

Françoise Rypens, MD
Thierry Metens, PhD
Nathalie Rocourt, MD
Pascale Sonigo, MD
Francis Brunelle, MD
Marie Pierre Quere, MD
Laurent Guibaud, MD
Brigitte Maugey-Laulom, MD
Chantal Durand, MD
Fred E. Avni, MD, PhD
Danièle Eurin, MD

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Abbreviation:

FLV = fetal lung volume

¹ From the Departments of Radiology, Hôpital Erasme, Université Libre de Bruxelles, route de Lennik 808, B-1070 Brussels, Belgium (F.R., T.M.); Hôpital Jeanne de Flandre, Lille, France (N.R., P.S.); Hôpital Necker Enfants-Malades, Paris, France (F.B.); CHU de Nantes, France (M.P.Q.); Hôpital Debrousse, Lyon, France (L.G.); CHU Pellegrin, Bordeaux, France (B.M.L.); CHU de Grenoble, France (C.D.); University Children's Hospital, Brussels, Belgium (F.E.A.); and Hôpital Charles Nicolle, Rouen, France (D.E.). Received April 13, 2000; revision requested June 6; revision received August 9; accepted September 11. Address correspondence to T.M. (e-mail:tmeters@ulb.ac.be).

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Author contributions:

Guarantors of integrity of entire study, D.E., F.R.; study concepts, D.E.; study design, T.M., F.R.; literature research, F.R., T.M.; clinical studies, F.R., N.R., P.S., F.B., M.P.Q., L.G., B.M.L., C.D.; data acquisition, F.R., T.M., N.R., P.S., F.B., M.P.Q., L.G., B.M.L., C.D.; data analysis/interpretation, F.R., T.M.; statistical analysis, T.M.; manuscript definition of intellectual content, T.M., F.R.; manuscript revision/review, D.E., F.E.A.; manuscript preparation, editing, and final version approval, F.R., T.M.

Fetal Lung Volume: Estimation at MR Imaging—Initial Results¹

PURPOSE: To plot normal fetal lung volume (FLV) obtained with fast spin-echo magnetic resonance (MR) images against gestational age; to investigate the correlation between lung growth and fetal presentation, sex, and ultrasonographic (US) biometric measurements; and to investigate its potential application in fetuses with thoracoabdominal malformations.

MATERIALS AND METHODS: In a prospective multicenter study, 336 fetuses suspected of having central nervous system disorders underwent fast spin-echo T2-weighted lung MR imaging. Data obtained at 21–38 weeks gestation in 215 fetuses without thoracoabdominal malformations and with normal US biometric findings were selected for an FLV normative curve. FLV measurements obtained at pathologic examination with an immersion method were compared with MR FLV measurements in 11 fetuses. MR FLV values in 16 fetuses with thoracoabdominal malformations were compared with the normative curve.

RESULTS: Normal FLV increased with gestational age as a power curve; the spread of values increased with age. Interobserver correlation was excellent ($R^2 = 0.96$). FLV measurements at MR imaging were 0.90 times those at pathologic examination. A constant ratio (0.78) between FLV on the left and right sides was observed. No significant difference in FLV was observed between fetal presentations. Normal FLV was observed in all fetuses with cystic adenomatoid malformations and in four of six with oligohydramnios. Lowest FLV values were observed in fetuses with diaphragmatic hernia.

CONCLUSION: In fetuses with normal lungs, FLV distribution against gestational age is easily assessed in utero with fast spin-echo T2-weighted MR imaging. These preliminary findings illustrate the potential for comparing FLV measurements in fetuses at risk of lung hypoplasia with normative values.

Proper evaluation of fetal development relies on morphologic analysis and biometric measurements. The comparison of these individual measurements with normal values obtained in a reference population allows the establishment of a growth pattern. To now, most of the measurements, including chest measurements, are performed at ultrasonography (US). However, US has some limitations, particularly in the determination of whether fetal lung has reached sufficient development to allow neonatal survival in cases of diaphragmatic hernia or oligohydramnios (1).

