

Prenatal prediction of pulmonary arterial hypertension in congenital diaphragmatic hernia

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ABSTRACT

Objective To evaluate the role of prenatal prognostic markers obtained routinely by ultrasound examination and magnetic resonance imaging (MRI) in the prediction of development of postnatal pulmonary arterial hypertension (PAH) in isolated congenital diaphragmatic hernia (CDH).

Methods One hundred and ten cases of isolated CDH were referred to our fetal medicine unit between January 2004 and April 2013. Mortality and morbidity rates were reviewed for those presenting with postnatal PAH. The following prenatal markers were evaluated as potential predictive factors of PAH: liver position, side of the CDH defect, lung area to head circumference ratio (LHR) and observed/expected LHR (o/e-LHR), which were measured by ultrasound, and observed/expected total fetal lung volume (o/e-TFLV), which was measured by MRI. Univariable logistic regression was used to assess associations.

Results PAH was significantly associated with perinatal mortality and morbidity ($P < 0.001$). The occurrence of PAH decreased significantly with an increasing LHR, o/e-LHR and o/e-TFLV and was significantly increased for cases with an intrathoracic liver, but not for those with right-sided defects. Univariable regression revealed that o/e-TFLV (odds ratio (OR), 0.9 (95% CI, 0.86–0.95); $P < 0.05$ for percentage unit change in o/e), LHR (OR, 0.19 (95% CI, 0.09–0.40); $P < 0.05$ for unit change), o/e-LHR (OR, 0.95 (95% CI, 0.93–0.98); $P < 0.05$ for percentage unit change in o/e) and liver position (OR, 2.82 (95% CI, 1.13–7.00); $P < 0.05$ for intrathoracic liver) were significant predictors of subsequent PAH. No differences were found after adjusting for gestational

age at delivery. The areas under the receiver–operating characteristics curve were 0.80 and 0.75 for o/e-TFLV and o/e-LHR, respectively.

Conclusion In cases of CDH, PAH is associated with high rates of mortality and morbidity. Routinely obtained prenatal markers, usually used for the assessment of pulmonary hypoplasia, are also relevant for the postnatal prediction of PAH. Copyright © 2014 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a severe fetal malformation, occurring in about 1 in 3000 live births, and is associated with high mortality and morbidity rates¹. In about 30% of cases, the condition is associated with genetic, chromosomal or structural anomalies that imply a poor prognosis overall². Despite the advances made in neonatal intensive care, the overall mortality rate ranges from 30% to 50%^{3–5}. Prenatal prognostic assessment of cases with CDH is of paramount importance since it is used not only for parental counseling but also when considering intrauterine surgery, i.e. fetal endoluminal tracheal occlusion (FETO). Prenatal prognostic assessment generally relies upon liver position, observed/expected lung area to head circumference ratio (o/e-LHR) (measured by ultrasound) and observed/expected total fetal lung volume (o/e-TFLV) (measured by magnetic resonance imaging (MRI))^{6–13}. Previous studies on CDH have concentrated mainly on the prenatal assessment of the likelihood of postnatal death. Severe pulmonary arterial hypertension (PAH) is a life-threatening complication of CDH in the context of pulmonary hypoplasia¹⁴ and is a leading cause of postnatal morbidity as well as

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mortality^{15,16}. Therefore, PAH may be a relevant outcome in prenatal assessment. Several studies have evaluated fetal pulmonary vasculature as a promising prognostic factor of postnatal PAH^{17–19}. In addition, the prenatal prediction of PAH by markers obtained at routine ultrasound examination has been evaluated in a few previous studies^{10,20}. However, these studies did not evaluate the prognostic value of MRI^{10,20}.

The objective of this study was to evaluate the relevance of routinely obtained fetal prognostic markers in the prediction of postnatal PAH.

