Prediction of Mortality and Need for Neonatal Extracorporeal Membrane Oxygenation in Fetuses with Congenital Diaphragmatic Hernia: Logistic Regression Analysis Based on MRI Fetal Lung Volume Measurements

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OBJECTIVE. The purpose of this study was to use logistic regression analysis of prenatal MRI fetal lung volume measurements to calculate mortality and the need for extracorporeal membrane oxygenation (ECMO) therapy among fetuses with congenital diaphragmatic hernia (CDH).

SUBJECTS AND METHODS. The fetal lung volume measurements of 65 fetuses with CDH were obtained between 32 and 34 weeks' gestation by means of MRI performed with multiplanar T2-weighted HASTE and true fast imaging with steady-state precession sequences. Logistic regression analysis was used to assess the prognostic value of the fetal lung volume measurements for prenatal prediction of fetal survival and need for neonatal ECMO.

RESULTS. Fetal lung volume was a highly significant predictor of survival ($p < 0.0001$) and neonatal ECMO requirement ($p = 0.0006$). The mortality was 84% and the ECMO requirement 80% among fetuses with a lung volume of 5 mL. The mortality was 0.4% and the ECMO requirement 20% among patients with a fetal lung volume of 30 mL.

CONCLUSION. Logistic regression analysis of MRI fetal lung volume measurements is highly valuable in predicting mortality among neonates with CDH, and it may help to estimate the need for neonatal ECMO. The method is feasible for facilitating parental guidance and may help in choosing postnatal therapeutic options, including ECMO therapy.

Congenital diaphragmatic hernia (CDH) occurs in approximately one in 2,000 to one in 4,000 live births, making it a relatively common congenital abnormality [1–3]. Despite increasing prenatal diagnosis and recent advances in postnatal care [3, 4], CDH continues to be a life-threatening anomaly with a high mortality rate. Predicting survival of the infants remains difficult. The reported mortality rates of CDH vary depending on whether survival statistics refer to fetuses, live-born infants, or infants admitted to neonatal intensive care units. Population-based studies [1, 2] have shown that approximately 52% of live-born infants, 32% of all infants, and 16% of all fetuses with a prenatal diagnosis survive.

The overall prenatal mortality of CDH is influenced by the rate of elective pregnancy termination [1, 2]. Among the population assessed by Colvin et al. [1], pregnancy was terminated in 49% of cases of prenatal diagnosis. In cases of postnatal diagnosis, however, the degree of pulmonary hypoplasia and associated abnormalities has the greatest influence on survival [5–7]. These conditions usually lead to death within the first 24 hours of life [2]. Although several surgical referral centers have reported survival rates up to 93% [1, 8–10], the results may have been influenced by patient selection bias. Colvin et al. reported that 35% of live-born infants died before referral and that the population of infants reaching the tertiary surgical center represented only 40% of the total cases of CDH.

A specialist involved in the care of a patient with CDH may find it difficult to provide detailed prognostic information and to individually counsel parents on therapeutic options. Few parameters have been defined to aid in predicting outcome for these infants. Although a variety of indexes have been suggested, no robust marker is available for accurate prediction of patient survival. Attention has been focused on the lung-to-head ratio assessed with sonography [11–15] and relative fetal lung volume calculated with biometric parameters based on MRI findings [16–19]. However, both parameters allow only a rough estimate of likelihood of survival. To our knowledge, no method is available for individually determining survival of infants with CDH. There

