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Tracheal diameter at birth in severe congenital diaphragmatic hernia treated by fetal endoscopic tracheal occlusion

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Objective To investigate tracheal dimensional differences seen at birth following fetal endoscopic tracheal occlusion (FETO) in cases of severe congenital diaphragmatic hernia (CDH) and to report on their clinical follow-up.

Patients and Methods In chest X-rays, taken within 48 h after birth, we measured the tracheal diameter at the level of the tracheal entry into the chest, 1 cm above the level of the carina and at middistance between these sites in 37 fetuses with severe CDH treated by FETO. These measurements were compared with those in 74 preterm and term neonates with no congenital lung abnormalities.

Results In the CDH group, compared to the controls, the tracheal diameter corrected for gestational age was significantly larger at all three levels of the trachea. Regression analysis showed that significant predictors of the tracheal diameter at the level of tracheal entry into the chest were the observed to expected (o/e) lung area to head circumference ratio (LHR) and the duration of tracheal occlusion. In the CDH group, postnatal follow-up until the age of 22 months (1–70) showed that 5 of 24 neonates had an effort-induced barking cough.

Conclusion A large number of infants with severe CDH surviving after FETO have a degree of tracheomegaly that is associated with the severity of CDH as assessed by pre-FETO LHR. This tracheomegaly does not constitute an obvious clinical problem. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS: diaphragmatic hernia; tracheal occlusion; tracheomegaly; fetal lung; prenatal diagnosis

INTRODUCTION

Congenital diaphragmatic hernia (CDH), with a birth prevalence of about 1 in 4000, is associated with a high perinatal mortality rate. In referral centers, the survival rate is about 50 to 70% for isolated cases and the remaining babies usually die in the neonatal period because of the consequences of pulmonary hypoplasia and persistent pulmonary hypertension (Metkus *et al*., 1996; Lipshutz *et al*., 1997; Stege *et al*., 2003; Jani *et al*., 2006; Deprest *et al*., 2009). Severely affected cases are defined with a fetal observed to expected (o/e) lung area to head circumference ratio (LHR) of 25% or less and intrathoracic liver with a predicted survival rate in left-sided cases of about 15% (Jani *et al*., 2007). Experimental studies have shown that pulmonary hypoplasia can be reversed by tracheal occlusion and human studies in more than 200 fetuses with CDH have suggested that the survival rate can be substantially improved by fetal endoscopic tracheal occlusion (FETO) (Harrison *et al*., 1990; Harrison *et al*., 2003; Deprest *et al*., 2004; Jani *et al*., 2009).

FETO is a fetoscopic percutaneous technique consisting of endotracheal occlusion using a detachable balloon. Fetal tracheal occlusion acts by preventing egress of lung liquid, leading to increased levels of lung tissue stretch thus triggering lung growth (DiFiore *et al*.,1994).

In FETO, the inflated balloon is about 8 mm in diameter and 22 mm in length. These dimensions exceed the fetal tracheal dimensions to ensure that the balloon remains occlusive as the trachea grows (Deprest *et al*., 1998). Animal studies, carried out before the introduction of FETO, showed that tracheal occlusion was associated with mild epithelial and inflammatory changes, elongation of the non-cartilaginous part, but no changes affecting the cartilage rings (Chiba *et al*., 2000; Deprest *et al*., 2000). In human beings, the description of tracheal side effects after FETO is only limited to case reports (Breysem *et al*., 2010; Deprest *et al*., 2010; Fayoux *et al*., 2010; McHugh *et al*., 2010).

The purpose of this study was to investigate tracheal dimensional changes seen at birth following FETO in cases of severe CDH and to report on their long-term clinical implications.

