjusted by gestational age at birth using multiple logistic regression analysis. Statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS 15.0; SPSS Inc., Chicago, IL, USA) software.

Data were analyzed using decision tree analysis provided by the SPSS Answer Tree version 2.1. The decision tree was developed using the Classification and Regression Trees QUEST method (Quick, Unbiased and Efficient Statistical Tree), which generates binary decision trees with the P inset at 0.05[27]. The classification and regression tree was constructed by splitting subsets of the dataset using all predictor variables to create two child nodes repeatedly. The best predictor was chosen using a variety of impurity and diversity measures. The stopping rules for the iterative process were that the tree should have a maximum of three levels, a minimum of 10 fetuses should be present for a split to be calculated and any given split should not generate a group with fewer than five fetuses. These allowed sequential analysis of variables to predict postnatal survival.

RESULTS

A total of 41 fetuses fulfilled the entry criteria. FETO was successfully performed in all fetuses (31 at Barcelona and 10 at Leuven) and the overall survival rate was 56.1% (23/41). Among the 18 newborns who died, the cause of death was pulmonary insufficiency and/or hypertension in 17, and sepsis at 90 days of age in the remaining newborn who had severe insufficiency and required chronic mechanical ventilation.

Table 1 shows the maternal and neonatal clinical characteristics of the population studied. No differences were observed in gestational age at FETO, occlusion time, postnatal balloon removal and mode of delivery between survivors and non-survivors. Fetuses that died showed significantly lower gestational age at delivery.

Table 2 shows the differences of distribution of O/E-LHR, and intrapulmonary artery PI, PEDRF and PSV between the study groups. Before FETO, survivors showed significantly lower PI (1.19 (SD 1.7) vs. 2.93 (SD 2.3); $P = 0.008$) and PEDRF (1.99 (SD 1.6) vs. 3.42 (SD 2.2); $P = 0.022$), and higher O/E-LHR (24.95% (SD 3.4) vs. 21.95% (SD 4.1); $P = 0.015$) than non-survivors. By contrast, CDH fetuses that survived had PSV values similar to those of non-survivors. Logistic regression analysis showed that O/E-LHR, and intrapulmonary artery PI and PEDRF were significantly and independently associated with postnatal survival. Table 3 depicts the individual odds ratio (OR) and individual thresholds for each parameter.

Decision-tree analysis was then used to determine the best predictive combination of parameters (Figure 2). The O/E-LHR was the best initial predictor of prognosis (O/E-LHR $\geq 26\%$, 90% survival; O/E-LHR $< 26\%$, 45% survival). For fetuses with an O/E-LHR of $< 26\%$, intrapulmonary artery PI and PEDRF allowed the discrimination of two groups with moderately good (66–71% survival) prognosis, and a group with all parameters abnormal and very poor (0% survival) prognosis.

DISCUSSION

This study provides evidence that Doppler of the intrapulmonary artery is an independent predictor of survival rates in fetuses with CDH treated with FETO. While preoperative O/E-LHR remained the most powerful predictor of survival, combination with Doppler parameters helped to stratify the probability of survival in a subset of CDH fetuses with an overall moderate to poor prognosis. Thus, in fetuses with an O/E-LHR of $< 26\%$ and an overall survival rate of 45%, Doppler allowed us to distinguish fetuses with moderately good prognosis from those with a very poor survival rate. By contrast, Doppler did not appear to add any benefit in fetuses with an O/E-LHR of $\geq 26\%$, which had a mean survival, after FETO, of 90%.

