

Lung and heart volumes by three-dimensional ultrasound in normal fetuses at 12–32 weeks' gestation

C. F. A. PERALTA, P. CAVORETTO, B. CSAPO, O. FALCON and K. H. NICOLAIDES

Harris Birthright Research Centre for Fetal Medicine, King's College Hospital Medical School, London, UK

KEYWORDS: 3D ultrasound; fetal heart volume; fetal lung volume; VOCAL

ABSTRACT

Objective To establish reference intervals for the fetal right, left and total lung volumes and heart volume between 12 and 32 weeks of gestation.

Methods Fetal lung and heart volumes were measured using three-dimensional (3D) ultrasound in 650 normal singleton pregnancies at 12–32 weeks. The VOCAL (Virtual Organ Computer-aided AnaLysis) technique was used to obtain a sequence of six sections of each lung and the heart around a fixed axis, each after a 30° rotation from the previous one. The rotation axis for the lungs extended from the apex to the upper limit of the diaphragm dome, and the rotation axis for the heart extended from its apex to its connection to the great vessels. The contour of each of these organs was drawn manually in the six different rotation planes to obtain the 3D volume measurement. In 60 cases the fetal lungs and heart volumes were measured by the same sonographer twice and also by a second sonographer once in order to compare the measurements and calculate intra- and interobserver agreement.

Results The total lung volume and heart volume increased with gestation, from respective mean values of 1.6 and 0.6 mL at 12 weeks to 10.9 and 4.3 mL at 20 weeks and 49.3 and 26.6 mL at 32 weeks. The right to left lung volume ratio did not change significantly with gestation (median, 0.7), whereas the heart to total lung volume ratio increased with gestation from about 0.3 at 12 weeks to 0.5 at 32 weeks. In the Bland–Altman plot, the difference between paired measurements by two sonographers was, in 95% of the cases, less than 0.05, 0.5 and 1.9 mL for each lung at 12–13, 19–22 and 29–32 weeks, respectively, and the corresponding values for the heart volumes were 0.04, 0.4 and 2.3 mL.

Conclusions In normal fetuses the lung and heart volumes increase between 12 and 32 weeks of gestation.

The extent to which in pathological pregnancies possible deviations in these measurements from normal prove to be useful in the prediction of outcome remains to be determined. Copyright © 2005 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Several sonographic studies have attempted to assess fetal lung volume, with the aim of improving prediction of pulmonary hypoplasia due to oligohydramnios or fetal defects, such as diaphragmatic hernia. In general, with two-dimensional (2D) ultrasound, efforts were focused on the measurement of the thoracic circumference or lung area in the cross-sectional plane of the thorax used for examination of the four-chamber view of the heart^{1–4}. With the advent of three-dimensional (3D) ultrasound it has become possible to assess lung volume, which could potentially provide more accurate assessment of normal and impaired lung development. However, studies of normal lung volume with gestation have reported inconsistent results, possibly because of the small number of patients examined and a lack of uniformity in methodology (Table 1)^{5–14}.

The aim of this cross-sectional study of 650 patients was to establish reference intervals for the right, left and total lung volumes and heart volume between 12 and 32 weeks of gestation.

METHODS

Fetal lung and heart volumes were measured using 3D ultrasound in 650 singleton pregnancies at 12–32 weeks. The inclusion criteria were uncomplicated pregnancy, well-defined gestational age by a known last menstrual period date and confirmed by a first-trimester scan, and normal fetal anatomy and growth demonstrated at routine

Correspondence to: Prof. K. H. Nicolaidis, Harris Birthright Research Centre for Fetal Medicine, King's College Hospital Medical School, Denmark Hill, London SE5 8RX, UK (e-mail: fmf@fetalmedicine.com)

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Table 1 Studies reporting on total lung volume with gestation