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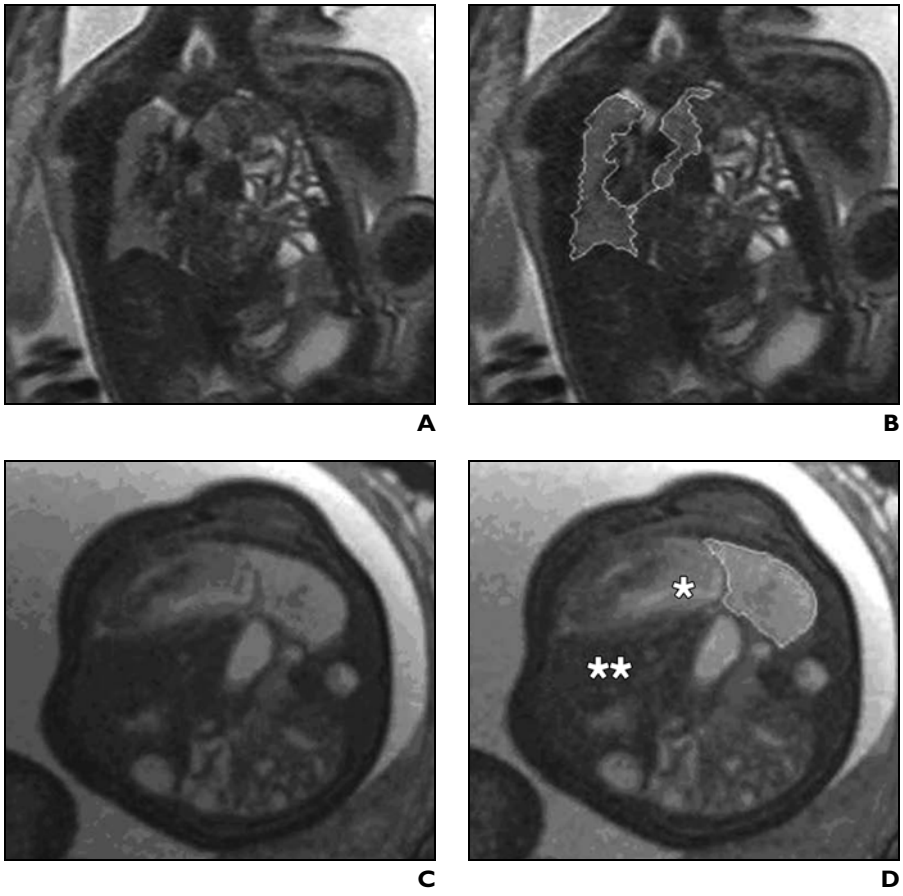

Fig. 1—Fetus at 33 weeks of gestation.
A and **B,** Coronal MR images obtained with HASTE sequence show fetal lung.
C and **D,** Transverse MR images obtained with true fast imaging with steady-state precession sequence and used for fetal lung volume assessment show fetal lung differentiated from heart (*single asterisk*) and herniated abdominal contents including fetal liver (*double asterisk*). Region of interest follows lung boundaries and does not include main vessels of pulmonary hila. Regions of interest with lung planimetry are shown in **B** and **D**.

also is no parameter for estimating the need for neonatal extracorporeal membrane oxygenation (ECMO) therapy. Among patients whose condition is refractory to conventional ventilation therapy, ECMO has been reported to improve the survival rate [20–23]. However, ECMO therapy is available at only a few specialized care centers, so prenatal transfer of the patient is desirable. Furthermore, and particularly for critically ill neonates, a generally higher survival rate has been observed at experienced tertiary care centers (high-volume centers) than at institutions where patients with CDH are treated less frequently [24]. Thus, even if ECMO therapy is not advocated, prenatal identification of patients at high risk of neonatal respiratory failure is essential to avoid delay in intensified postnatal care and to improve outcome for these patients.

The intention of our investigation was first to use logistic regression analysis of MRI fetal lung volume measurements for prenatal calculation of individual likelihood of survival of infants with CDH. We also assessed the applicability of this method to determine the corresponding probability of the need for neonatal ECMO therapy.

Subjects and Methods

Study Population

The study population comprised all pregnant women in whom fetal CDH was diagnosed from September 2001 to July 2006 and who underwent MRI fetal lung volume measurement at our institution between 32 and 34 weeks' gestation. The study received approval from the institutional review board. Informed consent to perform fetal MRI was obtained from all patients; separate consent was obtained if ECMO therapy was needed.

ECMO Therapy

All infants were intubated immediately after birth, and gentle conventional ventilation was administered. ECMO therapy was initiated if the postductal Pa_{O_2} was less than 40 mm Hg and preductal saturation did not rise above 80 mm Hg for more than 2 hours or if the postductal Pa_{O_2} did not rise above 50 mm Hg and preductal saturation stayed below 95% for more than 4 hours. During ECMO, heparin (Liquemin N5000, Roche) was given IV at a daily dose of 400 IU/kg. At decannulation the jugular vein was ligated, and the common carotid artery was reconstructed. Exclusion criteria for institution of ECMO therapy were evidence of ongoing bleeding or severe coagulopathy, fatal concomitant anomalies, and lactate levels of 20 mmol/L or greater.