SUBJECTS AND METHODS

This was a retrospective analysis of a single-center cohort examined between January 2004 and April 2013. We searched our database to identify all consecutive cases of CDH that were referred to the fetal medicine center of Necker Hospital, Paris. Potential predictors for the occurrence of pulmonary hypoplasia included LHR, lung volume on MRI, liver position and side of the CDH defect. LHR was measured using the method of Metkus *et al.*²¹, based on the product of the two longest perpendicular axes of the contralateral lung. LHR and lung volume as ascertained by MRI were converted into observed/expected (o/e) ratios. o/e-LHR was calculated using a formula derived by Peralta *et al.*²². Similarly, we considered o/e ratios for the MRI lung volume using the formula provided by Mahieu-Caputo *et al.*²³ in order to obtain o/e-TFLV. In our protocol, LHR was usually measured by ultrasound between 22 and 28 weeks' gestation, and MRI was performed between 28 and 34 weeks. Patients referred to our center after 28 weeks also had an LHR measurement that was converted into an o/e ratio. Several cases underwent multiple LHR measurements; in such cases the first value obtained was recorded for statistical analysis. We excluded all fetuses with associated chromosomal abnormalities or malformations, as well as cases undergoing medical termination of pregnancy and those resulting in intrauterine fetal death. Cases that underwent FETO were also excluded. All patients underwent karyotyping following amniocentesis.

After delivery, all babies were managed according to a standard protocol described by Datin-Dorriere *et al.*⁶. Neonates were intubated nasally in the delivery room and transferred immediately to the neonatal intensive care unit (NICU), and high-frequency oscillation was the first-line ventilation strategy used. In our protocol, persistent PAH was defined by a pre- and postductal saturation difference > 10%, together with a right-to-left shunt seen on echocardiography. The same definition was used by Ruano *et al.*¹⁰. PAH was managed by a high fraction of inspired oxygen and inhaled nitric oxide. Surgical repair was performed only once respiratory and hemodynamic stabilization had been obtained. The therapeutic strategy did not include exogenous surfactant therapy or extracorporeal membrane oxygenation (ECMO). Survival of the neonate

was defined by discharge from the NICU. In surviving infants, postnatal morbidity was defined using duration of assisted ventilation, a need for oxygen dependency at 28 days of age and the length of time spent in the NICU.

Results are presented as median (interquartile range (IQR)), median (range) or *n* (%), as appropriate. The relationship between PAH and survival/morbidity was compared using Student's *t*-test or the Mann–Whitney *U*-test for continuous variables, and the chi-square or Fisher's exact test for proportions. Two-sided $P \leq 0.05$ was considered statistically significant. Selected potential prenatal prognostic factors of mortality and PAH were liver position, side of the CDH defect, o/e-LHR and o/e-TFLV. Each predictor was assessed by univariable logistic regression to investigate its effect on the presence of postnatal PAH. Results were then adjusted by gestational age at delivery. Receiver–operating characteristics (ROC) curves were produced to compare the postnatal PAH prediction by o/e-TFLV and o/e-LHR. Statistical analysis was conducted using R software, version 2.0.0 (www.r-project.org, Foundation for Statistical Computing, Vienna, Austria).

This study was exempt from ethical review board approval because, at the time of prenatal diagnosis, LHR and MRI assessment were part of the routine diagnostic assessment.

