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COMMENTARY

Tracheal side effects following fetal endoscopic tracheal occlusion for severe congenital diaphragmatic hernia

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Despite optimal neonatal care and even in large referral centres, between 20% and 30% of neonates with isolated congenital diaphragmatic hernia (CDH) will not survive [1]. The leading causes of death remain in essence pulmonary hypoplasia and persistent pulmonary hypertension (PPHT). Prenatal medical imaging methods are used to predict individual outcome, which provides parents with prenatal options. For those with a predicted poor outcome this might include prenatal intervention, which aims to improve lung development rather than repairing the anatomical defect. Early attempts by prenatal surgical repair of the defect were abandoned as they required access by hysterotomy and because reducing liver herniation compromises the fetal circulation [2]. Tracheal occlusion (TO) prevents egress of lung liquid produced by the airway epithelium, hence induces tissue stretch, which acts as a signal for lung growth [3, 4]. Clinically TO was initially performed using extra-luminal clips with reversal during an ex-utero intrapartum tracheoplasty procedure [5]. Subsequently an endoluminal balloon was used, which allows easier reversal in utero, that itself triggers lung maturation according to experimental evidence [5–7]. Invasiveness was further reduced by using a completely percutaneous approach, small diameter instruments with a move towards regional or local anaesthesia. Up to 2008 the FETO consortium performed more than 200 percutaneous fetoscopic endoluminal TOs (FETO) [8]. Survival rate is twice as high as predicted, the latter based on lung size measurements in case of left-sided CDH [9]. Obviously this data is based on external controls and the procedure should be considered as investigational whilst a trial has not confirmed these early findings [10].

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A few lessons from this early experience can certainly already be drawn:

1. There are no known maternal safety issues.
2. Intra-operative tracheal complications such as laceration may occur. They are fortunately rare (2%), recover in utero but should be avoided by operator experience and using adequate diameter instruments.
3. The most important fetal risk is preterm delivery mainly because of preterm pre-labour rupture of membranes (16.7% within 3 weeks), the latter being operating time-related.
4. Preterm delivery may lead to the need for earlier than scheduled balloon removal. This means birth should take place in a centre appropriately trained for balloon removal and having a team available 24 h a day.
5. The leading cause of death following FETO remains pulmonary hypoplasia and PPHT. Postnatal death is best predicted prenatally by small lung size prior to the procedure and poor lung growth after the procedure. This may have may have consequences for patient selection or timing of the procedure. It is hoped that an earlier TO may lead to more lung growth. This might however be at the expense of extreme prematurity when membranes rupture or increased tracheal widening.
6. Early neonatal morbidity indicators do not suggest substitution of mortality by morbidity in comparison to same severity controls [11, 12]. As such, FETO may reduce pulmonary morbidity, such as oxygen requirement or number of ventilation days.
7. Long-term outcomes are, as with many congenital birth defects treated in utero, not well documented, despite knowledge about prenatal predictors of perinatal morbidity.

In our experience, symptomatic tracheal issues are very rare. Tracheal side effects were certainly one of our initial concerns with TO, whether this is by an external clip or endoluminal devices such as a foam plug or balloon. Tracheomalacia was once reported with the foam plug, but that device was mainly abandoned because of inappropriate occlusion, leading to insufficient pulmonary response [13, 14]. The currently used vascular occlusion balloons are, once inflated, about 7–8 mm in diameter and 20–22 mm in length, exceeding the tracheal dimensions during fetal life, both of normal fetuses as well as those with CDH [15, 16]. We, and others, have conducted experiments to define the properties of these balloons as well as the tracheal side effects [17–19]. In fetal lambs the tracheal side effects were limited to focal and mild epithelial and inflammatory changes, without visible changes in the cartilage rings. There was however tracheal dilatation, typically by elongation of the pars membranacea. Histological changes were superficial and focal and the effects seemed to recover following in utero unplugging. Dilatation was not confined to the balloon area, but the trachea was also wider (but to a lesser extent) distal to the occlusion.

McHugh et al. [20] report in this issue the clinical radiological findings of tracheal widening in a number of newborns and infants managed at Great Ormond Street Hospital for Children (London) and Queen's Medical Centre (Nottingham University Hospitals). On closer inspection, two of the babies' respiratory problems were likely due to the tracheal dilatation (numbers 1 and 3), but these problems eventually recovered. Two other babies died due to multiple issues, but also had a widened trachea. One other baby with tracheomegaly however has a tracheostomy and remains on CPAP at the moment of writing.

The tracheal enlargement McHugh et al. [20] describe is consistent with the widening we observed in sheep, and which we also documented in six consecutive infants who were managed in utero in Leuven, Belgium, and investigated with systematic fibre-endoscopic examination of the trachea during their neonatal intensive care unit stay in Lille, France [21]. Typically there is elongation and relaxation of the posterior tracheal wall. These changes were not symptomatic, except for a barking cough during increased respiratory effort. In non-survivors histology of that area revealed loss of epithelial folding and focal muscular disruption. There were no cartilage changes documented. We have also been able to follow-up infants and children who were managed locally during the perinatal period in Leuven. None of these cases so far has presented with clinical tracheal issues, although they had variable degrees of tracheal widening. On follow-up CT scan at a later date (Fig. 1), we documented that these to some extent persist, but appear to become much less pronounced with age; again their clinical relevance is unknown. As far as we were aware, obvious clinical postnatal tracheal problems have not been a problem in children managed so far by the FETO consortium, with the exception of the cases now reported by McHugh et al. [20]. Acute or incomplete removal problems, as in case 5, were already described in our first case series. Such situations are completely avoidable by controlling the airways pre-or peri-natally in optimal conditions. Therefore we urge our cases to remain under our care for as long as the trachea is occluded.

