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Diffusion-weighted MRI in lungs of normal fetuses and those with congenital diaphragmatic hernia

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KEYWORDS: diaphragmatic hernia; diffusion-weighted imaging; fetal lung; magnetic resonance imaging; prenatal diagnosis

ABSTRACT

Objective *To prospectively determine apparent diffusion coefficient (ADC) values of normally developing fetal lungs over gestation, as obtained by diffusion-weighted (DW) magnetic resonance imaging (MRI) and to investigate its potential application in fetuses with congenital diaphragmatic hernia (CDH).*

Methods *Informed consent was obtained for this cross-sectional study of 93 fetuses with normal lungs and 14 with isolated left-sided CDH, assessed between 18 and 40 weeks of gestation. MRI delineation of left and right lungs was performed on the native DW image, b0, and three values of ADC, corresponding to the overall value (ADC_{avg}), and values for low and high values of b (ADC_{low} and ADC_{high}, respectively) were calculated. Regression analysis was used to assess the relationship between gestational age and b0-values as well as calculated ADC values. The b0 and ADC values of normal and CDH fetuses were compared with normal ranges using the Mann–Whitney* U*-test.*

Results *In fetuses with normal lungs, there was a negative correlation between gestational age and b0 values as well as with ADC_{high}, a positive correlation with ADC_{low} but no correlation with ADC_{avg}. When measurable, ADC_{high} values were lower in CDH as compared to fetuses with normal lungs and ADC_{low} values were higher. ADC_{low} was unrelated to lung volume.*

Conclusions *There is a significant relationship between ADC_{low} and ADC_{high} values and gestational age in normal fetal lungs. This relationship is most probably explained by developmental changes during the last three stages of lung development, which involve intense peripheral growth of airways and vessels as well as maturation. In CDH, measurement of ADC_{low} might be useful as a predictor of postnatal outcome that is independent of lung volume. Copyright © 2009 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Diffusion-weighted (DW) magnetic resonance (MR) imaging uses the signal loss associated with the random thermal motion of water molecules in the presence of magnetic field gradients to derive a parameter that reflects the translational mobility of water molecules in tissues[1]. The apparent diffusion coefficient (ADC) is a quantitatively derived parameter calculated from DW-MR images and combines both the effect of capillary perfusion and water diffusion in the extracellular extravascular space[2] and can be used to differentiate normal from abnormal tissue structures[3].

So far, non-invasive evaluation of normal and pathological fetal lung development has relied mainly on biometric measurements of lung size such as the two-dimensional (2D) ultrasound lung area to head circumference ratio[4,5] or the three-dimensional (3D) ultrasound or MR imaging lung volume[6–8], but vascular evaluation of the lungs has also been used for this purpose[9–11]. Studies on the microstructural evaluation of the fetal lung using DW-MR imaging are rare, and none of them evaluated lungs in fetuses with congenital diaphragmatic hernia (CDH)[12–14]. DW-MR sequences need longer scanning times as compared to the more widely used T1- and T2-weighted images in fetal imaging. Consequently, they are more sensitive to motion artifacts, which may be one of the reasons they have been less widely used in fetal imaging.

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Thus, the purpose of our study was to prospectively determine the pattern of ADC values obtained with DW-MR imaging in normally developing fetal lungs and to investigate its potential application in fetuses with CDH.

PATIENTS AND METHODS

Study participants and design

The single-institution, cross-sectional prospective study was approved by the ethics committee on clinical studies of our hospital; informed consent was obtained. All consecutive patients referred between December 2004 and November 2006, undergoing fetal MRI examination as clinically indicated and matching the study criteria, were eligible to participate in the study. In all patients gestational age was estimated from the first-trimester scan. Fetuses with MR images degraded by fetal motion artifacts despite fetal sedation were excluded. During fetal MRI examination, the attending radiologist ensured that the entire fetus was imaged so that all biometric variables could be obtained. Two groups of fetuses were studied.

The inclusion criteria for the first group were singleton fetuses without thoracic or other structural abnormalities that potentially would affect lung volume, and that had biometric percentiles of 5–95% at the time of measurement at ultrasound within 2 weeks before MRI examination. The group consisted of fetuses with either central nervous system anomalies such as isolated ventriculomegaly ($n = 7$), agenesis of the corpus callosum ($n = 2$), aneurysm of the vein of Galen ($n = 2$), intraventricular hemorrhage ($n = 1$), craniosynostosis ($n = 1$), arachnoid cyst ($n = 1$), cerebell hypoplasia ($n = 1$), Dandy–Walker malformation ($n = 2$), porencephaly ($n = 2$), rhombencephalosynapsis ($n = 1$), myelomenigocele ($n = 3$), sinus thrombosis ($n = 1$) or cytomegalovirus seroconversion ($n = 33$), toxoplasmosis seroconversion ($n = 2$), renal cortical cyst ($n = 2$), ovarian cyst ($n = 3$), adrenal hemorrhage ($n = 1$), adrenal cyst ($n = 1$), gastrointestinal malformation ($n = 1$), sacrococcygial teratoma ($n = 3$), situs inversus ($n = 1$) and placental or maternal pelvic anomalies with normal fetal structures ($n = 22$).

Postnatal clinical follow-up in 87 fetuses and postmortem reports in six fetuses were available confirming normal clinical respiratory examination and lung development. This first group provided the normal range for lung volume and DW values.

The second group consisted of fetuses with isolated left-sided CDH as assessed by high-resolution level III ultrasonography prior to the MRI examination. The fetuses were all liveborn and expectantly managed in a tertiary neonatal care center with expertise in CDH. Postnatal survival was defined as the baby being alive at discharge from the hospital.

Of the 107 fetuses included in this study, the lung volumes of 58 fetuses had been previously reported without, however, reporting on the diffusion measurements in their lungs[15,16].