MRI Planimetry

All MR images were obtained with a 1.5-T supraconducting MRI system (Magnetom Sonata or Avanto, Siemens Medical Solutions) with a six-element phased-array surface coil. The mothers were positioned in either the supine or the partial left lateral position. No sedation was given to reduce fetal movement. The imaging protocol consisted of multiplanar T2-weighted images without respiratory triggering. A HASTE sequence (TR/TE, 1,000/85; flip angle, 150°; matrix size, 512 × 512) was performed on all patients. From June 2005 onward we also conducted a multiplanar true fast imaging with steady-state precession (true FISP) sequence on all of the patients (4.3/1.9; flip angle, 59°; matrix size, 512 × 512). Because its acquisition time (≤ 14 seconds) was shorter than that of the HASTE sequence (≤ 22 seconds), the true FISP sequence was particularly valuable if the fetus was agitated. All images were obtained with a 4-mm slice thickness. Sections were adjusted to the transverse, coronal, and sagittal planes relative to the fetal lungs. Imaging was monitored by an experienced radiologist to ensure that all of the anatomic features of interest were included. Sequences degraded by fetal motion artifacts were repeated to obtain images covering the whole thorax in a single acquisition and allowing clear identification of parietal and mediastinal boundaries.

Lung volumes were measured by two investigators using volume analysis software (ARGUS, Siemens Medical Solutions) on a workstation (Leonardo, Siemens Medical Solutions). A hand-tracing drawing tool was used to outline the region of interest following the lung boundaries on consecutive images covering the entire thorax (Fig. 1). A computer algorithm was used to calculate the area of the region of interest in square millimeters. The area was multiplied by the slice thickness to obtain the volume of the

TABLE 1: Patient Characteristics

Characteristic	Total Study Population (*n* = 65)	Survivors (*n* = 54)	Nonsurvivors (*n* = 11)	*p*	ECMO (*n* = 27)	No ECMO (*n* = 38)	*p*
Maternal age (y)	30.4 ± 5.4	30.0 ± 5.4	32.5 ± 5.1	0.166	31.3 ± 5.2	29.7 ± 5.4	0.241
Gestational age (wk)	33.8 ± 0.7	33.8 ± 0.7	33.7 ± 0.6	0.898	33.7 ± 0.7	33.8 ± 0.7	0.712
Left-sided congenital diaphragmatic hernia (*n*)	54 (83)	45 (83)	9 (82)	1.000	22 (81)	32 (84)	1.000
Fetal lung volume (mL)	21.5 ± 9.4	23.5 ± 8.8	11.7 ± 5.3	< 0.0001	16.9 ± 7.5	24.8 ± 9.4	0.0006
ECMO therapy (*n*)	27 (42)	18 (33)	9 (82)	0.005			
Survival rate (*n*)	54 (83)				18 (67)	36 (95)	0.005

Note—Values in parentheses are percentages. ECMO = extracorporeal membrane oxygenation.

entire lung. When different section orientations of high image quality were available, the best images were analyzed, and the mean fetal lung volume was calculated for subsequent evaluation.

Data Analysis

To assess the effect of fetal lung volume, maternal age, and the side of the defect on survival and neonatal ECMO requirement, we applied the Fisher's exact test and the Student's *t* test. Logistic regression analysis was used to express the association between mean fetal lung volume calculated with MR planimetry and mortality and likelihood of need for neonatal ECMO therapy. Statistical calculations were performed with SAS release 8.02 (SAS Institute). A value of $p < 0.05$ was considered to indicate a significant difference.

Results

The study group consisted of 66 singleton pregnancies and two twin pregnancies. All but one of the infants were delivered at our center. Of the 68 patients who underwent MRI fetal lung volume measurement at our institution, three had to be excluded from subsequent evaluation. One infant was lost to follow-up, one infant was excluded because of trisomy 18, and one because of transposition of the great vessels. Thus, 65 patients underwent further assessment. The mean maternal age in the study group was 30.4 ± 5.4 years (range, 19–41 years), and the mean gestational age at MRI was 33.8 ± 0.7 weeks. In 54 (83%) of the patients, the defect was left-sided; one infant had a bilateral hernia (Table 1).

