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Prenatal prediction of survival in isolated left-sided diaphragmatic hernia

J. JANI*, R. L. KELLER†, A. BENACHI‡, K. H. NICOLAIDES§, R. FAVRE¶, E. GRATACOS**, J. LAUDY††, V. EISENBERG‡‡, A. EGGINK§§, P. VAAST¶¶ and J. DEPREST* on behalf of the Antenatal-CDH-Registry Group***

*Fetal Medicine and Treatment Units of the *University Hospital Gasthuisberg, Leuven, Belgium, †University of California at San Francisco, San Francisco, CA, USA, ‡Hôpital Necker-Enfants Malades, Paris, France, §King's College Hospital, London, UK, ¶CMCO de Schiltigheim, Strasbourg, France, **Vall d'Hebron Hospital, Barcelona, Spain, ††Erasmus Medical Center, Rotterdam, The Netherlands, ‡‡Sheba Medical Center, Tel Hashomer, Israel, §§UMC Sint Radboud, Nijmegen, The Netherlands and ¶¶Hôpital Jeanne de Flandre, CHRU Lille, France. ***The ad-hoc Antenatal-CDH-Registry Group also includes: D. Van Schoubroeck, G. Naulaers (Leuven, Belgium); M. Harrison (San Francisco, CA, USA); H. Vandecruys (London, UK); D. Mitanchez (Paris, France); J. Matis (Strasbourg, France); A. Delelis (Lille, France); O. Moreno (Barcelona, Spain); D. Tibboel (Rotterdam, The Netherlands); A. van Heijst (Nijmegen, The Netherlands); S. Lipitz (Tel Hashomer, Israel)*

KEYWORDS: diaphragmatic hernia; lung area; lung to head ratio; prenatal diagnosis; pulmonary hypoplasia

ABSTRACT

Objective *To investigate the potential value of antenatally determined intrathoracic herniation of the liver and the ratio of fetal lung area to head circumference (LHR) in the prediction of postnatal survival in isolated, left-sided congenital diaphragmatic hernia (CDH).*

Methods *In this multicenter study, we searched the antenatal-CDH-Registry for fetuses with isolated left-sided CDH that were liveborn after 30 weeks of gestation and were followed up postnatally for at least 3 months after discharge from hospital. The patients were subdivided into those with and those without intrathoracic herniation of the liver and into subgroups according to the LHR that had been measured between 22 + 0 and 28 + 0 weeks of gestation. The rate of survival in each group and subgroup of patients was determined and compared.*

Results *The registry search identified 184 patients that fulfilled the entry criteria. Logistic regression analysis demonstrated that significant predictors of survival were the presence or absence of intrathoracic herniation of the liver and the LHR. In 86 cases there was liver herniation (Group A) and in 98 the liver was confined to the abdomen (Group B). In Group A, the survival rate was 50.0% and was significantly associated with LHR; in Group B the survival rate was 76.5% and was unrelated to LHR.*

Conclusion *In isolated, left-sided CDH, the postnatal mortality rate is substantially higher if there is intrathoracic herniation of the liver. In fetuses with liver herniation, measurement of LHR at 22–28 weeks of gestation is useful in the prediction of subsequent survival. Copyright © 2005 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Congenital diaphragmatic hernia (CDH), with a birth prevalence of about 1 in 4000, is associated with high perinatal mortality. Extensive animal and human studies have attempted to improve outcome by intrauterine surgical intervention[1–3]. One of the major challenges in the antenatal assessment of CDH is the prediction of the postnatal outcome. In about 30% of cases of CDH there are associated chromosomal and major defects and in this group the prognosis is poor[4]. In the group with apparently isolated CDH, the survival rate is about 60%, with the remaining babies usually dying in the neonatal period due to pulmonary hypoplasia and/or pulmonary hypertension[4–12].

Impaired lung development in CDH is thought to be the consequence of chronic intrauterine compression of the lungs. Consequently, attempts at antenatal prediction of outcome have focused on assessment of the degree of mediastinal shift. The method most extensively studied is that of measurement of the ratio of fetal lung area to

Correspondence to: Dr J. Deprest, Department of Obstetrics and Gynaecology, Unit of Prenatal and Gynaecological Ultrasound and Fetal Therapy, UZ Gasthuisberg, 3000 Leuven, Belgium (e-mail: Jan.Deprest@uz.kuleuven.ac.be)

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head circumference (LHR). However, the reported results have been inconsistent, possibly because of the varied methodologies used in the estimation of lung area, the wide range in gestational age and the small number of cases examined in each study (Table 1)[5–11].

In this multicenter study we investigated further the potential value of LHR in the prediction of the postnatal outcome of prenatally diagnosed, apparently isolated, left-sided CDH.