Study	n	Gestation (weeks)	Study design	Method of measurement	Median lung volume (mL) for gestation (weeks)					
					12	16	20	24	28	32
Lee <i>et al.</i> (1996) ⁵	108*	14–41	Mixture	Multiplanar: thorax–heart	6.8	15.2	26.4	42.0	60.3	
D'Arcy <i>et al.</i> (1996) ⁶	20	24–36	Cross-sectional	Multiplanar: each lung			5.1	17.2	29.3	
Laudy <i>et al.</i> (1998) ⁷	29	19–39	Cross-sectional	Multiplanar: thorax–heart			6.0	24.1	42.3	60.5
Pohls and Rempen (1998) ⁸	57	20–34	Cross-sectional	Multiplanar: each lung			9.9	19.3	33.4	53.1
Bahmaie <i>et al.</i> (2000) ⁹	234*	18–40	Longitudinal	Multiplanar: each lung			5.8	12.5	25.3	40.0
Osada <i>et al.</i> (2002) ¹⁰	125	15–40	Cross-sectional	Multiplanar: each lung	1.2	6.6	14.5	29.1	41.4	
Chang <i>et al.</i> (2003) ¹¹	152	20–40	Cross-sectional	Multiplanar: each lung			8.3	18.6	33.0	51.3
Sabogal <i>et al.</i> (2004) ¹²	167*	20–30	Longitudinal	Multiplanar: each lung			10.3	26.9	43.3	
Ruano <i>et al.</i> (2004) ¹³	109	20–37	Cross-sectional	VOCAL: each lung			10.0	21.3	39.8	61.7
Moeglin <i>et al.</i> (2005) ¹⁴	39	17–34	Cross-sectional	VOCAL: each lung			8.5	16.7	26.8	36.8
Present study	650	12–32	Cross-sectional	VOCAL: each lung	0.8	3.1	9.4	21.1	35.6	45.0

*Total measurements. VOCAL, Virtual Organ Computer-aided AnaLysis.

ultrasound examination. Each patient was included once in this study, which was carried out in the authors' center during a 16-month period (between December 2003 and April 2005). All scans were performed by sonographers with extensive experience in 3D ultrasound.

Several 3D volumes of the fetal chest were acquired by transabdominal sonography (RAB 4-8L probe, Voluson 730 Expert, GE Medical Systems, Milwaukee, WI, USA) and the volumes with the best image quality were chosen for analysis. Volume acquisition was performed when the fetus was facing towards the transducer and was not moving. The transducer was held over the mid-sagittal plane of the fetal thorax and slightly tilted cranially to allow better identification of the diaphragm. The same 3D settings (high for both quality and harmonics) were used to obtain the lung and heart volumes. This guaranteed a sufficiently fast acquisition time to avoid motion artifacts, with minimal compromise of image resolution. The sweep angle was set from 40° to 85°, depending on the gestational age. 2D settings were defined for better visualization of the limits of the lungs and heart (first trimester: persistence filter = 3, line filter = low, dynamic contrast = 8, enhance = 3, rejection = 25; second and third trimesters: persistence filter = 2, line filter = low, dynamic contrast = 8, enhance = 3, rejection = 30).

The VOCAL (Virtual Organ Computer-aided AnaLysis) technique was used to obtain a sequence of six sections of each lung and the heart around a fixed axis, each after a 30° rotation from the previous one (Voluson 730 Expert Operation Manual, GE Medical Systems). The rotation axis for the lungs extended from the apex to the upper limit of the diaphragm dome, and the rotation axis for the heart extended from its apex to its connection to the great vessels (Figure 1). The contour of each of these organs was drawn manually in the six different rotation planes to obtain the 3D volume measurement. The starting plane of rotation for each lung included their biggest anteroposterior diameters, and the starting plane for the heart included the four-chamber view. Every

measurement was done offline after the scan by the same operator.

In 60 randomly selected cases (20 at 12–13 weeks, 20 at 19–22 weeks and 20 at 29–32 weeks) the fetal lungs and heart volumes were measured by the same sonographer twice and also by a second sonographer once in order to compare the measurements and calculate intra- and interobserver agreement.

