Cross-sectional Study of Tracheomegaly in Children after Fetal Tracheal Occlusion for Severe Congenital Diaphragmatic Hernia[1]

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Purpose: To measure tracheal dimensions in children with congenital diaphragmatic hernia (CDH) who had undergone fetoscopic endoluminal tracheal occlusion (FETO) or were treated expectantly during gestation.

Materials and Methods: The study was approved by the local ethics committee. Computed tomography was performed in 23 patients (14 boys and nine girls) aged 1 month to 6.5 years, and the anteroposterior diameter, width, area, and perimeter of the trachea were determined. Seven of the 23 patients had undergone FETO and 16 had been treated expectantly. The relative difference of each parameter between the two most proximal concentric sections of the trachea, just below the larynx, and the two sections on which the trachea was the largest was compared between both groups (Mann-Whitney *U* test). Regression statistics were applied to maximum and mean tracheal areas as a function of age. Each trachea was divided into quartiles, and mean areas normalized to 3 years of age were analyzed for each quartile as a function of its relative position on the trachea (Student *t* test).

Results: Tracheal width, area, and perimeter were significantly different between both groups. A linear relationship was observed between the maximum and mean tracheal areas and age for both the FETO group (maximum tracheal area: $R^2 = 0.83$, $P = .0045$; mean tracheal area: $R^2 = 0.92$, $P = .0005$) and the non-FETO group (maximum tracheal area: $R^2 = 0.66$, $P = .0001$; mean trachea area: $R^2 = 0.66$, $P = .0001$). The maximum tracheal area in both groups tended to decrease toward the age of 5 years. Significantly different mean tracheal areas per tracheal quartile ($P < .05$) were found for all quartiles except for the proximal one-fourth.

Conclusion: The relative difference between proximal and largest tracheal width, area, and perimeter was significantly larger in patients who underwent FETO than in those treated expectantly, demonstrating tracheal dilatation in the former. Measurements of tracheal dimensions at different levels indicate a maximum dilatation in the lower half of the trachea, which tends to level off toward the age of 5 years.

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Congenital diaphragmatic hernia (CDH) is a severe congenital malformation that occurs in approximately one in 2500 births (1–3). It can occur alone or as part of a spectrum of other anomalies. Despite continuous improvement and new insights in the neonatal management of CDH, the mortality rate of the isolated form remains around 30% and is influenced by the severity of lung hypoplasia and the presence of persistent pulmonary hypertension (2). Once CDH is diagnosed in the prenatal period, medical imaging is used to predict individual mortality and early neonatal morbidity (1–3). Antenatal therapy can be offered in a select group of fetuses predicted to have lethal pulmonary hypoplasia, in whom the chances for survival are low (<15%). Antenatal intervention is performed to trigger lung growth rather than to correct the diaphragmatic defect, which can be easily repaired after birth. Tracheal occlusion prevents egress of lung liquid produced by the airway epithelium and induces tissue stretch, which acts as a signal for lung growth (4,5). Prenatal release of the occlusion stimulates lung maturation (6). Currently, temporary fetal tracheal occlusion is achieved clinically by means of percutaneous fetoscopic endoluminal tracheal occlusion (FETO) with use of a balloon (7). The survival rates reported in the literature are stable at approximately 50% (7,8). Some of the initial concerns of tracheal occlusion are the tracheal side effects (epithelial damage, cartilage and/or muscular damage) caused by the occluding technique (use of either an external clip or an endoluminal balloon, the latter being attractive because it can be easily punctured in utero). Experimental work defined the features of an endoluminal balloon as well as predominantly local epithelial pressure and inflammatory effects (9,10). The balloons used are inflated once to approximately 7–8 mm in diameter and 22 mm in length, exceeding as such the tracheal dimensions. In fetal lambs (9), the tracheal side effects were limited to focal and mild epithelial and inflammatory changes (without visible changes in the cartilage rings) as well as tracheal dilatation, typically due to elongation of the pars membranacea. Histologic changes were transient and recovered after the occlusion was removed in utero. We performed a cross-sectional study in children born and still living in Belgium who were treated locally in the perinatal period. At the postnatal follow-up visits, we assessed the tracheal dimensions by means of computed tomography (CT) and compared measurements obtained in patients who had undergone FETO with those in patients who were treated expectantly during pregnancy. The purpose of the present study was to measure tracheal dimensions in children with CDH, some of whom had undergone FETO.

