CLINICAL STUDY

Predicting Neonatal Outcome in Isolated Congenital Diaphragmatic Hernia Using Ultrasonographic Pulmonary Measurements

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Abstract

Objective: To study the potential of different methods of evaluating pulmonary measurements to predict neonatal outcome in cases with isolated congenital diaphragmatic hernia (CDH).
Materials and Methods: Between January 2002 and December 2004, thirty-one fetuses with isolated CDH were prospectively evaluated. Fetal lung volumes were estimated by the rotational technique on three-dimensional ultrasonography (3D-US) and fetal weight by the Hadlock equation on two-dimensional ultrasound examinations, which allowed calculating the ultrasonographic fetal lung/body weight ratio (US-FLW), the observed/expected fetal lung volumes (o/e-FLV) and the lung-over-head ratio (LHR). These measurements were compared to each other and to neonatal outcome.
Results: Good correlations were observed between the US-FLW ratio and the o/e-FLV (r=0.90, $p<0.001$) and the LHR (r=0.64, $p<0.001$). The US-FLW ratio was significantly lower in neonatal death cases (median: 0.009, range: 0.004-0.021) than in survivals (median: 0.011, range: 0.008-0.020, $p=0.018$), as well as the o/e-FLV ($p=0.03$) and the LHR ($p=0.03$). Accuracies of the US-FLW, the o/e-FLV and the LHR in predicting neonatal outcome were 64.52% (21/31), 80.65% (25/31) and 77.42% (24/31), respectively.
Discussion: In isolated CDH, fetal size is directly related to neonatal outcome, which can be evaluated by different methods. However, the o/e-FLV seems to be the best parameter for this purpose.

Keywords: prenatal diagnosis, fetal lung, congenital diaphragmatic hernia, three-dimensional ultrasound, ultrasound, pulmonary hypoplasia

Özet

Ultrasonografik Akciğer Ölçümleri ile İzole Konjenital Diyafram Hernisinin Yenidoğan Sonucunda Tahmini

Amaç: İzole konjenital diyafram hernisi (CDH) olaylarında doğum sonrası sonucun tahmin edilmesinde değişik akciğer ultrasonografi ölçümlerinin değerlendirilmesi.
Materyal ve Metot: Ocak 2002 ve Aralık 2004 arasında izole CDH tanılı 31 fetus doğum sonrasına kadar izlendi. Üç boyutlu ultrasonografiyle rotasyonel teknikle fetus akciğerlerinin hacmi ölçüldü ve fetus beden ağırlığı iki boyutlu ultrason tetkikine dayana Hadlock denklemi ile hesaplandı ve bundan fetusta akciğer/beden ağırlığı orantısı (US-FLW), ölçülen/beklenen fetus akciğer hacmi (o/e-FLV) ve de akciğer/kafa orantısı (LHR) elde edildi. Bu ölçümler, birbirleri ile ve yenidoğan sonuçları ile karşılaştırıldı.
Sonuçlar: US-FLW orantısı ile o/e-FLV arasında (r=0.90, $p<0.001$) ve LHR arasında (r=0.64, $p<0.001$) kuvvetli karşılıklı ilişki bulundu. US-FLW orantısı yenidoğanda ölüm olgularında (medyan: 0.009, yayılım aralığı: 0.004-0.021) hayatta

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kalanlara kıyasla (medyan: 0.011, yayılım aralığı: 0.008-0.020, *p*=0.018) anlamlı oranda düşük çıktı. Aynı şekilde o/e-FLV (*p*=0.03) ve LHR (*p*=0.03) değerleri de düşüktü. Yenidoğan sonuçlarında US-FLW, o/e-FLV ve LHR tahmin doğruluğu sırasıyla, 64.52% (21/31), 80.65% (25/31) ve 77.42% (24/31) olarak saptandı.

Tartışma : İzole CDH'de, fetus boyutu doğrudan yenidoğan sonucu ile ilişkilidir ve bu değişik metotlarla değerlendirilebilir. Ancak, bu amaç için en iyi parametre o/e-FLV olarak görünmektedir.