PATIENTS AND METHODS

This was a cross-sectional retrospective study of 37 neonates with CDH treated by FETO and 74 preterm

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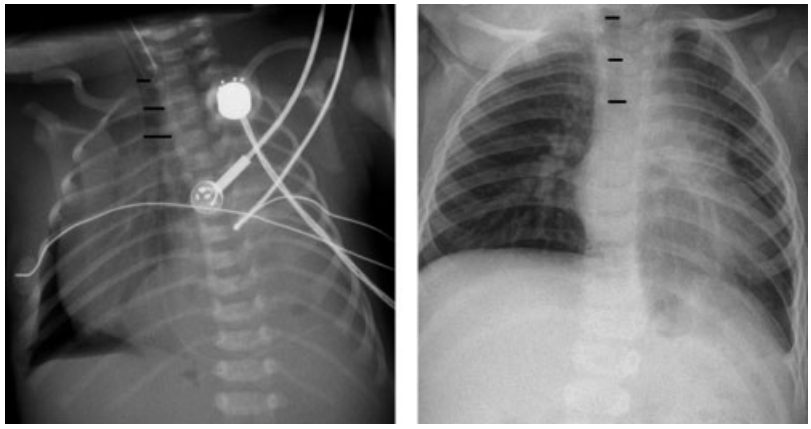

Figure 1—Antero-posterior X-rays at the level of the chest in neonates born at 38 weeks' gestation illustrating the measurement of tracheal diameter (continuous lines) at the level of the tracheal entry into the chest, 1 cm above the carina and at middistance between the two sites. On the left is the image from a case of left-sided congenital diaphragmatic hernia and on the right is the image from a case with no congenital lung lesion

and term neonates admitted at the neonatal intensive care unit (NICU) with various pathologies including spontaneous or induced prematurity for feto-maternal conditions ($n = 37$), respiratory distress ($n = 18$), and non-pulmonary defects ($n = 19$). Tracheal diameters were measured on chest X-rays within 48 h after birth.

The CDH group were consecutive cases of CDH treated by FETO between October 2001 and September 2008, managed in the neonatal period at the King's College Hospital, London, UK, and in whom a chest X-ray was available within 48 h from birth. The control group were admitted between September 2007 and September 2008 at the NICU of the Hôpital Universitaire des Enfants Reine Fabiola (HUDERF), Brussels, Belgium. They were born after 28 weeks' gestation, had no congenital lung, trachea of diaphragmatic abnormalities, and they had a chest X-ray within 48 h from birth.

All measurements of the tracheal diameter were performed by a single operator (M.C.). Measurements were performed off-line on facial chest X-rays uploaded into the Picture Archiving and Communication System (PACS; Impax, Agfa-Gevaert, Mortsel, Belgium). Tracheal diameters were measured at tracheal entry into the chest, 1 cm above the level of the carina and at middistance in between these two sites (Figure 1).

Statistical analysis

In the control group, regression analysis was performed to examine the significance of the association between each of the three tracheal diameters in millimeters and gestational age at delivery in weeks. Each regression line used a least squares approximation of the line to the points. In each case and control the observed tracheal diameter was expressed as a percentage of the expected normal mean for gestation (o/e). Mann–Whitney U-test was then used to compare the mean o/e ratios between cases and controls. In the CDH group, regression analysis was used to investigate the effect on o/e tracheal diameter of o/e LHR measured in percentage values before FETO, gestation at FETO in weeks, duration of the FETO procedure in minutes, and duration of tracheal occlusion in weeks, as continuous numerical variables. Data on longer term outcomes were collected during the clinical follow-up of these infants and children.

Data were analyzed with the statistical softwares SPSS, version 16.0 (Chicago, Illinois, USA), Statistica, version 6.0 (StatSoft, Tulsa, Okla) and Excel, version 9.0 (Microsoft, Redmond, Washington).

RESULTS

In the CDH group, the lesion was left sided in 32 cases and right sided in 5. Their median o/e LHR measured before FETO was 20% (range 12–39), the median gestational age at FETO was 26 weeks (range 23–33), and the duration of the FETO procedure was 10 min (range 4–82). The duration of the tracheal occlusion was 49 days (3–100), and the gestational age at delivery was 33 weeks (range 26–41). There were 24 survivors (64.9%) and 13 deaths (35.1%) at discharge from the hospital.

