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Prenatal prediction of neonatal morbidity in survivors with congenital diaphragmatic hernia: a multicenter study

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KEYWORDS: congenital diaphragmatic hernia; lung area; lung to head ratio; postnatal morbidity; prenatal diagnosis

ABSTRACT

Objectives *To investigate the value of the observed to expected fetal lung area to head circumference ratio (o/e LHR) and liver position in the prediction of neonatal morbidity in survivors with congenital diaphragmatic hernia (CDH).*

Methods *Neonatal morbidity was recorded in 100 consecutive cases with isolated CDH diagnosed in fetal medicine units, which were expectantly managed in the prenatal period, were delivered after 30 weeks and survived until discharge from hospital. Regression analysis was used to identify the significant predictors of morbidity, including prenatal and immediate neonatal findings.*

Results *The o/e LHR provided significant prediction of the need for prosthetic patch repair, duration of assisted ventilation, need for supplemental oxygen at 28 days, and incidence of feeding problems. An additional independent prenatal predictor of the need for patch repair was the presence of fetal liver in the chest.*

Conclusions *In isolated CDH the prenatally assessed size of the contralateral lung is a significant predictor of the need for prosthetic patch repair, the functional consequences of impaired lung development and occurrence of feeding problems. Copyright © 2008 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a surgically correctable anatomical defect occurring in about one in 5000 live births. In about 40% of cases there are multiple other defects and in this group the rate of neonatal death is about 85%[1–3]. In 60% of cases the defect is isolated and in this group the survival rate is between 50 and 70%[3–5]. In some series higher survival rates have been reported, but there is uncertainty whether this is the consequence of improved neonatal care, high case load or reflection of a selection bias with the most severe cases undergoing termination of pregnancy[4–6].

The widely accepted approach to neonatal care includes respiratory support until the baby is stable and then surgery. At surgery the aim is to close the diaphragmatic defect by primary repair, but in severe cases the application of a patch is necessary. Respiratory support essentially relies on oxygen supplementation, mechanical ventilation and, in cases with evidence of pulmonary hypertension, the administration of nitric oxide among others[7]. Pulmonary hypoplasia, abnormal pulmonary vasculature and lung injury secondary to mechanical ventilation are thought to be the underlying cause of both mortality as well as long-term respiratory morbidity[8]. A commonly encountered problem in both the neonatal period and in the long term is gastroesophageal reflux requiring antacid medication, fundoplication and occasionally chronic gastric feeding[9].

Several studies of CDH infants have reported on the prenatal prediction of postnatal survival, which essentially relies on the indirect assessment of fetal lung volume and whether there is intrathoracic herniation of the liver[10–14]. The most commonly used method for assessment of lung volume is measurement of the contralateral lung area to head circumference ratio (LHR)[10,12]. However, the LHR increases with gestation and it is therefore preferable to

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use the observed to expected normal mean for gestation (o/e) LHR to obtain a gestation-independent prediction of postnatal survival[15]. In a multicenter study, involving 329 fetuses with isolated left-sided CDH, we found that the rate of postnatal survival increased from 18% at o/e LHR < 25% to 66% at o/e LHR 26–45% and 89% at o/e LHR > 45%[15].

In this multicenter study we examined the potential value of o/e LHR and position of the liver in the prediction of neonatal morbidity.

METHODS

This is an ongoing multicenter study in fetal medicine and neonatal units on the antenatal findings and postnatal outcome of fetuses diagnosed with isolated CDH. 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. The study was approved by the hospital ethics committee.

Inclusion criteria

We searched the database to identify all consecutive cases of CDH, diagnosed in the participating fetal medicine units and fulfilling the following criteria: first, prenatal determination of liver herniation and measurement of fetal LHR, second, expectant antenatal management, third, gestational age at delivery more than 30 weeks, fourth, live birth between January 1996 and December 2005, fifth, no major congenital defects other than CDH and, sixth, survival at discharge from the hospital.