MRI examination

MRI was performed on a clinical 1.5-T whole-body unit (Siemens Magnetom Sonata, Erlangen, Germany) with gradient switching capabilities of 25 mT/m in 300 μsec. The mother was given flunitrazepam (0.5 mg) orally 30 min before the procedure to reduce fetal movements and related motion artifacts. Patients were positioned in the left-lateral position to prevent supine hypotension syndrome, with a combination of a six-channel phased-array body coil and two coil elements of the spine coil positioned over the lower pelvic area. The MRI protocol consisted of T2-weighted images in order to confirm normal lung development with normal thorax and without structural abnormalities potentially affecting lung volume. The T2- weighted images consisted of 38 contiguous slices with a 4-mm slice thickness, an intersection gap of 0 mm, a field-of-view of 380 × 380 mm, a matrix of 173 × 256, TR (repetition time)/TE (echo time) of 1000/88 ms, partial Fourier factor of 5/8, resulting voxel resolution of $1.8 \times 1.5 \times 4.0$ mm^3 and a bandwidth of 475 Hz/pixel. T2-weighted images were obtained using a half Fourier acquisition single shot turbo spin echo (HASTE) sequence in orthogonal transverse, coronal and sagittal planes according to the fetal orientation. No breath hold was requested of the mother. A diffusion-weighted echo-planar imaging (EPI) sequence was acquired in the transverse plane with the following parameters: 10 slices with a 5-mm slice thickness and a 1.25 mm intersection gap, a field-of-view of 309 × 380 mm, a matrix of 104 × 128, TR/TE of 1500/84 ms and a bandwidth of 1502 Hz/pixel; four averages were acquired. The images were acquired using six different b-values (b = 0, 100, 250, 500, 750 and 1000 s/mm^2). The resulting voxel resolution was $3.0 \times 3.0 \times 5.0$ mm^3 in a total acquisition time of 1 min 42 s. All diffusion-sensitizing gradients were applied in three orthogonal directions, creating a three-scan trace. The mean examination time was 20 ± 4 min per patient.

Image delineations

The structural and anatomical MRI evaluation was carried out by a single operator (M.C.) using T2- weighted images and the DW imaging measurements were done in consensus by two operators (M.C. with 3 years and I.R. with 1 year of experience in image delineation at the start of the study). Planimetric measurements of left and right lung volumes were all performed by M.C. Lung volumes were calculated on the T2 HASTE sequences as previously described[15].

Analysis of the DW images was performed off-line on a LINUX workstation using dedicated software (BioMAP, Novartis, Basel, Switzerland). The delineations were performed on transverse slices, relative to the fetal position, of the native DW images acquired using a b-value of 0 s/mm^2 (b0 images). All visible areas of each lung on all slices were delineated, and combined to create one 3D region of interest (ROI) per lung. These ROIs (one for

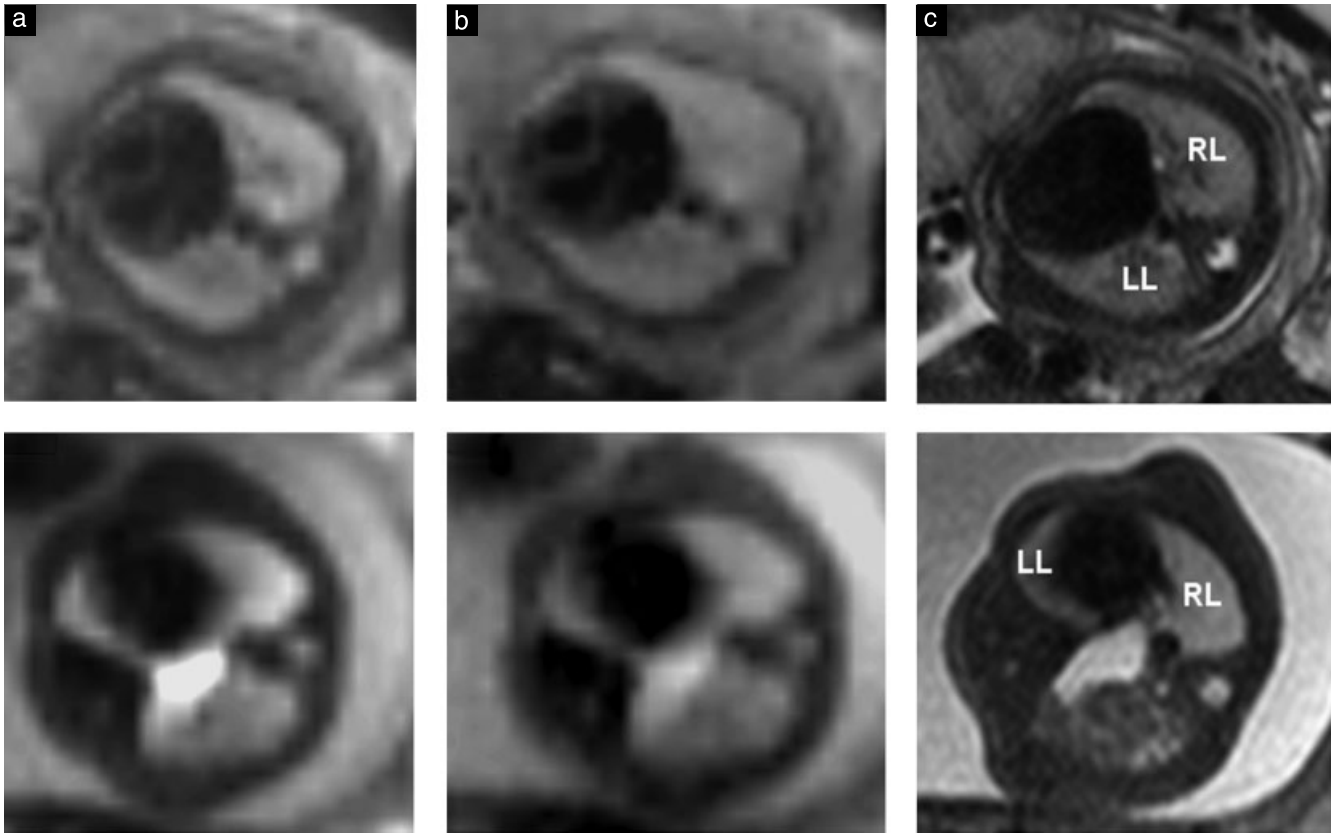

Figure 1 Axial diffusion weighted (DW) images with native b0 (a) and overall apparent diffusion coefficient (b) and T2-weighted single-shot turbo spin echo magnetic resonance (MR) images (c) (repetition time/echo time, 1000 ms/88 ms) from the thoracic level in a fetus at 31 weeks' gestation with normal lungs (top row) and in a fetus at 29 weeks with left-sided congenital diaphragmatic hernia (CDH) (bottom row). Note the lower resolution in the DW compared with the T2-weighted MR images and the very small size of the ipsilateral lung compared with the contralateral side in the CDH fetus. (LL, left lung; RL, right lung).