Lung hypoplasia is characterized by insufficient development of pulmonary airways, alveoli, and vessels, and it correlates with low lung volume and poor outcome (2). Therefore, accurate measurement of fetal lung volume (FLV) may have important clinical applications. Assessment of lung volume or lung hypoplasia by means of conventional US remains difficult and inaccurate (3). More recently, measurements of FLV in normal amniotic fluid environment have been performed with three-dimensional US (4,5). However, in cases of congenital diaphragmatic hernia and oligohydramnios, accurate visualization of lung parenchyma is not always possible with US.

Magnetic resonance (MR) imaging has been shown (6–8) to have applications in such circumstances. FLV measurements are also possible at MR imaging, and findings of a longitudinal study involving echo-planar imaging techniques in a healthy fetal population have been recently published (9–11). Unfortunately, echo-planar techniques lack the



Figure 1. Coronal fast spin-echo T2-weighted MR image (5,900/140; 3-mm thickness; spatial resolution, 1.2×1.5 mm) in a 32-week-old fetus clearly depicts the trachea (arrowhead), carina, and main bronchi.

spatial resolution offered by other more widely available fast imaging sequences (6). The purpose of the present multicenter study was to establish a curve of normal FLV values plotted against gestational age on the basis of fast spin-echo T2-weighted MR images, for normative reference, and to investigate the correlation between lung growth and fetal presentation, sex, and US biometric measurements. To demonstrate its potential clinical interest, the normal FLV curve was compared with FLV data obtained in a group of fetuses with disease.

MATERIALS AND METHODS

Patients

A multicenter (seven hospitals in France and Belgium) prospective study was conducted. In this study, two groups of patients were examined. The first group included 320 fetuses (gestational age range, 21–38 weeks; mean, 31 weeks; maternal age range, 16–43 years; mean, 29 years) referred for brain MR imaging between January 1996 and July 1999 because they were suspected of having central nervous system disorders (at US or pregnancy at risk). During this examination, they underwent complementary T2-weighted fast spin-echo MR imaging

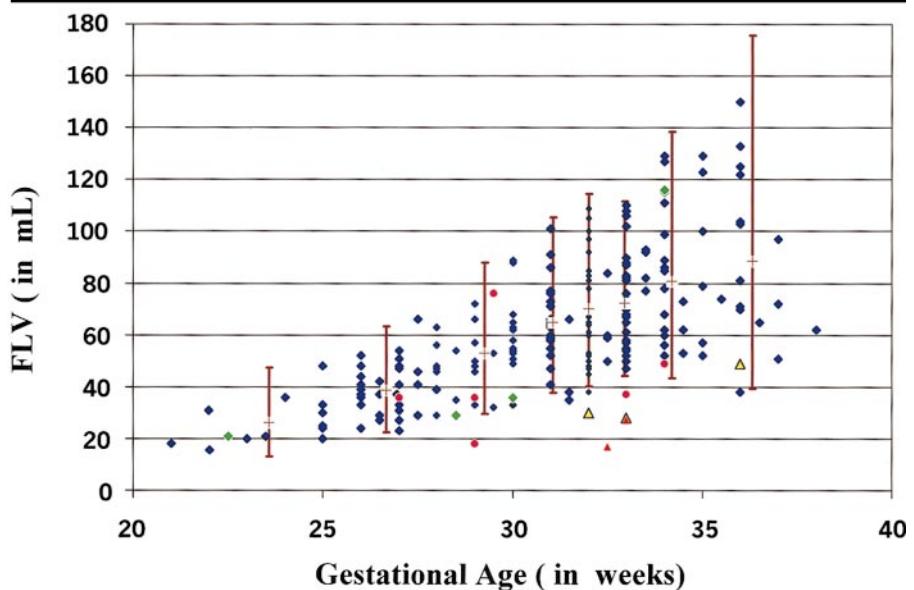


Figure 2. Normative FLV distribution plotted against gestational age (blue diamonds). Mean FLV (+) values were calculated for eight age classes of comparable size. In each age class, the asymmetric 95% CI for the FLV is shown with bars below and above the mean value. In addition, the FLVs measured in fetuses with thoracoabdominal malformation were compared with the FLV normative curve. Red circles indicate fetuses with oligohydramnios; green diamonds, fetuses with adenomatoid malformation; red triangles, fetuses with diaphragmatic hernia (did not survive); and yellow triangles, fetuses with diaphragmatic hernia (survived).

