OBSTETRICS

Prenatal prognosis in isolated congenital diaphragmatic hernia

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OBJECTIVE: A monocentric retrospective study of 79 neonates with isolated diaphragmatic hernia antenatally diagnosed was performed to identify prenatal parameters that may characterize the severity of the disease.

STUDY DESIGN: Postnatal treatment protocol included early high frequency ventilation, inhaled nitric oxide, and delayed surgery. Postnatal survival rate was 63.3%.

RESULTS: Age at diagnosis, polyhydramnios, and left ventricle/right ventricle index were not related with survival. None of the 9 left diaphragmatic hernias with intraabdominal stomach died. Neonatal mortality was significantly related with the side of the defect, intrathoracic position of the liver, the ratio of fetal lung area to head circumference value, and fetal lung volume ratio measured by resonance magnetic imaging.

CONCLUSION: No prenatal factor alone firmly predicts neonatal outcome. Clinicians should help stratify the severity of the disease and compare accurately different postnatal therapeutic strategies.

Key words: congenital diaphragmatic hernia, lung to head ratio, magnetic resonance imaging, prenatal diagnosis, pulmonary hypoplasia

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The sensitivity of prenatal ultrasound screening for congenital diaphragmatic hernia (CDH) reaches 60% in Europe.[1] This has 2 major advantages: the exclusion of commonly associated defects and the possibility of planning delivery at hospital with appropriate facilities for neonatal intensive care and surgical repair of the defect. Associated major congenital defects and chromosomal anomalies are most often predictive of lethal prognosis. In the case of isolated CDH, survival rate remains a matter of debate.[2] Death is mainly due to associated pulmonary hypoplasia and subsequent persistent pulmonary hypertension. Prenatal identification of the severity of pulmonary hypoplasia remains a challenge, and this can be partly achieved by ultrasonography or magnetic resonance imaging (MRI).[3] A wide variety of indices recorded by conventional ultrasound has been suggested, but most of them remain under debate.[3] Three-dimensional ultrasound is under investigation to evaluate fetal lung volume.[4] Recently a prospective multicenter study involving 77 fetuses with isolated CDH investigated the correlation between fetal lung volume measured by MRI and postnatal mortality.[5] However, postnatal management varied widely between institutions and postnatal outcome partly depends on the therapeutic modalities.

We reported a series of 79 patients with isolated CDH diagnosed prenatally. They were managed in the same institution between January 2000 and November 2005 by the same therapeutic protocol. Therapeutic modalities included early high-frequency ventilation and delayed surgery. Extracorporeal membrane oxygenation (ECMO) was not used. We analyzed the relationship among prenatal ultrasound factors currently recorded in our prenatal center, the fetal lung volume measured by MRI, and the postnatal outcome. Our purpose was to evaluate these factors in the prediction of postnatal mortality in a large group of patients treated with the same therapeutic modalities.

Materials and Methods

Between January 2000 and November 2005, 118 patients were referred to the fetal medicine center of Necker Hospital in Paris after antenatal diagnosis of CDH. Among them, there were 99 pregnancies with isolated CDH and 79 liveborn infants were admitted in the neonatal intensive care unit (NICU). Fetal karyotype obtained by amniocentesis was normal in all 79 cases. The following data were recorded prospectively according to the institutional protocol for prenatal investigations for CDH: (1) gestational age at ultrasound diagnosis; (2) potential prognosis features recorded by a detailed prenatal sonographic examination including the side of the hernia, amniotic fluid volume (normal vs polyhydramnios, defined as a large pocket of fluid of 8 cm or more), stomach position, and determination of thoracic liver herniation for the left CDH, left ventricle (LV)/right ventricle (RV) index estab-