Prenatal ultrasound findings

The position of the fetal liver and the LHR measurement were determined by ultrasonographic examination. Measurement of the lung area was as described by Metkus *et al.*[10]. This essentially involves, first, obtaining a transverse section of the fetal chest demonstrating the four-chamber view of the heart and, second, multiplying the longest diameter by the longest perpendicular of the contralateral lung. In each case the observed LHR was divided by the appropriate normal mean for gestation[16] and multiplied by 100 to derive the o/e LHR, which was expressed as a percentage[15].

Outcome measures

The following outcome measures were examined: duration of hospitalization, need for a prosthetic patch for surgical repair of the defect in the diaphragm, duration of assisted ventilation, need for supplementary oxygen for at least 28 days after delivery, occurrence of pulmonary hypertension with evidence on cardiac ultrasound imaging of predominant unidirectional right to left shunt[17], and age at full enteral feeding. We did not include the use of extracorporeal membrane oxygenation (ECMO) as one of our outcome measures because the majority of patients were managed in centers that did not offer this technique.

Statistical analysis

Logistic regression analysis was used to identify significant contributors in the prediction of duration of hospitalization including year of delivery, prenatal findings (o/e LHR and gestational age in weeks as continuous variables, side of diaphragmatic hernia and intrathoracic herniation of the liver as binary variables), immediate neonatal findings (gestational age at delivery in weeks, birth weight in kilograms and Apgar score at 5 min as continuous variables, and sex as a binary variable), the need for prosthetic patch repair as a binary variable, duration of assisted ventilation in days as a continuous variable, presence of evidence of pulmonary hypertension as a binary variable, and age at full enteral feeding as a continuous variable. For prediction of the need for a prosthetic patch in the surgical repair of the diaphragmatic hernia we examined the contribution of the year of delivery, prenatal findings (as above) and immediate neonatal findings (as above). For prediction of duration of assisted ventilation and need for supplementary oxygen for at least 28 days after delivery, we examined the contribution of year of delivery, prenatal findings (as above), immediate neonatal findings (as above), and presence of evidence of pulmonary hypertension (yes or no). For prediction of pulmonary hypertension, we examined the contribution of year of delivery, prenatal findings (as above) and immediate neonatal findings (as above). For prediction of age at full enteral feeding, we examined the contribution of year of delivery, prenatal findings (as above), immediate neonatal findings (as above), need for antacid medication at discharge and need for fundoplication before discharge from hospital as binary variables.

The data were analyzed using the statistical software packages SPSS 14.0 (Chicago, Illinois, USA) and Excel for Windows 2000 (Microsoft Corp., Redmond, WA, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Search of the registry identified 127 cases fulfilling the entry criteria but all details on selected outcome measures were available in only 100 cases and these subjects were included in the study. There were no significant differences in prenatal and delivery data between the 100 cases included in the study and the 27 excluded cases.

The gestational age, and findings at prenatal assessment, at delivery and in the neonatal period are summarized in Table 1.

Prenatal ultrasound findings

In 95 cases the CDH was left sided and in five it was right sided. There was intrathoracic herniation of the liver in

Table 1 Prenatal and neonatal findings in 100 cases of isolated diaphragmatic hernia

Prenatal and neonatal findings	*Median (range) or* n *(%)*
Gestational age at prenatal ultrasound imaging (weeks)	27 (20–39)
Observed to expected LHR (%)	43 (15–83)
Left-sided diaphragmatic hernia	95 (95)
Intrathoracic herniation of the liver	24 (24)
Gestational at delivery (weeks)	39 (34–42)
Infant gender male	63 (63)
Birth weight (kg)	3.0 (1.8–4.3)
Apgar score at 5 min*	8 (1–10)
Age at surgery (days)	3 (1–16)
Need for prosthetic patch repair	23 (23)
Duration of hospitalization (days)	38.5 (10–184)
Duration of assisted ventilation (days)	13 (2–130)
Duration of high-frequency ventilation (days)†	2 (1–20)
Duration of supplemental oxygen (days)	14 (0–423)
Need for supplemental oxygen at 28 days	23 (23)
Pulmonary hypertension	31 (31)
Age at full enteral feeding (days)	23 (4–210)
Antacid medication at discharge	52 (52)
Fundoplication before discharge	10 (10)

*Recorded in 73 of the neonates. †Used in 77 of the neonates. LHR, lung area to head circumference ratio.