The study confirms and extends previous observations supporting the value of LHR to stratify the likelihood of

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Table 1 Maternal and neonatal clinical characteristics of the study groups

Characteristic	*Survivors* (n = *23*)	*Non-survivors* (n = *18*)	P*
GA at ultrasound (weeks)	27.3 (2.5)	25.9 (1.9)	0.07
Maternal age (years)	30.1 (6.1)	28.6 (6.5)	0.49
Primiparous	47.8	27.8	0.19
Non-Caucasian ethnicity	13.0	11.1	0.85
GA at FETO (weeks)	29.3 (2.0)	28.4 (2.4)	0.20
Occlusion time (days)	30.2 (11.2)	34.8 (18.5)	0.35
GA at occlusion removal (weeks)	33.6 (1.6)	33.5 (2.3)	0.82
Postnatal balloon removal	4.3	22.2	0.08
PPROM	30.4	50.0	0.20
Cesarean section	17.4	44.4	0.06
GA at delivery (weeks)	36.9 (2.4)	35.0 (3.0)	0.03
Birth weight (g)	2601 (601)	2252 (581)	0.09
Male/female ratio	12/11	9/9	0.89
5-min Apgar score < 7	4.3	33.3	0.01
Extracorporeal membrane oxygenation	4.3	22.2	0.08
Inhaled nitric oxide	39.1	83.3	0.01
High-frequency ventilation	87	88.9	0.85
Neonatal age when CDH repaired (days)	1.9 (1.7)	1.3 (0.5)	0.47
Length of stay in neonatal unit (days)	27.2 (26.9)	14.9 (26.7)	0.17

Results are expressed as mean (SD) or %. *Student's *t*-test for independent samples or Pearson's chi-square test. CDH, congenital diaphragmatic hernia; FETO, fetoscopic tracheal occlusion; GA, gestational age; PPROM, preterm premature rupture of membranes.

Table 2 Lung ultrasound parameters in the study groups

Parameter	*Survivors* (n = *23*)	*Non-survivors* (n = *18*)	P*
O/E-LHR (mean (SD))	24.95 (3.4)	21.95 (4.1)	0.015
Intrapulmonary artery			
PI (*Z*-score (SD))	1.19 (1.7)	2.93 (2.3)	0.008
PEDRF (*Z*-score (SD))	1.99 (1.6)	3.42 (2.2)	0.022
PSV (*Z*-score (SD))	0.22 (1.0)	0.14 (1.1)	0.821

*Student's *t*-test. O/E-LHR, observed to expected lung-to-head ratio; PEDRF, peak early diastolic reversed flow; PI, pulsatility index; PSV, peak systolic velocity.

Table 3 Individual risk of survival for each parameter studied

Dependent variable	*Odds ratio*	*95% CI*	P*
O/E-LHR ≥ 26%	14.24	1.52–133.4	0.020
Intrapulmonary artery			
PI < 1.0 *Z*-score	8.41	1.79–39.39	0.007
PEDRF < 3.5 *Z*-score	5.66	1.44–22.28	0.013

*Adjusted for gestational age at delivery by multiple logistic regression. O/E-LHR, observed to expected lung-to-head ratio; PEDRF, peak early diastolic reversed flow; PI, pulsatility index.