Patient Survival and Neonatal ECMO Requirement

The influence of certain factors on survival and the need for ECMO are presented in Table 1. The global survival rate was 83%. The location of the defect in neonates who survived did not differ from that in infants who did not. Among the 11 patients who died, including the patient with a bilateral defect, eight deaths occurred because of respiratory failure, and three infants died of major hemorrhage during ECMO therapy (two cases of intracerebral and one of cervical bleeding, 11% of all ECMO patients). The mean fetal lung volume of the infants whose deaths were related to ECMO did not differ significantly from that of infants who died of respiratory failure (10.5 ± 6.4 mL vs 12.1 ± 5.2 mL, $p = 0.610$). The fetal lung volume calculated with prenatal MRI was the only parameter that significantly influenced infant survival ($p < 0.0001$). The average lung volume of survivors was 23.5 ± 8.8 mL, whereas that of nonsurvivors was 11.7 ± 5.3 mL.

Because of respiratory distress, 27 (42%) of the newborns received arteriovenous ECMO therapy. The fetal lung volume measured on prenatal MRI again was found to be the only predictive parameter for estimating postnatal course. Higher fetal lung volume was significantly associated with a lower neonatal ECMO requirement ($p = 0.005$). All other parameters, including location of the hernia, were of no consequence.

The association between individual fetal lung volume and postnatal mortality ($R_{\text{mortality}}$) and neonatal ECMO requirement (R_{ECMO}) was determined using logistic regression analysis performed with SAS release 2.0 and was expressed as follows:

$$R_{mortality} = \frac{e^{3.0513 - 0.2828 \times \text{fetal lung volume}}}{1 + e^{3.0513 - 0.2828 \times \text{fetal lung volume}}}$$

$$R_{ECMO} = \frac{e^{1.9039 - 0.1093 \times \text{fetal lung volume}}}{1 + e^{1.9039 - 0.1093 \times \text{fetal lung volume}}}$$

Application of these formulas indicated an 84% mortality among infants with a prenatal fetal lung volume of 5 mL and a 0.4% mortality among infants with a 30-mL lung volume. The corresponding need for ECMO therapy was estimated at 80% and 20%, respectively. Table 2 and Figure 2 provide an overview of the data.

TABLE 2: Results of Logistic Regression Analysis for Prediction of Mortality and Need for Neonatal ECMO Among Fetuses Evaluated Between 32 and 34 Weeks of Gestation

Fetal Lung Volume (mL)	Mortality (%)	ECMO Requirement (%)
5	84	80
10	56	69
15	23	57
20	7	43
25	1.8	30
30	0.4	20
35	0.1	13
40	0.02	7.8

Note—EMCO = extracorporeal membrane oxygenation.

Discussion

Once any associated fatal defects such as chromosomal abnormalities have been ruled out, perinatal outcome among infants with CDH depends primarily on the degree of lung hypoplasia and persistent pulmonary hypertension [5–7, 13, 25, 26]. With the introduction of conventional ventilation strategies and a substantial increase in the proportion of patients with a prenatal diagnosis [3] who are delivered at specialized centers, the prognosis of CDH has improved over the past decade [1, 8–10, 27]. Particularly among patients with respiratory failure within the first 24 hours of life,

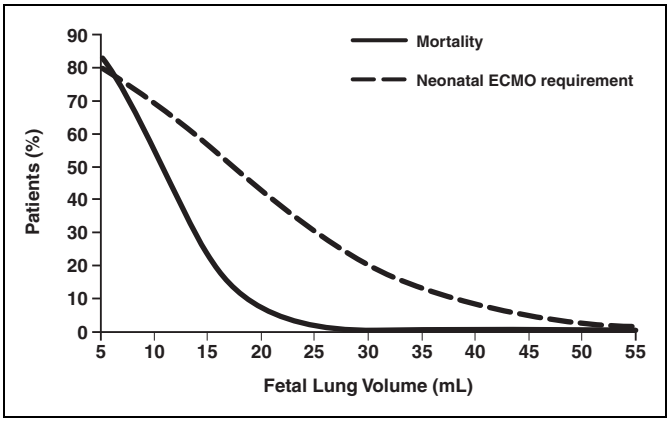

Fig. 2—Graph shows results of logistic regression analysis of mortality and probability of need for neonatal extracorporeal membrane oxygenation (ECMO).

prompt, intensified care is known to improve survival rate [28–32]. It has proved difficult, however, to accurately assess prenatal prognostic markers, and predicting survival among these infants continues to be a challenge.