In the controls, tracheal diameter at 1 cm above the level of the carina increased significantly with gestational age (diameter $= 0.083 \times$ gestation in weeks $+ 1.37$; $r = 0.35$, $p < 0.005$), but tracheal diameters at tracheal entry and at middistance did not change significantly with gestation ($r = 0.15$, $p = 0.21$; and $r = 0.17$, $p = 0.15$, respectively) (Figure 2). In the CDH group, compared to controls, the mean o/e tracheal diameter was significantly larger at all three levels of the trachea (Table 1, Figure 3).

Regression analysis showed that significant prediction of increased o/e tracheal diameter at the level of tracheal entry into the chest were provided by the o/e LHR and the duration of tracheal occlusion but not the gestation at FETO or the duration of the FETO procedure (Table 2). Significant predictors of increased o/e tracheal diameter size at the level of the midtrachea as well as at 1 cm above the level of the carina were provided only by o/e LHR (Table 3).

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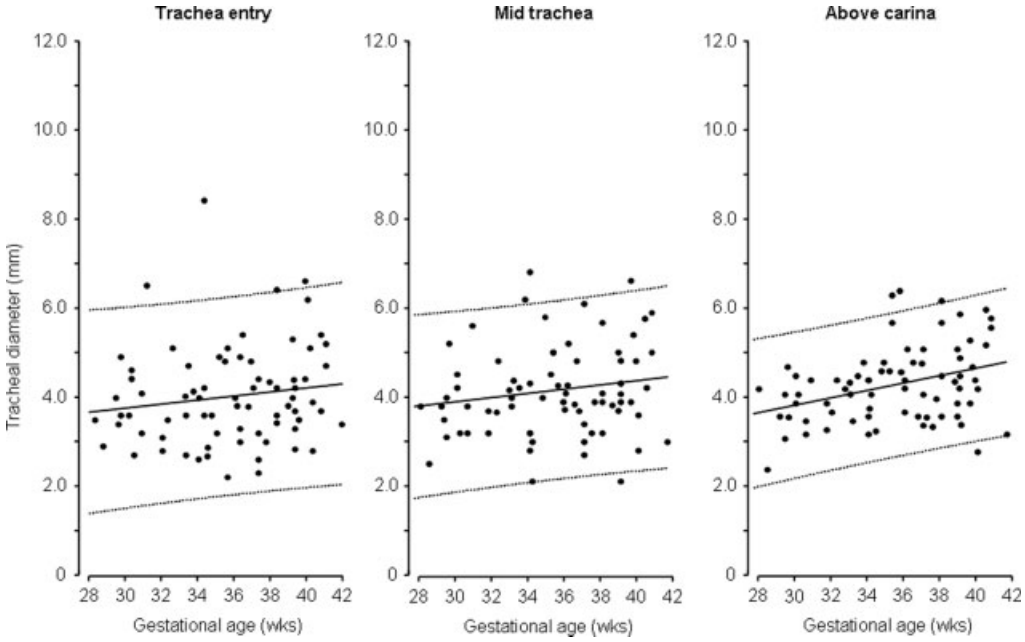

Figure 2—Mean and 95% confidence intervals of tracheal diameter with gestational age at birth at the level of the tracheal entry into the chest, the midtrachea, and above the carina for preterm and term neonates. Black dots represent control neonates