of the lungs. All fetuses underwent US biometry (including measurement of biparietal diameter, abdominal circumference, and femoral length) performed the same day or within the week before MR study. At both MR imaging and US, none of these fetuses had thoracoabdominal abnormalities. In 11 fetuses, pathologic results, including measurement of the lung volume obtained with an immersion method, were available within the 2 weeks following MR examination. After dissection of the pulmonary hilum, each lung was separately immersed in a graduated water column, and its volume was determined. The sum of volumes in the left and right sides was then computed. Pathologic results were correlated with MR FLV measurements. Only data from fetuses ($n = 215$) with normal amniotic fluid volume, with biometric percentiles of 5%–95% at the time of measurement at US, and with normal lungs confirmed with postnatal follow-up were incorporated to establish the FLV normative curve.

The second group included 16 patients referred for complementary MR imaging of thoracoabdominal malformations detected at US. This group included five fetuses with cystic adenomatoid malformation, five fetuses with diaphragmatic hernia (three left-sided, two right-sided), and six fetuses with oligohydramnios. In

all these patients, MR FLV measurement was performed.

The examination procedure was explained to the parents of the 336 fetuses, and they provided informed consent. Approval of the respective institutional review boards was obtained for the entire study.

MR Imaging

MR studies were performed with a phased-array body coil or a surface coil by using 1.5-T systems from different manufacturers (CompactPlus, Philips Medical Systems, Best, the Netherlands; Signa Echo Speed, GE Medical Systems, Milwaukee, Wis; and Magnetom Vision, Siemens Medical Systems, Erlangen, Germany). T2-weighted fast spin-echo MR imaging of the lungs consisted of the acquisition of 12–20 sections of 3–5-mm thickness oriented in at least one of the transverse or coronal planes relative to the fetal lungs. Images were acquired in 23–35 seconds without respiratory triggering (repetition time msec/echo time msec, 5,900 or 9,600/140; echo train length, 47–128; half-scanning percentage, 55%–70%; in-plane spatial resolution, 1.2×1.5 mm). Multishot (multi-section acquisition encompassing six repetition times) or single-shot (consecutive single-section acquisition) techniques were applied, and the specific absorption rate

FLV: Descriptive Statistical Data for Gestational Age Classes

Age Class (wk)	FLV Range (mL)	Mean FLV (mL)	Median FLV (mL)	SD	Skewness	95% CI
21.0–25.0 (n = 13)	16–48	26.15	24	9.15	1.18	13.00, 47.55
26.0–27.5 (n = 29)	23–66	38.83	37	10.12	0.57	22.33, 63.27
28.0–30.0 (n = 34)	29–89	52.97	53	14.20	0.59	29.73, 88.00
31.0–31.5 (n = 26)	35–101	65.04	64	15.91	0.18	37.71, 105.53
32.0 (n = 32)	38–109	70.22	67.5	18.16	0.41	40.30, 114.62
32.5–33.0 (n = 34)	47–110	72.29	69	17.18	0.69	44.38, 111.73
33.5–35.0 (n = 30)	52–129	80.73	77.50	24.32	0.73	43.34, 138.38
35.5–38.0 (n = 16)	38–150	88.63	77.50	31.77	0.42	39.45, 175.58

always remained below 3.0 W per kilogram of body weight.

Maternal sedation with flunitrazepam (1 mg) or hydroxyzine hydrochloride (25 mg) was administered orally 30–45 minutes before the beginning of the examination to reduce fetal movements and related volume measurement errors. The mothers were positioned in either the supine or partial left decubitus position. Respiratory and video monitoring were systematically used.

Image Analysis

FLV was computed on images covering the entire thorax, from the area of regions of interest following the lung boundaries and drawn on consecutive images multiplied by the section thickness. The regions of interest were independently measured in the left and right lungs; they did not include the main vessels of the pulmonary hila. When different section orientations were available, the orientation corresponding to the best image quality was chosen for FLV measurement. The criteria for a high-quality image included coverage of the whole thorax on a single acquisition; absence of motion artifacts; and clear identification of parietal and mediastinal boundaries, including the thymus, heart, main pulmonary veins and arteries, esophagus, trachea, main and lobar bronchi, diaphragm, and thoracic wall (Fig 1).