For the future we need to determine; (1) the "denominator", i.e. whether this is present in all children and how likely this is in (premature) CDH newborns who did not undergo FETO; (2) what the clinical consequences are of the radiographic tracheal widening; (3) what the pathologic substrate of this condition is, and whether it is an entity that is different from what is currently understood as trache-

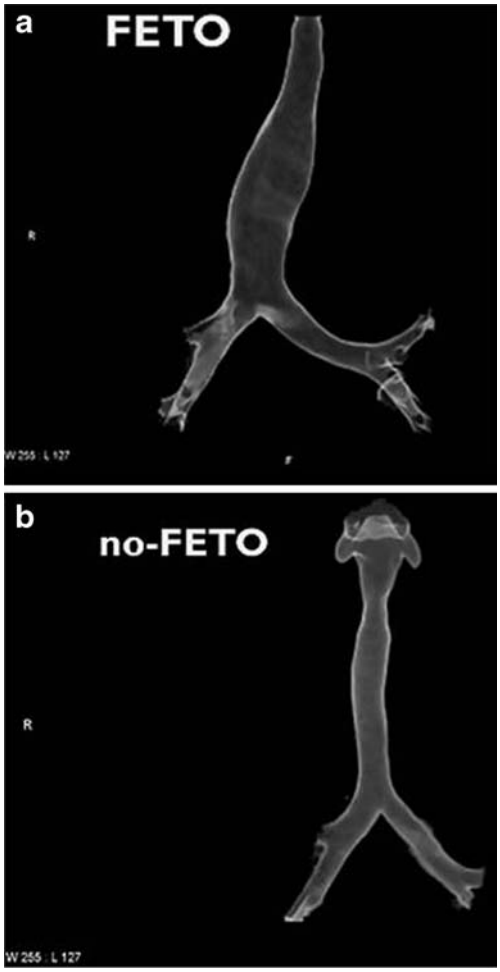

Fig. 1 Comparison of a 3-D reconstruction of the trachea of a child between 4.5 and 5 years of age either (**a**) having undergone FETO or (**b**) expectantly managed during pregnancy, both asymptomatic. The FETO patient (**a**) has distal tracheal widening as compared to the control (**b**). Low-dose/ 2 mGy spiral chest CT was performed with the child in a supine position and during quiet respiration at near functional residual lung capacity. CT parameters: tube voltage 100 kVp, tube load 45 mAs, collimation 64×0.6 mm, pitch 1.4, rotation time 0.5 s and CTDIvol 2 mGy. The upper limit of the field of view was situated at the vocal cords and the lower limit at the base of the lungs (Somatom Sensation 64, Siemens Medical Solutions, Erlangen, Germany)

omegaly and/or tracheomalacia; (4) to work on its prevention by adapting the diameter in early gestation or the design of the TO device; and (5) to develop potential solutions for established problems, if this would prove to be a (however rare) complication. Of note is that three cases were occluded at 24 weeks' gestation or less, and the remaining two <26 weeks' gestation with balloon removal only at birth. This may indicate that tracheomegaly is more likely to occur early in pregnancy when the airways are highly compliant, or with insufficient in utero recovery time [22]. Alternative devices need to keep the balance between complete occlusion without unnecessarily oversizing the tracheal dimensions during the occlusion period. Unfortunately, the interest of the medical industry in such "orphan" devices is minimal. In terms of tracheal solutions, tissue engineering techniques are already being explored for tracheal reconstruction in cases with similar problems but different causes such as prolonged intubation, recurrent pneumonia and bronchiectasis [23].

The absence of longer-term follow-up of survivors following FETO is certainly a lack of the current FETO programme. Plausible reasons for this are the international nature of the programme, where children typically are in one centre during the occlusion period but referred back to their national referral centre once stabilized in the neonatal period. In addition the European 6th Framework Programme support of the current trial does not include funding for recalling patients [24]. Although initially we also lacked guidelines for standardizing follow-up, this has recently been addressed by the American Academy of Pediatrics [25]. We certainly join the recommendations made by McHugh et al. [20], that this particular aspect should be part of the standardized follow-up of children having undergone FETO in the prenatal period. This might include performing tracheal measurements on follow-up CT scans, or in symptomatic children, liberal use of fibre-endoscopy.

Our group is currently gathering comprehensive data on this and other aspects of the entire programme rather than casuistic reporting, as well as performing a trial documenting the potential benefit of FETO in moderate and severe forms of hypoplasia. To us, the North American randomized trial did not answer the latter question [26]. In that study, only three cases with severe hypoplasia were included (i.e. a lung-head-ratio (LHR) <1.0 and liver herniation), a group we have been operating on so far. The majority were moderate cases, but no benefit of fetal therapy was shown. However, today FETO is performed via a single, 3.3-mm port, as a percutaneous procedure that can be performed under local anaesthesia. Seventy-percent of patients deliver ≥34 weeks, which compares favourably to the outcomes in the NIH-trial, where the rupture rate was 100% and delivery took place at about 30 weeks. Moreover, despite the early gestational age at birth, the alveolar-arterial oxygen difference and pulmonary compliance was improved in the TO group of the American trial [27]. Improved lung function in those moderate cases, as well as in those with severe hypoplasia that we operated on, led us to design a randomized trial in this group as well. To avoid the side effects of prematurity, we propose fetal therapy late (30–32 weeks) in gestation, which, in addition to avoiding prematurity, may also lessen the impact of the balloon on the tracheal diameter.

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