the left lung and one for the right lung) were then copied to the other b-value images and a mean signal intensity value for each lung and for each b-value was acquired. The ROI delineations of the left and right lungs consisted of on average 14 (range, 3–31) voxels (Figure 1).

Data and statistical analysis

Interobserver variability (M.C. and I.R., one delineation each) and intraobserver variability (M.C., two delineations with 3 months in between) was assessed for the b0 and the b-1000 values on 20 randomly chosen lungs from the first group of fetuses without thoracic pathologies, using intraclass correlation coefficient (ICC).

For each ROI, from the average signal intensity values for each of the six b-values, an overall ADC, i.e. ADC_{avg}, was calculated. In addition, separate ADC values were calculated for the low b-values ($b = 0$, 100 and 250 s/mm^2; ADC_{low}) and the high b-values ($b = 500$, 750 and 1000 s/mm^2; ADC_{high}) in order to assess the relative influence of the microstructural and true molecular diffusion of the tissue.

The ADC values were calculated using a least squares solution of the following system of equations: $S(i) = S_0 \times \exp^{(-bi \times ADC)}$, where S(i) is the signal intensity measured on the ith b-value image and b_i is the corresponding b-value. S_0 is a variable estimating the exact signal intensity (without noise induced by the MRI measurement) for $b = 0$ s/mm^2. To reduce the influence of the noise and minimize the effects of any fetal movement on the calculations, the diffusion images of at least three b-values were used for each ADC calculation.

Delineations of the left and right lungs were performed separately. Linear regression analysis was performed for left and right lungs separately between gestational age and lung volume; the native DW-MR images acquired with a b0-value; and each of the calculated ADC values (ADC_{avg}, ADC_{low} and ADC_{high}). Each regression line used a least squares approximation of the line to the points. For all fetuses the observed/expected (o/e) left and right lung volume ratios were calculated by expressing the observed left and right lung volume as a percentage of the expected normal mean left and right value for gestational age. Similarly, for both groups of fetuses and for both lungs, the o/e b0, ADC_{avg}, ADC_{low} and ADC_{high} were calculated by expressing the observed value as a percentage of the expected normal mean for gestation.

For each of the left and right lungs, the median o/e ratios based on gestational age of lung volume, b0, ADC_{avg}, ADC_{low} and ADC_{high} were compared between fetuses with normal lungs and those with CDH as well as between left and right lungs in fetuses with CDH using

Table 1 Regression formulae, correlation coefficients and *P*-values for left and right lung volume, b0 and different apparent diffusion coefficient (ADC) values with gestation in 93 fetuses with normal lungs

Variable	*Regression formula*	*Correlation coefficient*	P
Left lung volume (mL)	$-33.13 + (1.82 \times GA)$	0.82	< 0.001
Right lung volume (mL)	$-44.76 + (2.45 \times GA)$	0.82	< 0.001
b0-left (au)	$223.01 - (3.34 \times GA)$	−0.39	< 0.001
b0-right (au)	$227.38 - (3.38 \times GA)$	−0.40	< 0.001
ADC_{low}-left (mm^2/s)	$0.003 + (0.00005 \times GA)$	0.21	0.0461
ADC_{low}-right (mm^2/s)	$0.002 + (0.00005 \times GA)$	0.23	0.0242
ADC_{avg}-left (mm^2/s)	$0.002 - (0.00001 \times GA)$	−0.14	0.169
ADC_{avg}-right (mm^2/s)	$0.002 + (0.000002 \times GA)$	0.02	0.832
ADC_{high}-left (mm^2/s)	$0.002 - (0.00004 \times GA)$	−0.42	< 0.001
ADC_{high}-right (mm^2/s)	$0.002 - (0.00003 \times GA)$	−0.29	0.0056

ADC_{avg}, overall ADC; ADC_{low}, ADC for low values of b; ADC_{high}, ADC for high values of b; au, arbitrary units; GA, gestational age (in weeks).

the Mann–Whitney *U*-test. Finally, in fetuses with CDH, linear regression analysis was performed between the b0-value and each of the calculated ADC values and lung volume. The data were expressed as medians and ranges. Statistical calculations were performed with software packages Statistica, version 6.0 (StatSoft, Tulsa, OK) and Excel, version 9.0 (Microsoft, Redmond, WA). $P < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

The first group consisted of 93 fetuses that were imaged at between 18 and 40 weeks' gestation. The second group included 14 fetuses, 10 that survived and four that subsequently died at discharge from the hospital. For the latter group MRI was performed at between 22 and 35 weeks' gestation. Nine from the first and two fetuses from the second group were earlier excluded because of fetal motion artifacts at DW-MRI. Interobserver and intraobserver agreement for the b0-values were both high, with ICCs of 0.93 and 0.95, respectively ($P < 0.01$ for both). Interobserver and intraobserver agreement for the b1000-values were both high, with ICCs of 0.89 and 0.92, respectively ($P < 0.01$ for both).