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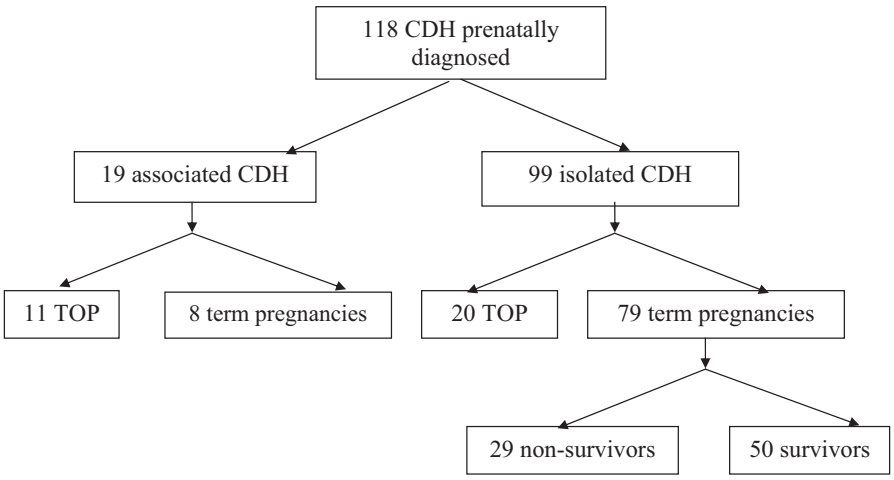
FIGURE 1
Outcome of CDH pregnancies



Outcome of pregnancies with prenatal diagnosis of CDH registered in Necker-Enfants Malades hospital between January 2000 and November 2005. *TOP*, termination of pregnancy.

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lished at mean gestational age of 32.1 weeks (range 22-37) by measuring the size of the LV and the RV on a 4-chamber view at the level of the ventricle annulus[6]; and (3) data recorded by fetal MRI including fetal lung volume (FLV) ratio measured by MRI in 62 cases during the third trimester (31.7 weeks [range 27-37]). The technique of MRI has been described previously.[7] Pulmonary volume was calculated according to the following formula: expected fetal lung volume (milliliters) = exp (1.24722 + 0.08939 × gestational age in weeks). The FLV ratio was expressed as the ratio of the measured to the expected fetal lung volume for the gestational age.

During the last 2 years of the study, the ratio of fetal lung area to head circumference (LHR) was measured by ultrasound in 28 cases of left CDH between 22 and 28 weeks of gestation. Measurement of the lung area was as described first by Metkus et al.[8] This involves first obtaining a transverse section of the fetal chest demonstrating the 4-chamber view of the heart, and second, multiplying the longest diameter by the longest perpendicular of the contralateral lung.

Postnatal management

All in-born babies were treated with the same strategy (1 infant born out of our institution was converted to this strategy on arrival). Neonates were nasally intubated in the delivery room and immediately transferred to the NICU. The first ventilator strategy used was high-frequency oscillation (Dräger 8000+, Dräger, Anthony, France), designed to limit barotrauma and lung distention. Sedation was performed by sufentanil and midazolam, but muscle paralyzing agents were avoided. Persistent pulmonary hypertension evaluated by echocardiography was managed by high FiO_2 and inhaled nitric oxide. Patients underwent surgical repair only after respiratory and hemodynamic stabilization had been achieved. The treatment protocol did not include prenatal corticosteroids, exogenous surfactant therapy, or ECMO.

Statistical analysis

Results are presented as mean and range or percentage. Estimates of survival were computed by using the Kaplan-Meier method. The relationship between mortality and the potential risk factors was investigated by using log-rank test for dichotomous variables or by using Cox proportional-hazard model for continuous variables, after proportionality of hazards had been checked. Multivariate analyses were made by using Cox proportional-hazard model. Comparison of fetal lung volume values between neonates with intraabdominal stomach and neonates with intrathoracic stomach was performed with use of Wilcoxon sum rank test.

A 2-sided P value of .05 or less was considered to indicate statistical significance. Statistical analyses were conducted with the R software, version 2.0.0.

This study was approved by the institutional review board.

RESULTS

Between January 2000 and November 2005, 118 patients with antenatal diagnosis of CDH were referred to the fetal medicine unit. Nineteen cases had associated anomalies and were eliminated. Elective termination of pregnancy was performed for 11 of them. Ninety-nine cases had isolated diaphragmatic hernia diagnosed at mean gestational age of 25.2 weeks (range 12-37). Termination of pregnancy was performed in 20 cases (20%). All 79 newborn infants with isolated CDH were admitted in the NICU (Figure 1). Only 1 infant was born out of our hospital after a short labor.

