Tracheomegaly in Infants with Severe Congenital Diaphragmatic Hernia Treated with Fetal Endoluminal Tracheal Occlusion

Augusto Zani, MD, PhD[1], Maria Sellars, MB, ChB[2], Pamela Allen, MB, ChB[2], Athanasios Tyraskis[1], Kypros Nicolaides, MD[3], Anne Greenough, MD (Cantab)[4], Shailesh Patel, MB, BS[1], Mark Davenport, ChM[1], and Niyi Ade-Ajayi, MPhil[1]

Objective To measure and evaluate the effects of tracheal dimensions on survival and ventilation in a large series of infants with congenital diaphragmatic hernia (CDH) treated antenatally with fetal endoluminal tracheal occlusion (FETO).

Study design Tracheal dimensions on chest radiograph (CR) were measured by 2 blinded radiologists. Survival, day 1 best oxygenation index and duration of ventilation, continuous positive airway pressure, and hospital stay were recorded. Survivors with a minimum 12-month follow-up were longitudinally compared for incidence of gastroesophageal reflux, chest infections, chest deformities, and hernia recurrence.

Results Seventy infants with CDH (41 who underwent FETO) were treated between 2004 and 2010. Hernia repair was performed in 26 infants without FETO (8 with patch repair) and 35 infants with FETO (26 with patch repair; $P = .0015$). Infants with FETO had a wider trachea than those without FETO at T1 ($P < .0001$) and between T1 and the carina ($P < .0001$). Tracheal diameter was similar in survivors and nonsurvivors in the FETO group. Tracheal size was not correlated with day 1 best oxygenation index in the FETO group ($R^2 = 0.17$) or the non-FETO group ($R^2 = 0.07$). There were no between-group differences in duration of mechanical ventilation ($P = .30$), continuous positive airway pressure ($P = .20$), or hospital stay ($P = .30$). In the longitudinal study, tracheal widths were larger on the last CR than on preoperative CR in patients without FETO (T1, $P = .02$; widest point, $P = .001$; carina, $P = .0001$), and for patients with FETO at the widest point ($P < .0001$) and at the carina ($P < .0001$), but not at T1 ($P = .12$). There were no differences in clinical variables between the FETO and non-FETO groups.

Conclusion FETO has a significant impact on tracheal size of infants with CDH; however, tracheal size does not affect survival or the requirement for early respiratory support. *(J Pediatr 2014;164:1311-5)*.

Congenital diaphragmatic hernia (CDH) is a complex anomaly with significant risk of mortality, due mainly to pulmonary hypoplasia.[1] Intrauterine tracheal occlusion appears to ameliorate and even reverse impaired lung growth in experimental models[2] and in the human condition.[3] The technique appears to work by preventing the egress of liquid from the lung, increasing airway pressure, causing cellular proliferation, and increasing alveolar airspace and maturation of pulmonary vasculature.[4] In many centers in Europe and Brazil,[5,6] intratracheal placement of a detachable balloon, known as fetal endoluminal tracheal occlusion (FETO), has replaced the earlier method of external tracheal clipping.

The FETO Task Force initiated a clinical program in which this technique was performed on fetuses with CDH and a poor prognosis, with a "liver-up" position and a lung-to-head ratio ≤1.0.[5] According to stratified data from the Antenatal CDH Registry, FETO increased survival in severe cases with left-sided CDH by up to 49% and in cases with right-sided CDH by up to 35%.[7]

The most common complication associated with FETO is premature rupture of the membranes, with an incidence of 17% within 3 weeks after the procedure.[7] The resultant preterm labor and delivery in this subset of fetuses with CDH is associated with higher mortality. A more recently reported side effect of FETO is tracheomegaly, although animal studies initially suggested that the balloon does not cause significant tracheal damage.[8-12]

King's College Hospital (KCH), London is part of the European FETO Task Force and currently the sole center in the United Kingdom that performs FETO, which has been performed on fetuses with CDH and a poor prognosis since 2002. A collaborative study with the University Hospital Brugmann compared the presence of tracheomegaly in a cohort of infants who underwent FETO and a cohort of infants with no congenital lung abnormalities.[13]

CDH	Congenital diaphragmatic hernia
CPAP	Continuous positive airway pressure
CR	Chest radiograph
CT	Computed tomography
d1-BOI	Day 1 best oxygenation index
FETO	Fetal endoluminal tracheal occlusion
KCH	King's College Hospital
WTP	Widest tracheal point

From the Departments of [1]Pediatric Surgery and [2]Radiology, and [3]Harris Birthright Research Center for Fetal Medicine, King's College Hospital; and [4]Division of Asthma, Allergy, and Lung Biology, King's College London, London, United Kingdom

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The aim of the present study was to determine whether any such effects are more common in infants with CDH who underwent FETO compared with those who did not undergo FETO. We also examined possible implications for clinical outcomes in a large cohort of infants with CDH by relating tracheal size to outcome in infants with FETO and those without FETO in the newborn period and at follow-up.

