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Follow-up of fetuses with congenital diaphragmatic hernia: The quantitative lung index

Carlota Rodó[a,*], Tamara Illescas[a], Silvia Arévalo[a], Santiago Pérez-Hoyos[b], Elena Carreras[a]

[a] Maternal-fetal Medicine Unit, Department of Obstetrics, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Spain
[b] Department of Statistics and Preventive Medicine, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Spain

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ABSTRACT

Objective: To assess the longitudinal behavior of Quantitative Lung Index (QLI) for the follow-up of fetuses with congenital diaphragmatic hernia.
Study design: Retrospective study of fetuses with isolated left congenital diaphragmatic hernia. The fetuses were assessed by ultrasound at different gestational ages and QLI was retrospectively calculated by means of previous lung-to-head ratio measurements. We used a random effects model (mixed model with repeated measurements) to compare the performance of the QLI in operated and non-operated fetuses throughout pregnancy.
Results: Fifty-eight cases of isolated left diaphragmatic hernia with complete follow-up were assessed in Hospital Universitari Vall d'Hebron in Barcelona (2003–2015). Thirty-eight of them were managed expectantly (non-TO) and the other 20 underwent tracheal occlusion (TO). All fetuses undergoing tracheal occlusion had lung-to-head ratio (LHR) <1, observed-to-expected LHR (o/eLHR) $\leq 45\%$, QLI <0.6 and liver up inside the thorax. The survival rate was 87% for the non-TO group and 60% for the TO group ($p = 0.02$). The QLI remained constant throughout pregnancy in both groups. The QLI in the TO group had lower values than the non-TO group ($p < 0.03$).
Conclusion: The quantitative lung index was constant during pregnancy. This index was lower in fetuses undergoing tracheal occlusion but no significant changes were seen in its performance during pregnancy.

Introduction

Congenital diaphragmatic hernia (CDH) is a rare disease with high perinatal mortality, mainly related to pulmonary hypoplasia and pulmonary hypertension. In the recent years all the efforts in prenatal diagnosis of CDH have been focused on developing prenatal indexes to identify the fetuses with the poorest prognosis, therefore the best candidates for fetal therapy, in an attempt to improve survival rates.

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 the best candidates for prenatal surgery and for the ulterior follow-up of these fetuses.

The LHR was first described in 1996 by Metkus [1], but it turned out to increase exponentially with gestational age (GA) [2,3] therefore reference values for right and left LHR in normal fetuses were established [2] and Jani et al. 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]. In 2011 Quintero et al. demonstrated that the o/eLHR is also dependent on gestational age [4,5] and they developed another sonographic tool based in a mathematical model, the quantitative lung index (QLI), which was theoretically independent of gestational age [4]. They defined the 50th percentile for the QLI being constant at 1.0 (for the right lung, from 16 to 32 weeks), and a small lung when was stated when the QLI was less than 0.6 (the first percentile) [4].

Later on, Ruano observed that the QLI is not totally independent of GA, but its variation throughout the pregnancy is much lower than the other indexes' [6].

The main objective of this study was to assess the longitudinal behavior of QLI throughout pregnancy. We hypothesised that QLI would remain constant and independent of gestational age. A secondary objective of the study was to determine if tracheal occlusion might influence the behavior of QLI throughout gestation.

* Corresponding author at: Maternal-fetal Medicine Unit, Department of Obstetrics, Hospital Universitari Vall d'Hebron, Passeig Vall d'Hebron 119-129, 08035 Barcelona, Spain.
E-mail address: crodo@vhebron.net (C. Rodó).

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Methods

This is a descriptive retrospective study on singleton pregnancies with fetuses carrying an isolated left CDH that had been referred to our center (Hospital Universitari Vall d'Hebron, Barcelona, Spain) as candidates for prenatal surgery (fetoscopic balloon placement for tracheal occlusion) from January 2003 to February 2015. A normal karyotype or targeted arrays were ascertained for every patient included in this study.

The fetal measurements originally obtained by ultrasound (US) for the assessment and management of the CDH cases were: Lung-to-head ratio (contralateral-to-the-hernia lung area to head circumference ratio) [1] and observed-to-expected LHR, which is calculated as o/eLHR = (observed LHR/expected LHR) × 100^3. The expected values were obtained from those described by Peralta [2]. The lung area was obtained using the 2 perpendicular diameters measured at the four-chamber view.

The allocation into surgery or expectant management had been based on: gestational age (fetuses older than 32 weeks old were excluded), LHR (<1), observed-to-expected LHR (<25% + liver down the abdomen and/or <45% and liver up into the thorax for left CDH; <45% for right CHD) and presence/absence of intrathoracic liver.

Demographic data of the patients, the status regarding surgery (operated/non-operated) and the outcomes of the pregnancy, namely neonatal survival in the first 180 days of life, were recorded.

Operated and non-operated fetuses were scanned twice weekly for the assessment of the CDH, to obtain biometric measurements, to rule out any other malformations and for the surveillance of the lung volume throughout gestation.

All fetal US scans in which the measurements of the cephalic circumference and the 2 perpendicular diameters of the lung were available were included. They were used for the retrospective calculation of the QLI (right lung area/(head circumference/10)^2) [4]. A QLI below 0.6 was used to define a small lung [4]. The LHR was already available since it had been previously obtained for the clinical decision-making process.