Statistical analysis

For the construction of the reference intervals for lung and heart volume with gestation, the mean and SD for these parameters were initially calculated for each complete week of gestation. Regression analysis was used to fit separate curves to the means and the SDs and to determine the significance of the association between the lung and the heart volume and the gestational age. The best fit to the means of the lung volume was obtained using quadratic regression equations, and the best fit to the means of the heart volume was obtained using a cubic curve. For the SDs, quadratic regression equations were the best fit for the lung and heart volumes. To check the final model for each parameter, the values of volumes were expressed as Z-scores [(actual value – estimated mean for gestation)/estimated SD for gestation]. The Kolmogorov–Smirnov test confirmed a normal distribution of the Z-scores, and therefore the goodness of fit of each model. To obtain the 95% reference intervals for each parameter with gestation the following formula was used: centile = mean ± 1.96 × SD, where both the mean and the SD were obtained using the regression formulae¹⁵. The Bland–Altman analysis was used to compare the measurement agreement and bias for a single examiner and between different examiners¹⁶. The data were analyzed using the statistical software package SPSS 13.0 (SPSS Inc., Chicago, IL, USA) and Excel for Windows 2000 (Microsoft Corp., Redmond, WA, USA). A value of $P < 0.05$ was considered statistically significant.

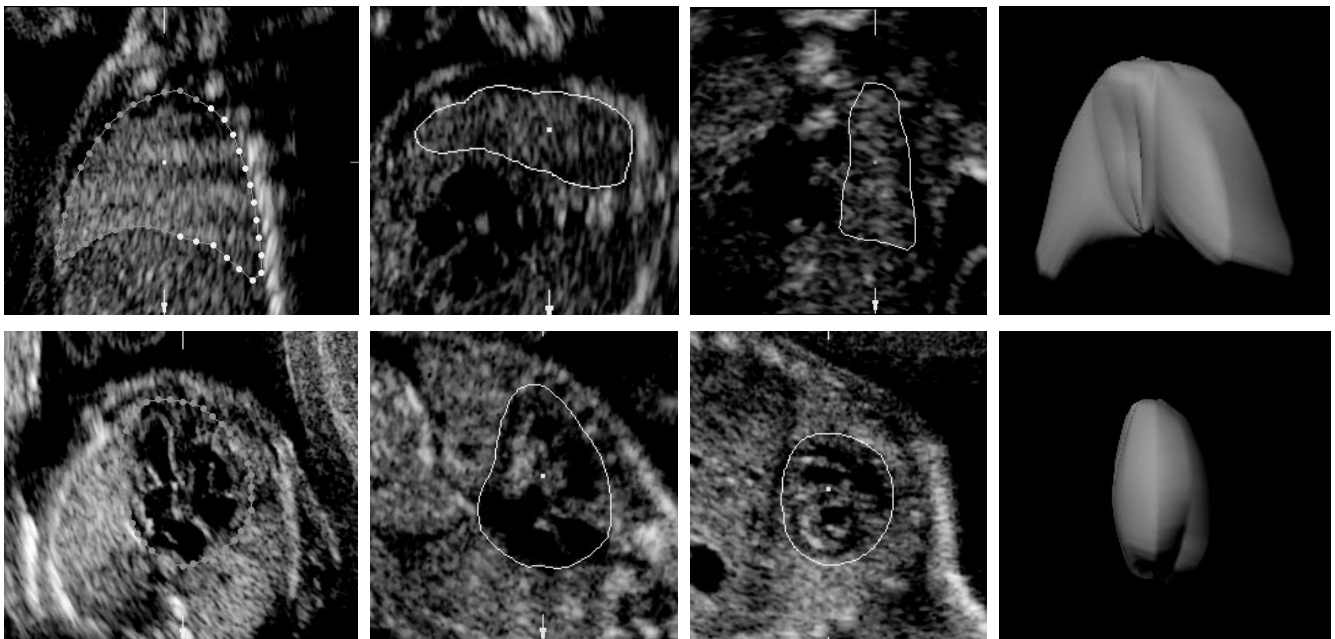


Figure 1 Three-dimensional ultrasound measurement of the fetal lung volume (upper images) and fetal heart volume (lower images) obtained using the VOCAL (Virtual Organ Computer-aided AnaLysis) technique.