RESULTS

Between January 2004 and April 2013, 165 patients with an antenatal diagnosis of CDH were referred to our center for perinatal care. Outcomes of these 165 patients are presented in Figure 1. Fifty-five cases that did not meet the inclusion criteria were excluded: 21 patients had medical termination of pregnancy, six neonates were born with malformations, one case of eventration was diagnosed after birth, one intrauterine fetal death occurred and 25 cases underwent FETO procedures. In one case, early postnatal death prevented any assessment of pulmonary arterial pressure. Included in the cohort were 110 live births with an isolated CDH that underwent pulmonary arterial pressure assessment (Table 1). The median gestational age at birth was 39 (range, 33–41) weeks and median birth weight was 3000 g (range, 1480–4220 g). Among the 110 neonates included, 62 (56.4%) were male. There were 17 (15.5%) cases of right-sided CDH, 93 (84.5%) cases of left-sided CDH and no cases of bilateral CDH. The o/e-LHR was assessed in 101 cases, the o/e-TFLV in 96 cases, and 91 cases had both an o/e-TFLV and an o/e-LHR measurement. The median gestational age at the time of the LHR measurement was 27 (IQR, 24–32) weeks and the median gestational age at o/e-TFLV measurement was 31 (IQR, 28.5–33) weeks. The liver was intrathoracic in 36/110 (32.7%) cases, the median LHR was 1.7 (IQR, 1.3–2.3), the median o/e-LHR was 45.6% (IQR, 38.5–63.4%) and the median o/e-TFLV was 37.3% (IQR, 28.0–46.0%).

The overall postnatal survival rate was 63/110 (57.3%). All neonates underwent high-frequency ventilation. The

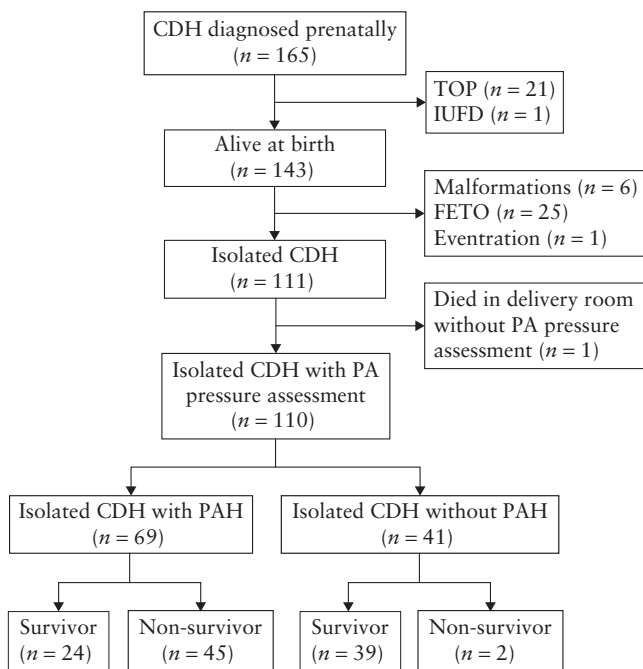


Figure 1 Flowchart showing outcome of pregnancies with prenatal diagnosis of congenital diaphragmatic hernia (CDH), according to occurrence of postnatal pulmonary arterial hypertension (PAH). FETO, fetal endoluminal tracheal occlusion; IUID, intrauterine fetal death; PA, pulmonary artery; TOP, termination of pregnancy.

Table 1 Prenatal characteristics and outcome of 110 cases with isolated congenital diaphragmatic hernia (CDH) referred consecutively to the fetal medicine unit of Necker Hospital, Paris, between January 2004 and April 2013

Characteristic	Value
Male neonate	62 (56.4)
Gestational age at birth (weeks)	39 (33–41)
Birth weight (g)	3000 (1480–4220)
Right-sided CDH	17 (15.5)
Intrathoracic liver	36 (32.7)
LHR*	1.7 [1.3–2.3]
o/e-LHR* (%)	45.6 [38.5–63.4]
o/e-TFLV† (%)	37.3 [28.0–46.0]
Neonatal survival	63 (57.3)
PAH development	69 (62.7)

Data are given as *n* (%), median (range) or median [interquartile range]. *Measured in 101 patients. †Measured in 96 patients. LHR, fetal lung-to-head ratio; o/e, observed to expected; PAH, pulmonary arterial hypertension; TFLV, total fetal lung volume.

rate of postnatal mortality was assessed according to the side of the CDH defect, location of the liver, LHR, o/e-LHR and o/e-TFLV using univariable logistic regression (Table 2). The mortality rate significantly decreased as LHR, o/e-LHR and o/e-TFLV increased and increased significantly for cases with an intrathoracic liver, but not in those with right-sided CDH defects. No significant difference was found when adjusting by gestational age at delivery.