Advances in Knowledge

- In children treated with fetal tracheal occlusion, CT enabled accurate measurements and demonstrated a fusiform dilated trachea.
- Compared to that in children with severe left-sided congenital diaphragmatic hernia (CDH) without antenatal intervention, the dilatation effect on the trachea of patients with CDH is most pronounced in the 1st year of life and decreases thereafter (assessment up to 5 years of age).

Materials and Methods

The study and, in particular, the FETO procedure were approved by the local ethics committee. Written informed consent was obtained from the parents and guardians of all children.

Implication for Patient Care

- A dilated trachea seen at chest CT of a very young child (mean age, 22.7 months; age range, 1.1–72.2 months) with a history of severe left-sided CDH and fetal tracheal occlusion can be considered a temporary finding.

Patients

This is a single-center, cross-sectional study in a cohort of 23 infants and children (mean age, 35.5 months; age range, 1.1–79.3 months) admitted to our neonatal intensive care unit between 2002 and 2008. It included 14 boys (mean age, 23.5 months; age range, 1.1–79.3 months) and nine girls (mean age, 42.7 months; age range, 5.4–72.2 months).

Between January 1, 2002, and June 30, 2008, 65 patients with CDH were admitted to our neonatal intensive care unit. Fifty-nine of those 65 patients were born at our institution. Thirty-eight of the 65 patients (58%) survived the neonatal period, and six of those 38 patients (16%) were transferred abroad back to the referring center. The 32 patients who lived in our country were cared for in a follow-up program at our institution. The parents of four of the 32 patients (12%) declined follow-up, and one patient (3.1%) was lost to follow-up. Thus, 27 patients were eligible for this study. Two of the 38 patients (5.3%) were unable to attend the follow-up visits within the requested time and were excluded from this study. Twenty-five of the 38 patients (66%) underwent CT; two of those 25 patients (8%) were excluded from analysis owing to incomplete visualization of the trachea. Of the remaining 23 patients, seven (30%) had undergone FETO and 16 (70%) had been treated expectantly during gestation (non-FETO group) (Table 1).

Published online before print
10.1148/radiol.10092388

Radiology 2010; 257:226–232

Abbreviations:
CDH = congenital diaphragmatic hernia
FETO = fetoscopic endoluminal tracheal occlusion

Author contributions:
Guarantors of integrity of entire study, L.B., J.D.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, L.B., M.H.S.; clinical studies, L.B., A.D., M.P., M.H.S., J.D.; statistical analysis, F.D., P.L., J.D.; and manuscript editing, L.B., A.D., F.C., M.P., P.L., M.H.S., J.D.

Authors stated no financial relationship to disclose.

Patients were included in this study if they were born at our institution and if CDH had been diagnosed prenatally no later than the 2nd trimester. At that time, the isolated nature and severity of the condition was assessed with ultrasonography (US) (2). In addition, US was used to assess lung size and the presence of liver herniation. Measurement of the lung area–to–head circumference ratio, as described by Metkus et al (11), essentially involves obtaining a transverse image of the fetal chest demonstrating the four-chamber view of the heart and then multiplying the two longest perpendicular diameters (width and anteroposterior diameter) of the right lung (2,11). The effect of gestational age on the lung area–to–head circumference ratio can be corrected for by expressing the measured value over what is expected in a gestational age–matched control subject (observed-to-expected lung area–to–head circumference ratio) (12). The condition was classified as severe when the predicted survival was less than 20% (1). Prenatal therapy—which involved fetoscopic placement of an endotracheal balloon at 26–29 weeks of gestation and its removal at no later than 34 weeks (7)—was offered in those cases in which the predicted outcome was poor.