Anahtar sözcükler: doğum öncesi tanı, fetus akciğeri, konjenital diyafram hernisi, üç boyutlu ultrasonografi, ultrason, pulmoner hipoplazi

Introduction

Congenital diaphragmatic hernia (CDH) occurs in approximately 1 in 2200 livebirths with an overall neonatal mortality rate of 50% in prenatally diagnosed cases (1). Prenatal prediction of neonatal prognosis remains a challenge, being crucial for immediate neonatal care and for the selection of candidates for minimally invasive therapeutic interventions such as intermittent tracheal occlusion by fetoscopy (2,3).

As neonatal mortality is directly related to severe pulmonary hypoplasia, many prognostic factors have been suggested based on the prenatal assessment of lung size (fetal lung volumes and lung-over-head ratio) (4-10). The lung-over-head ratio (LHR) is widely used to predict outcome. When it is less than 1.0, high neonatal mortality is observed (almost 100%) (4,5). Recent studies have demonstrated that total fetal lung volume, being statistically correlated with neonatal outcome, can be estimated in cases with CDH using magnetic resonance imaging (MRI) or three-dimensional ultrasonography (3D-US) (6-10). These authors have been proposing the use of the relative lung volume ratio, in which the observed lung volume is compared to the expected value for each specific gestational age, suggesting that observed/expected fetal lung volume ratio (o/e-FLV) less than 0.35 is associated with poorer outcome.

Recently, Tanigaki et al. (11) proposed to use the ratio between the fetal lung volume estimated by MRI and the sonographic estimated fetal body weight for the prediction of pulmonary hypoplasia. This authors' suggestion is based on the pathological definition of pulmonary hypoplasia which is considered when the ratio of the lung weight to the body weight-fetal lung/body weight, ratio (FLW ratio) is less than 0.012 (12-14). In this study, a high accuracy (88%) of this method in predicting pulmonary hypoplasia was observed.

Previous experiences demonstrated that fetal lung volumes can be measured precisely using 3D-US in CDH cases with similar results to those of MRI estimation (15) and to post-mortem fetal lung weights (16). Based on these findings, we proposed a prospective study to evaluate the potential of the ultrasonographic "FLW", the o/e-FLV and the LHR to predict neonatal outcome in 31 fetuses with isolated CDH.

Materials and Methods

From January 2002 to December 2004, a prospective observational study was conducted in two tertiary centers at Université de Paris, France, and at Universidade de São Paulo, Brazil, in which ultrasound examinations were performed on 31 cases with isolated CDH (26 left and 5 right). All pregnant women volunteered to undergo ultrasonographic examination after being fully informed about the study protocol and the technique. This protocol was approved by the local Ethical Committees of both hospitals.

In all cases, gestational age was based on the date of the last maternal menstruation and by ultrasonographic measurement of the crown-rump length in the first trimester. All cases with CDH were submitted to detailed ultrasound examination and fetal amniocentesis for karyotyping. Gestational age at diagnosis ranged from 16 to 35 weeks. Only, cases with a normal karyotype and without any other associated malformations were included in the study. Ultrasound examination was performed with the cases in between 22 and 36 weeks of gestation. All women were informed that the results of the study would not be used to modify perinatal management. The perinatologists, ultrasonographers and surgeons in charge were unaware of the results of the lung volume measurements. The prenatal diagnostic investigations, obstetrical care and postnatal treatment were provided with similar postnatal protocol at both centers. All cases delivered at term (mean: 37.3 weeks; range: 31-40). Immediately after birth, all neonates were intubated and high-frequency oscillatory ventilation was started in every case, being subsequently changed to conventional ventilation when appropriate. Nitric oxide (NO) was used in infants (n=21) with pulmonary hypertension. CDH repair was only performed after preoperative respiratory and hemodynamic stabilization (n=12). When autopsy was performed, the pathologic diagnosis of pulmonary hypoplasia was made by histopathological analysis and when the lung/body weight ratio was less than 0.012 (11-14).