Measurements were performed independently by two observers (F.R., T.M.) in the first 60 fetuses to determine interobserver variability (only measurements performed by F.R. were incorporated into the study). The remaining measurements were performed in each site by the local observer (N.R., P.S., F.B., M.P.Q., L.G., B.M.L., C.D.) in charge of the analysis.

Statistical Analysis

Our population sample (n = 215) from whom data were used to draw our FLV

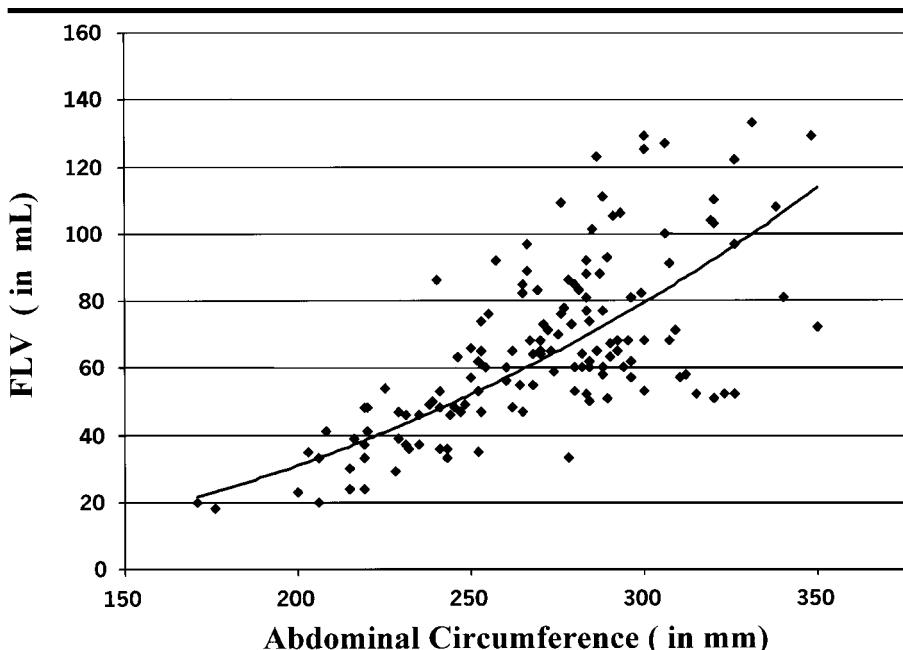


Figure 3. FLV distribution plotted against abdominal circumference measured at US. Data were best fitted with the following power curve: $FLV = 0.0001c^{2.32}$ ($R^2 = 0.57$), where c represents abdominal circumference. The correlation between these variables appears to be limited, especially for large values and correspond mostly to the end of the gestation.

normative curve was divided into eight age classes of comparable size. For each age class, the mean value of the FLV—as well as the values of the median, SD (unbiased s), and skewness (estimate by the unbiased Fisher g_1 asymmetry coefficient)—were calculated. The Fisher g_1 asymmetry coefficient is given by the following equation:

$$g_1 = \frac{n}{(n-1)(n-2)} \sum_{i=1}^n \left(\frac{x_i - \bar{x}}{s} \right)^3,$$

where n is the population sample, x_i is an individual FLV measurement, \bar{x} is the mean value, and s is the SD (12). For each age class, an approximate value of the 95% CI for the predicted values of FLV was obtained by considering the distribution of the logarithm of the observed FLV

(13). This distribution did not significantly differ from a normal distribution (Lilliefors test, $P > .1$) its 95% CI was then computed and retransformed into original FLV values (Fig 2, Table).