Morphologic evaluation

On the T2-weighted images left and right lung volume could be delineated in all fetuses with normal lungs and those with CDH. Both left and right lung volumes showed a strong correlation with gestational age and increased according to the following linear fits: left LV $= -33.13 + (1.82 \times GA)$ ($r = 0.82$, $P < 0.001$) and right LV $= -44.76 + (2.45 \times GA)$ ($r = 0.82$, $P < 0.001$), where LV = lung volume and GA = gestational age (Table 1, Figure 2).

Both the median o/e left and right lung volume in fetuses with CDH were significantly smaller than the corresponding o/e for fetuses with normal lungs (Table 2). The median o/e ipsilateral lung volume was significantly smaller than the corresponding o/e contralateral lung volume in fetuses with CDH (Table 3).

Microstructural evaluation

On the DW-MR images, ROIs could be delineated for both left and right lung volume in all 93 fetuses with normal lungs, and in all 14 for the right (contralateral) lung volume but only in nine (64%) out of 14 left (ipsilateral) lung volumes in fetuses with CDH. Consequently comparisons between DW-MR image variables in fetuses with normal lungs and in fetuses with CDH were only made when the appropriate measurements could be obtained.

The regression formulae, correlation coefficients and *P*-values for b0 and different ADC values with gestational age in the 93 fetuses with normal lungs are displayed in Table 1. Both b0 and ADC_{high} decreased significantly, ADC_{low} increased significantly while ADC_{avg} remained stable with gestational age (Table 1, Figures 3–6).

Comparison between fetuses with normal lungs and those with CDH showed no differences for the left or right lung o/e b0 values. For left as well as right lung o/e ADC_{low} was higher in fetuses with CDH than the corresponding lung in fetuses with normal lungs. The median left lung values tended to be higher than the right lung values, but this difference was not significant. In fetuses with CDH, o/e ADC_{high} was smaller for the left lung as compared to the corresponding normal lungs as well as to the right lung, and o/e ADC_{avg} was higher for the right lung as compared to the corresponding normal lungs, but values from left and right lungs were similar (Tables 2 and 3, Figures 3–6). In fetuses with CDH, neither o/e b0, nor o/e ADC_{low} was correlated with o/e lung volume. In contrast, o/e ADC_{avg} and o/e ADC_{high} were positively correlated with o/e lung volume (Table 4).

The number of fetuses with isolated CDH that subsequently died in the neonatal period was too small to allow any statistical analysis, however their o/e ADC_{low} tended

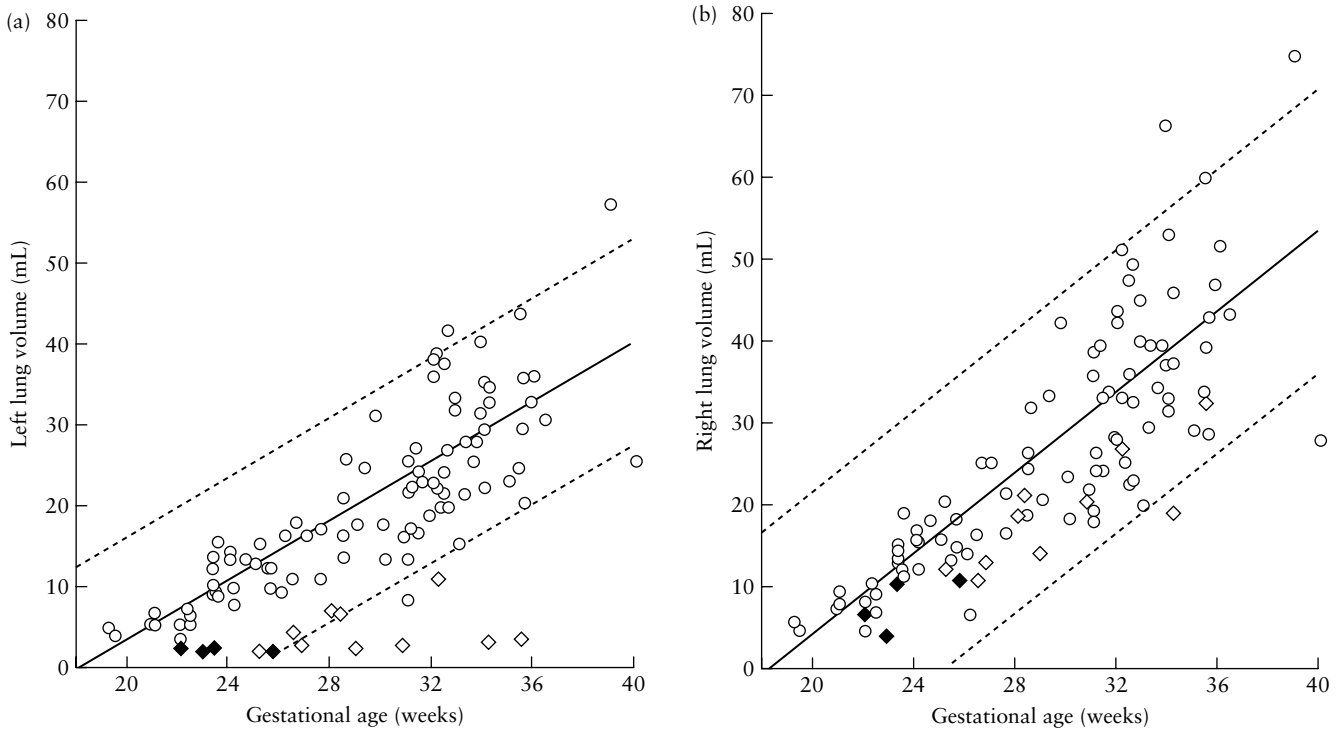

Figure 2 Plot of fetal left (a) and right (b) lung volume against gestational age for fetuses with normal lungs (○), showing a strong linear correlation between these two parameters. ———, mean value; - - - - , 95% CIs for prediction. On the same plot are data from fetuses with isolated left-sided congenital diaphragmatic hernia: ◊, fetuses that subsequently survived; ♦, fetuses that subsequently died in the neonatal period.