Among the 110 cases with CDH, 69 (62.7%) infants subsequently developed PAH. The relationship between

Table 2 Prenatal factors associated with postnatal mortality (with and without adjustment for term delivery) in 110 cases with isolated congenital diaphragmatic hernia (CDH)

Variable	OR (95% CI)	Adjusted OR (95% CI)
LHR*	0.12 (0.04–0.33)	0.13 (0.05–0.35)
o/e-LHR*	0.95 (0.92–0.98)	0.95 (0.92–0.98)
o/e-TFLV†	0.90 (0.85–0.94)	0.90 (0.85–0.94)
Intrathoracic liver	3.69 (1.60–8.51)	3.88 (1.65–9.13)
Right-sided CDH	2.15 (0.65–7.09)	1.92 (0.57–6.44)

*Measured in 101 patients. †Measured in 96 patients. LHR, fetal lung-to-head ratio; o/e, observed to expected; OR, odds ratio; TFLV, total fetal lung volume.

Table 3 Outcome of 110 cases with isolated congenital diaphragmatic hernia (CDH) and neonatal measures of morbidity in the 63 survivors, according to presence of postnatal pulmonary arterial hypertension (PAH)

Postnatal outcome	CDH with PAH (n = 69)	CDH without PAH (n = 41)	P
Survival at discharge	24/69 (34.8)	39/41 (95.1)	< 0.001
Need for supplemental oxygen at 28 days	13/24 (54.2)	3/39 (7.7)	< 0.001
Duration of hospitalization (days)	32 (23–48)	12 (8–19)	< 0.001
Duration of assisted ventilation (days)	23 (17–25)	6 (3–10)	< 0.001

Data are given as *n/N* (%) or median (interquartile range).

the presence of PAH and outcome, especially survival and neonatal morbidity in surviving infants, is detailed in Table 3. PAH was significantly associated with postnatal mortality ($P < 0.001$). Among the 63 surviving infants, 24/63 (38.1%) developed PAH. The median duration of nitric oxide inhalation among the 24 surviving infants who developed PAH was 11 (IQR, 5–18) days. Cases that developed PAH had a significantly higher morbidity than those that did not; they needed longer NICU hospitalization ($P < 0.001$), prolonged assisted ventilation ($P < 0.001$) and developed oxygen dependency more often ($P < 0.001$).

The rate of development of PAH was assessed according to the side of the CDH defect, liver location, LHR, o/e-LHR and o/e-TFLV using univariable logistic regression (Table 4). Significant predictors for postnatal PAH were o/e-TFLV (odds ratio (OR), 0.9 (95% CI, 0.86–0.95); $P < 0.05$ for percentage unit change in o/e), LHR (OR, 0.19 (95% CI, 0.09–0.40); $P < 0.05$ per unit change), o/e-LHR (OR, 0.95 (95% CI, 0.93–0.98); $P < 0.05$ for percentage unit change in o/e) and liver location (OR, 2.82 (95% CI, 1.13–7.00); $P < 0.05$ for intrathoracic liver). The side of the CDH defect (OR, 2.15 (95% CI, 0.65–7.09) for right-sided defect) was not found to be statistically significant. The results were similar when adjusted for gestational age at delivery. In summary, the occurrence of PAH decreased significantly as LHR, o/e-LHR and o/e-TFLV increased and was

Table 4 Prenatal factors associated with occurrence of postnatal pulmonary arterial hypertension (with and without adjustment for term delivery) in 110 cases with isolated congenital diaphragmatic hernia (CDH)