Assessment of fetal lung volumes by 3D-US

Fetal lung volumes were estimated by the same technique previously described (8,9,15,16), using a Voluson 730 ultrasound machine (Kretztechnik, General-Electric, Zipf, Austria) with a 4 to 8 MHz transducer for three-dimensional volume scanning. A transverse section of the fetal thorax at the level of the four chamber view, with the fetal heart proximal to the

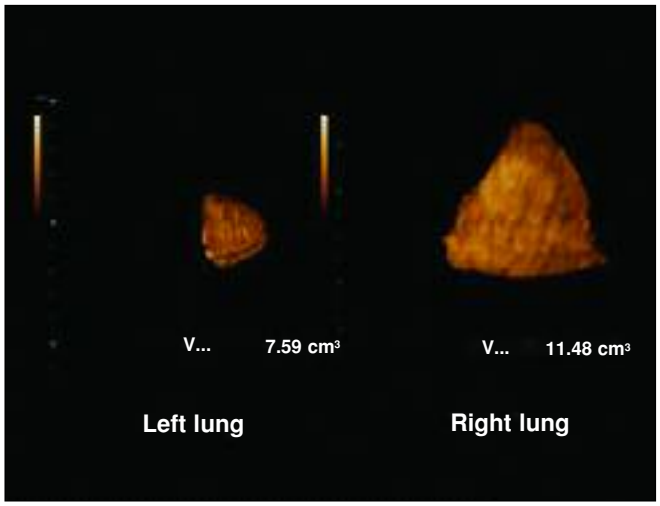

Figure 1. Three-dimensional (rendered) image of right (contrateral) and left (ipsilateral) lungs of a fetus with left-sided CDH at 31 weeks of gestation.

transducer, was identified by 2D-ultrasound and the volume box was adjusted in order to scan the entire fetal thorax. After scanning the volume, the three orthogonal ultrasound sections were analyzed and stored on a removable hard disk. Each lung was carefully identified in the three orthogonal multiplanar imaging. A transverse section of the fetal thorax in the multiplanar imaging was chosen and each lung volume was measured by the rotational technique which consists of outlining the contour of the lung repeatedly after rotating its image 6 times by 30°. Left and right lung volumes were automatically measured four times by the same operator (R. R.), and the total fetal lung volumes were then calculated in cm³ (Figure 1).

Estimation of fetal lung weight by 2D-US

At the same examination, fetal weight was estimated using the same equipment, by the Hadlock mathematical equation

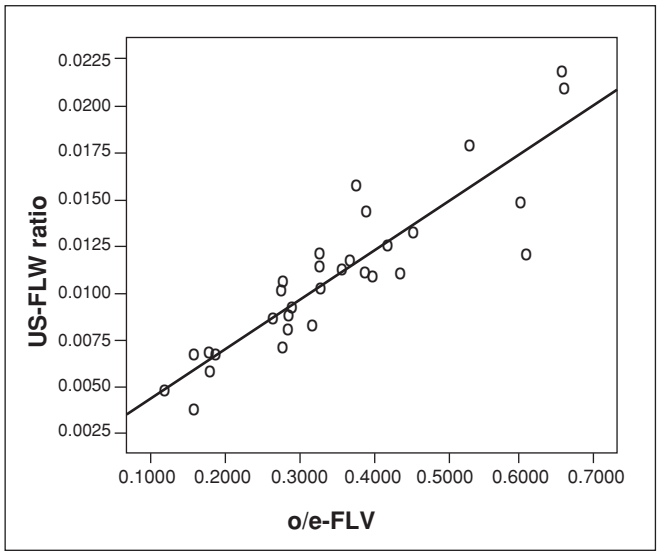

Figure 2. Regression line of "ultrasonographic fetal lung/body weight ratio" (US-FLW) versus observed/expected fetal lung volume (o/e-FLV)..