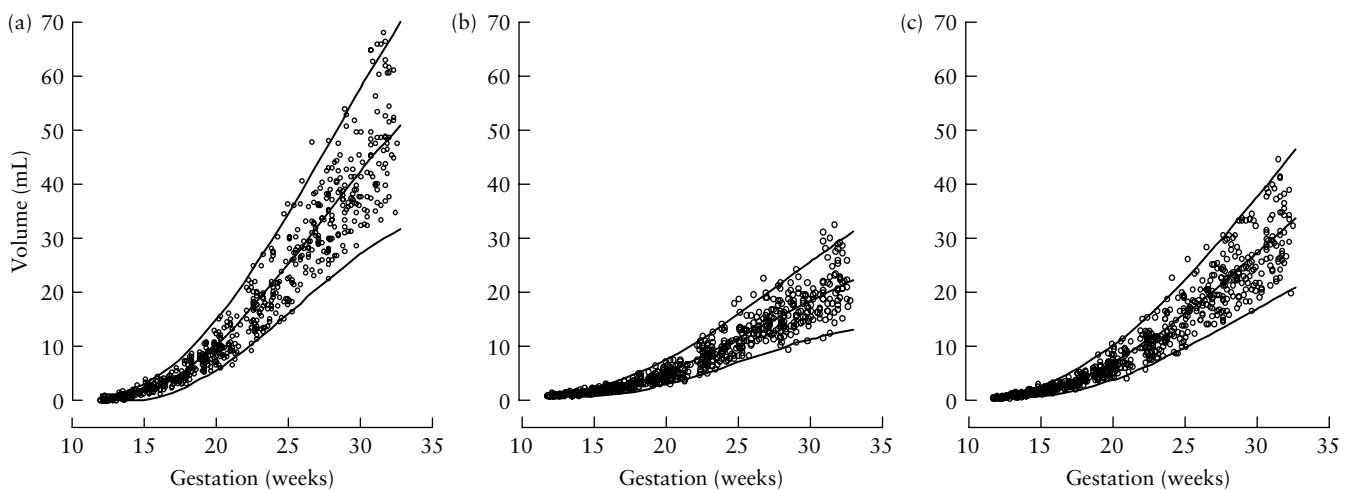


Figure 2 Mean and 95% reference intervals of (a) total, (b) left and (c) right lung volumes with gestation.

RESULTS

The fetal lung and heart volumes were successfully measured in all 650 pregnancies that fulfilled the entry criteria. The mean left, right and total lung volume increased with gestation, from 0.6, 0.6 and 1.6 mL at 12 weeks to 4.6, 6.3 and 10.9 mL at 20 weeks and 20.5, 30.0 and 49.3 mL at 32 weeks (left lung volume (mL) = $17.686614 - 2.777019 \times \text{gestation in weeks} + 0.116851 \times \text{gestation in weeks}^2 - 0.000026682 \times \text{gestation in weeks}^4$, $r = 0.9960$, $P < 0.001$; SD (mL) = $-0.2928 - 0.0463 \times \text{gestation in weeks} + 0.0059 \times \text{gestation in weeks}^2$, $r = 0.9260$, $P < 0.001$; right lung volume (mL) = $8.486184 - 1.070747 \times \text{gestation in weeks} + 0.003578 \times \text{gestation in weeks}^3 - 0.00005867 \times \text{gestation in weeks}^4$, $r = 0.9971$, $P <$