Best-fit curves and corresponding R^2 coefficients (resulting in the proportion of the variance of the dependent variable explained by the regression curve) were obtained to compare dependent variables (FLV, gestational age, and US biometric measurements) and to compare FLV measurements by two independent observers (interobserver variations). In cases of linear regression, the 95% CI for the regression coefficient was calculated; when appropriate, mean values were compared with the Student t test, and the intercept was verified to be nonsignificantly differ-

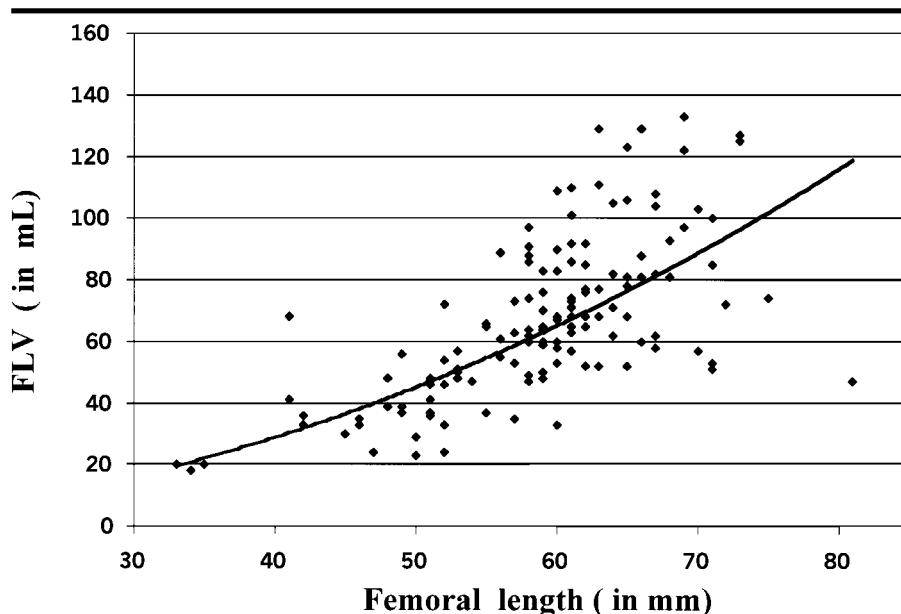


Figure 4. FLV distribution plotted against femoral length measured at US. Data were best fitted by the following power curve: $FLV = 0.0174f^{2.01}$ ($R^2 = 0.53$), where f represents the femoral length. The correlation between FLV and f remains of the same order as that of the correlation between FLV and abdominal circumference.

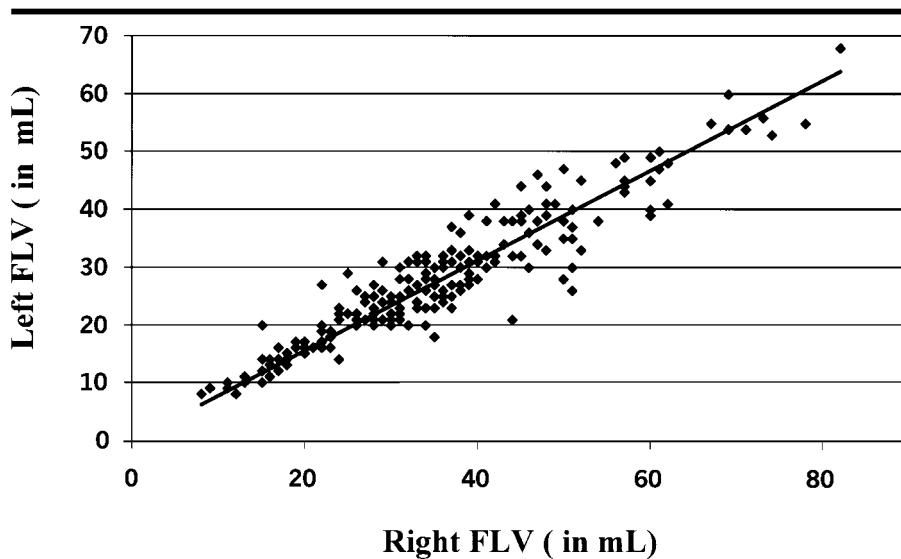


Figure 5. Left FLV plotted against right FLV. The best fit is given by a linear regression curve, as follows: Left FLV equals 0.78 times the right FLV; R^2 is 0.87. The ratio between the left and right FLV remains approximately constant throughout gestation.

ent from zero. FLVs of male and female fetuses were compared in the different age classes with the Mann-Whitney U test. The level of statistical significance was fixed at a P value of .05. Regression curves were generated with EXCEL 98 (Microsoft, Redmond, Wash), inference tests were performed with STATISTICA (StatSoft, Tulsa, Okla), and all calculations were performed on a Macintosh Power PC G3 (Apple Computer, Cupertino, Calif).