Table 2 Comparison between observed to expected (o/e) lung volume, b0 and different apparent diffusion coefficient (ADC) values for left and right lungs between fetuses with normal lungs and those with isolated left-sided congenital diaphragmatic hernia (CDH)

Variable	*Normal lungs*	*CDH*	P
o/e left lung volume	98.0 (35.8 to 257.8)	20.0 (10.6 to 42.4)	< 0.001
o/e right lung volume	98.7 (34.4 to 259.7)	86.3 (39.2 to 112.5)	0.035
o/e b0-left	98.8 (40.2 to 148.5)	86.2 (67.6 to 113.2)	0.325
o/e b0-right	96.6 (45.5 to 189.8)	93.3 (65.0 to 137.2)	0.746
o/e ADC_{low}-left	97.6 (42.1 to 210.2)	141.6 (64.1 to 225.7)	0.0038
o/e ADC_{low}-right	100.3 (40.0 to 205.3)	121.4 (101.5 to 170.6)	< 0.001
o/e ADC_{avg}-left	97.5 (52.3 to 187.5)	87.5 (44.9 to 130.5)	0.616
o/e ADC_{avg}-right	95.1 (55.6 to 171.9)	109.8 (78.9 to 142.9)	0.043
o/e ADC_{high}-left	96.3 (−10.7 to 238.8)	47.5 (−21.9 to 160.8)	0.025
o/e ADC_{high}-right	99.2 (−2.8 to 245.2)	109.0 (38.8 to 179.7)	0.406

Data are given as median (range) %. ADC_{avg}, overall ADC; ADC_{low}, ADC for low values of b; ADC_{high}, ADC for high values of b.

Table 3 Comparison between observed to expected (o/e) lung volume, b0 and different apparent diffusion coefficient (ADC) values between left and right lungs in fetuses with isolated left-sided congenital diaphragmatic hernia (CDH)

Variable	*Left lung*	*Right lung*	P
o/e lung volume	20.0 (10.6 to 42.4)	86.3 (39.2 to 112.5)	< 0.001
o/e b0	86.2 (67.6 to 113.2)	93.3 (65.0 to 137.2)	0.659
o/e ADC_{low}	141.6 (64.1 to 225.7)	121.4 (101.5 to 170.6)	0.413
o/e ADC_{avg}	87.5 (44.9 to 130.5)	109.8 (78.9 to 142.9)	0.059
o/e ADC_{high}	47.5 (−21.9 to 160.8)	109.0 (38.8 to 179.7)	0.023

Data are given as median (range) %. ADC_{avg}, overall ADC; ADC_{low}, ADC for low values of b; ADC_{high}, ADC for high values of b.

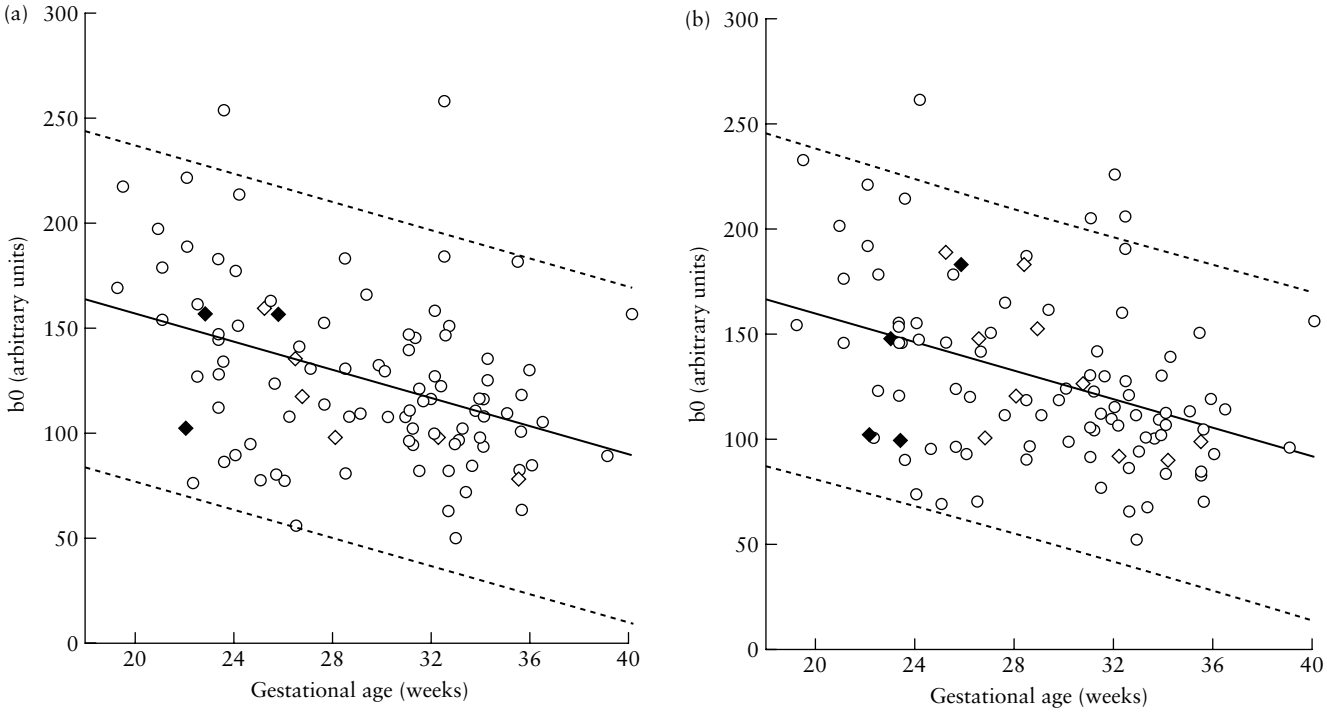

Figure 3 Plot of fetal left (a) and right (b) lung b0 values against gestational age for fetuses with normal lungs (○), showing a strong positive linear correlation between these two parameters. ———, mean value; - - - - 95% CIs for prediction. On the same plot are data from fetuses with isolated left-sided congenital diaphragmatic hernia: ◊, fetuses that subsequently survived; ♦, fetuses that subsequently died in the neonatal period.