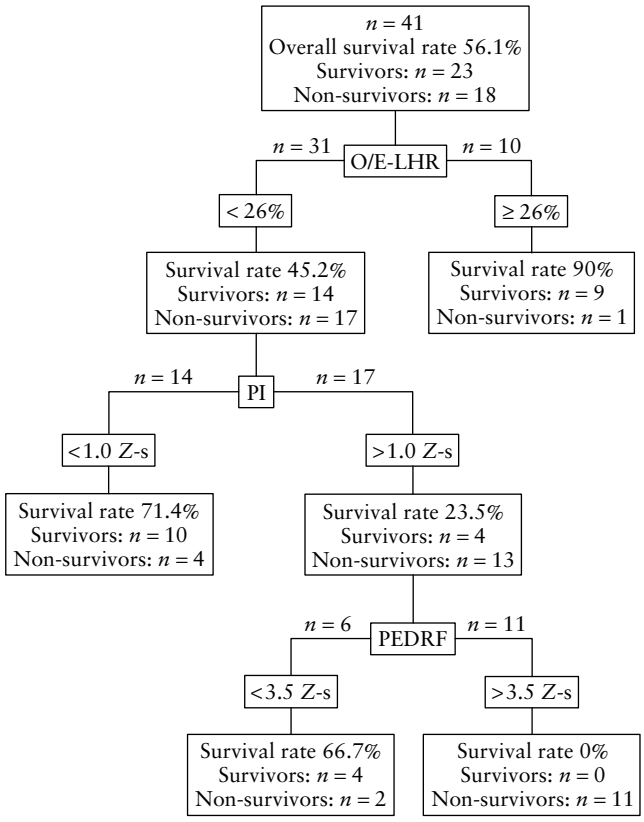

Figure 2 Clinical algorithm for prediction of survival in fetuses with congenital diaphragmatic hernia (CDH) using decision-tree analysis. O/E-LHR, observed/expected lung-to-head ratio; PEDRF, peak early diastolic reversed flow; PI, pulsatility index; *Z*-s, *Z*-score.

survival after FETO[12,13]. There are no previous studies assessing the value of Doppler findings to predict the response to FETO. Our findings are in line with a variety of studies including patients with CDH managed expectantly *in utero*[14–17] and oligohydramnios associated with preterm premature rupture of membranes[28–30]. Although the methodology and specific vessel vary among studies, there is general agreement that cases with a high risk of pulmonary hypoplasia had significant changes in Doppler parameters. In this study, we decided to use the proximal branch of the pulmonary artery. We and others have demonstrated that middle and distal intrapulmonary branches can also be visualized and insonated, even in fetuses with severe forms of CDH. However, the precise level at which middle and distal vessels are explored can be less reliably identified, and optimal insonation with angles near 0 is not possible. By contrast, the proximal branch is clearly identified, and it can be insonated at a consistent location with small angles on virtually all occasions. Furthermore, reference values throughout gestation are available for the parameters used in this study[22,31] and this allows the use of *Z*-scores for gestational age[21,32].

From a pathophysiological perspective, Doppler changes in CDH are likely to reflect both mechanical lung compression and intrinsic changes in the pulmonary vascular tree. In support of the concept of mechanical compression, in animal models immediate pulmonary

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Doppler changes are consistently observed after surgical induction of CDH, before any histological change may have taken place[33]. In humans we have previously reported a substantial increase in lung tissue perfusion, as measured by fractional moving blood volume, 1 week after tracheal occlusion, and the opposite is observed immediately after removal of the balloon[34]. However, in addition to the mechanical component, the data of the present study strongly support that Doppler changes also reflect intrinsic lung developmental changes. Our findings demonstrate that fetuses with similar lung sizes, as assessed by O/E-LHR, may present substantial differences in pulmonary Doppler parameters. These findings support the notion that CDH is associated with differences in the type of pulmonary hypoplasia, which are not reflected in the lung size. Thus, fetuses with abnormal Doppler values could reflect earlier and more severe insults in pulmonary development, but they could also represent the existence of forms of CDH with primary lung hypoplasia, as previously proposed by several authors. Investigation of histological and genetic patterns in these subgroups might help us to understand the differences observed in the lung response and survival after FETO and to further refine prognostic prediction with and without prenatal treatment.

This study has several limitations. First, although the study group is similar to or larger than those of most previous reports considering the rarity of this condition[12], the sample size was not large enough to evaluate other associations, such as the potential existence of differences in morbidity in survivors according to Doppler values. Second, because there was no control group we cannot establish comparisons with contemporary cases managed expectantly, although the historical survival rates used were collected in recent multinational series. Third, although we[18] and others[31] have previously reported good reproducibility for pulmonary artery Doppler, it was not tested in this study for each participating center. As with any Doppler measurement, intrapulmonary Doppler requires not only a trained examiner, but also very strict guidelines for acquisition and measurement. A high degree of compliance with important aspects, such as the insonation angle, is essential to ensure reproducibility and should be required for comparability among studies.

In conclusion, intrapulmonary artery Doppler improves the prediction of the response to FETO in fetuses with severe CDH. Pulmonary Doppler seems to be particularly informative in those fetuses with smaller lung areas (O/E-LHR of $< 26\%$) where it helps to identify the subgroup of fetuses that are very unlikely to respond to FETO. Integration of Doppler in clinical prognosis algorithms at the time of considering FETO could facilitate clinical and patient decisions, and help to refine the design of future clinical trials.

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