Mean gestational age at birth was 38.4 weeks (range 32-41) and mean birthweight was 3017 g (range 1665-4210). Among the 79 patients, 54 were male infants (68%, sex ratio 2:1). Thirteen were right (16.5%) and 66 were left CDH (83.5%). There was no anterior or bilateral diaphragmatic hernia. No associated anomaly was diagnosed after birth. Main prenatal characteristics of the 79 patients (survivor and nonsurvivors) are shown in Table 1.

Among the 79 patients managed in the NICU, the survival rate was 63.3% (range 53.5 to 74.9) at 1 month. None of the infants died after this period. Among the 29 patients who died, 24 were preoperative deaths and 5 were postoperative deaths. Twenty-eight patients died because of severe uncontrolled persistent pulmonary hypertension. In the last case, septic shock was responsible for the death.

Estimates of possible prenatal predictive factors (as individual relative

TABLE 1
Prenatal characteristics of 79 patients with congenital isolated diaphragmatic hernia according to the neonatal outcome

	Nonsurvivors (n = 29)	Survivors (n = 50)
Sex, number of males (%)	21 (72)	33 (66)
Mean gestational age at diagnosis, wks	23.6 (12-35)	26.1 (17-37)
Prenatal diagnosis less than 25 wks, n	21	28
Right diaphragmatic hernia, n	8	5
Intraabdominal stomach, n[a]	0	9
Intrathoracic liver, n[a]	11	10
Polyhydramnios, n (%)	12 (41)	21 (42)
LV/RV index	0.79 (0.47-1)	0.81 (0.5-1)
LHR[b]	1.1 (0.31-1.8)	1.7 (0.7-3.03)
FLV ratio, %	27.8 (7-78)	41.5 (16-82.6)

[a] Among left-sided defect.

[b] LHR ratio was measured for 10 nonsurvivors and 18 survivors.

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risks) for neonatal mortality are shown in Table 2. Age at the ultrasound diagnosis, polyhydramnios, and LV/RV index were not associated with mortality. Neonatal mortality was significantly associated with the side of the hernia, the intrathoracic position of the stomach, the intrathoracic position of the liver, LHR, and the FLV ratio. The FLV ratio equal to 30% appeared to be the threshold below which mortality was worse and above which survival rate was better. For this threshold, the positive predictive value was 60.8%, the negative predictive value was 71.8%, the sensitivity was 56%, and the specificity was 75.7%. We adjusted the analysis on those factors associated with significant risk of mortality, including position of the liver, LHR, and FLV ratio. As a consequence, right CDH was excluded. The multivariate analysis, performed for the 28 subjects who had antenatal measure of the LHR and MRI, demonstrated that only the LHR and the FLV ratio provide significant independent prediction of survival (Table 2). Postnatal outcome according to LHR value and FLV ratio are shown in Figures 2 and 3.

COMMENT

The aim of this study was to analyze the association between postnatal mortality and potential prenatal predictive factors in a series of 79 patients with isolated CDH managed in the same center during pregnancy and postnatal period. The measure of FLV ratio by MRI was the most accurate prognosis factor for left and right CDH. Intrathoracic liver and LHR were also accurate prognosis factors for left CDH.

We do not confirm the purported significance of some predictors previously reported in the literature, such as age at antenatal diagnosis,[6,8] polyhydramnios,[6,9] and LV/RV ratio.[6] Gestational age at diagnosis depends on screening programs efficacy. Recent multicenter studies report that the prenatal detection rate of CHD is approximately 60%.[1] The quality of ultrasound examination is the most significant factor contributing to the missed diagnosis.[10] One study suggested that LV hypoplasia, as determined by the LV/RV index, correlates with poor outcome. The difference between survivors and nonsurvivors was statistically significant between 31 and 40 weeks of gestation.[6] In our study, the LV/RV in-