CT Evaluation

Between November 2007 and November 2008, the children underwent unenhanced low-dose spiral chest CT (Somatom Sensation 64; Siemens Medical Solutions, Erlangen Germany). CT was performed as part of a clinical follow-up plan to evaluate the size of the lungs and trachea and the presence of collapse, consolidation, bullae, emphysema, mosaic perfusion during quiet respiration, (peri)bronchial thickening, bronchiectasis, and thickening of the interlobular septa (13). In addition, CT can enable the evaluation of repeat herniation or hiatus hernia after surgery. CT was performed with the child in the supine position during quiet respiration or, when necessary, conscious sedation at near-functional residual lung capacity. CT parameters were as follows: 100 kV, 45 mAs with an automatic exposure control system (Care Dose, Siemens Medical Solutions), 64 × 0.6-mm collimation, pitch of 1.4, 0.5-second rotation time, and volume CT dose index of 2 mGy. The upper limit of the field of view was situated at the vocal cords, and the lower limit was situated at the

Table 1

Demographic Data and Results of CT Measurements in the FETO and Non-FETO Groups

Group and Patient No.	Age at Follow-up CT (mo)	Trachea Length (cm)	Trachea Width		Trachea Perimeter		Trachea Area	
			Mean (mm)	Difference (%)*	Mean (mm)	Difference (%)*	Mean (cm^2)	Difference (%)*
Non-FETO								
1	9.5	74.5	0.7	14.6	2.2	8.7	0.3	9.4
2	60.2	121.0	0.9	40.7	2.7	28.6	0.5	68.6
3	73.0	122.0	0.9	24.2	2.9	26.5	0.6	85.5
4	35.7	87.0	0.8	1.9	2.4	4.6	0.4	6.0
5	60.1	101.0	0.8	0.0	2.7	7.9	0.6	18.6
6	34.4	88.8	0.7	7.5	2.8	26.7	0.6	65.9
7	23.8	86.8	0.8	20.3	2.7	0.7	0.5	7.7
8	23.6	87.9	0.8	27.1	2.4	14.3	0.4	55.7
9	38.1	99.0	0.9	1.7	2.9	−3.9	0.6	−5.9
10	41.8	100.0	0.7	2.9	2.5	9.9	0.4	22.8
11	35.5	98.5	0.8	17.7	2.7	13.4	0.5	50.0
12	18.5	83.0	0.7	13.1	2.2	5.6	0.4	14.9
13	19.2	79.0	0.7	19.9	2.3	12.5	0.4	39.1
14	79.3	123.0	1.0	25.3	3.3	16.3	0.8	46.3
15	69.0	125.0	0.9	18.0	3.3	5.2	0.8	20.4
16	47.3	97.5	0.8	14.2	2.5	7.5	0.4	22.5
FETO								
17	14.0	74.0	0.9	60.9	2.5	45.4	0.4	145.8
18	22.4	86.5	1.0	63.3	3.3	24.8	0.7	87.6
19	51.1	96.0	1.2	92.8	3.5	67.8	0.8	176.2
20	56.0	100.0	1.4	110.2	4.0	72.2	1.0	155.9
21	23.0	81.0	1.1	128.6	3.2	80.9	0.7	196.0
22	5.5	66.5	0.8	70.4	2.9	23.2	0.4	115.2
23	1.1	43.5	0.9	88.4	2.5	56.9	0.4	88.9

* Data are the relative percentage differences between the measurements obtained on the two most proximal consecutive concentric axial sections of the trachea and those obtained on the two largest consecutive axial sections ([mean of measurements on the two largest areas − mean of measurements on the first two sections]/[mean of measurements on the first two sections] × 100). The percentage differences for tracheal width, perimeter, and area were significantly larger in the FETO group than in the non-FETO group ($P = .0011$, $P = .0062$, and $P = .0025$, respectively, as determined with the two-tailed Student *t* test).

bases of the lungs. Reconstructions in the axial, coronal, and sagittal planes were performed and three-dimensional reconstructions of the tracheobronchial tree and lungs were generated. To facilitate the measurements, we used the coronal and axial reconstruction data set to identify the most proximal level of the cylindrical-shaped trachea, just below the larynx, and defined the proximal level as the second consecutive section with a cylindrical-shaped trachea. The most distal level of the trachea was defined as two sections or 6 mm above the bifurcation to the main bronchi to avoid false-positive enlargement of the trachea due to branching into the main bronchi. The anteroposterior diameter, width, and perimeter of the trachea were determined manually by one investigator (L.B., with more than 10 years of experience in pediatric radiology and CT scan interpretation) from contiguous 3-mm-thick axial images as previously described by Griscom (14). The tracheal area was calculated automatically by the software of the CT scanner (Fig 1).