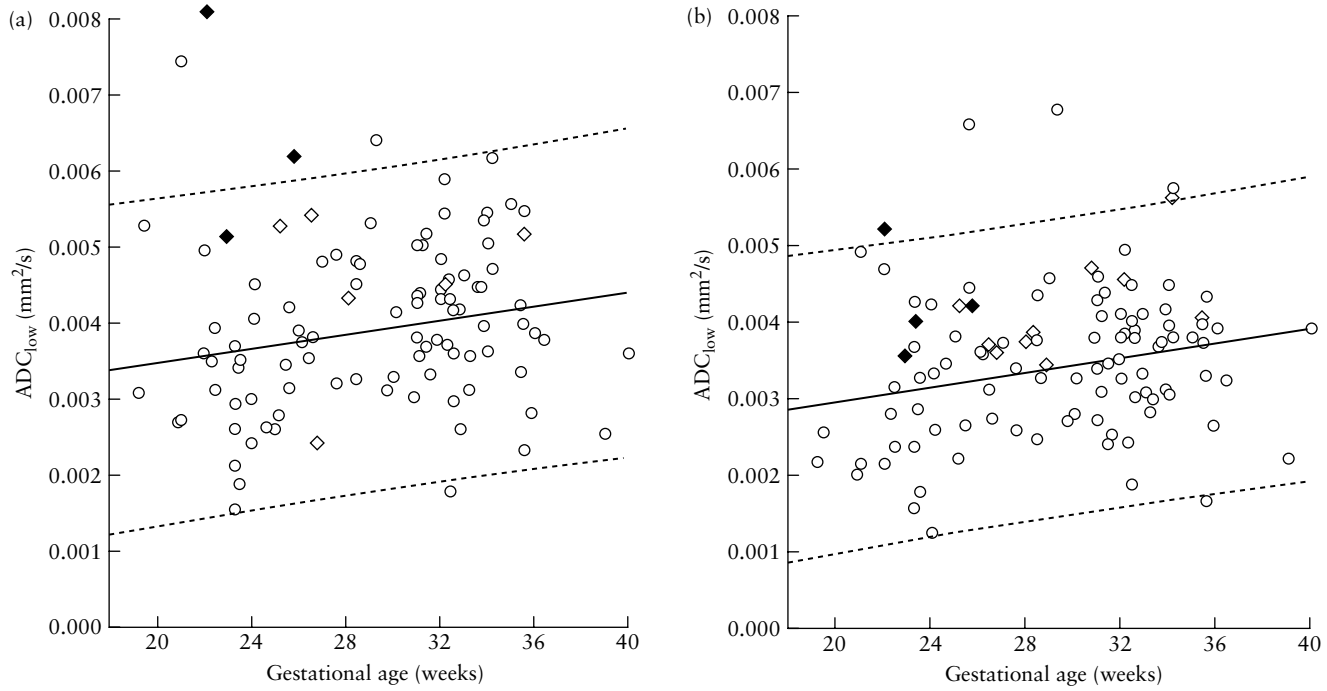

Figure 4 Plot of fetal left (a) and right (b) lung apparent diffusion coefficient for low values of b (ADC_{low}) against gestational age for fetuses with normal lungs (○), showing a positive linear correlation between these two parameters. ———, mean value; - - - - 95% CIs for prediction. On the same plot are data from fetuses with isolated left-sided congenital diaphragmatic hernia: ◊, fetuses that subsequently survived; ♦, fetuses that subsequently died in the neonatal period.

to be higher and their ADC_{high} tended to be lower as compared to the respective o/e ADC values from fetuses with CDH that subsequently survived in the neonatal period.

DISCUSSION

In this study we determined the normal pattern of b0 and calculated ADC values from 18 weeks' gestation onwards.