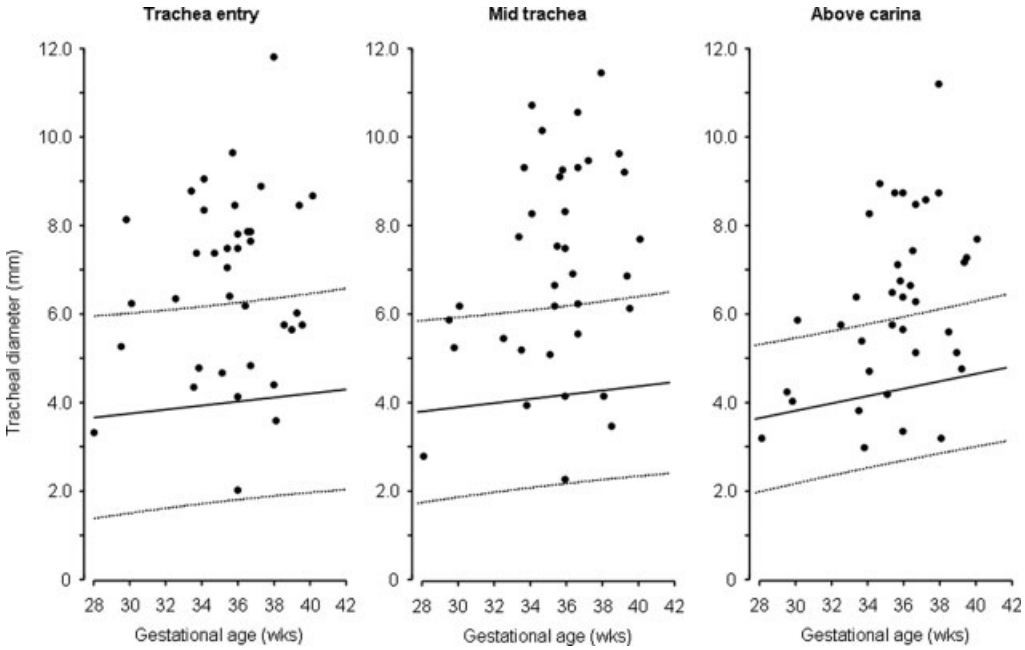

Figure 3—Tracheal diameter at the level of the tracheal entry into the chest, the midtrachea, and above the carina for neonates with congenital diaphragmatic hernia treated by fetal endoscopic tracheal occlusion plotted on the mean and 95% confidence intervals of the range with gestational age in neonates with no congenital lung lesion. Black dots represent fetuses with congenital diaphragmatic hernia treated by fetal endoscopic tracheal occlusion

Table 1—Comparison of o/e tracheal diameter at birth between fetuses with congenital diaphragmatic hernia treated by fetal endoscopic tracheal occlusion and preterm and term control neonates

o/e tracheal diameter	Diaphragmatic hernia	Controls	*P* value
Tracheal entry, median (range) in %	173.7 (49.3–282.9)	95.6 (54.6–211.5)	<0.01
Middistance, median (range) in %	166.6 (54.6–284.5)	97.4 (48.8–167.1)	<0.01
1 cm above carina, median (range) in %	147.2 (71.1–248.7)	100.8 (59.7–147.6)	<0.01

o/e, observed to expected.

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Table 2—Regression analysis in the prediction of increased tracheal diameter at birth at the level of the tracheal entry into the chest in fetuses with CDH treated by FETO

Variable	Median (range)	o/e tracheal diameter at tracheal entry into the chest			
		Univariate analysis		Multivariate analysis	
		Coefficient of regression (95% CI)	*P* value	Coefficient of regression (95% CI)	*P* value
o/e LHR (%)	20 (12–39)	−3.766[(−6.364) to (−1.167)]	<0.01	−4.000[(−6.415) to (−1.585)]	<0.01
Duration of tracheal occlusion (days)	49 (3–100)	0.007 (0.000 to 0.014)	0.045	0.008 (0.002 to 0.014)	0.013
Gestation at FETO (weeks)	26 (23–33)	−0.051[(−0.11) to (−0.009)]	0.094	—	—
Duration of FETO (min)	10 (4–82)	−0.002[(−0.012) to (0.008)]	0.751	—	—

CI, confidence intervals; LHR, lung area to head circumference ratio; FETO, fetal endoscopic tracheal occlusion; o/e, observed to expected.

