

Observed to expected lung area to head circumference ratio in the prediction of survival in fetuses with isolated diaphragmatic hernia

J. JANI*, K. H. NICOLAIDES†, R. L. KELLER‡, A. BENACHI§, C. F. A. PERALTA†, R. FAVRE¶, O. MORENO**, D. TIBBOEL††, S. LIPITZ‡‡, A. EGGINK§§, P. VAAST¶¶, K. ALLEGAERT*, M. HARRISON‡ and J. DEPREST* on behalf of the Antenatal-CDH-Registry Group

Fetal Medicine and Treatment Units of the *University Hospital Gasthuisberg, Leuven, Belgium, †King's College Hospital, London, UK, ‡University of California at San Francisco, San Francisco, CA, USA, §Hôpital Necker-Enfants Malades, Paris, France, ¶CMCO de Schiltigheim, Strasbourg, France, **Hospital Clinic, Barcelona, Spain, ††Erasmus Medical Center, Rotterdam, The Netherlands, ‡‡Sheba Medical Center, Tel Hashomer, Israel, §§UMC Sint Radboud, Nijmegen, The Netherlands and ¶¶Hôpital Jeanne de Flandre, CHRU Lille, France

KEYWORDS: diaphragmatic hernia; lung area; lung to head ratio; prenatal diagnosis; pulmonary hypoplasia

ABSTRACT

Objective To assess the value of antenatally determined observed to expected fetal lung area to head circumference ratio (LHR) in the prediction of postnatal survival in isolated, congenital diaphragmatic hernia (CDH).

Methods Two groups of fetuses were examined. The first group included 650 normal fetuses at 12–32 weeks' gestation, and the data collected were used to establish a normal range of observed to expected LHR with gestational age. The second group included the data of a retrospective multicenter study of 354 fetuses with isolated CDH in which the LHR was measured on one occasion at 18–38 weeks' gestation. The patients were divided into those with left-sided CDH with and without intrathoracic herniation of the liver and right-sided CDH. Regression analysis was used to determine the significant predictors of postnatal survival.

Results In both the normal fetuses and those with CDH the LHR increased but the observed to expected LHR did not change significantly with gestational age. In normal fetuses the mean observed to expected LHR in the left lung was 100% (95% CI, 61–139%) and in the right lung it was 100% (95% CI, 67–133%). In fetuses with CDH the mean observed to expected LHR was 39% (range 7–79%). Regression analysis demonstrated

that significant predictors of survival were the observed to expected LHR (odds ratio (OR) 1.09, 95% CI, 1.06–1.12), side of CDH (left side OR 11.14, 95% CI, 3.41–36.39) and gestational age at delivery (OR 1.18, 95% CI, 1.02–1.36).

Conclusion In CDH, the LHR increases while observed to expected LHR is independent of gestational age. In fetuses with both left- and right-sided CDH, measurement of the observed to expected LHR provides a useful prediction of subsequent survival. Copyright © 2007 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

In congenital diaphragmatic hernia (CDH) prenatal prediction of postnatal survival relies on indirect assessment of fetal lung volume. The most commonly used method for such assessment is measurement of the two-dimensional lung area to head circumference ratio (LHR)^{1,2}. A multicenter study, involving 184 fetuses with isolated, left-sided CDH, reported that in those cases with intrathoracic herniation of the liver, measurement of LHR at 22–28 weeks' gestation provided a useful prediction of subsequent survival². In contrast, in the group without liver herniation, LHR was not significantly different between those that subsequently died and those

Correspondence to: Prof. J. Deprest, Department of Obstetrics and Gynaecology, Unit of Prenatal and Gynaecological Ultrasound and Fetal Therapy, UZ Gasthuisberg 3000 Leuven, Belgium (e-mail: Jan.Deprest@uz.kuleuven.ac.be)

The 'ad hoc' Antenatal-CDH-Registry Group further includes: D. Van Schoubroeck and G. Naulaers (Leuven, Belgium); F. Molina (London, UK); V. Datin (Paris, France); J. Matis (Strasbourg, France); A. Delelis (Lille, France); E. Gratacos (Barcelona, Spain); J. Laudy (Rotterdam, The Netherlands); A. van Heijst (Nijmegen, The Netherlands); V. Eisenberg (Tel Hashomer, Israel).

Accepted: 8 March 2007

that survived. A study of 650 normal fetuses demonstrated that the LHR increases exponentially with gestational age³. Consequently, in the assessment of fetuses with CDH it would be preferable to correct for the gestational age-related change in LHR.