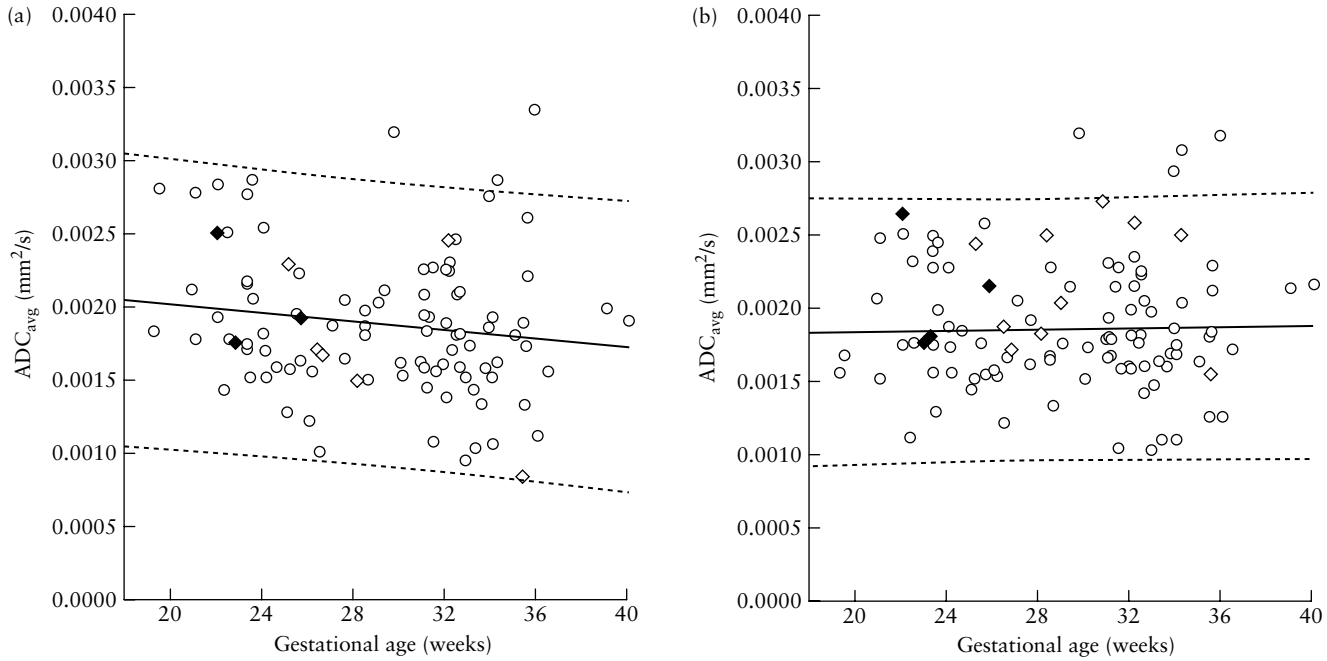

Figure 5 Plot of fetal left (a) and right (b) lung overall apparent diffusion coefficient (ADC_{avg}) against gestational age for fetuses with normal lungs (○), showing no correlation between these two parameters. ———, mean value; - - - - 95% CIs for prediction. On the same plot are data from fetuses with isolated left-sided congenital diaphragmatic hernia: ◊, fetuses that subsequently survived; ♦, fetuses that subsequently died in the neonatal period.

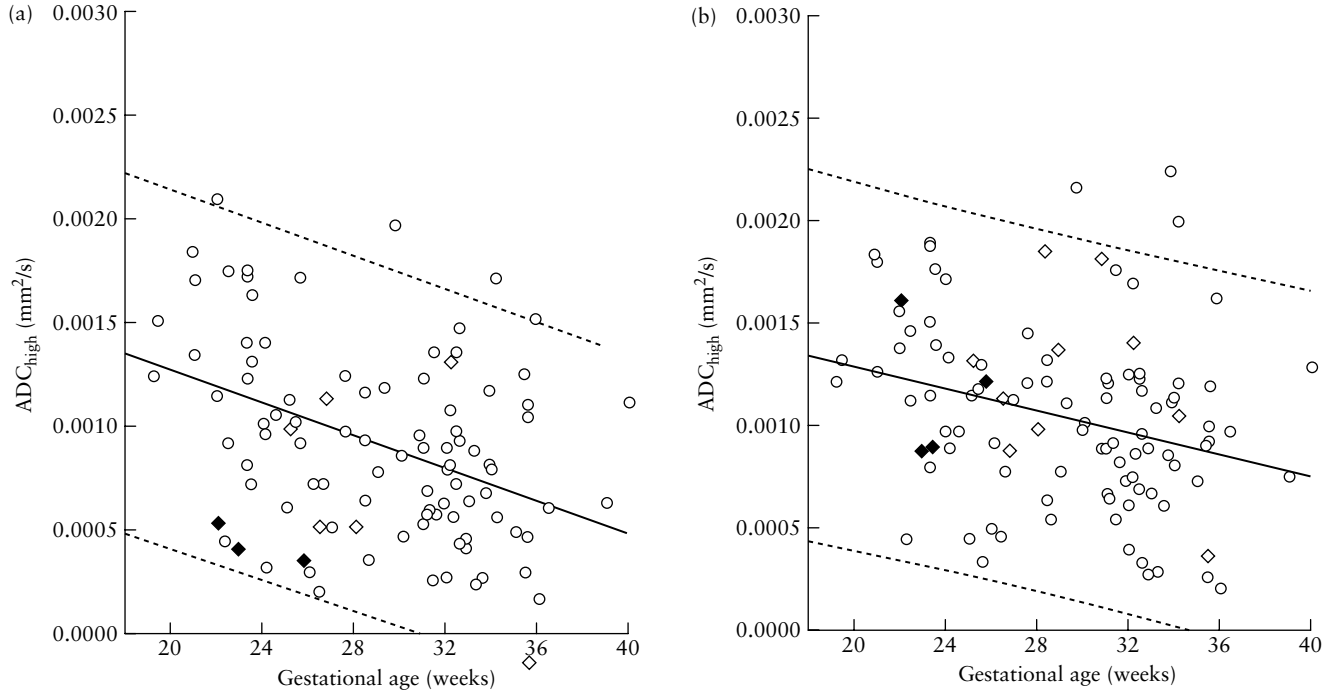

Figure 6 Plot of fetal left (a) and right (b) lung apparent diffusion coefficient for high values of b (ADC_{high}) against gestational age for fetuses with normal lungs (○) showing a negative linear correlation between these two parameters. ———, mean value; - - - - 95% CIs for prediction. On the same plot are data from fetuses with isolated left-sided congenital diaphragmatic hernia: ◊, fetuses that subsequently survived; ♦, fetuses that subsequently died in the neonatal period.

We have shown that b0 and ADC_{high} decreased with gestation and ADC_{low} increased, while ADC_{avg} remained stable. Moreover, in a small number of fetuses with CDH we observed that ADC_{high} and ADC_{low} values were at the limit of the normal range, in particular for the ipsilateral lung. ADC_{low} measurement was unrelated to lung size.

We present both morphologic and microstructural evaluation of the lungs of 107 fetuses, 93 with normal and 14 with hypoplastic lungs as a consequence of CDH. This allowed the correlation of the microstructural with the morphologic findings. We confirmed by the present series that both the ipsi- and contralateral lung size is affected

Table 4 Regression formulae, correlation coefficients and *P*-values for observed to expected (o/e) b0 and different apparent diffusion coefficient (ADC) values for left and right lung volume (LV) in fetuses with isolated left-sided congenital diaphragmatic hernia

Variable	*Regression formula*	*Correlation coefficient*	P
o/e b0	0.91 + (0.042 × o/e LV)	0.067	0.76
o/e ADC_{low}	1.38 − (0.13 × o/e LV)	−0.15	0.50
o/e ADC_{avg}	0.86 + (0.32 × o/e LV)	0.44	0.037
o/e ADC_{high}	0.42 + (0.79 × o/e LV)	0.54	0.008

ADC_{avg}, overall ADC; ADC_{low}, ADC for low values of b; ADC_{high}, ADC for high values of b.

in CDH, however the ipsilateral is more affected than the contralateral lung[17]. We also used different b values to assess the lungs. The subdivision of ADC into ADC_{avg}, ADC_{low} and ADC_{high} was made for a particular reason, i.e. ADC_{high} approximates the true diffusion coefficient of tissue while ADC_{low} provides comparable information, but in addition it provides valuable knowledge on structural effects, i.e. movement in microvessels or tubular structures[18].