Table 3—Regression analysis in the prediction of increased tracheal diameter at birth at the level of the midtracheal and 1 cm above the carina in fetuses with CDH treated by FETO

Variable	Median (range)	o/e tracheal diameter at midtrachea		o/e tracheal diameter at 1 cm above the carina	
		Univariate analysis		Univariate analysis	
		Coefficient of regression (95% CI)	*P* value	Coefficient of regression (95% CI)	*P* value
o/e LHR (%)	20 (12–39)	−3.406[(−6.619) to (−0.194)]	0.038	−2.383[(−4.733) to (−0.034)]	0.047
Duration of tracheal occlusion (days)	49 (3–100)	0.006 [(−0.002) to (0.015)]	0.146	0.005 [(−0.001) to (0.011)]	0.098
Gestation at FETO (weeks)	26 (23–33)	−0.033[(−0.105) to (−0.04)]	0.368	−0.024[(−0.077) to (0.028)]	0.352
Duration of FETO (min)	10 (4–82)	−0.005[(−0.017) to (0.007)]	0.388	−0.005[(−0.013) to (0.003)]	0.242

CI, confidence intervals, LHR, lung area to head circumference ratio; FETO, fetal endoscopic tracheal occlusion; o/e, observed to expected.

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The 24 survivors of the CDH fetuses were followed up until the mean age of 22 months (range 1–70), and in five cases there was an effort-induced barking cough. Their o/e tracheal diameter at the midlevel of the trachea ranged between 129 and 224% of the expected normal mean for gestation. There were no reported clinical tracheal problems in the follow-up of the remaining 32 neonates.

DISCUSSION

The finding of this study shows that in CDH fetuses undergoing FETO, tracheal diameter at birth is increased in its whole length as compared with preterm and term controls matched for gestational age. Furthermore, this study has shown that this increase in tracheal diameter in its upper, middle, and lower part was mainly related to the severity of the CDH as measured by the o/e LHR before FETO and in its upper part to the duration of the tracheal occlusion. In about 20% of cases, clinical follow-up to the age of 22 months showed an effort-induced barking cough.

Tracheomegaly or an abnormally dilated trachea may result from connective tissue disorders, rare congenital abnormalities with manifestation described only in children aged 18 months and more, or prolonged positive pressure ventilation (Adam and Dixon, 2008; Menon *et al*., 2008). All neonates included in our study had their chest X-rays taken within a few hours from birth, excluding the effect of long-term ventilation on tracheal diameter. Furthermore, a bronchoscopy study including 39 cases of CDH described anatomic anomalies of the tracheobronchial tree such as bronchial hypoplasia in up to 38% of cases, however, did not describe tracheomegaly (Nose *et al*., 2000). It is, therefore, very likely that the described tracheomegaly in our study is the consequence of FETO and not of any other underlying anomalies, including CDH itself.

Successful clinical implementation of prenatal treatment requires a reliable, reversible, and atraumatic technique of occluding the fetal trachea. Earlier attempts to occlude the trachea using foam plugs were abandoned because they did not provide consistently reliable fetal tracheal occlusion (Bealer *et al*., 1995), and the use of clips is associated with several surgical complications (Flake *et al*., 2000). The use of the vascular endoluminal balloon as in the FETO technique seemed, therefore, to be the best alternative. Earlier experimental studies in fetal lambs showed that tracheal occlusion was not associated with visible changes in the cartilage rings (Deprest *et al*., 2000). There were limited side effects with macroscopically dilated trachea secondary to the elongation of the *pars membranacea*, mild epithelial and local inflammatory changes, but these changes nearly disappeared during the rest of the pregnancy after *in utero* unplugging (Deprest *et al*., 2000).