The aim of this extended multicenter study involving 354 fetuses with isolated CDH was to re-examine the value of LHR, corrected for gestational age, in the prediction of postnatal survival both in fetuses with left-sided lesions, with and without intrathoracic herniation of the liver, and in those with right-sided CDH.

PATIENTS AND METHODS

This is an ongoing multicenter study by fetal medicine units of the antenatal findings and postnatal outcome of fetuses diagnosed with isolated CDH. The participating centers provide the necessary data, which are entered in a central antenatal-CDH-registry at the Fetal Medicine Unit in the University Hospital of Leuven, Belgium.

We searched the database to identify all consecutive cases of CDH, diagnosed from the year 1995 onwards, that fulfilled the following criteria: first, no major abnormalities diagnosed either prenatally or postnatally; second, live birth after 30 weeks' gestation and postnatal follow-up until discharge from the hospital; and third, determination of liver herniation and measurement of the fetal LHR. In all the centers measurement of the lung area was as described by Metkus *et al.*, which essentially involves obtaining a transverse section of the fetal chest

demonstrating the four-chamber view of the heart, and then multiplying the contralateral lung area's longest diameter by the longest perpendicular to it¹.

Statistical analysis

The data from a previous study, in which we measured the LHR for the left and right lungs of 650 normal fetuses at 12–32 weeks' gestation³, were used to establish a normal range of observed to expected LHR with gestational age. In each fetus the observed LHR in the left and right lungs was expressed as a percentage of the appropriate expected mean for gestational age (observed/expected LHR × 100). Regression analysis was then used to calculate the mean and the 95% confidence intervals of the observed to expected LHR for gestational age for the left and right lungs.

In each fetus with CDH the observed LHR was expressed as a percentage of the expected normal mean for gestational age. The patients were then divided into three groups: left-sided CDH with intrathoracic herniation of the liver, left-sided CDH without intrathoracic herniation of the liver and right-sided CDH. Each group was subdivided into those that died postnatally either before or after surgery and those that survived. In each subgroup regression analysis was used to determine whether there was a significant association between LHR and observed to expected LHR with gestational age. Regression analysis was used to investigate the effect on survival of observed to expected LHR and gestational age at delivery as continuous numerical variables, and side of the diaphragmatic hernia (left or right) and intrathoracic