TABLE 2
Prenatal factors and risk of mortality in isolated CDH

	n	RR (95% CI)	*P* value	Adjusted RR (95% CI)[a]	*P* value
Gestational age at diagnosis[a]	76	0.94 (0.87-1.01)	.088		
Side of the hernia[b]	79	0.36 (0.16-0.82)	.011		
Intrathoracic stomach[b]	66	ND	.043		
Intrathoracic liver[b]	66	3.14 (1.33-7.40)	.006	0.83 (0.15-4.61)	.83
Polyhydramnios[b]	79	1.08 (0.57-2.27)	.83		
LV/RV index[a]	65	0.74 (0.05-10.40)	.83		
LHR[a]	28	0.36 (0.17-0.77)	.009	0.43 (0.19-0.94)	.034
FLV ratio[a]	62	0.53 (0.37-0.74)	.0003	0.41 (0.19-0.85)	.018
FLV greater than 30%[b]	62	0.37 (0.17-0.81)	.010		

CI, confidence interval; *ND*, not determined because all nonsurvivors had an intrathoracic stomach.

[a] Cox proportional-hazard model. Relative risk (RR) was calculated for a 0.5 increase of LHR; RR was calculated for a 10% increase of FLV ratio.

[b] Log rank test. For intrathoracic stomach and intrathoracic liver, RR was calculated only for left CDH.

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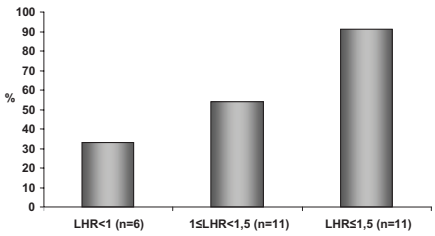
FIGURE 2
Survival of patients with CDH by LHR value



Survival of patients with congenital diaphragmatic hernia according to LHR value (n = 28). LHR was measured by ultrasound between 22 and 28 weeks.

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dex did not reach statistical significance in predicting outcome, but it was measured before 30 weeks in about 25% of the fetuses. On the other hand, VanderWall et al[11] showed that left heart dimensions and LV volume in fetuses with CDH did not predict postnatal outcome.

As described previously, right-sided CDH had a worse outcome.[12,13] The presence of intraabdominal stomach may be one of the most accurate predictor of outcome in left CDH. In our series, the 100% survival rate of the infants with intraabdominal stomach confirms previous studies reporting a survival rate better than 90%.[14,15] However, the practical interest of this element is limited because intraabdominal stomach was infrequent (9 of 66).

Other factors, such as liver position, LHR value, and FLV ratio measured by MRI, are currently under investigation to better assess their capacity in predicting outcome.[3] Our study confirms the influence of antenatal herniation of the liver on neonatal outcome of left CDH.[8,16-18] In multivariate analyses including parameters evaluating fetal lung size, liver position did not provide significant independent prediction. However, we consider that this multivariate analysis performed for only 28 subjects was not powerful enough because of the relatively small number of patients in the subgroup.

