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The quantitative lung index and the prediction of survival in fetuses with congenital diaphragmatic hernia

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ABSTRACT

Introduction: The lung-to-head ratio (LHR) is routinely used to select the best candidates for prenatal surgery and to follow-up the fetuses with congenital diaphragmatic hernia (CDH). Since this index is gestation-dependent, the quantitative lung index (QLI) was proposed as an alternative parameter that stays constant throughout pregnancy. Our objective was to study the performance of QLI to predict survival in fetuses with CDH.

Materials and methods: Observational retrospective study of fetuses with isolated CDH, referred to our center. LHR was originally used for the prenatal surgery evaluation. We calculated the QLI and compared the performance of both indexes (QLI and LHR) to predict survival.

Results: From January-2009 to February-2015 we followed 31 fetuses with isolated CDH. The mean QLI was 0.66 (95% CI: 0.57–0.75) for survivors and 0.41 (95% CI: 0.25–0.58) for non-survivors ($p < 0.01$) and the mean LHR was 1.38 (95% CI: 1.17–1.60) for survivors and 0.91 (95% CI: 0.57–1.25) for non-survivors ($p < 0.02$). All operated fetuses ($n = 12$) had a LHR <1 and a QLI <0.5 and none of them survived when the QLI was <0.32. When separately considering the prenatal surgery status, the mean values of the QLI (but not those of the LHR) were still significantly different between survivors and non-survivors. The comparative ROC curves showed a better performance of the QLI with respect to the LHR for the prediction of survival, especially in the group of operated fetuses, although differences were not statistically significant.

Comment: The QLI seems to be a better predictor for survival than the LHR, especially for the group of fetuses undergoing prenatal surgery.

Introduction

The high perinatal mortality rate in congenital diaphragmatic hernia (CDH) is mainly related to lung hypoplasia and pulmonary arterial hypertension. For almost 20 years the efforts in prenatal diagnosis of CDH have been focused on developing the optimal algorithms to identify the best candidates for fetal therapy among the fetuses with the poorest prognosis and to predict survival after birth.

Lung-to-head ratio (LHR) is one of the best-known indexes to predict neonatal outcome in fetuses with congenital diaphragmatic hernia. It is routinely used to select fetuses for prenatal surgery of CDH, for the follow-up throughout pregnancy either in operated or non-operated fetuses, and to predict outcomes, namely postnatal survival.

The lung-to-head ratio was first described in 1996 by Metkus [1]. Some years later, the group of Peralta [2] and Jani [3] demonstrated that the LHR increases exponentially with gestational age (GA). They proposed to correct the observed LHR by the expected LHR (o/eLHR) in order to minimize the effect of gestational age on the LHR [3]. However, in 2011 Quintero et al. [4,5] demonstrated that the o/eLHR is also dependent on gestational age. To overcome this problem, they developed another sonographic tool, the quantitative lung index (QLI), based in a

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mathematical model and theoretically independent of gestational age [4]. Quintero found that the 50th percentile for the QLI was constant at 1.0 from 16 to 32 weeks for the right lung, and he defined a small lung when the QLI has less than 0.6, which is the first percentile [4].

Our objective was to study the performance of the QLI to predict survival among fetuses with CDH.

Materials and methods

We conducted an observational retrospective study on singleton pregnancies with fetuses carrying an isolated congenital diaphragmatic hernia, referred to our center (Hospital Universitari Vall d'Hebron, Barcelona, Spain) as candidates for prenatal tracheal occlusion (TO) with balloon placement.

All fetuses were scanned for the assessment of the CDH, to obtain biometric measurements and to rule out any other malformations, although the ones evaluated for the first time after 32 weeks of gestation were systematically excluded for TO. A normal genetic study consisting of karyotype or targeted arrays was ascertained for every patient included in this study. We selected one scan for each patient: For fetuses undergoing TO, we selected the scan made immediately before the intervention. For fetuses with expectant management, we chose the first scan made for the evaluation of the CDH in our center.