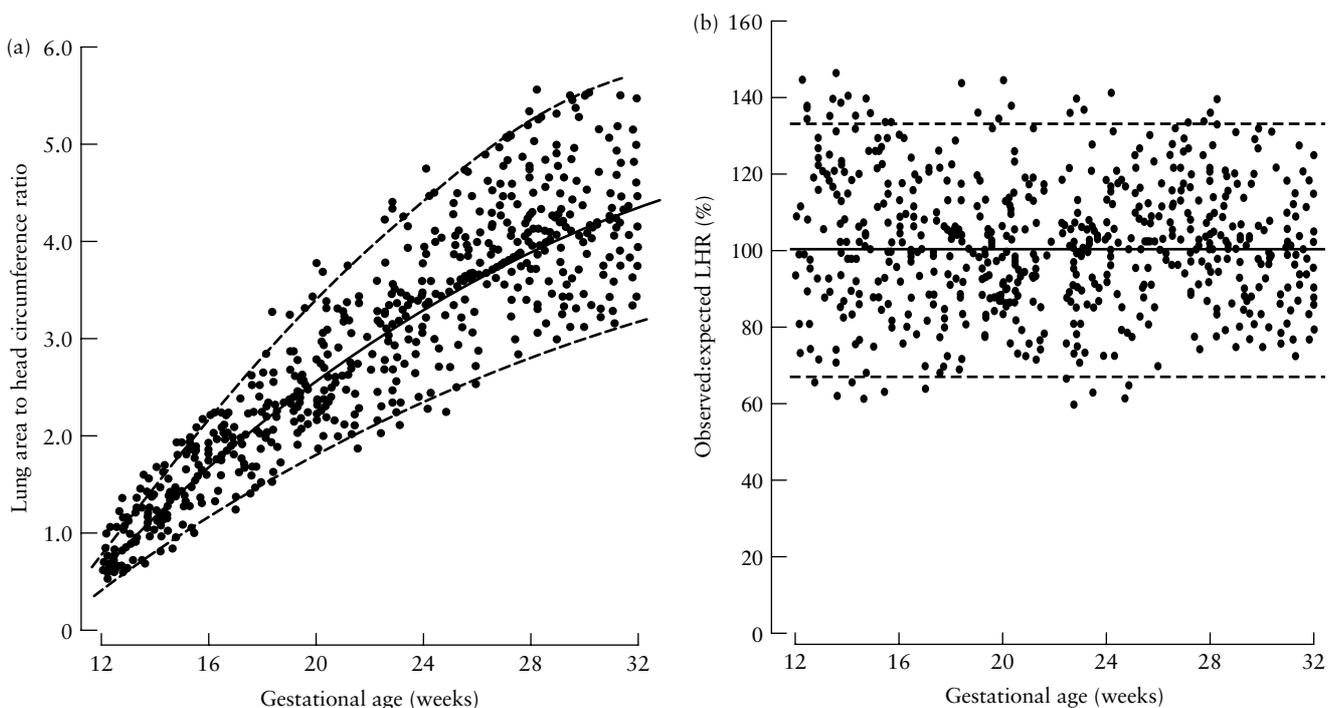


Figure 1 Relationship between right lung area to head circumference ratio (LHR) (a) and observed to expected LHR (b) with gestational age in normal fetuses. Lines represent mean and 95% CI.

Table 1 Relationship between lung area to head circumference ratio (LHR) and observed to expected (O/E) LHR with gestational age in fetuses with congenital diaphragmatic hernia

Type of diaphragmatic hernia	Outcome	n	LHR with gestational age		O/E LHR with gestational age	
			r	P	r	P
Left-sided, liver up	Alive	85	0.486	< 0.001	0.092	NS
Left-sided, liver up	Dead	76	0.312	< 0.01	-0.138	NS
Left-sided, liver down	Alive	126	0.406	< 0.001	-0.082	NS
Left-sided, liver down	Dead	42	0.334	< 0.05	-0.156	NS
Right-sided	Alive	11	0.0977	NS	-0.237	NS
Right-sided	Dead	14	0.1352	NS	-0.121	NS

NS, not significant.