METHODS

This is an ongoing multicenter study of fetal medicine units on the antenatal findings and postnatal outcome of fetal diaphragmatic hernia. The participating centers provide the necessary data, which are entered in a central antenatal-CDH-Registry at the fetal medicine unit in the University Hospital of Leuven, Belgium.

We searched the database to identify all consecutive cases of left-sided CDH, diagnosed from the year 1995 onwards, that fulfilled the following criteria: firstly, no major abnormalities diagnosed either prenatally or postnatally; secondly, live birth after 30 weeks of gestation and postnatal follow-up for at least 3 months after discharge from the hospital; thirdly, determination of liver herniation and measurement of fetal LHR at between $22+0$ and $28+0$ weeks of gestation. In all centers, measurement of the lung area was as described first by Metkus *et al.*[5] Essentially this involves firstly, obtaining a transverse section of the fetal chest demonstrating the four-chamber view of the heart, and secondly, multiplying the longest diameter by the longest perpendicular of the contralateral lung[5].

Statistical analysis

The patients were subdivided into those with and those without intrathoracic herniation of the liver and into subgroups according to the LHR. The rate of survival in each group and subgroup of patients was determined and compared. Univariate regression analysis was used to investigate the effect on survival of LHR, gestational age at the time of measurement of LHR, gestational age at delivery and year of management (between 1995 and 2004) as continuous numerical variables, and the place at which the patient was managed (USA and non-USA), and intrathoracic herniation of the liver (yes or no) as categorical variables. Multiple logistic regression analysis was performed subsequently to determine the significant independent contribution of those variables yielding a P-value of < 0.05 in the univariate analysis. Statistical analysis of data was performed with SPSS for Windows (V.12, Chicago, IL, USA).

RESULTS

The search of the antenatal-CDH-Registry identified 184 patients who fulfilled the entry criteria. These patients were examined antenatally in one of the following non-USA units: University Hospital Gasthuisberg, Leuven, Belgium; Hôpital Necker Enfants Malades, Paris, France; King's College Hospital, London, UK; Vall d'Hebron Hospital, Barcelona, Spain; CMCO, Schiltigheim, Strasbourg, France; Erasmus Medical Center, Rotterdam, The Netherlands; Sheba Medical Center, Tel-Hashomer, Israel; UMC Sint Radboud, Nijmegen, The Netherlands; Hôpital Jeanne de Flandre, Lille, France; in the USA they were examined in the University of California at San Francisco, San Francisco, CA, USA. Survival rates

Table 1 Studies reporting on the value of fetal lung area to head circumference ratio (LHR) in the prediction of survival in isolated left-sided congenital diaphragmatic hernia

Reference	n	*Percentage with intrathoracic liver herniation*	*Gestational age at LHR measurement (weeks)*	*LHR cut-off*	*Survival (%)*
Metkus *et al.* 1996[5]	38	≥ 80	≤ 25	< 0.6	0
				0.6–1.35	57
				> 1.35	100
Lipshutz *et al.* 1997[6]	15	Not given	24–26	< 1.0	0
				1–1.4	38
				> 1.4	100
Harrison *et al.* 1998[7]	13	100	20	< 1.0	20
				1.0–1.4	57
Flake *et al.* 2000[8]	47	Not given	23–25	< 1.0	0
				1–1.4	56
				> 1.4	85
Sbragia *et al.* 2000[9]	20	0	16–26	< 1.4	89
				≥ 1.4	73
Laudy *et al.* 2003[10]	21	Not given	28–37	< 1.0	0
				1–1.4	38
				> 1.4	100
Heling *et al.* 2005[11]	22	64	16–38	< 1.0	67
				1.0–1.4	60
				> 1.4	40

Table 2 Regression analysis in the prediction of survival in fetuses with isolated left-sided congenital diaphragmatic hernia

		Survival			
		Univariate analysis		*Multivariate analysis*	
Variable	n *(%) or median (range)*	*OR (95% CI)*	P	*OR (95% CI)*	P
Intrathoracic herniation of liver					
No (Group B)	98 (53.3)	1	< 0.0001	1	
Yes (Group A)	86 (46.7)	0.31 (0.16–0.58)		0.48 (0.24–0.95)	0.035
Place of neonatal management					
Non-USA	107 (58.2)	1			
USA	77 (41.8)	1.75 (0.93–3.27)	0.081		
LHR	1.2 (0.4–2.6)	11.6 (4.12–32.79)	< 0.0001	8.77 (3.0–25.6)	< 0.0001
Gestation at LHR (weeks)	25 (22–28)	1.07 (0.90–1.27)	0.425		
Gestation at delivery (weeks)	38 (31–42)	1.12 (0.95–1.33)	0.174		
Year of management	2001 (1995–2004)	1.03 (0.92–1.16)	0.612		

LHR, lung area/head circumference; OR, odds ratio.

of these patients were comparable between places of neonatal management (Table 2). This remained so when comparing survival rates of individual centers (data not shown).