Variable	OR (95% CI)	Adjusted OR (95% CI)
LHR*	0.19 (0.09–0.40)	0.19 (0.09–0.42)
o/e-LHR*	0.95 (0.93–0.98)	0.95 (0.92–0.98)
o/e-TFLV†	0.90 (0.86–0.95)	0.90 (0.86–0.95)
Intrathoracic liver	2.82 (1.13–7.00)	3.11 (1.20–8.09)
Right-sided CDH	2.15 (0.65–7.09)	1.92 (0.57–6.44)

*Measured in 101 patients. †Measured in 96 patients. LHR, fetal lung-to-head ratio; o/e, observed to expected; OR, odds ratio; TFLV, total fetal lung volume.

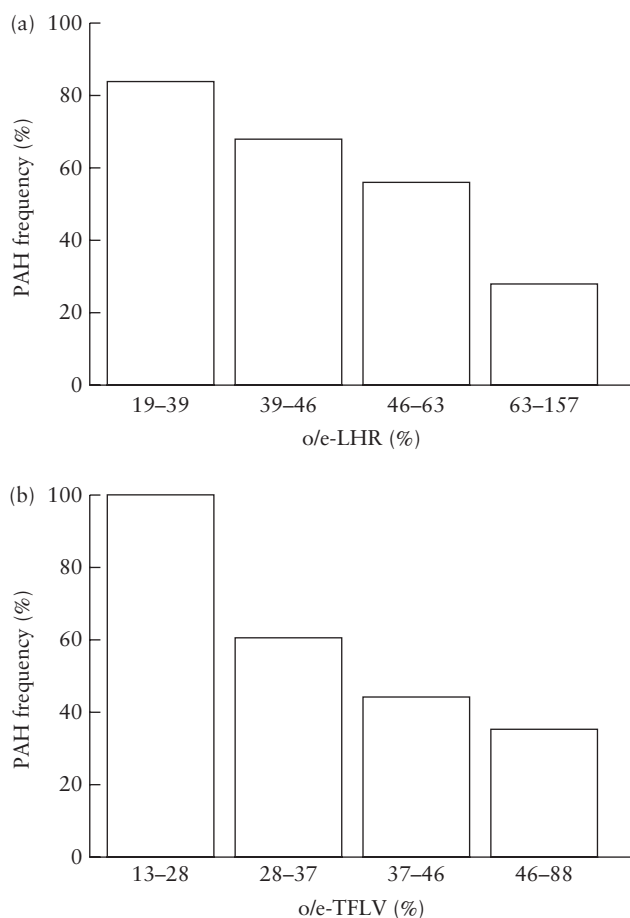


Figure 2 Frequency of postnatal pulmonary arterial hypertension (PAH) according to: (a) observed/expected fetal lung-to-head ratio (o/e-LHR) and (b) observed/expected total fetal lung volume (o/e-TFLV).

increased significantly for cases with an intrathoracic liver, but not for those with right-sided defects. Figure 2 illustrates the frequency of PAH occurrence according to o/e-LHR and o/e-TFLV. A ROC curve was produced from the 91 patients that underwent both an o/e-TFLV and an o/e-LHR assessment. The ROC curve (Figure 3) revealed that o/e-TFLV was slightly more accurate than was o/e-LHR for the prediction of postnatal PAH (area under the ROC curve (AUC), 0.80 vs 0.75).