Three recent studies described case series of neonatal tracheal changes following FETO. The first study described morphological and dynamic changes during breathing using flexible endoscopy in seven cases that had a FETO at 26 weeks' gestation or more (Fayoux *et al*., 2010). The duration of tracheal occlusion ranged between 2.4 and 9.0 weeks and in all, but one case, the balloon was removed prenatally. The study described intermittent collapse and obstruction of the trachea during tidal breathing caused by an abnormal displacement of the posterior wall with segmental widening of the *pars membranacea*. Histological studies in the two neonates who died revealed focal loss of fibro-elastic network and muscular disruption of the *pars membranacea* but the cartilage space was normal. Survivors were followed up till the age of 38 months and were asymptomatic except for the presence of a barking cough during increased respiratory efforts. The second study described radiological findings mainly at bronchography in five cases that had a FETO at 23.7 to 25.9 weeks' gestation (McHugh *et al*., 2010). The duration of tracheal occlusion ranged between 5.3 and 10.7 weeks and in three cases the balloon was removed postnatally. This study described severe tracheomegaly up to four times the size of a vertebral thoracic body extending into the right bronchus. In the latter case, the fetus was ventilated for several minutes while the balloon was still in place. Two of the five infants died as a consequence of respiratory complications, two are alive and well at the age of 1 and 2 years and one was still on overnight continuous positive airway pressure (CPAP) at the age of 32 months. The third study evaluated the tracheal size by computed tomography at 1 to 56 months of age in seven neonates with CDH treated by FETO as compared with 23 neonates with CDH without prenatal FETO assessed at 9 to 79 months of age and showed tracheal dilatation in the FETO group (Breysem *et al*., 2010). The authors in this study failed to show a comparable duration of ventilation during the stay in the NICU between the two groups, which could have biased their results on tracheal size.

On the basis of the data from our study and the three above studies it becomes clear that a large number of CDH neonates and infants treated by FETO, even if asymptomatic, might have a certain degree of tracheomegaly associated with subtle lesions of the tracheal epithelium that were not reported before because cases were not, until recently, systematically documented. These lesions seem to be related to the duration of tracheal occlusion. However, because we aimed to remove the balloon at 34 weeks, there seems to be an age-related effect of occlusion with enlargement found more frequently when FETO is performed before 26 weeks' gestation at a time when the airways are highly compliant and there is insufficient time for *in utero* recovery (Cullen *et al*., 2006). With the exception of the cases described by McHugh *et al*. (2010) the enlargement found in the trachea do not constitute an obvious clinical problem and seem to become less pronounced with age (Deprest *et al*., 2010).

The finding that tracheomegaly is associated with the severity of CDH, as measured by o/e LHR, suggests that in fetuses with very severe lung hypoplasia there may be a coexistence of hypoplastic bronchial tree (Nose *et al*., 2000). Therefore, because we used the same size of balloons inflated systematically to 0.8 mL in all cases

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this balloon might have caused more enlargement in those with smaller tracheas. One option is to inflate the balloon according to the individual fetal tracheal diameter and repeat the procedure one or more times in the subsequent weeks as the trachea enlarges with gestation. There is some evidence from animal studies that such cyclical tracheal occlusion may allow optimal alveolar development as compared to a temporary or sustained occlusion (Nelson *et al.*, 2005). However, such a cyclical occlusion is not clinically applicable at the moment because the potential benefit of reducing tracheal damage and improving pulmonary development is likely to be counterbalanced by the adverse effects of early delivery because of repeated fetoscopies.

Our study had some limitations. Firstly, we used chest X-rays rather than computed tomography for measurement, the latter may be more accurate and our tracheal measurements are not necessarily true dimensions but rather a proportion of measurements in controls. On the other hand, we used a similar method in our FETO group as compared with the controls which overcomes this limitation. Second, we did not use a CDH control group. However, a proper CDH group used as controls should be a group with comparable severity based on prenatal LHR measurement, which is difficult to achieve outside of a randomized study.

The findings of our study suggest that in infants surviving after FETO it is necessary to undertake close tracheal surveillance. Early tracheal occlusion before 26 weeks' gestation seems to predispose to tracheomegaly if the same type of balloon is used as for those at 26 to 29 weeks. The extent to which FETO-induced tracheomegaly is associated with a certain degree of long-term tracheal morbidity remains to be determined in future studies.

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