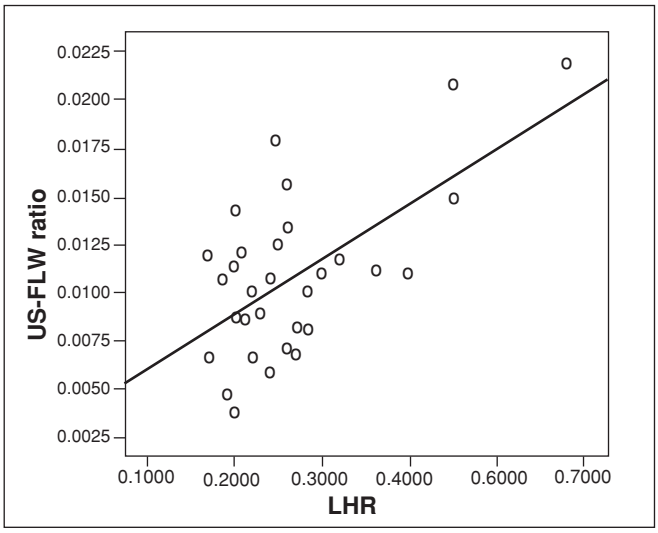

Figure 3. Regression line of "ultrasonographic fetal lung/body weight ratio" (US-FLW) versus lung-over-head ratio (LHR).

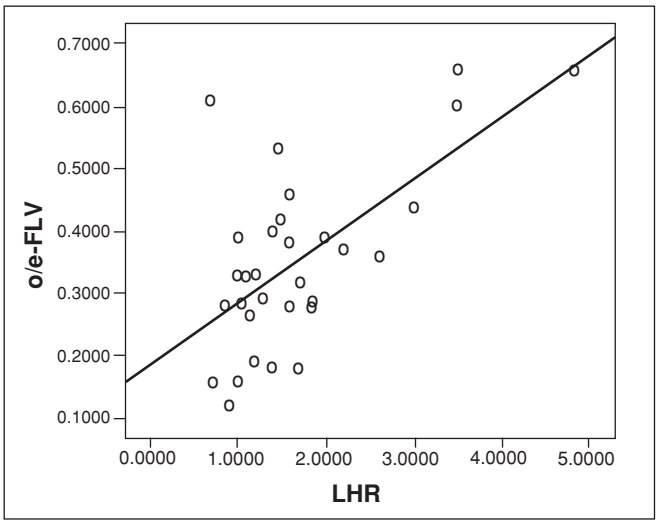

Figure 4. Regression line of observed/expected fetal lung volume (o/e-FLV) versus lung-over-head ratio (LHR).

(17), which includes the measurements of biparietal diameter, head circumference, abdominal circumference and femur length.

Statistical analyses

The US-FLW was calculated by the ratio between estimated fetal lung volumes on 3D-US and estimated fetal weights on 2D-US. The observed/expected FLV and the LHR were also calculated in each case, following the method previously described (4,5,8). These three parameters were correlated to each other by analysing the Pearson's correlation test and they were compared with neonatal outcome using the Mann-Whitney U test (SPSS 13, Microsoft, USA). Accuracies of US-FLW, o/e-FLV and LHR in predicting neonatal deaths were also evaluated. Statistical differences were considered to be significant when the *p* value was less than 0.05.

Table 1. Prediction of neonatal death in isolated CDH using sonographic parameters

Parameter	Sensitivity	Specificty	PPV	NPV	Accuracy
US-FLW	68.42% (13/19)	58.33% (7/12)	72.22% (13/18)	53.85% (7/13)	64.52% (21/31)
o/e-FLV	78.95% (15/19)	83.33% (10/12)	88.24% (15/17)	71.43% (10/14)	80.65% (25/31)
LHR	89.47% (17/19)	58.33% (7/12)	77.27% (17/22)	77.78% (7/9)	77.42% (24/31)

US-FLW: ultrasonographic fetal lung/body weight ratio
o/e-FLV: observed/expected total fetal lung volume ratio
LHR: lung-over-head ratio

Results

Among the 31 fetuses with isolated CDH, neonatal deaths occurred in 19 cases (61.29%).