Methods

We conducted a review of all neonates born with CDH at KCH between January 2004 and December 2010. The study was approved by the KCH Institutional Review Board (approval no. 2938). A proportion of the neonates had been diagnosed antenatally with severe CDH (defined as a lung-to-head ratio ≤1.0 and a "liver-up" position[5,7]) and had undergone FETO at KCH's Harris Birthright Research Centre for Fetal Medicine. We excluded infants who underwent FETO at KCH but were then delivered at other centers. Demographic data for the patients included in this study were retrieved from the clinical notes. The patients were divided into 2 groups: FETO and non-FETO (internal control).

Tracheal Size

Tracheal size and clinical outcome were assessed at 2 separate time points, in the neonatal period and at last follow-up. Tracheal size was assessed by 2 pediatric radiologists (M.S. and P.A.), who blindly reviewed the chest radiographs (CRs) of the entire cohort. Images were viewed on GE-PACS workstations (GE Healthcare, Buckinghamshire, United Kingdom) with high-definition monitors. Tracheal measurements were obtained at 3 levels: T1 vertebral body, carina, and widest tracheal point (WTP). Tracheal measurements were evaluated in more depth in patients who also had undergone a chest computed tomography (CT) scan during the study period. The results on CT were compared with those on the CRs obtained at the date closest to the CT scan.

Neonatal Cross-Sectional Study

The FETO and non-FETO groups were compared in terms of tracheal measurements, days of mechanical ventilation (including continuous positive airway pressure [CPAP]), and length of hospital stay. In addition, each patient's WTP was correlated to day 1 best oxygenation index (d1-BOI) and duration of mechanical ventilation, CPAP, and hospital stay using linear regression analysis. The d1-BOI was calculated as described previously, as fraction of inspired oxygen times mean airway pressure, divided by the partial pressure of oxygen in arterial blood; the best (ie, lowest) value on day 1 of life is the d1-BOI.[14]

Longitudinal Study

This aspect of the study focused on patients with CDH born and treated at KCH between January 2006 and December 2009. This population comprises survivors with imaging data available on KCH's high-specification picture archiving and communications system (PACS) with at least a 12-month follow-up. Tracheal measurements at T1, the carina and the WTP on CRs from birth to the last review of infants with and without FETO were compared using logistic regression analysis (slope difference and deviation from zero). The location of the WTP at the last follow-up was also recorded and compared with that at birth.

In addition, data on severe gastroesophageal reflux requiring fundoplication, severe chest infections prompting hospital admission, severe chest wall deformities, and diaphragmatic hernia recurrence were compared in the FETO and non-FETO groups.

Statistical Analyses

Data are expressed as median (range) or mean ± SEM as appropriate, following determination of normality with the D'Agostino-Pearson test. Categorical data were compared using the χ^2 or Fisher exact test. Ordinal data were compared with 2-tailed parametric tests (eg, *t* test) or nonparametric tests (eg, Mann-Whitney test) as appropriate. Nonparametric data correlation is expressed as Spearman rank correlation coefficient (*r*). Linear regression analysis was used to study the correlation between tracheal size and clinical variables in the neonatal study and the progression of tracheal growth over the years in the longitudinal study. $P < .05$ was considered to indicate statistical significance.

Results

Neonatal Cross-Sectional Study

During the study period, 70 infants with CDH were born and treated at KCH. Of these, 41 (59%) had undergone FETO in utero (**Table**). The FETO group had an earlier median gestational age compared with the non-FETO group (35 weeks [range, 31-40 weeks] vs 38 weeks [range, 29-41 weeks]; $P < .0001$). Six infants in the FETO group (15%) and 3 infants in the non-FETO group (11%) died before undergoing surgical repair ($P = .73$).

On CR review, the trachea was wider at T1 (8.6 ± 0.3 mm vs 6.4 ± 0.2 mm; $P < .0001$) and at the WTP (8.9 ± 0.4 mm vs 6.9 ± 0.3 mm; $P < .0001$) in the FETO group compared with the non-FETO group (**Figure 1**). However, there was no between-group difference in tracheal width at the level of the carina (6.4 ± 0.2 vs 6.0 ± 0.2 mm; $P = .26$) (**Figure 1**). The WTP was most commonly at the level of T1 (75%) and less commonly at the level of T4 (8%), T2 (7%), T3 (7%), or C7 (3%) (**Figure 2**).

There was no difference in tracheal width between survivors and nonsurvivors in the FETO group at all 3 points (T1: 8.4 ± 0.4 vs 9.4 ± 0.7 mm, $P = .15$; WTP: 8.8 ± 0.4 vs 9.5 ± 0.7 mm, $P = .19$; carina: 6.4 ± 0.2 vs 6.6 ± 0.5 mm, $P = .60$).

Tracheal size did not correlate with d1-BOI ($r = 0.004$; $P = .98$). This was confirmed in an independent test of the correlation between tracheal size and d1-BOI in the FETO group ($r = 0.017$; $P = .52$) and non-FETO group ($r = 0.07$; $P = .52$).

A chest CT scan was performed in 3 infants (2 in the FETO group) for diagnostic purposes, to exclude congenital airway