RESULTS

FLV measurement with fast spin-echo sequences was easily feasible. The duration of image acquisition was short and well tolerated by patients. However, measurements with planimetry were time-consuming; approximately 10 minutes were needed for one FLV measurement in our series.

FLV (range, 16–150 mL) increased with gestational age, as illustrated in Figure

2. The spread of values increased with age according to a power fit: $FLV = 0.0033g^{2.86}$ ($R^2 = 0.58$), where g is gestational age in weeks. For the eight age classes, the Table shows the mean value of the FLV, as well as the values of the median, SD, asymmetry coefficient (unbiased Fisher g_1 coefficient), and error bars (used in Fig 2).

FLV was correlated with US fetal biometric measurements, as shown in Figures 3 and 4. FLV was correlated with fetal abdominal circumference c and femoral length f according to the following power fits: $FLV = 0.0001c^{2.32}$ ($R^2 = 0.57$) and $FLV = 0.0174f^{2.01}$ ($R^2 = 0.53$). FLV was correlated with the Shepard et al (14) estimation of the fetal weight w according to the following power fit: $FLV = 0.1157w^{0.84}$ ($R^2 = 0.61$). Abdominal circumference and femoral length correlated well with gestational age ($R^2 = 0.75$ and 0.74, respectively), but biparietal diameter did not ($R^2 = 0.57$). Also, the best-fit curve between FLV and biparietal diameter revealed a poor correlation ($R^2 = 0.40$).

Throughout gestation, a constant ratio between volumes on the left and right sides was observed, as shown in Figure 5. A linear fit was demonstrated between left and right FLV: Left FLV was 0.78 times the right FLV; R^2 was 0.87. (The 95% CI for the regression coefficient was 0.77, 0.79.) Right FLV accounted for 56% of the total FLV. There was no significant difference in FLV between fetal presentations where the fit curves superimposed.

Toward the end of gestation, FLV values of male fetuses increased more than FLV values of female fetuses; a statistically significant difference was observed after 35 weeks gestation (unilateral Mann-Whitney U test, $P = .051$). Measurements performed independently by two observers were linearly correlated: R^2 was 0.96. Their mean FLV values, 74.48 and 73.97, were not significantly different (bilateral paired Student t test, $P = .56$), and the intercept was not significantly different from zero ($P = .9$); for each age class, individual differences remained inside the SD around the mean value.

FLV measurements at MR imaging and pathologic examination were linearly correlated: FLV at MR imaging was 0.90 times the FLV at pathologic examination; R^2 was 0.75. The mean FLV at MR imaging and pathologic examination was not significantly different (Student t test, $P = .25$), and the 95% CI for the regression coefficient was 0.80, 1.00.

The FLV measured in fetuses with thoracoabdominal malformation was compared with the FLV normative curve (Fig

2). The five fetuses with adenomatoid malformation had normal FLV values; they all survived. The six fetuses with oligohydramnios had values within the normal range in all but two cases; one had severe intrauterine growth retardation, and the other had autosomal recessive polycystic kidney disease (confirmed at pathologic examination) and died. Four of five fetuses with diaphragmatic hernia had a low FLV; the two fetuses with a right-sided diaphragmatic hernia died. The three other fetuses had left-sided hernia and survived.