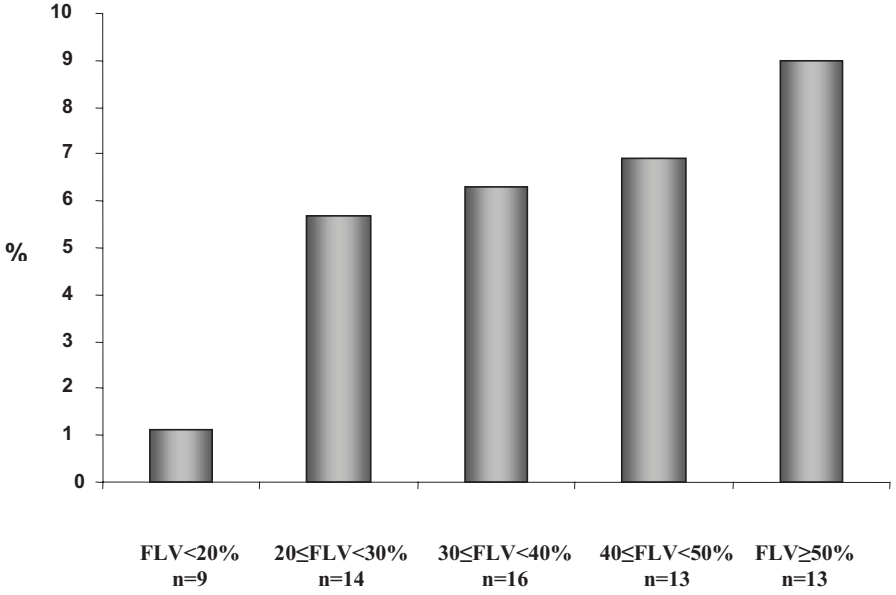
Although the predictive value of LHR is controversial,[8,18,19] it is a strong predictive factor in our study. It was significantly related with the outcome, although recorded in only 28 patients. We also found that FLV ratio was significantly related with mortality. Our findings are very similar to those quoted by Gorincour et al.[5] In their study, the survival gap became significant when the ratio value for FLV was below 25%. We found that mortality was worse when the FLV ratio was below 30%. This information may help parents during pregnancy to anticipate the severity of their fetus's disease. However, the statistical data do not allow assessing firmly the postnatal outcome in individual case during prenatal counseling.

The goal of LHR and FLV measures is to evaluate pulmonary hypoplasia based on the estimation of fetal pulmonary volume, but it does not allow functional evaluation of pulmonary vasculature. This is illustrated in our series by the postnatal death of 1 infant with LHR greater than 1.5 and 5 infants with FLV 40% or greater and the survival of 2 infants with LHR less than 1 and 1 infant with FLV greater than 20%. It is also confirmed by the poor sensitivity and the poor predictive value when the threshold for FLV was 30%.

We are aware that information obtained by MRI was established late in pregnancy, reflecting the fact that most patients were not referred until the third trimester. This may be of limited relevance in decision making relative to prenatal therapeutic intervention and to termination of pregnancy, especially in countries in which third-trimester medical termination of pregnancy is illegal. Fetal endoscopic tracheal occlusion by an inflatable balloon is a new strategy in the management of CDH that may improve survival.[20] It requires the ability to detect those fetuses more severely affected as soon as the second trimester. A second-trimester prospective study is needed to establish the prognosis value of FLV ratio by MRI. This data associated with LHR measure between 22 and 28 weeks may help to better stratify patients with CDH.

The postnatal survival rate in this study is consistent with those reported in the literature, although all reported cases were exclusively prenatally diagnosed, which is usually considered of worse prognosis.[2,21] The postnatal survival rate

FIGURE 3
Survival of patients with CDH by FLV ratio



Survival of patients with CDH according to FLV ratio. MRI was performed in 62 of 79 patients between 27 and 37 weeks.

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also did not differ from those reported with the use of ECMO, although we did not offer this therapy because we were aware of resulting poor outcome and severe morbidity.[22–24] In newborns for which CDH is an isolated anomaly, the degree of associated pulmonary hypoplasia remains the major determinant of survival. Current evidence suggests that better outcome may be achieved by delivering infants with CDH at experienced centers, delaying surgery until an acceptable degree of hemodynamic and respiratory stability is achieved, and judicious utilization of nonaggressive mechanical ventilation.[22,25] However, comparing survival rates between institutions according to therapeutic modalities is not really informative if the severity of the disease among the different populations is not estimated.

We have shown that prenatal investigations such as fetal ultrasound and MRI allow analyzing anatomic factors with statistical predictive value for the outcome. We propose the use of these prenatal factors to characterize the severity of pulmonary hypoplasia in patients with isolated CDH managed among the different institutions. A stratification scheme based on these prenatal parameters should be designed to allow better comparison of outcome data from the different NICUs.

In conclusion, some prenatal factors may help evaluate the outcome of infants with CDH, but because none of these factors strictly allow establishing prognosis during pregnancy, they should be used with caution in prenatal management. However, these factors could be used in the postnatal course to estimate the risks for populations with isolated CDH. This will allow clinicians to compare more accurately the different therapeutic modalities and improve the quality of the research for the future therapeutics. ■

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