Univariate regression analysis demonstrated that significant predictors of survival were the presence or absence of intrathoracic herniation of the liver and LHR (Table 2). Multiple logistic regression analysis demonstrated that liver herniation and LHR provided significant independent prediction of survival. However, the prediction of survival based on LHR was better in those with liver herniation than it was in those without herniation (odds ratio, 26.56 vs. 3.25).

In 86 cases there was intrathoracic herniation of the liver (Group A) and in 98 the liver was confined to the abdomen (Group B). In Group A, 43/86 (50.0%) babies survived after delivery at 31–42 (median, 38) weeks of gestation and the rate of survival increased with LHR (Table 3; Figure 1). In the 43 babies that died, the primary cause of death was pulmonary hypoplasia and/or hypertension in all cases.

In Group B, 75/98 (76.5%) babies survived after delivery at 32–42 (median, 39) weeks of gestation. In the 23 babies that died, the primary cause of death was pulmonary hypoplasia and/or hypertension in 21 cases and sepsis in two. There was no significant difference in median LHR between those who survived (median, 1.4; range, 0.6–2.6) and in those who died (median, 1.3; range, 0.7–2.3) (Table 3; Figure 1).

Table 3 Survival rate according to the fetal lung area to head circumference ratio (LHR) at 22–28 weeks in fetuses with and without intrathoracic herniation of the liver

	Intrathoracic herniation of the liver			
	Yes (Group A)		*No (Group B)*	
LHR	n	*Survival* (n *(%))*	n	*Survival* (n *(%))*
0.4–0.5	2	0		
0.6–0.7	6	0	4	3 (75.0)
0.8–0.9	19	3 (15.8)	15	8 (53.3)
1.0–1.1	23	14 (60.9)	11	11 (100.0)
1.2–1.3	19	13 (68.4)	15	10 (66.7)
1.4–1.5	11	8 (72.7)	25	18 (72.0)
≥ 1.6	6	5 (83.3)	28	25 (89.3)
	86	43 (50.0)	98	75 (76.5)

DISCUSSION

The findings of this study demonstrate that isolated, left-sided CDH is associated with a high rate of postnatal death (about 40%), due primarily to pulmonary hypoplasia and/or hypertension. Furthermore, the data show that the mortality rate is substantially higher if there is intrathoracic herniation of the liver (about 50% vs. 24%). In fetuses with intrathoracic herniation of the liver, measurement of LHR at 22–28 weeks of gestation is useful in the prediction of subsequent survival. In contrast, in the group without liver herniation, LHR is not significantly different between those that die subsequently and those that survive.

The overall mortality rate of about 40% is compatible with the results of previous reports[4–11]. A recent review of a British-based regional case registry reported that the overall mortality rate of antenatally diagnosed CDH was 64% and in those with isolated lesions that were liveborn the subsequent mortality rate was 30%[12]. Our study showed the survival rates to be consistent for all participating centers, irrespective of their location. Contrary to claims that the introduction of new postnatal therapies, such as extracorporeal membrane oxygenation, has improved survival, in reality, such improved rates have coincided with an increase in the rate of termination of pregnancy. Consequently, the apparent improvement in postnatal survival may be the result of case selection bias because of prenatal diagnosis and selective termination of pregnancies with likely poor outcome[12]. Furthermore, in studies reporting improved survival there was a concomitant increase in morbidity[13,14].

The findings of our study highlight the major influence on postnatal survival of antenatally detectable