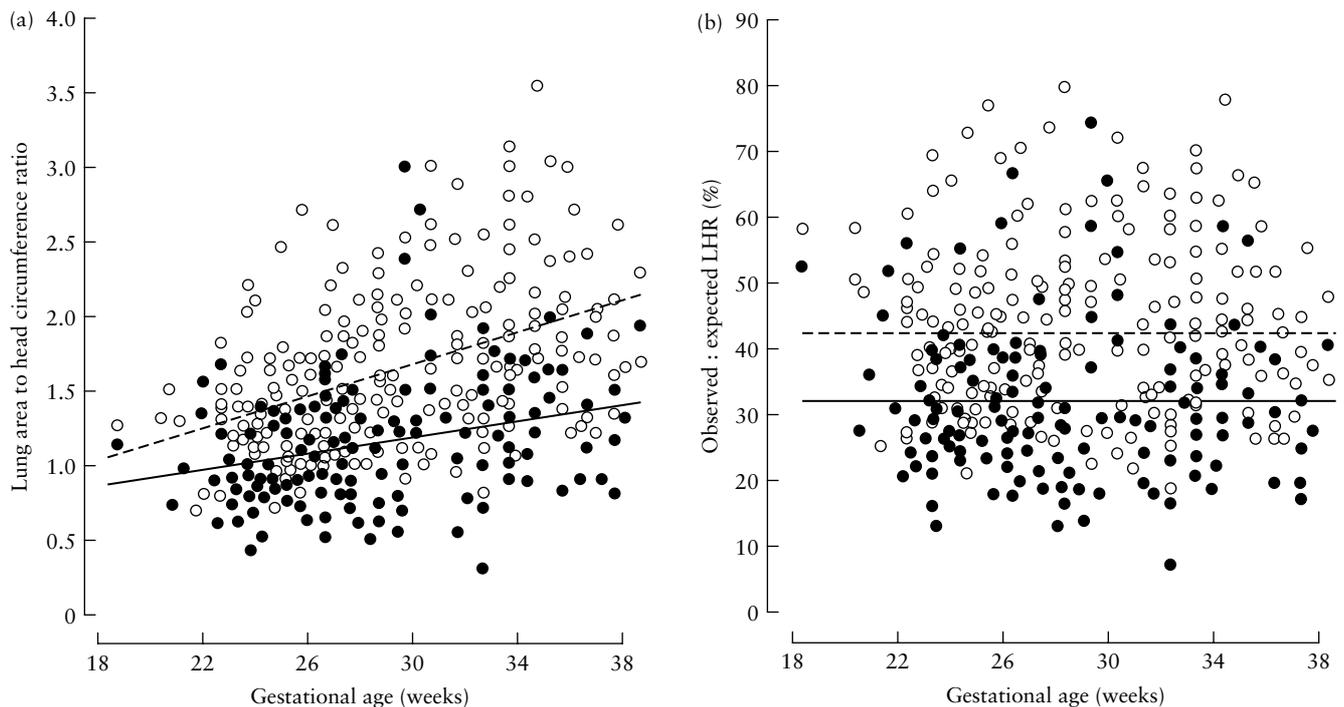


Figure 2 Relationship between lung area to head circumference ratio (LHR) (a) and observed to expected LHR (b) with gestational age in fetuses with left-sided congenital diaphragmatic hernia. The closed circles and solid regression lines are the values for the babies that died and the open circles and dashed regression lines represent the survivors.

position of the liver (yes or no) as categorical variables. A receiver-operating characteristics (ROC) curve was constructed for the prediction of survival by the observed to expected LHR.

Statistical analysis of the data was performed with SPSS for Windows (V.13, Chicago, IL, USA) and Excel for Windows 2003 (Microsoft Corp., Redmond, WA, USA). A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

In normal fetuses, in both the left and right lungs the LHR increased significantly with gestational age³, but the observed to expected LHR did not change significantly with gestational age (left lung: $r = -0.029$, $P = 0.464$; mean observed to expected LHR 100%, 95%

CI, 61–139%; right lung: $r = -0.039$, $P = 0.320$; mean observed to expected LHR 100%, 95% CI, 67–133%, Figure 1).

The search of the antenatal-CDH-registry identified 354 fetuses that fulfilled the entry criteria². The median gestational age at prenatal sonographic assessment was 27 (range, 18–38) weeks and the median gestational age at delivery was 38 (range, 31–42) weeks. In each of the four subgroups of fetuses with left-sided CDH there was a significant association between LHR and gestational age, but not between observed to expected LHR and gestational age (Table 1; Figure 2). For the two subgroups with right-sided CDH there was no significant association of either LHR or observed to expected LHR with gestational age (Table 1).

In the group with left-sided CDH and intrathoracic herniation of the liver, 85 of the 161 (52.8%) babies

Table 2 Regression analysis in the prediction of survival in fetuses with isolated diaphragmatic hernia

Variable	n (%) or median (range)	Multivariate analysis	
		OR (95% CI)	P
Side of diaphragmatic hernia			
Right	25 (7.1)	1	
Left	329 (92.9)	11.14 (3.41–36.39)	< 0.001
Intrathoracic herniation of the liver			
No	168 (47.5)	1	
Yes	186 (52.5)	0.76 (0.45–1.30)	NS
Observed to expected LHR (%)	36.6 (6.8–79.4)	1.09 (1.06–1.12)	< 0.001
Gestational age at delivery (weeks)	38 (31–42)	1.18 (1.02–1.36)	< 0.05

LHR, lung area to head circumference ratio; NS, not significant; OR, odds ratio.