Good correlation were observed between US-FLW and o/e-FLV (r=0.90, p<0.001) (Figure 2), between US-FLW and LHR (r=0.63, p<0.001) (Figure 3) as well as between o/e-FLV and LHR (r=0.64, p<0.001) (Figure 4).

The US-FLW ratio was significantly lower in neonatal death cases (median: 0.009, range: 0.004-0.021) than in survivals (median: 0.011, range: 0.008-0.020, p=0.018) (Figure 5).

The o/e-FLV and the LHR were also significantly lower in cases that died (median o/e-FLV: 0.28, range: 0.12-0.66; median LHR: 1.1, range: 0.7-4.8) than in survivals (median o/e-FLV: 0.40, range: 0.29-0.66; median LHR: 1.9, range: 1.2-3.5; p=0.03 and p=0.03, respectively) (Figures 6 and 7).

Accuracies of US-FLW, o/e-FLV and LHR in predicting neonatal outcome were 64.52% (21/31), 80.65% (25/31) and 77.42% (24/31), respectively (Table 1).

Figure 6. Box-plot of the "the observed/expected fetal lung volume" (o/e-FLV in CDH-cases that died and lived. The horizontal bar within the box corresponds to the median. The upper and lower bars of the boxes correspond to the 1st and 3rd quartiles (Q1 and Q3), respectively. The two vertical lines (called whiskers) outside the box extend to the smallest and largest observations within 1.5xIQR of the quartiles (IQR=Q3-Q1).

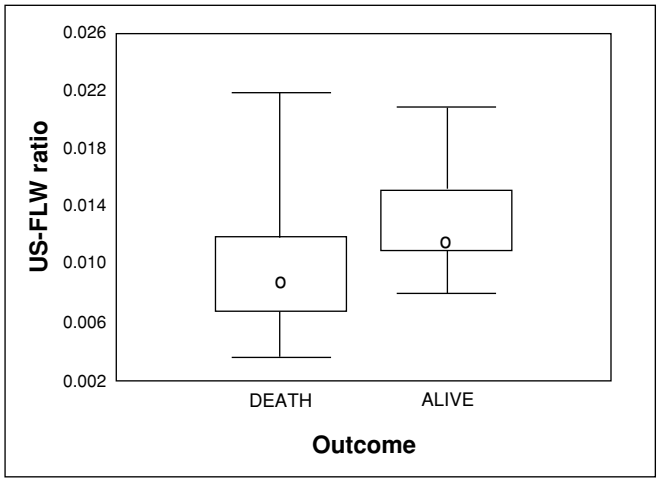

Figure 5. Box-plot of the "ultrasonographic estimated fetal lung/body weight ratio" (FLW) in CDH-cases that died and lived. The horizontal bar within the box corresponds to the median. The upper and lower bars of the boxes correspond to the 1st and 3rd quartiles (Q1 and Q3), respectively. The two vertical lines (called whiskers) outside the box extend to the smallest and largest observations within 1.5xIQR of the quartiles (IQR=Q3-Q1).