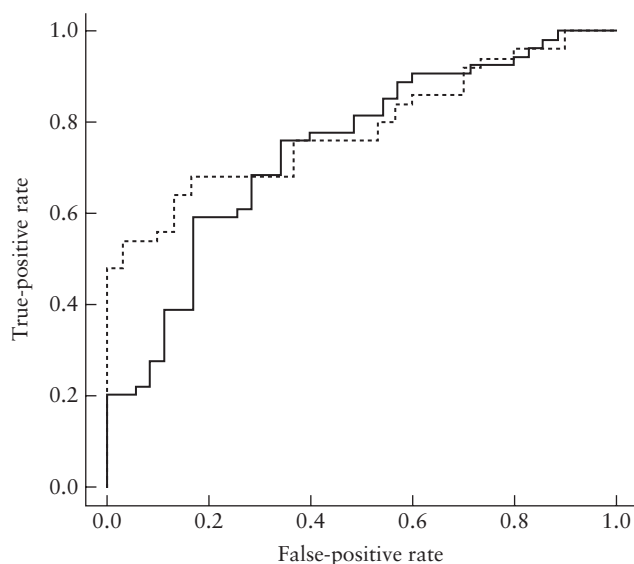


Figure 3 Receiver–operating characteristics curve evaluating accuracy of observed/expected total fetal lung volume (o/e-TFLV) (-----) and observed/expected fetal lung-to-head ratio (o/e-LHR) (—) for the prediction of pulmonary arterial hypertension in fetuses with isolated congenital diaphragmatic hernia. Areas under the curve for o/e-TFLV and o/e-LHR were 0.80 and 0.75, respectively.

DISCUSSION

The vast majority of studies that have assessed the prenatal prognosis of CDH focused on the prediction of postnatal survival. Moreover, many investigators still focus on the severity of pulmonary hypoplasia and overlook PAH as an important part of the outcome. Since CDH may be responsible for significant morbidity among surviving children, merely predicting survival seems insufficient. Indeed, surviving children remain at high risk of developing secondary morbidity, and particularly pulmonary morbidity. Among the survivors, 30% to 50% will present pulmonary sequelae such as chronic lung disease²⁴. Our results have shown that PAH is associated with a high rate of both mortality and morbidity, in agreement with the literature^{14–16}. In our study, infants who developed PAH required longer NICU hospitalization and developed significant pulmonary morbidity. Indeed, in our series, the duration of assisted ventilation observed was prolonged significantly in cases with PAH, thus increasing ventilation-related lung damage and pulmonary sequelae^{24,25}. Although ECMO is not part of our protocol because of the controversy concerning patient selection and the risk of associated neurodevelopmental morbidity^{26–28}, it is used routinely for severe PAH in some centers²⁶. Therefore, our results may facilitate counseling regarding this specific part of postnatal therapy, for centers routinely using ECMO.

Some have attempted to evaluate postnatal PAH by studying the fetal pulmonary vasculature using prenatal ultrasonography. In 2006, Ruano *et al.*¹⁷ evaluated fetal pulmonary vasculature using three-dimensional (3D) power Doppler ultrasonography. They reported that using

fetal pulmonary vascular indices could help to predict the development of postnatal PAH. Similar results were obtained in a more recent study¹⁰. The same team (Ruano *et al.*^{10,29}) studied the prognostic value of fetal pulmonary artery diameter, but the prediction of PAH was inferior to that of 3D power Doppler ultrasonography¹⁰. An interesting tool for the prediction of PAH may be a maternal hyperoxygenation test³⁰, but to date, it has been evaluated only in selected cases of severe CDH that underwent FETO. Further studies are required to confirm these results and to extend the technique to less severe cases of CDH.

The development of PAH results from pulmonary arterial abnormalities that are characterized by a reduced number of pulmonary arteries and an increased thickness of the vascular walls^{31,32}. It has been demonstrated that pulmonary vascular lesions are closely related to pulmonary hypoplasia^{33,34}. For this reason we chose to evaluate the prenatal prediction of PAH using the classical markers of pulmonary hypoplasia. Moreover, the side of the CDH defect, liver position, o/e-LHR and o/e-TFLV have become part of the routine diagnostic work-up in the management of CDH used by most teams involved in the prenatal management of CDH. We analyzed both right- and left-sided CDH together since one aim of our study was to evaluate the side of CDH as a predictive factor of postnatal PAH. Our results show that the postnatal development of PAH is not associated with the side of the defect. In fact, in most cases of right-sided CDH, if not in all, the liver is intrathoracic. Therefore, liver position seems to be more relevant than is the side of the defect.