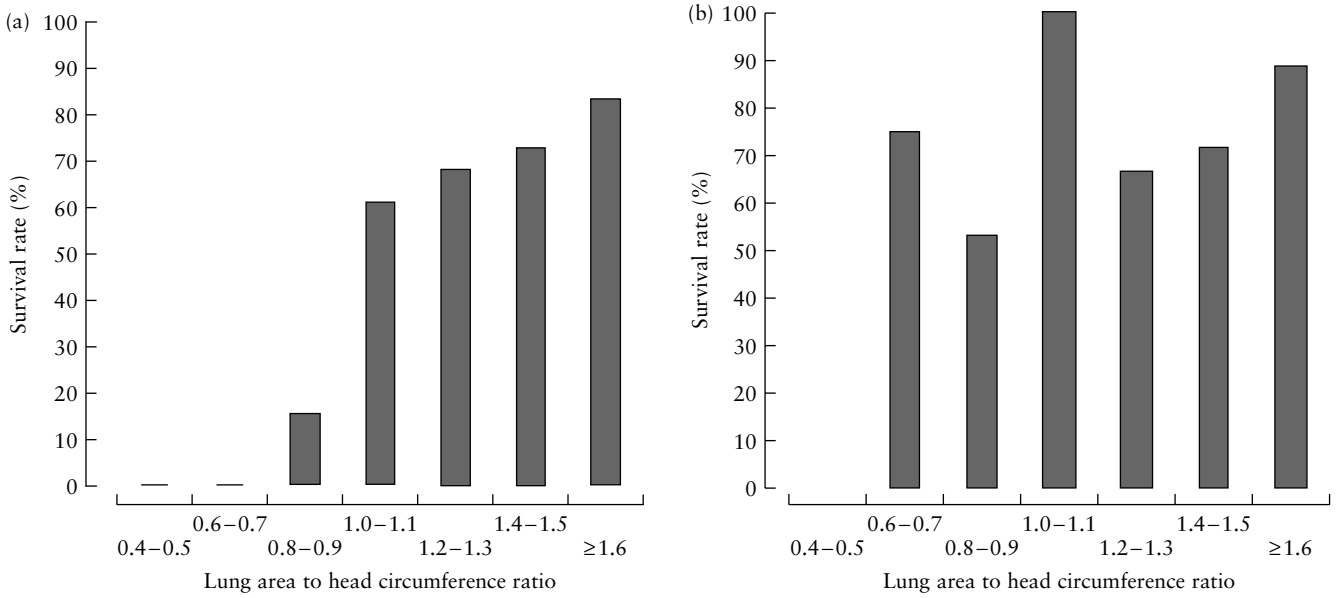

Figure 1 Survival rate according to the fetal lung area to head circumference ratio in fetuses with isolated left-sided diaphragmatic hernia (a) with intrathoracic herniation of the liver and (b) without herniation.

Table 4 Studies reporting on the value of intrathoracic liver herniation in the prediction of survival in prenatally diagnosed isolated left-sided congenital diaphragmatic hernia

Reference	*Method of assessment*	n	*Gestational age at assessment (weeks)*	*Survival* (n *(%))*	
				Intrathoracic liver	*No liver herniation*
Metkus *et al.* 1996[5]	Ultrasound	55	Not given	25/45 (56)	10/10 (100)
Albanese *et al.* 1998[15]	Ultrasound	42	Not given	13/27 (48)	14/15 (93)
Heling *et al.* 2005[11]	Ultrasound	22	16–38	6/14 (43)	7/8 (88)
Walsh *et al.* 2000[16]	MRI	41	20–39	9/22 (41)	15/19 (79)
Mahieu-Caputo *et al.* 2001[17]	MRI	11	28–37	0/5 (0)	4/6 (67)
Total		171		53/113 (46.9)	50/58 (86.2)

MRI, magnetic resonance imaging.

intrathoracic herniation of the liver. These results are compatible with previous reports (Table 4)[5,11,15–17]. In the combined data from five previous studies in fetuses with isolated, left-sided CDH, the respective survival rates were 46.9% (53/113) and 86.2% (50/58) in those with and those without intrathoracic liver herniation.

In the group with intrathoracic herniation of the liver there was an inverse correlation between LHR at 22–28 weeks of gestation and subsequent survival. Essentially, the survival rate increased from 0% for those with an LHR of 0.4–0.7 to about 15% for an LHR of 0.8–0.9, 65% for an LHR of 1.0–1.5 and more than 80% for an LHR of 1.6 or more. The poor prognosis for fetuses with LHR below 1.0 has also been reported in all but one of the previous studies examining the association between fetal LHR and outcome (Table 1). Consequently, in fetuses with LHR below 1.0, the parents should be counseled as to the likely poor prognosis and in countries where late termination is legal they should be given this option. If abortion is not legal or if the parents choose to continue with the pregnancy, then avoiding Cesarean section for fetal indications may be preferred. Preliminary data suggest that another strategy in the management of such patients is fetoscopic tracheal occlusion (FETO) by means of an inflatable balloon that may improve survival. In consecutive reports on prenatally treated fetuses with LHR below 1.0 and intrathoracic herniation of the liver, approximately 50% of babies survived after fetal surgery, both for left- as well as right-sided CDH[3,18].

In pregnancies with a fetal LHR of 1.6 or more the parents should be reassured that the likely outcome is good and they should be encouraged to continue with the pregnancy without the need for any intrauterine therapeutic intervention. In fetuses with intermediate LHR (1.0–1.5) the overall survival is 65% and the extent to which this could be improved by prenatal intervention remains to be determined.

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