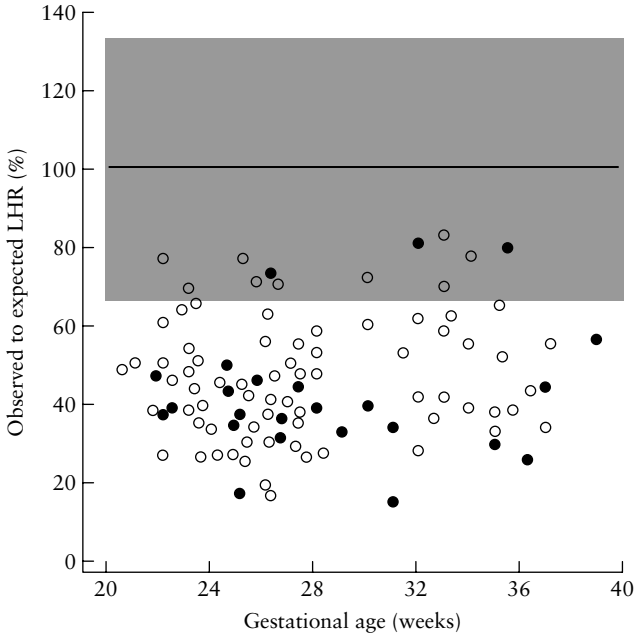

Figure 1 Relationship between observed to expected lung area to head circumference ratio (LHR) and gestational age in fetuses with congenital diaphragmatic hernia with (●) and without (○) intrathoracic liver herniation. The shaded area corresponds to the normal range (mean, 5th and 95th centiles)[16].

24 cases and the liver was confined to the abdomen in 76 cases. The median o/e LHR was 43.4 (range, 14.9–82.7)%; it was < 25% in four cases including two with intrathoracic herniation of the liver, 26–45% in 50 cases including 15 with liver herniation, and > 45% in 46 cases including seven with liver herniation (Figure 1).

Outcome measures

The significant independent contributors to the prediction of neonatal measures of morbidity are summarized in Table 2. The predicted outcomes are presented according to o/e LHR in Table 3. The o/e LHR was significantly associated with the duration of assisted ventilation (o/e LHR (%) = 51.49 − 0.37 × duration of ventilation in days; $r = -0.3596$, $P < 0.001$) (Figure 2). The position of the fetal liver provided significant additional contribution to the o/e LHR in the prediction of the need for patch repair; this was required in 10/24 (41.7%) cases with intrathoracic liver herniation and in 13/76 (17.1%) with no herniation.

DISCUSSION

This study has demonstrated that in isolated CDH the antenatally assessed size of the contralateral lung is a significant predictor of, first, the need for prosthetic patch repair and therefore the size of the diaphragmatic defect, second, the need for postnatal assisted ventilation and therefore the degree of impaired prenatal development of the lungs and, third, the incidence of feeding problems. An additional prenatal predictor of the need for patch repair was the presence of fetal liver in the chest.

The duration of hospitalization was determined by the presence of both respiratory and feeding problems. We chose duration of hospitalization, rather than duration of stay in the intensive care unit, as an endpoint for our study because the participating centers varied in their policy in terms of keeping babies with feeding problems without assisted ventilation in the intensive care or a lower-level care unit before discharge from hospital.