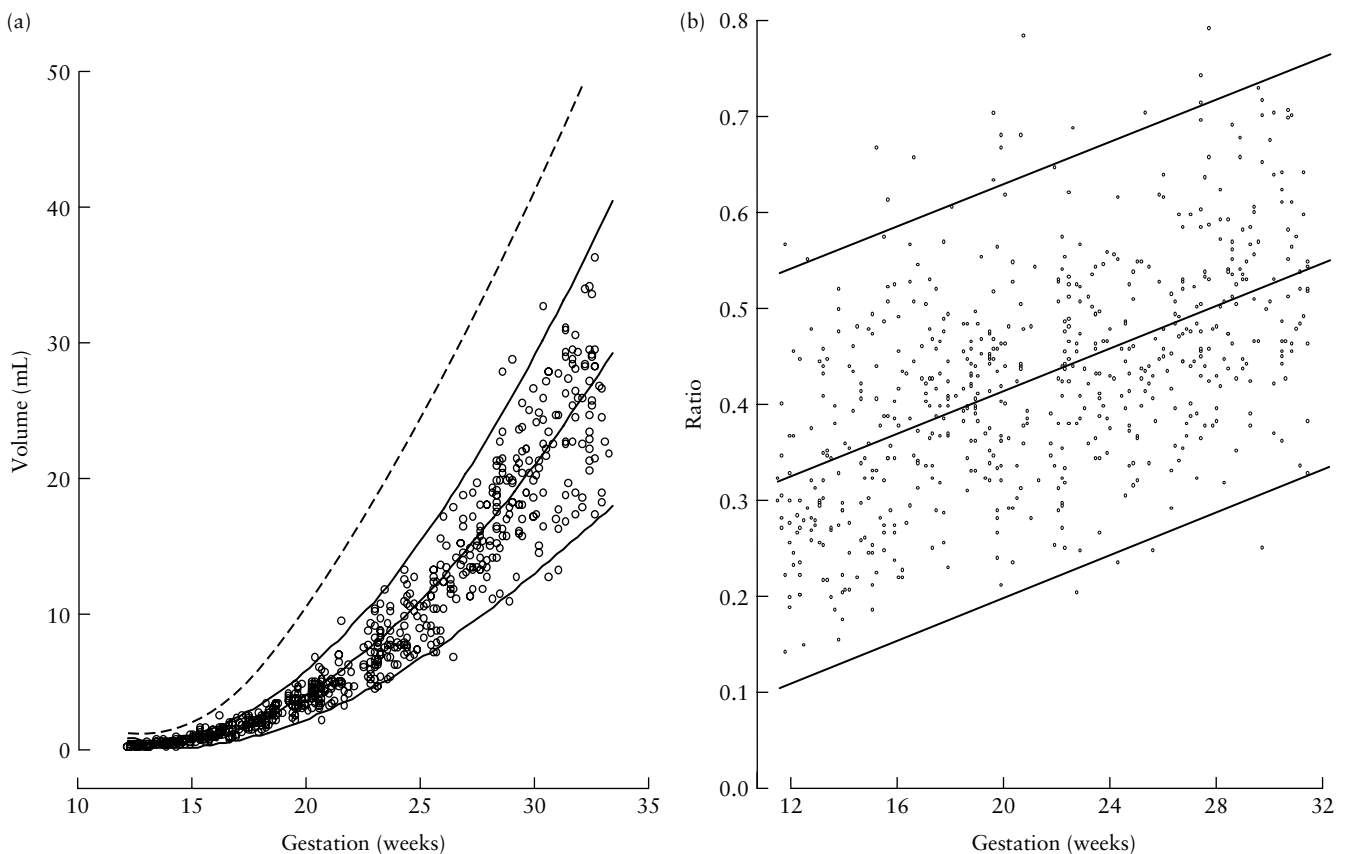
0.001 , SD (mL) = $-0.0491 - 0.1021 \times \text{gestation in weeks} + 0.0089 \times \text{gestation in weeks}^2$, $r = 0.9867$, $P < 0.001$; total lung volume (mL) = $41.822982 - 6.536788 \times \text{gestation in weeks} + 0.273906 \times \text{gestation in weeks}^2 - 0.000060877 \times \text{gestation in weeks}^4$, $r = 0.9967$, $P < 0.001$, SD (mL) = $0.1804 - 0.1797 \times \text{gestation in weeks} + 0.0144 \times \text{gestation in weeks}^2$, $r = 0.9657$, $P < 0.001$; Figure 2, Table 2).

The mean heart volume increased significantly with gestation, from 0.6 mL at 12 weeks to 4.3 mL at 20 weeks and 26.6 mL at 32 weeks (heart volume (mL) = $18.66 - 2.8983 \times \text{gestation in weeks} + 0.1271 \times \text{gestation in weeks}^2 - 0.0009 \times \text{gestation in weeks}^3$, $r = 0.9981$, $P < 0.001$, SD (mL) = $1.7937 - 0.2874 \times \text{gestation in weeks} + 0.0123 \times \text{gestation in weeks}^2$, $r = 0.9802$, $P < 0.001$; Figure 3, Table 2).