The measurements originally obtained for the assessment of the CDH and to select the best candidates for TO were: Lung-to-head ratio (ratio of 2 perpendicular diameters measured, in the lung contralateral to the hernia at the level of the four-chamber view, to the head circumference) [1] and observed/expected LHR, which is calculated as o/eLHR = (observed LHR/expected LHR) × 100. The expected values were obtained from those described by Peralta [2].

The allocation into TO or expectant management was based on the values of the LHR (<1), the o/e LHR (<25–45% for left CDH, <45% for right CHD) and the presence of intrathoracic liver (liver-up cases).

The formula for the calculation of the QLI was then applied retrospectively (QLI = right lung area/(head circumference/10)^2) with the measurements already available of the lung area, contralateral to the hernia, and the cephalic circumference. We used the 2 perpendicular diameters of the lung that had been used to obtain the LHR.

We first described the characteristics of the survivors and the non-survivors. We then assessed the QLI with respect to survival in the first 180 days after birth, in both groups with and without prenatal balloon placement.

We also evaluated the area under the curve (AUC) of the comparative receiver operating characteristic (ROC) curves for QLI and LHR to predict survival in the whole sample and also separately for the operated and non-operated groups.

As this was an observational retrospective study with previously taken measurements, no Ethics Approval was needed. We used the Student's test to compare means between groups and expressed the data obtained as mean (95% confidence interval). The statistical analyses were performed using the STATA 13.1 software package. A p value <0.05 was considered statistically significant.

Results

From January 2009 to February 2015 we assessed 56 fetuses with CDH at the Fetal Medicine Unit in Hospital Universitari Vall d'Hebron. Four cases were excluded since they were twin pregnancies, non-isolated cases of CDH or bilateral hernias. Twenty pregnancies were electively terminated before 22 weeks. We had 1 case lost to follow-up among the non-operated fetuses.

Among the remaining 31 fetuses with complete follow-up, there were a total of 12 with an indication for TO, based on a LHR below 1 and o/eLHR ≤45%; all of these cases had liver up inside the thorax, 10 were left-sided and 2 were right-sided.

Among the non-operated fetuses, 4 of them were more than 32 weeks at the time of referral therefore automatically excluded for surgery. Other 2 fetuses, both with right-sided hernias, had liver-up but were not allocated to TO because of their LHR and o/eLHR far above the cut-offs for surgery (LHR of 1.64 and 1.41 and o/eLHR of 85% and 75%, respectively).

The overall mortality rate in our study group was 25.8% (8/31) for the first 180 days of life. Table 1 describes the characteristics of both groups of surviving and non-surviving neonates.

Table 2 shows the characteristics of the 8 non-survivors. The cause of death was always directly related to hypoxia due to lung hypoplasia and severe pulmonary hypertension; in three cases, nosocomial sepsis was documented.

Table 3 shows the mean values and the 95% confidence interval of the QLI and the LHR and the p value for the mean difference

Table 1
Characteristics of the survivors and the non-survivors. CDH side was expressed as the percentage of left hernias vs the percentage of right hernias in each group. TO: Tracheal occlusion. GA: Gestational age. NS: Non-significant.

	N	CDH side (LvsR)	Liver-up	TO	GA at birth	Weight at birth
Survivors	23	83% vs 17%	44%	30%	37.5 w	2913 g
Non-survivors	8	75% vs 25%	88%	63%	35.7 w	2361 g
p Value		NS	0.03	NS	NS	NS

Table 2
Characteristics of the babies dead in the first 180 days of life. Case 3 was referred after 32 weeks of gestation therefore the o/eLHR is not available. TO: Tracheal occlusion. GA: Gestational age.

Case	CDH-side	Liver	LHR	OE-LHR	QLI	TO	GA at birth	Weight at birth	Days of life
1	Right	Up	1.64	85	0.83	No	39	2730	27
2	Right	Up	0.4	30	0.30	Yes	34	1490	66
3	Left	Up	0.8	–	0.26	No	37	2500	1
4	Left	Up	0.78	30	0.31	Yes	34	1780	1
5	Left	Down	1.38	56	0.60	No	39	3090	2
6	Left	Up	0.61	29	0.31	Yes	30	1500	10
7	Left	Up	0.84	30	0.34	Yes	37	3000	11
8	Left	Up	0.8	32	0.37	Yes	36	2800	2