The following calculations were performed to assess tracheal diameter: *(a)* Mean values for anteroposterior diameter, width, and area were calculated by averaging all measurements obtained for the entire tracheal length. *(b)* To quantify the degree of fusiform tracheal dilatation, we calculated the percentage difference between the measurements obtained on the two most proximal consecutive concentric axial sections and those on the two sections on which the trachea was largest for each parameter in all patients ([mean of measurements obtained on the two largest sections − mean of measurements obtained on the first two axial levels]/[mean of measurements obtained on the first two axial levels] × 100). *(c)* To determine the location of any conformational change along the trachea, the trachea was divided into four zones, as follows: First, the tracheal length was measured by determining the number of sections (section thickness = 3.0 mm) acquired between the most proximal level under the larynx and the area just above the bifurcation to the main bronchi. Then, each individual trachea was divided into quartiles. Between the measuring levels, the first quartile corresponds with the proximal one-fourth of the trachea and the fourth quartile with the distal one-fourth of the trachea. In between, the second and third quartiles correspond with the second one-fourth and the third one-fourth of the trachea, respectively. To locate the area with maximum widening, the mean tracheal areas were calculated for each quartile. These values were compared between patients in the FETO and non-FETO groups.

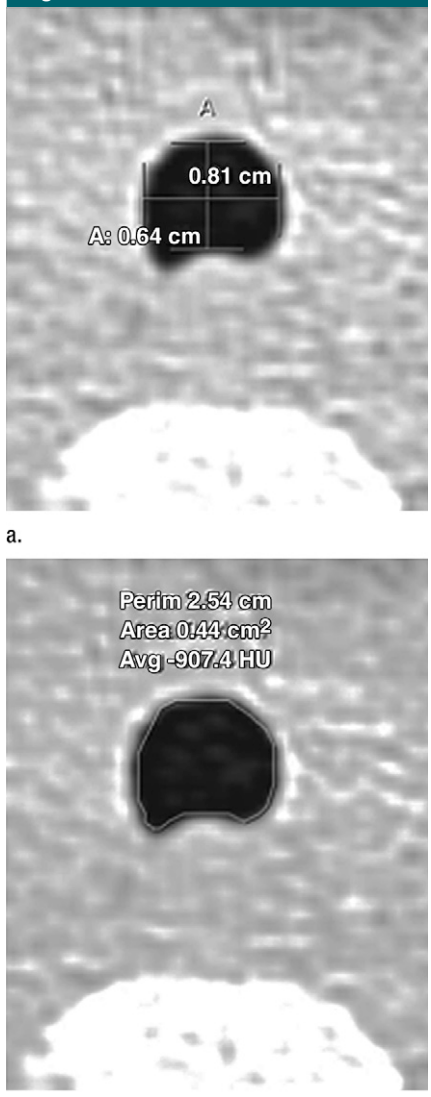
Statistical Analysis

Statistical analysis was performed by using SPSS (SPSS, Chicago, Ill), JMP 7 (SAS Institute, Cary, NC), MLwiN (Centre for Multilevel Modeling, University of Bristol, Bristol, England), and Prism 5 (GraphPad Software, La Jolla, Calif) software. Results from patients who were treated expectantly and those who underwent FETO were compared by using the Mann-Whitney *U* test. Regression analysis was used to assess the ratio of the maximum and mean areas in the FETO group to those in the non-FETO group as a function of age. The relationships between the maximum and mean tracheal areas and age were assessed for the FETO and non-FETO groups: A linear regression analysis was applied to the maximum and mean areas of the FETO and non-FETO groups as a function of age. To correct for the different ages at assessment, tracheal measurements of individual patients were normalized to 3 years of age by using linear regressions of area on age for the FETO and non-FETO groups. To evaluate mean area to relative location on the trachea, mean areas normalized to 3 years of age were computed for each quartile of relative trachea position and differences between mean areas analyzed with the Student *t* test. Relative position was defined as follows: [(number of sections × 3 mm)/trachea length (in millimeters)] × 100.