Table 2 Mean (95% reference interval) of lung and heart volumes with gestation

GA (weeks)	Volume (mL)			
	Left lung	Right lung	Total lung	Heart
12	0.64 (0.63–0.65)	0.60 (0.59–0.62)	1.56 (1.37–1.75)	0.63 (0.40–0.86)
13	0.57 (0.37–0.77)	0.75 (0.50–1.00)	1.40 (0.85–1.94)	0.48 (0.22–0.75)
14	0.69 (0.26–1.11)	1.06 (0.54–1.58)	1.65 (0.70–2.61)	0.53 (0.17–0.88)
15	0.97 (0.31–1.64)	1.53 (0.70–2.36)	2.32 (0.90–3.74)	0.75 (0.26–1.24)
16	1.42 (0.49–2.35)	2.16 (1.00–3.33)	3.36 (1.42–5.31)	1.14 (0.46–1.81)
17	2.02 (0.79–3.24)	2.96 (1.42–4.51)	4.77 (2.25–7.29)	1.70 (0.79–2.61)
18	2.76 (1.22–4.30)	3.92 (1.97–5.87)	6.52 (3.36–9.67)	2.42 (1.24–3.61)
19	3.63 (1.75–5.51)	5.04 (2.64–7.44)	8.57 (4.72–12.4)	3.30 (1.79–4.82)
20	4.62 (2.38–6.85)	6.31 (3.43–9.19)	10.9 (6.31–15.5)	4.33 (2.44–6.23)
21	5.71 (3.09–8.33)	7.73 (4.33–11.1)	13.5 (8.10–18.9)	5.51 (3.19–7.83)
22	6.90 (3.87–9.92)	9.28 (5.34–13.2)	16.3 (10.1–22.6)	6.83 (4.04–9.62)
23	8.16 (4.71–11.6)	11.0 (6.45–15.5)	19.3 (12.2–26.5)	8.28 (4.97–11.6)
24	9.49 (5.58–13.4)	12.8 (7.64–17.9)	22.5 (14.4–30.7)	9.87 (5.99–13.8)
25	10.9 (6.49–15.3)	14.7 (8.90–20.5)	25.8 (16.6–35.0)	11.6 (7.08–16.1)
26	12.3 (7.40–17.2)	16.7 (10.2–23.2)	29.2 (18.9–39.5)	13.4 (8.24–18.6)
27	13.7 (8.31–19.1)	18.8 (11.6–26.0)	32.7 (21.2–44.1)	15.4 (9.47–21.2)
28	15.1 (9.19–21.1)	21.0 (13.0–29.0)	36.1 (23.5–48.7)	17.4 (10.8–24.0)
29	16.6 (10.0–23.1)	23.2 (14.4–32.0)	39.6 (25.7–53.4)	19.6 (12.1–27.0)
30	17.9 (10.8–25.0)	25.5 (15.9–35.1)	42.9 (27.7–58.1)	21.8 (13.5–30.1)
31	19.3 (11.5–27.0)	27.7 (17.2–38.2)	46.2 (29.6–62.7)	24.1 (14.9–33.4)
32	20.5 (12.1–28.9)	30.0 (18.6–41.3)	49.3 (31.3–67.3)	26.6 (16.4–36.8)

GA, gestational age.

**Figure 3** (a) Mean and 95% reference interval of heart volume with gestation. The dotted line is the mean total lung volume with gestation. (b) Plot of the heart volume to total lung volume ratio with gestation.