Ruano *et al.*¹⁰ evaluated several ultrasound markers such as o/e-LHR, TFLV assessed by 3D ultrasound and liver location to predict postnatal PAH. They reported that o/e-LHR, TFLV and liver position are associated with the presence of postnatal PAH. They found an AUC of 0.78 for o/e-LHR, a value strikingly close to ours (AUC, 0.75). However, prenatal MRI was not part of their evaluation. In our study, MRI accurately predicted PAH, with an AUC of 0.80. Ultrasonographic measurement of LHR can be difficult³⁵, and is probably more prone to high inter- and intraoperator variability and is therefore probably less reliable than MRI in assessing pulmonary hypoplasia. Indeed, many factors may impair the reliability of ultrasound measurements of LHR, such as an accurate reference plane, visualization of the limits of the lungs, rib ultrasound shadowing as well as caliper placement. Moreover, MRI allows volume evaluation of both lungs, while LHR assesses only one lung³⁶. Our results show that o/e-TFLV by MRI is slightly more accurate than is o/e-LHR for predicting the postnatal development of PAH. o/e-TFLV can also be measured by 3D ultrasound, and was found to have an AUC of 0.85 for the prediction of postnatal PAH in one study¹⁰. However, measuring o/e-TFLV by 3D ultrasound can be difficult technically, and MRI is likely to be more reliable.

The ORs regarding prediction of the development of PAH and mortality from the o/e-LHR and o/e-TFLV are similar, and differ mainly with respect to the impact of

liver position. Nonetheless, it should be borne in mind that 34.7% of newborns diagnosed with severe PAH survived. Therefore, the similarity of the ORs reflects the close relationship that exists between the occurrence of PAH and subsequent death, but in addition this finding suggests that the prognostic value of routine prenatal markers of pulmonary development for predicting postnatal PAH is comparable with what is found when considering overall survival as the outcome of interest.

Several potential biases and limitations of the study should be acknowledged. In the study, LHR assessment by ultrasound and MRI were performed at different gestational ages. However, the first measurement of LHR is normally used as the basis for further management, while MRI is generally performed later, at around 28 weeks' gestation. This is why we compared the first LHR measurement and the MRI performed later. However, using o/e for both LHR and MRI makes these measurements comparable theoretically, adjusting for differences in gestational age.

Our survival rate is low compared to some centers that have a survival rate of 80%, and we have no explanation for this³⁷. Because prenatal surgery disrupts the natural history of CDH, we chose to remove from the study cases that were treated by FETO. Although this introduces a bias, decreasing the observed mortality rate artificially, we do not think that it impacts on the intrinsic performance of o/e-LHR and MRI in terms of sensitivity and specificity, and also it should not affect the ORs.

Our results may improve prenatal counseling, especially in the era of prenatal therapy. FETO is likely to play an increasing role in the prognosis and management of CDH, and has been advocated mainly for cases with expected poor survival. However a randomized controlled trial is at present underway with the objective of assessing its effect on morbidity in cases with an intermediate prognosis (www.totaltrial.eu). In our protocol, MRI was usually performed between 28 and 34 weeks, which is too late for pre-FETO assessment. Therefore, MRI could be performed at around 27 weeks in order to help in the decision and counseling over FETO, with regards not only to survival, but also to the prospects of severe morbidity.

In conclusion, the presence of postnatal PAH in cases of CDH is associated with severe mortality and morbidity, justifying its inclusion in prenatal assessment. Moreover, prediction of PAH by routinely obtained prognostic markers may standardize practice regarding prenatal management of CDH. Prenatal care and indication for intrauterine interventions such as FETO may also benefit from considering the probability of PAH in preoperative assessment.

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