Results

Table 1 displays the demographic data for the 23 patients and the CT measurements obtained at the postnatal examination. Multiplanar reconstructions (axial, coronal, and sagittal) were available in all patients. The percentage difference between the measurements obtained on the two consecutive most proximal concentric axial sections of the trachea and those obtained on the two largest consecutive axial sections was

Figure 1



a.

b.

Figure 1: Contiguous 3-mm-thick axial CT scans of the trachea between the proximal and distal levels. **(a)** Tracheal dimensions (anteroposterior diameter [0.64 cm] and width [0.81 cm]) and **(b)** perimeter (*Perim*) were determined manually. Tracheal area was calculated automatically by standard CT software. *Avg* = average attenuation.

significantly larger in the FETO group than the non-FETO group with regard to tracheal width, perimeter, and area (P = .0011, P = .0062, and P = .0025, respectively) (Table 1).

To evaluate the evolution of tracheal area with age, maximum and mean tracheal areas were plotted against age for the FETO and non-FETO groups. Because similar figures were obtained with maximum and mean data, only graphs for the maximum areas are shown herein (Fig 2).

A linear relationship was found between maximum and mean tracheal areas and age for both the non-FETO group (maximum tracheal area: R^2 = 0.66, P = .0001; mean tracheal area: R^2 = 0.66, P = .0001) (Fig 2a) and the FETO group (maximum tracheal area: R^2 = 0.83, P = .0045; mean tracheal area: R^2 = 0.93, P = .0005) (Fig 2b). The ratio between the maximum and mean tracheal areas for the FETO and non-FETO groups tended to decrease slightly as a function of age (Fig 3).

The relationship between tracheal areas normalized to the age of 3 years and the relative position on the trachea was almost quadratic (R^2 = 0.47, P < .005) for the FETO group and cubic (R^2 = 0.13, P < .005) for the non-FETO group. The graph shown in Figure 4 shows that tracheal enlargement in the patients who underwent FETO was most obvious in the lower half of the trachea. This was confirmed with the calculation of mean normalized area per tracheal quartile: Significant differences (P < .05) were found for all quartiles of the trachea except the first (Table 2), with the largest difference in the proximal segment of the lower half of the trachea.

The 95% confidence intervals of the estimated ratios of maximum area in the FETO and non-FETO groups were derived by means of the "delta rule" by using the coefficients of the linear regressions of maximum area versus age and their corresponding standard errors.