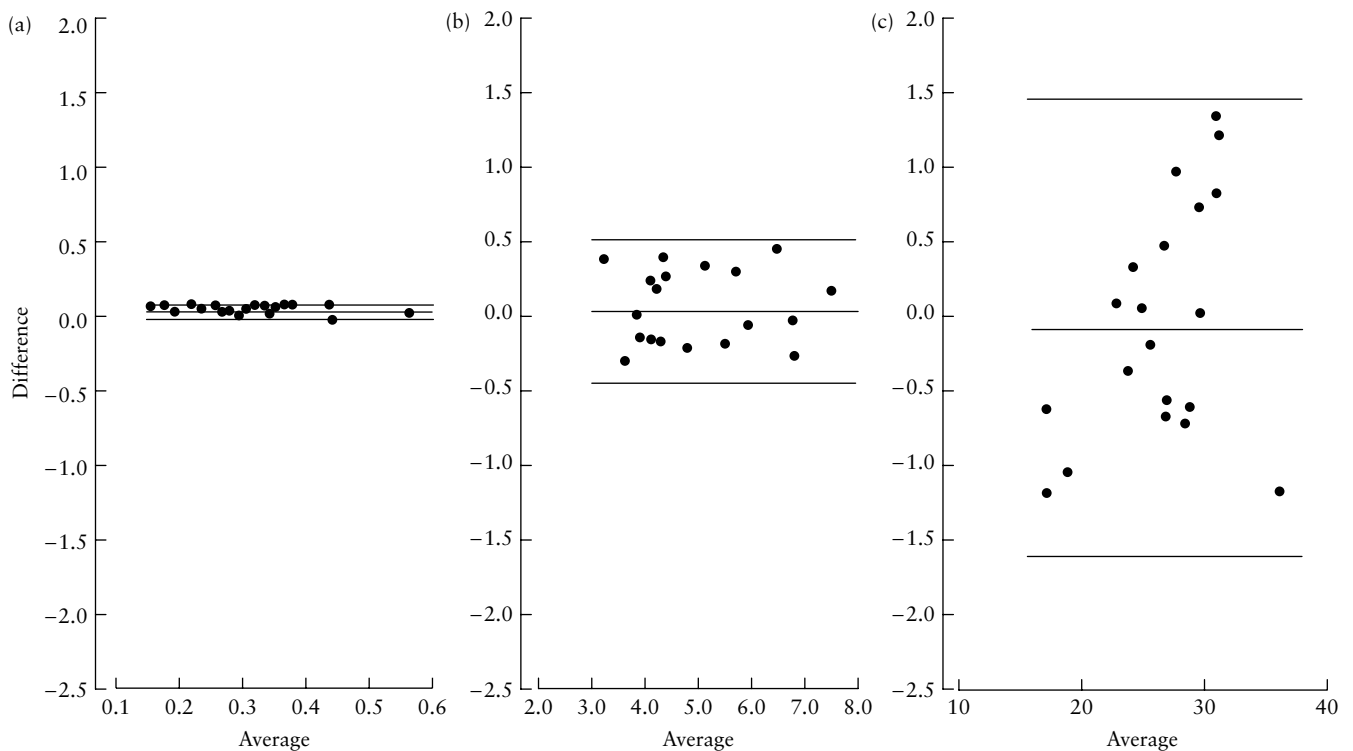
The right to left lung volume ratio did not change significantly with gestation (mean 0.74, SD = 0.12, $r = 0.027$, $P = 0.500$), whereas the heart to total lung volume

ratio increased with gestation (ratio = $0.185 + 0.011 \times$ gestation in weeks, $r = 0.520$, SD = 0.11, $P < 0.001$; Figure 3).

Table 3 Mean difference and the 95% limits of agreement between paired measurements by two sonographers and between paired measurements by the same sonographer

GA (weeks)	Mean difference and 95% CI (mL)	
	Interobserver	Intraobserver
Right lung volume		
12–13	0.01 [–0.05 (–0.07 to –0.03) to 0.06 (0.04–0.08)]	0.00 [–0.05 (–0.07 to –0.03) to 0.05 (0.03–0.07)]
19–22	0.03 [–0.46 (–0.69 to –0.27) to 0.51 (0.33–0.71)]	–0.03 [–0.51 (–0.70 to –0.32) to 0.45 (0.27–0.64)]
29–32	–0.36 [–2.25 (–2.98 to –1.52) to 1.53 (0.80–2.26)]	–0.08 [–1.63 (–2.23 to –1.03) to 1.48 (0.88–2.08)]
Left lung volume		
12–13	–0.01 [–0.05 (–0.07 to –0.03) to 0.04 (0.02–0.05)]	0.00 [–0.04 (–0.06 to –0.02) to 0.04 (0.02–0.05)]
19–22	0.05 [–0.46 (–0.66 to –0.26) to 0.56 (0.36–0.76)]	0.01 [–0.43 (–0.60 to –0.26) to 0.44 (0.27–0.61)]
29–32	0.23 [–1.39 (–2.02 to –0.76) to 1.86 (1.23–2.49)]	0.13 [–1.48 (–2.11 to –0.86) to 1.75 (1.12–2.37)]
Heart volume		
12–13	0.00 [–0.04 (–0.06 to –0.02) to 0.05 (0.03–0.06)]	–0.01 [–0.04 (–0.06 to –0.03) to 0.03 (0.02–0.04)]
19–22	0.02 [–0.49 (–0.67 to 0.31) to 0.45 (0.27–0.63)]	–0.02 [–0.29 (–0.39 to –0.18) to 0.25 (0.14–0.35)]
29–32	–0.16 [–2.73 (–3.73 to –1.73) to 2.41 (1.42–3.41)]	0.15 [–2.08 (–2.94 to –1.22) to 2.37 (1.51–3.23)]