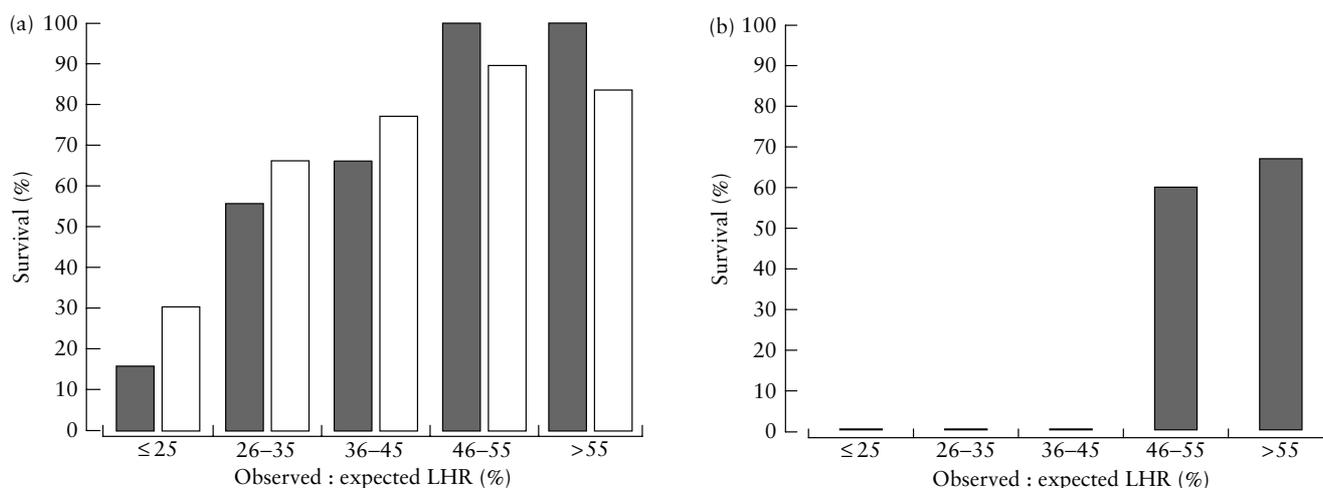


Figure 3 Survival rate according to the fetal observed to expected lung area to head circumference ratio (LHR) in fetuses with isolated left-sided (a) and right-sided (b) diaphragmatic hernia. The filled bars represent fetuses with intrathoracic herniation of the liver and the open bars represent those without herniation.

survived after delivery at 31–42 (median 38) weeks' gestation and in those with left-sided CDH and the liver confined to the abdomen 126 of the 168 (75.0%) babies survived after delivery at 32–41 (median, 38) weeks. In all 25 fetuses with right-sided CDH there was intrathoracic herniation of the liver and 11 (44.0%) babies survived after delivery at 35–41 (median, 38) weeks. Regression analysis demonstrated that significant predictors of survival were the side of diaphragmatic hernia, the observed to expected LHR and the gestational age at delivery (Table 2). The relationship between observed to expected LHR and survival in each group is shown in Figure 3.

In our previous report on expectantly managed fetuses with isolated, left-sided CDH, we found that postnatal survival was very poor when the LHR at 22–28 weeks' gestation was less than 1.0, which is equivalent to an observed to expected LHR of $\leq 25\%$ in the present study².

The area under the ROC curve for prediction of survival from the observed to expected LHR in fetuses with left-sided CDH was 0.761 ($P < 0.001$; standard error = 0.027) and for a false positive rate of 10% the sensitivity was 46% (Figure 4).

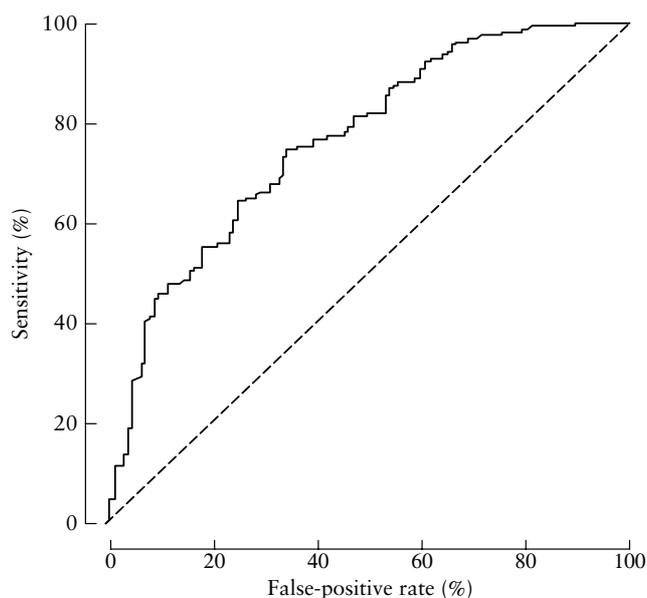


Figure 4 Receiver–operating characteristics curve for the prediction of survival in fetuses with left-sided congenital diaphragmatic hernia according to cut-off values of observed to expected lung area to head circumference ratio (continuous line). The dashed line is the reference line.

DISCUSSION

The findings of this study demonstrate that in both normal fetuses and in those with CDH the LHR changes with gestational age at assessment, whereas the observed to expected LHR is independent of gestational age. Furthermore, the data show that in both left- and right-sided CDH, measurement of observed to expected LHR provides useful prediction of subsequent survival.

In CDH prenatal prediction of postnatal survival relies on the indirect assessment of lung size. The LHR was initially thought to be independent of the gestational age at assessment⁴. However, a study of 650 normal fetuses has shown that between 12 and 32 weeks' gestation there is an 18-fold increase in lung area but only a 4-fold increase in head circumference³. Consequently, the left and right LHR increase exponentially with gestational age. By introducing the observed to expected LHR, the effect of gestational age at assessment has been eliminated. In normal fetuses, the 2.5th percentile of the observed to expected LHR for both the left and right lungs is about 60%.