Figure 2

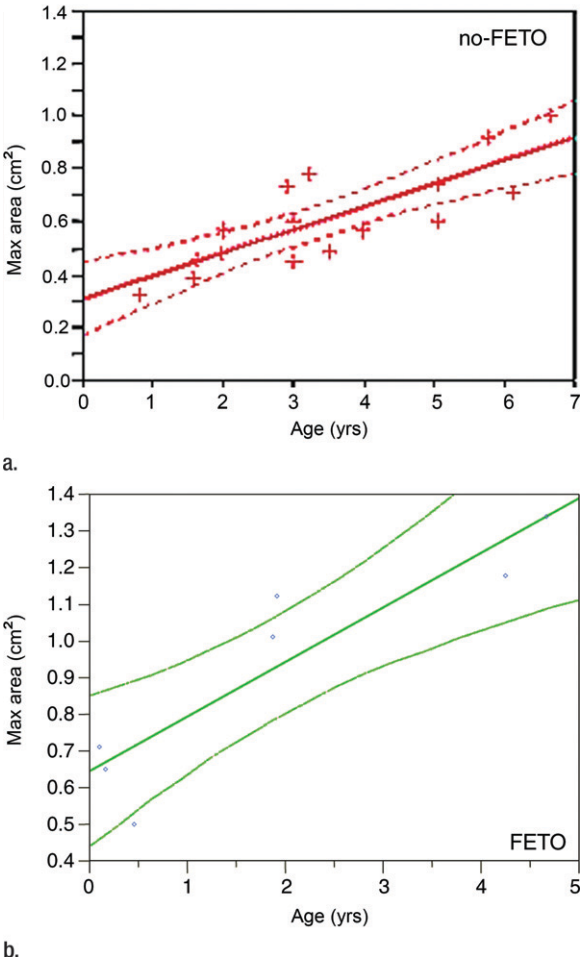


Figure 2: Graphs show the maximum (*Max*) tracheal area (+ for the non-FETO group and • for the FETO group) plotted against age, the fitted curves (continuous lines), and the 95% confidence intervals (dashed lines in **a** and light green lines in **b**) in the **(a)** non-FETO and **(b)** FETO groups. There was a linear relationship between maximum tracheal area and age in both groups. The difference between the maximum tracheal areas of the FETO and non-FETO groups becomes less pronounced with age. Similar correlations were obtained with use of mean tracheal area (data not shown).

Discussion

To our knowledge, this is the first longitudinal study in which the tracheal deformity in a consecutive group of children with CDH who had undergone FETO or were treated expectantly was investigated with CT. Studies in healthy children have shown that tracheal dimensions determined with CT are reliable and accurate (15). The dimensions of the trachea relate best to body height, postnatal growth is proportionally greatest early in infancy, the trachea is more flattened in children up to the age of 6 years, and the differences in tracheal cross-sectional areas are small. Until the age of 14 years, tracheal dimensions are unrelated to sex (14–19).

Recently, a series of five selected patients with tracheal enlargement after FETO has been described (20). All patients in that study presented with severe respiratory problems after birth. In our study, we reported on an unselected group of patients who had undergone FETO or were treated expectantly in gestation; none of the children were symptomatic. Our findings indicated that the tracheal width, perimeter, and area were significantly increased in children with CDH who had undergone prenatal tracheal occlusion with a balloon. Their tracheal area was significantly larger in the lower trachea—most so in the proximal part of its lower half. Furthermore, the difference was smaller toward the age of 5 years.

Tracheomegaly in children is a rare finding. It is sporadically reported in the literature within the clinical context of the Mounier-Kuhn syndrome or as an acquired condition in infants born prematurely who are on ventilation,

Figure 3

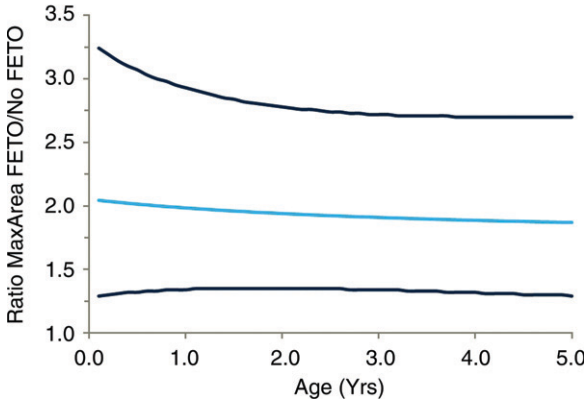


Figure 3: Graph shows the estimated ratio between maximum (*Max*) tracheal areas in the FETO and non-FETO groups (blue line) and 95% confidence intervals (black lines) as a function of age. The maximum area of the trachea in the FETO versus non-FETO groups is expressed as a ratio, and this curve shows us that the difference demonstrates a slightly decreasing trend with age.

Figure 4

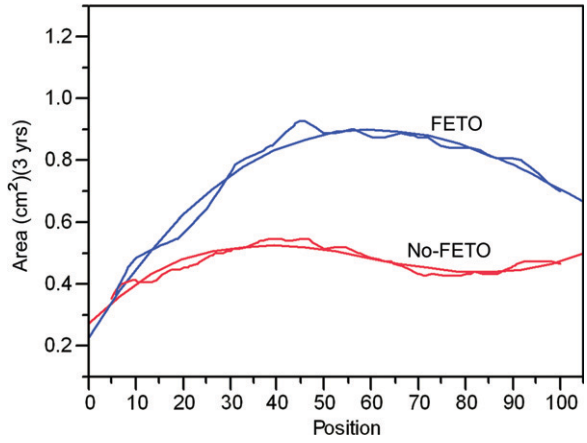


Figure 4: Graph shows the relationship between tracheal areas normalized to the age of 3 years as a function of relative position on the trachea (0 = proximal level of trachea, 100 = distal level of trachea). Smooth lines represent cubic fits of area on relative position for the non-FETO and FETO groups. Wavy lines represent spline fits to area as a function of relative position on the trachea by using a smoothing factor (lambda) of 100.