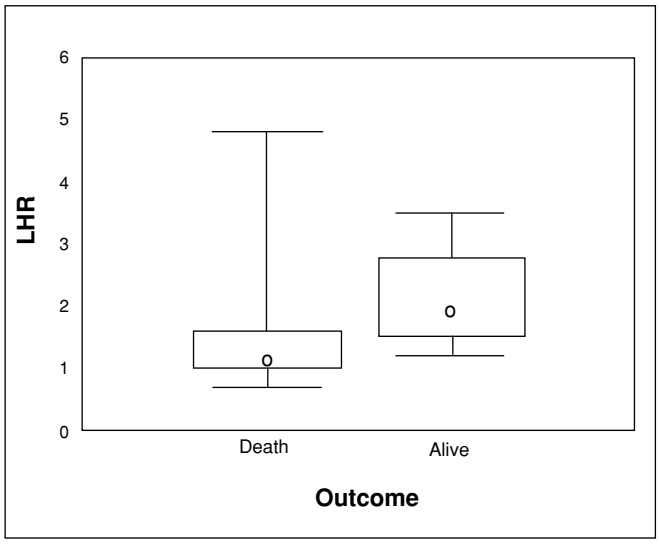

Figure 7. Box-plot of the "lung-over-head ratio" (LHR) in CDH-cases that died and lived. The horizontal bar within the box corresponds to the median. The upper and lower bars of the boxes correspond to the 1st and 3rd quartiles (Q1 and Q3), respectively. The two vertical lines (called whiskers) outside the box extend to the smallest and largest observations within 1.5xIQR of the quartiles (IQR=Q3-Q1).

Discussion

Our results suggest that FLW, o/e-FLV and LHR are significantly correlated to each other, but the o/e-FLV predicts more accurately postnatal outcome than the FLW ratio and the LHR in isolated CDH.

The LHR, which is the ratio between the area of the contralateral lung and the head circumference, is widely used to predict outcome. Nowadays it is considered one of the best and the main prenatal sonographic criteria for selecting cases of isolated CDH with worse prognosis for fetal therapy (2,3), which is as an indirect marker of severe postnatal pulmonary hypoplasia is such cases. However, many authors suggest that this ratio may not evaluate and represent the entire pulmonary condition in such cases (6-8). Because of the great advance in sonographic imaging quality, the ispsilateral lung can be identified, which lead many authors to investigate the fetal lung volume as a potential prenatal predictor of severe pulmonary hypoplasia and, consequently, neonatal outcome.

Different nomograms of fetal lung volumes using MRI and 3D-US have been proposed (7,8,18-21). In isolated CDH, the o/e-FLV has been used to predict outcome, which represents the relation between the observed and the expected fetal lungs based on nomograms.

Tanigaki et al. (10) proposed to use the ratio between the fetal lung volume estimated by MRI and the sonographic estimated fetal body weight for the prediction of pulmonary hypoplasia, based on the pathological definition of pulmonary hypoplasia. Our group is also describing the FLW ratio but estimated only on ultrasound examination, in which fetal lung was measured here by 3D-US and fetal weight by 2D-US.

In the present study, the o/e-FLV ratio predicted more accurately neonatal outcome than the LHR and the FLW ratio. The FLW ratio had lower sensitivity, specificity and accuracy for predicting neonatal deaths than both the o/e-FLV and the LHR. Although the o/e-FLV had a higher accuracy, the LHR has more sensitivity for predicting neonatal deaths in isolated CDH. Although the specificity of the LHR and the FLW were similar for predicting outcome, the first had a higher sensitivity and negative predictive value, being more accurate than the FLW ratio.

The good correlations between these three ultrasonographic parameters confirm that they evaluate fetal pulmonary size directly (o/e-FLV ad FLW ratio) or indirectly (LHR). Besides, the o/e-FLV ratio had the best performance probably because it considers the entire lung and compares it with a normal expected fetal lung volume at determined gestational age. The fact that these three sonographic parameters correlated significantly with neonatal deaths confirms that fetal pulmonary size is directly related to neonatal outcome and that severe pulmonary hypoplasia is one of the main causes of neonatal death in isolated CDH.

Evaluating the LHR is easier and probably more reproducible than estimating fetal lung volumes using the rotational technique (VOCAL™). The main difficulty of the volumetric method is the necessity to identify precisely the organ borders. In fetuses with CDH, this difficulty may be seen principally when analyzing the lungs ipsilaterally to the diaphragmatic defect (22,23). To avoid this limitation and to improve the precision of the method, our proposal is to acquire the fetal thorax block at the level of the four chamber view with the fetal heart proximal to the transducer, to evaluate the quality of the acquired volumetric image and then to rotate the reference image (transverse section of fetal thorax-image A on the three orthogonal multiplanar imaging) by 30 degrees (16,24).

In conclusion, both o/-e-FLV, FLW and LHR correlate significantly to each other. The o/e-FLV predicts more accurately the neonatal deaths than the FLW and the LHR in isolated CDH.

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