The lung-to-head ratio measured with sonography has been proposed as a reliable means of helping to predict postnatal survival. In isolated left-sided CDH, the lung-to-head ratio is the product of the orthogonal diameters of the right lung at the level of the cardiac atria divided by the head circumference. Several prospective and retrospective studies have shown that cutoff levels of lung-to-head ratio of 1 and 1.4 can be applied in predicting fetal outcome. The predicted survival rate is 100% for a lung-to-head ratio greater than 1.4, and the predicted mortality is 100% for a lung-to-head ratio less than 1 [11–13, 33]. A considerable number of these patients, however, have intermediate values, and our ability to predict outcome among these patients is limited, survival rates ranging from 38% to 61% [11, 13, 33]. Jani et al. [34] described a detailed association between lung-to-head ratio and postnatal outcome, the survival rate ranging from 17% to 78%. The data in that study, however, were limited to fetuses in early pregnancy (25–29 weeks' gestation) with associated liver herniation and a lung-to-head ratio of only 0.9 or less. Other studies [14, 35, 36] did not confirm a predictive value of the lung-to-head ratio for either survival or postnatal clinical course, including the need for ECMO therapy.

Relative fetal lung volume assessed with prenatal MR planimetry has been described as a prognostic marker. Gorincour et al. [17] observed marked impairment in the survival rate among infants with a relative fetal lung volume less than 25% of the expected volume. Those authors, however, did not provide more accurate calculation of individual survival likelihood, nor did investigators in subsequent studies on this topic [16–19].

The first aims of our study were to evaluate a new technique of prenatal estimation of individual likelihood of survival among infants with isolated CDH and to determine the corresponding probability of need for ECMO therapy. Using logistic regression analysis, we found that fetal lung volume assessed with prenatal MR planimetry at 32–34 weeks' gestation is significantly associated with survival and need for neonatal ECMO. These findings show that fetal lung volume assessed with MR planimetry can be used for reliable estimation of the postnatal course of each patient. MRI fetal lung volume measurement may even be preferable to lung-to-head ratio as a predictive parameter because measurement accuracy and reliability have been shown to be high, with a low intraobserver and interobserver variability [37]. Moreover, imaging quality is almost unaffected by maternal obesity, oligohydramnios, and an unfavorable fetal position.

The main limitation of our study was that we restricted the patient cohort to fetuses between 32 and 34 weeks' gestation, that is, late pregnancy. However, we imposed this restriction deliberately to first assess the prognostic power of the method free from a potential effect of gestational age. Our study was designed not to identify infants who might benefit from prenatal high-risk interventions such as fetal endotracheal balloon implantation [38, 39] but to improve prenatal parental counseling and decisions on postnatal therapy, including ECMO therapy.

Ability to identify fetuses most severely affected in the perinatal period would be invaluable in selecting patients for high-risk interventions. Although an initial randomized trial by Harrison et al. [40] was terminated early by the steering committee because of unexpectedly good outcome in the control group, fetal tracheal occlusion continues to be explored in Europe because further technical refinement may produce survival benefits among patients at high risk [39, 41]. Thus, further evaluation of logistic regression analysis based on MRI fetal lung volume measurements is necessary to assess the prognostic value of this method in early pregnancy to possibly identify fetuses who may benefit from minimally invasive fetal surgery.

Another limitation of our study was that the estimated risk of need for ECMO therapy calculated cannot necessarily be assigned to other centers because there are no universally accepted ECMO criteria. The inclusion and exclusion criteria used at our institution correspond to classic objective criteria for the need to institute ECMO therapy [20, 42, 43]. Nevertheless, procedures may vary among tertiary care centers.

Logistic regression analysis based on MRI fetal lung volume measurements in late pregnancy may serve as a reliable tool to help in prediction of fetal outcome and, consequently, in counseling of clinicians and parents facing difficult decisions in pre- and postnatal care.

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