DISCUSSION

Fast spin-echo T2-weighted MR images of the fetal thorax used in this study provided outstanding contrast between lung parenchyma and the surrounding structures, including the trachea, main bronchi, heart and hila, thymus, esophagus, diaphragm, and thoracic wall structures (Fig 1). This contrast allowed accurate delineation of the boundaries of the lungs, which probably accounted for the good interobserver agreement in the measurement of FLV. In our study, MR measurements were 10% less than the FLV measured at pathologic examination ($n = 11$). Similarly, our MR values remained less than the published (15) pathologic data ($n = 42$, including neonates). Compared with recent MR echo-planar data obtained in a longitudinal study (11), our measurements were systematically greater at any gestational age and were better correlated with fetopathologic standards.

The best fit of FLV against gestational age differed between the echo-planar study findings and those of the present study. However, in both studies, the spread of values increased with age, resulting in a low correlation between FLV and gestational age. The differences between our results and those of the echo-planar series might be partially explained by the differences in image quality and study design (longitudinal vs transverse). Interestingly, enlargement of the inferior length of the FLV 95% CI observed in our study after 33.5 weeks gestation might reflect the decrease of FLV toward the term reported in the longitudinal study (11).

One could argue about the possible effect of amniotic breathing on the large dispersion of observed FLV in fetuses close to term. It might be expected that movement artifacts could occur when the fetus is breathing amniotic fluid, but in the few fetuses included in the 35.5–38.0-week gestational age class ($n = 16$),

we made all measurements on images that were free of movement artifact, and no respiratory-like feature could be detected. However, we did not systematically repeat FLV measurement in the same fetus in the same plane; therefore, we cannot make conclusions.

In fetuses and infants, lung volume is correlated with fetal body volume or fetal body weight (16). These two parameters were not available in our study, and we used biometric parameters currently applied in a fetal survey that are only indicative of fetal body weight or volume. Despite the fact that the included reference population had normal lungs (confirmed at postnatal follow-up), a biometric finding of 5%–95%, and normal amniotic fluid, it was not a strictly healthy population because the fetuses were suspected of having central nervous system disease and because confounding factors involving head biometry were probably present. These limitations might explain the poor correlation observed in our study between FLV and US biometric measurements.

A constant linear relation was observed between left and right FLVs throughout pregnancy. The left and right lung volumes corresponded, respectively, to 44% and 56% of the total FLV. These results are in agreement with published (16,17) pathologic data obtained in infants and fetuses and with echo-planar volumes measured in infants.

A significant difference between male and female fetuses was observed only after 35 weeks gestation in our series. The difference between both sexes is well documented in adults, but it is not well established in children and in fetuses. In the pathology literature data from a small series (15) that included fetuses and neonates showed no difference between males and females. However, according to the findings of a postnatal pathologic study of lung growth (18), boys have larger lungs than girls, and the difference is significant at about the age of 2 years.

Among 16 fetuses with thoracoabdominal malformations or oligohydramnios, 10 fetuses had normal FLV and survived, while three of six fetuses with an abnormally low FLV died. The fetus with oligohydramnios and severe intrauterine growth retardation survived despite a low FLV value measured at 29 weeks gestation. The other fetus with oligohydramnios and a low FLV at 33 weeks gestation died; he had autosomal recessive multicystic kidney disease, which is known to be associated with lung hypoplasia.

As expected, FLV measured in fetuses with diaphragmatic hernia was less than the normal range in four of five fetuses. All three fetuses with a left-sided hernia survived. The two fetuses with a right-sided hernia died shortly after birth before any surgical treatment. One of these two had a low FLV value at 32 weeks gestation, whereas the other had a FLV value that was close to the FLV of a surviving fetus with left-sided diaphragmatic hernia. However, interestingly, there was a difference between these last two fetuses: The lung-to-liver signal intensity ratio was lower in the fetus with a right-sided hernia. This finding could be related to differences in the intrapulmonary liquid content or lung histologic characteristics, which eventually could explain the different outcomes. Therefore, in addition to FLV estimation, other information provided at fetal MR imaging (19), such as relative lung signal intensity, and spectroscopy (20) should probably be considered in future studies for the assessment of the fetal lung.

In conclusion, these MR findings demonstrate the distribution of FLV measured in utero compared with fetal age and US biometric measurements in fetuses with normal lungs; a potential application in the evaluation of fetuses with thoracic malformations, diaphragmatic hernia, or oligohydramnios is suggested.

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