Statistical analysis

The values of the QLI throughout gestation were studied (QLI values against gestational age in weeks). As it was a repeated measurements problem, a random effects model was used to compare the performance of the QLI in operated vs non-operated fetuses, taking into account possible interactions with gestational age.

The χ^2 test was used to compare categorical variables and the t Student test for the quantitative ones. Statistical analyses were performed using STATA 13.1 and a p value <0.05 was considered statistically significant. As it was a retrospective study with previously taken measurements, no ethics approval by the local Review Board was needed.

Results

From January 2003 to February 2015, 155 fetuses with CDH were assessed at the Fetal Medicine Unit in Hospital Universitari Vall d'Hebron in Barcelona, Spain. Of them, 56 cases underwent termination of pregnancy before 22 weeks. Among the non-terminated cases, right-sided CDH (18 cases), bilateral hernias (1 case) and non-isolated cases of CDH (1 case) were excluded. We had 2 sets of twins and 2 cases that were more than 32 weeks at the time of evaluation, therefore not eligible for prenatal surgery and also excluded from the analysis. In addition, 13 patients were lost to follow-up. Finally, another 2 cases of failed fetoscopy and 2 cases of death not related to lung hypoplasia were excluded (one fetal death during tracheal occlusion and another at birth, before the balloon could be deflated).

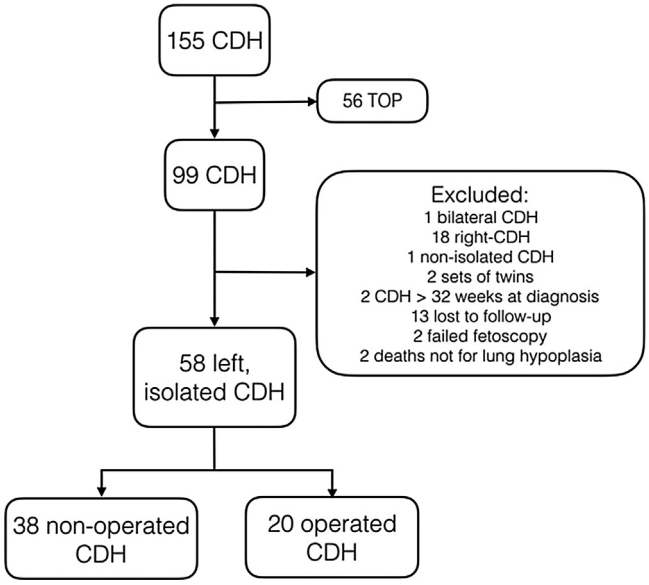

Fig. 1. Flowchart showing the included cases of congenital diaphragmatic hernia. CDH: congenital diaphragmatic hernia.

This led to a final sample of 58 cases of isolated left congenital diaphragmatic hernia with complete follow-up that were included for the analysis. Thirty-eight of them were managed expectantly (non-TO) and in the other 20 we performed a tracheal occlusion (TO) (Fig. 1).

Table 1 describes the characteristics of both groups: gestational age at diagnosis was similar in both groups of management (25.1 weeks in the non-TO group vs 22.9 in the TO group, $p > 0.05$), whereas maternal age (31.1 years in the non-TO vs 27.8 years in the TO group, $p = 0.03$); gestational age at delivery (38.7 weeks in non-TO vs 34.7 weeks in TO, $p < 0.01$); and birthweight (3118 g vs 2311 g in TO, $p < 0.01$) were significantly different for operated and non-operated fetuses. All fetuses undergoing TO had the LHR below 1, the o/eLHR ≤45% and the QLI below 0.6; all cases had liver up inside the thorax (against 35% of the non-operated fetuses, $p < 0.01$). For the TO group, the mean gestational age at tracheal occlusion was 26.8 weeks and the mean gestational age at balloon removal was 32.6 weeks. We performed elective balloon removal in all except two fetuses. The survival rate was 87% for the non-TO group and 60% for the TO group ($p = 0.02$).

During the follow-up of these 58 cases of left CDH, at least one and up to 14 ultrasound scans were performed from 16 weeks 5 days to 39 weeks 4 days of gestation. From these scans we obtained 305 ultrasound measurements of the cephalic circumference and the lung area for the ulterior calculation of LHR and QLI

Table 1
Characteristics of the pregnancies according to the type of management. Continuous variables are depicted as *mean (standard deviation)*.

	No TO (n = 38)	TO (n = 20)	*p* value
Maternal age (years)	31.05 (4.58)	27.75 (6.86)	0.03
GA at diagnosis (weeks)	25.09 (5.47)	22.93 (3.31)	>0.05
Liver up (%)	35	100	<0.01
GA at tracheal occlusion (weeks)	–	26.82 (2.22)	–
GA at balloon removal (weeks)	–	32.60 (2.85)	–
GA at delivery (weeks)	38.67 (1.78)	34.69 (2.75)	<0.01
Birthweight (grams)	3118.37 (548.53)	2311.57 (472.03)	<0.01
Survival rate (%)	87	60	0.02

TO: Tracheal occlusion. GA: Gestational age. NS: Not significant.