A previous study documented DW images in the lungs of 26 normal fetuses[12]. In that study Moore *et al.*[12] used an ADC based on low b values, which is equivalent to ADC_{low} that we used. Their calculated ADC increased between 19 and 39 weeks' gestation, which is in agreement with our findings. In the canalicular, but mainly the saccular and alveolar phases of normal lung development, there is a tremendous increase in terminal air sacs, both in number as well as structural complexity of the respiratory acinus. In parallel to that numerous additional generations of peripheral pulmonary vessels are formed, and the future air–blood barrier thins increasingly. Both the airway and vascular changes can explain the increase in ADC_{low}. An increase in terminal tubules and coinciding ADC_{low} has been experimentally suggested by the *in-vivo* simulation studies of Moore *et al.*[12].

Fetuses with CDH essentially have lung hypoplasia. This means that their lungs have a reduced number of conducting airways as well as vessels. They also have fewer alveoli, thickened alveolar walls and increased interstitial tissue, with markedly diminished alveolar air space. There is a reduced number of vessels, the latter showing adventitial thickening, medial hyperplasia and peripheral extension of the muscle layer of vessels as distal as the intra-acinary arterioles[19]. Both lungs are affected, the ipsilateral one more so than the contralateral one. This more dense structure at the ultrastructural level coincides with an increase in ADC_{low} values, which shows an increased limitation of hydrogen ions to move freely within the structures present.

The finding that ADC_{low} values were unrelated to lung volume is very interesting. This means that there might be additional information in this measurement, apart from what can be deduced from lung volumetry, which is an independent predictor of outcome in CDH[5]. There was a tendency towards higher values in fetuses that subsequently died in the neonatal period as compared to fetuses that subsequently survived, which may relate to the observed difference in lung compliance between survivors and non-survivors[20]. Whether ADC_{low} can be used as an indirect measure of lung compliance should be further investigated.

No previous studies documenting b0 and ADC_{high} in normal or CDH fetal lungs have been published. We found a significant negative correlation between gestational age and the signal intensity on the native DW image acquired using a b-value of 0 s/mm^2 but also with the calculated ADC_{high}. This decrease in signal intensity might be attributable to a decrease in extracellular fluid content during the normal process of lung development, but could also be explained by an increase in macromolecules such as surfactant, phospholipids and lecithin. In CDH fetuses b0 values are *not* affected when compared to fetuses with normal lungs. However ADC_{high} values are at the lower range of normal. This leads us to speculate on the above as follows. CDH lungs have a decreased number of respiratory airways and peripheral vessels, as well as thickened septa and increased wall thickness. This leads to a proportionally increased cell density in a relatively much smaller lung with less architectural complexity. However they are not deficient in surfactant, as has recently been shown[21]. The decrease in ADC_{high} with gestation would therefore be attributable to the increased cell density and the unchanged b0 values, as compared to the normal values, with the normal maturation process of CDH lungs by term.

Our study revealed no significant correlation between the ADC_{avg} in the left or right lung and gestational age, which is in agreement with the results of Balassy *et al.* on 53 fetuses with normal lungs[13]. Balassy *et al.* used only two b values with a factor of 0 and 700 s/mm^2 for the calculation of their ADC values, and therefore the latter would correspond to the average values we observed. Looking at all our results, it is not surprising that ADC_{avg} did not relate to gestational age since it is a combination of ADC_{low} and ADC_{high}, which had a tendency to change in opposite directions. Our observations stress the potential gain in information when one uses six b values rather than two during the same sequence, which can then be secondarily partitioned in calculated ADC values such as low, average and high, but more importantly allows comparison between studies.

Our study has some limitations. First, we did not include fetuses from healthy volunteers but used available MR images obtained from pregnancies requiring fetal MRI for structural anomalies other than those of the fetal lungs. Obviously, when the dataset becomes available from healthy fetuses, additional work will be necessary. Second, we used fetal sedation to perform our MRI examination in order to decrease our examination time. However, theoretically the examination could also be performed without fetal sedation at the expense of a longer examination time. Third, in one third of our

fetuses with CDH, we could not perform DW image measurement in the ipsilateral lung. The most obvious reason for this is the small lung size. Volumetric lung measurements were possible on these lungs, but for the DW measurements a large slice thickness and gap were used, which may have created a resolution problem. These limitations may be overcome by advances in technology decreasing the acquisition time. Fourth, our data showed that gestational age at the time that CDH was seen on MRI is predictive of survival, since all fetuses in which this was detected before 24 weeks' gestation died, while those in which it was detected after 27 weeks survived. Such a finding is more likely to be due to the small number of CDH fetuses included that died rather than a true relationship, however it needs to be further investigated.

In conclusion, we have demonstrated a significant increase in ADC_{low} and decrease in ADC_{high} values in normal fetal lungs between 18 weeks' gestation and term, which are most probably explained by structural and maturational changes in the fetal lung. We have derived normal ranges for different calculated ADC values with gestation. Our preliminary results in fetuses with CDH showed deviations from this normal pattern mainly for the ipsilateral lungs and for ADC_{high} and ADC_{low}, and the latter were unrelated to lung size. These findings can theoretically be explained by the structural differences in hypoplastic lungs of CDH fetuses. These early observations suggest the need for confirmation in larger numbers as well as experimental research as to the structural or molecular basis for these observations. However, since ADC_{low} is independent of other predictors of outcome such as lung volume, it could potentially be used as an alternative or additional tool in predicting postnatal outcome.

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