There are no previous reports on prenatal prediction of the need for prosthetic patch repair. Recently it has been shown that the need for patch repair is a measure of the severity of diaphragmatic hernia and of long-term

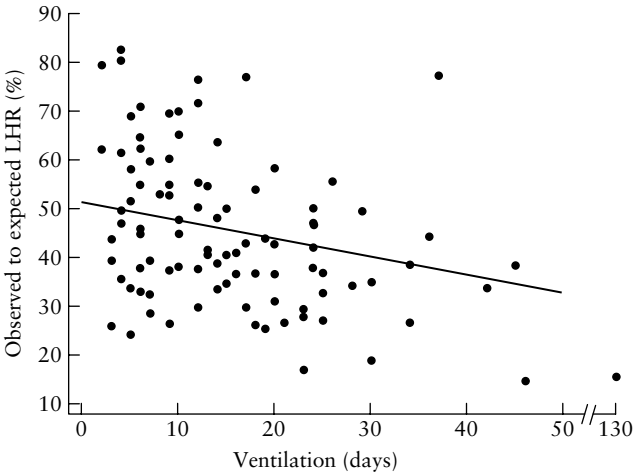

Figure 2 Relationship between observed to expected lung area to head circumference ratio (LHR) and duration of assisted ventilation in fetuses with congenital diaphragmatic hernia. The regression line is indicated.

Table 2 Significant predictors of neonatal measures of morbidity in 100 fetuses with isolated congenital diaphragmatic hernia from prenatal and neonatal variables

Neonatal measure of morbidity	*Median (range) or* n *(%)*	*Multivariate analysis*	*Coefficient of regression or OR (95% CI)*	P
Duration of hospitalization (days)	38.5 (10–184)	Duration of assisted ventilation	1.144 (0.858–1.431)	< 0.001
		Age at full enteral feeding	0.344 (0.176–0.513)	< 0.001
		Evidence of pulmonary hypertension	8.950 (0.083–17.818)	0.048
Need for prosthetic patch repair	23 (23)	Observed to expected LHR	0.943 (0.905–0.983)	0.006
		Intrathoracic herniation of the liver	2.991 (1.025–8.734)	0.045
Duration of assisted ventilation (days)	13 (2–130)	Observed to expected LHR	−0.345 (−0.516 to −0.173)	< 0.001
		Evidence of pulmonary hypertension	10.866 (5.098–16.634)	< 0.001
Need for supplemental oxygen at 28 days	23 (23)	Observed to expected LHR	0.954 (0.917–0.992)	0.020
		Birth weight	0.999 (0.998–1.000)	0.046
		Evidence of pulmonary hypertension	3.165 (1.099–9.116)	0.033
Evidence of pulmonary hypertension	31 (31)	Gestational age at delivery	1.426 (1.034–1.968)	0.031
Age at full enteral feeding (days)	23 (4–210)	Observed to expected LHR	−0.386 (−0.637 to −0.135)	0.003
		Antacid medication at discharge	12.018 (4.082–19.955)	0.003
		Fundoplication before discharge	42.288 (29.033–55.544)	< 0.001

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

Table 3 Neonatal measures of morbidity in 100 fetuses with isolated congenital diaphragmatic hernia according to prenatally determined observed to expected lung area to head circumference ratio (o/e LHR)

		o/e LHR		
Neonatal measure of morbidity	*Overall*	*≤ 25* (n = *4)*	*26–45* (n = *50)*	*> 45* (n = *46)*
Duration of hospitalization (days, median (range))	38.5	73 (60–184)	44 (13–180)	31 (10–112)
Need for patch repair (%)	23.0	75.0	32.0	8.7
Duration of assisted ventilation (days, median (range))	12.5	38 (23–130)	16 (3–45)	9 (2–37)
Need for supplemental oxygen at 28 days (%)	23.0	75.0	30.0	10.9
Age at full enteral feeding (days, median (range))	23.0	51 (24–210)	27 (5–70)	19 (4–92)

morbidity. In a 2-year follow-up study on infants with CDH, the incidence of chronic lung disease was 50% in the group with patch repair, compared with 11% in those not requiring patch repair, and the respective incidences of gastroesophageal reflux were 79% and 11%[18].