GA, gestational age.

**Figure 4** Bland–Altman plot: the mean difference and the 95% limits of agreement between paired measurements by the same sonographer of the right lung at (a) 12–13, (b) 19–22 and (c) 29–32 gestational weeks.

In the Bland–Altman plot, the mean difference and the 95% limits of agreement between paired measurements by the same sonographer and between paired measurements by two sonographers are shown in Table 3 and Figure 4.

DISCUSSION

The study data demonstrate that both the lung and heart volumes increase with gestation from respective mean values of about 1.6 and 0.6 mL at 12 weeks to 49 and 27 mL at 32 weeks. The rate of growth of the left and

right lungs is similar and the ratio of the two volumes does not change with gestation. In contrast, the heart to total lung volume ratio increases with gestation.

The essential prerequisites for measurement of lung volume are: first, acquisition of the volume with the fetus facing the transducer and in the absence of fetal movements, and second, accurate definition of the whole diaphragm at the lower end, the apex of the lungs at the level of the clavicles, the medial border of the lungs and distinction from the heart and mediastinal organs and the lateral border of the lungs and distinction from

the thoracic cage. We found that the measurement of lung volumes in early pregnancy is easy and reproducible. In contrast, in the third trimester the measurements can be difficult and less reproducible because the fetus is often with the spine up, there are many fetal breathing movements, and the ossified ribs and consequent shadows they produce may obscure accurate definition of the limits of the lungs. We did not examine patients beyond 32 weeks of gestation because of these technical problems, which have also been highlighted in previous studies^{7,11,14}. However, this limitation does not have any clinical implications because the diagnosis of pulmonary hypoplasia and decisions concerning the management of such pregnancies should be made before 32 weeks.

In this study we used the VOCAL technique to measure each lung separately. Previous studies have demonstrated that the results obtained by the multiplanar and VOCAL techniques are similar^{14,17}. An advantage of the VOCAL technique is that the whole lung is visualized simultaneously so that first, the lowermost parts of the lungs that extend below the dome of the diaphragm can be included, and second, after the initial calculation of the lung volume it is possible to modify the contour in each plane so that a more accurate final measurement can be obtained. In the multiplanar technique, once the contour is drawn it cannot be subsequently modified. We chose the VOCAL 30° rotation step because this was faster than the other available steps and guaranteed the inclusion of the whole organ in the final volume measurement, as long as the starting plane of rotation for each lung included their biggest anteroposterior diameters and the starting plane for the heart included the four-chamber view.

The differences in the present measurements from previous reports can be explained by the small number of cases the other researchers examined. The early studies, in which lung volume was estimated by subtracting the heart volume from the thoracic volume, reported substantially higher values than in the present study, because the measurement of thoracic volume included mediastinal organs such as the thymus, great vessels, trachea and esophagus^{5,7}.

The fetal heart volume increased with gestation, from the mean value of 0.6 mL at 12 weeks to 4.3 mL at 20 weeks and 26.6 mL at 32 weeks. These volumes are considerably higher than those in one previous 3D ultrasound study, which examined 50 fetuses at 20–30 weeks and reported a linear increase with gestation from 1.6 mL at 20 weeks to 13.8 mL at 30 weeks¹⁸. We found that the heart to total lung volume ratio increased linearly with gestation from about 0.3 at 12 weeks to 0.6 at 32 weeks.

The present study has established reference ranges for the lung and heart volumes between 12 and 32 weeks of gestation. The extent to which in pathological pregnancies possible deviations in these measurements from normal prove to be useful in the prediction of outcome remains to be determined.

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