In fetuses with CDH, LHR changes with gestational age and this effect is removed by introducing the observed to expected LHR. In more than 90% of our cases the observed to expected LHR was below the 2.5th percentile of the normal range. Although there was a highly significant association between the observed to expected LHR for both left- and right-sided CDH there was a considerable overlap in values between individual fetuses. Consequently the sensitivity of observed to expected LHR in the prediction of survival was only 46% for a false positive rate of 10%.

On the assumption that this relatively weak correlation is a consequence of trying to assess lung size through a two-dimensional measurement of lung area, research is now examining the potential value of volumetric assessment of the lungs by three-dimensional (3D) ultrasound and magnetic resonance imaging⁵⁻⁷. Furthermore, prediction of survival is improved by examining the pulmonary response to tracheal occlusion. Thus, in a study of 30 fetuses with isolated severe CDH treated by fetoscopic tracheal occlusion (FETO) the volume of the contralateral lung was measured by 3D ultrasound the day before and 2 and 7 days after FETO^{8,9}. In the prediction of postnatal survival, with a sensitivity of 95%, the false positive rate was 78% for lung volume measurements before FETO, 22% for measurements at 2 days after FETO and 11% for measurements at 7 days after FETO.

In this study, as in previous reports, in fetuses with left-sided CDH the survival rate was substantially lower in those with intrathoracic herniation of the liver than in those with the liver confined to the abdomen (53% vs. 75%). However, logistic regression analysis demonstrated that the position of the liver did not provide a significant contribution, independent of the observed to expected LHR, in the prediction of survival.

ACKNOWLEDGMENT

This research was funded by the European Commission within the 5th (QLG1 CT2002 01632; EuroTwin2Twin) and the 6th (EuroSTEC; LSHC-CT-2006-037409) Framework Programme.

REFERENCES

1. Metkus AP, Filly RA, Stringer MD, Harrison MR, Adzick NS. Sonographic predictor of survival in fetal diaphragmatic hernia. *J Pediatr Surg* 1996; 31: 148-151.
2. Jani J, Keller RL, Benachi A, Nicolaides KH, Favre R, Gratacos E, Laudy J, Eisenberg V, Eggink A, Vaast P, Deprest J. Prenatal prediction of survival in isolated left-sided diaphragmatic hernia. *Ultrasound Obstet Gynecol* 2006; 27: 18-22.
3. Peralta CFA, Cavoretto P, Csapo B, Vandercruys H, Nicolaides KH. Assessment of lung area in normal fetuses at 12-32 weeks. *Ultrasound Obstet Gynecol* 2005; 26: 718-724.
4. Laudy JAM, Van Gucht M, Van Dooren MF, Wladimiroff JW, Tibboel D. Congenital diaphragmatic hernia. An evaluation of the prognostic value of the lung-to-head ratio and other prenatal parameters. *Prenat Diagn* 2003; 23: 634-639.
5. Peralta CFA, Jani J, Cos T, Nicolaides KH, Deprest J. Left and right lung volumes in fetuses with diaphragmatic hernia. *Ultrasound Obstet Gynecol* 2006; 27: 551-554.
6. Jani J, Peralta CFA, Van Schoubroeck D, Deprest J, Nicolaides KH. Relation between lung-to-head ratio and lung volume in normal fetuses and fetuses with diaphragmatic hernia. *Ultrasound Obstet Gynecol* 2006; 27: 545-550.
7. Cannie M, Jani J, De Keyzer F, Devlieger R, Van Schoubroeck D, Witters I, Marchal G, Dymarkowski S, Deprest J. The use of fetal body volume at magnetic resonance imaging to accurately quantify fetal relative lung volume in fetuses with suspected pulmonary hypoplasia. *Radiology* 2006; 241: 847-853.
8. Deprest J, Gratacos E, Nicolaides KH. Fetoscopic tracheal occlusion (FETO) for severe congenital diaphragmatic hernia: evolution of a technique and preliminary results. *Ultrasound Obstet Gynecol* 2004; 24: 121-126.
9. Peralta CFA, Jani J, Van Schoubroeck D, Nicolaides KH, Deprest J. Fetal lung volume after endoscopic tracheal occlusion in the prediction of postnatal outcome. *Am J Obstet Gynecol* 2007 (in press).