Table 2

Mean Areas Computed for Each Quartile of Relative Trachea Position

	Estimated Mean Area (cm^2)*		Non-FETO Group vs FETO Group		
Quartile	Non-FETO Group	FETO Group	Difference (cm^2)	Standard Error (cm^2)	*P* Value
1	0.443	0.552	0.112	0.064	.096
2	0.529	0.833	0.304	0.065	<.0001
3	0.470	0.891	0.421	0.053	<.0001
4	0.441	0.821	0.380	0.079	.0001

Note.—There were 16 patients in the non-FETO group and seven in the FETO group. Quartile 1 = position 1–25, quartile 2 = position 25–50, quartile 3 = position 50–75, and quartile 4 = position 75–100.

* Area was normalized to 3 years of age.

in children with chronic lung disease who are on ventilation, and in children with cystic fibrosis (21).The membranous part of the trachea, including the smooth muscle layer, is usually involved in the acquired form of tracheomegaly. Stretching of the smooth muscles may alter the function, and, as such, the posterior wall of the trachea can become less supportive, causing the configuration of the trachea to change (22). However, these findings seem to be less pronounced in the premature infant on ventilation because of the physiologically increased compliance and decreased contractility of the immature airway (23). A morphologic US study in neonatal lambs (24) demonstrated that the internal diameter of the trachea increased on mechanical ventilation; in addition, there was evidence of thinning of the posterior layer.

In our series, the most likely cause of tracheomegaly was the prenatal placement of a balloon for up to 8 weeks (the median gestational age at balloon removal is 33 weeks when it is placed as an elective procedure or 34.3 weeks in case of an emergency procedure [8]). Before the clinical introduction of the procedure, the side effects of tracheal balloon placement were experimentally documented in fetal lambs in both the acute (postmortem examination after an endoluminal balloon was placed for a median of 2 weeks) and delayed (postmortem examination approximately 3 weeks after in utero removal of the balloon) periods (9). The balloon widened the trachea without causing major histologic abnormalities in the cartilage and pars membranacea. The histologic changes were most pronounced in the epithelium. In those animals examined 3 weeks after the balloon was released, there were no longer any measurable changes (9). Despite that fact, the findings at reversal of occlusion suggest that applying forces to the immature trachea can affect the normal configuration.

This study has some limitations. First, because of the nature of this type of abnormality, a selection bias was introduced. In general, the fetuses in the FETO group had less chance of survival, as estimated with the lung area–to–head circumference ratio, than did the fetuses in the non-FETO group. This bias is present because ethical guidelines prohibit us from performing a possibly dangerous intervention if the chances of survival without it are high enough. Therefore, the baseline characteristics of both groups cannot be compared. Second, the number of patients in our study was small, especially in the lower and higher ranges of included infant age.

This is due to the low prevalence of the disease and the difficulty of CT-based follow-up in infants. In addition, we included only children who survived long enough to undergo follow-up CT after birth, which probably led to the lower number of children in the FETO group than in the non-FETO group as mortality was higher in the most severe cases. It is possible that more pronounced or other tracheal abnormalities were present in the deceased children. However, because ethical guidelines do not allow real randomized studies in this regard, the bias in this study is currently unavoidable. Another possible bias is the difference in postmenstrual age at birth between patients treated with FETO and those treated expectantly. It is, however, very unlikely that the difference in tracheal dimension would only be secondary to a more premature birth and the consequential need for invasive ventilation. Last, although CT was not performed in patients with a uniform postnatal age, it allowed us to have an impression of diminishing difference in tracheal area between the FETO and non-FETO groups in later ages.

In conclusion, the tracheal dimensions in children with CDH who underwent FETO were significantly larger than those in children with CDH who were treated expectantly in pregnancy. The differences tended to diminish over time. We recommend that additional studies be performed to investigate the potential causes of this observation.

Acknowledgments: We thank Walter Coudyzer and Herman Pauwels for their skills in image postprocessing.

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