There was a significant association between o/e LHR and duration of assisted ventilation as well as the need for supplemental oxygen at 28 days. One previous study has also demonstrated an association between prenatal LHR and postnatal neonatal respiratory problems. In that study, ECMO was available and the incidence of severe respiratory problems in infants requiring ECMO was inversely associated with the fetal LHR at 23–25 weeks of gestation. ECMO was needed in all cases with a LHR ≤ 1.0 (equivalent to o/e LHR of ≤ 25%), in 78% of those with a LHR of 1.1–1.4 (equivalent to o/e LHR of about 26–45%) and in 33% of those with a LHR > 1.4 (equivalent to o/e LHR of more than 45%)[19]. Another 2-year follow-up study of infants with CDH reported that the incidence of chronic lung disease was 56% in the group with ECMO treatment, compared with 3% in those not requiring ECMO, and the respective incidences of cerebral palsy and developmental delay were 22% and 6%[18]. Another follow-up study evaluating infants with corrected CDH at 0.5–3.2 years of age reported that the incidence of pulmonary and non-pulmonary morbidity was related to the duration of ventilation during the neonatal period[20]. Consequently, it is likely that prenatally assessed size of the contralateral lung is a predictor not only of neonatal respiratory difficulties but also long-term pulmonary and non-pulmonary morbidity.

Pulmonary hypertension, in contrast to the need for ventilation and prolonged supplemental oxygen, was not predicted by the prenatal o/e LHR. The finding that pulmonary hypertension was associated with gestational age at delivery is compatible with the findings of an anatomical study which reported that in aborted fetuses or neonatal deaths with CDH, compared with abortions or neonatal deaths without CDH, the distal pulmonary arterial wall was significantly thicker only after 30 weeks, and this became worse with advancing gestation[21].

Feeding problems in the neonatal period, mainly related to gastroesophageal reflux, are commonly encountered

in infants with CDH and their incidence is related to the severity of pulmonary hypoplasia[9]. Actually, the incidence of feeding problems is related to oral aversion, a behavioral disorder that is directly related to the need for and duration of noxious oral stimulants such as endotracheal tubes and feeding tubes, the use of which is indirectly related to the severity of pulmonary hypoplasia requiring prolonged respiratory support. As demonstrated in our study there was an inverse association between o/e LHR and age at full enteral feeding. In the long-term gastroesophageal reflux is also associated with failure to thrive. The weight of infants with corrected CDH is below the 5th centile for age in about 30% of cases during the first year of postnatal life[9] and in 20% of cases during the second year[18].

The findings of this study and our previous investigation[15] of the relationship between o/e LHR and survival can be used as the basis for counseling parents. Thus, in expectantly managed fetuses with isolated CDH, if the prenatally assessed o/e LHR is $< 25\%$ only about 18% of the babies will survive and 75% of these will require patch repair; 75% will require supplemental oxygen for at least 28 days after birth and full enteral feeding will be achieved only after about 50 days of birth. In contrast, if the o/e LHR is $> 45\%$ about 89% of the babies will survive and $< 10\%$ of these will require patch repair; about 10% will require supplemental oxygen for at least 28 days after birth and full enteral feeding will be achieved on average within 20 days of birth.

Preliminary data suggest that intrauterine therapy by endoscopic placement of a balloon in the trachea at 26–29 weeks of gestation in fetuses with o/e LHR $< 25\%$ improves survival to about 50%[22,23]. The extent to which intrauterine therapy in these most severely compromised fetuses reduces postnatal respiratory morbidity compared with that in controls matched for o/e LHR remains to be determined. It is possible that the indications for intrauterine therapy may be expanded to include fetuses with an o/e LHR $> 25\%$ because, as demonstrated in the present study, a high proportion of such cases also have respiratory problems.

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