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Technical aspects of fetal endoscopic tracheal occlusion for congenital diaphragmatic hernia☆

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Abstract In isolated congenital diaphragmatic hernia, prenatal prediction is made based on measurements of lung size and the presence of liver herniation into the thorax. A subset of fetuses likely to die in the postnatal period is eligible for fetal intervention that can promote lung growth. Rather than anatomical repair, this is now attempted by temporary fetal endoscopic tracheal occlusion (FETO). Herein we describe purpose-designed instruments that were developed thanks to a grant from the European Commission. The feasibility and safety of FETO have now been demonstrated in several active fetal surgery programs. The most frequent complication of the procedure is preterm premature rupture of the membranes, which is probably iatrogenic in nature. It does have an impact on gestational age at delivery and complicates balloon removal. FETO is associated with an apparent increase in survival compared with same severity controls, although this needs to be evaluated in a formal trial. The time has come to do so.

Congenital diaphragmatic hernia (CDH) occurs sporadically, with an incidence of 1/2500 to 1/5000 of newborns, depending on whether stillbirths are included. The vast majority of cases are left-sided CDHs, whereas 13% are right-sided CDHs; bilateral lesions, complete agenesis, and other rarities comprise less than 2%. In approximately 40% of cases, there are associated anomalies. Their presence is an independent predictor of neonatal death, with less than 15% of babies surviving in this group. The majority are thus

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apparently *isolated*. Although CDH is a surgically correctable defect, it is the developmental arrest of both airway and vessels that causes problems in the postnatal period. Depending on the degree of pulmonary hypoplasia, neonates will experience severe respiratory insufficiency and develop pulmonary hypertension. Currently, 2 of 3 cases are diagnosed prenatally; the parents of an affected fetus should be referred to a tertiary care center experienced in assessing this anomaly and managing CDH in the perinatal period [1]. Based on a comprehensive diagnostic and prognostic assessment, parents will make their decisions [2]. There is still controversy regarding the natural history of this disease, which today may be difficult to define given that parents may request termination of the pregnancy. In utero referral to centers that offer highly specialized neonatal care may impact the survival rate [3-5]. The current mortality for prenatally diagnosed, isolated left-sided CDH is probably under or around 30% at tertiary care centers (Table 1).

1. Prediction methods

Prediction of mortality is crucial for attempting fetal intervention. Roughly speaking, this is based on estimation of lung size, the degree of liver herniation, and, increasingly, evaluation of the pulmonary circulation. We refer to recent reviews of the imaging methods used for this purpose [12,13]. These novel methods are still being validated, and currently fetal treatment programs still rely on the widest validated method for patient selection: the lung-to-head ratio, first described by Metkus et al [14]. It involves a 2-dimensional measurement of the lung area contralateral to the lesion, in proportion to the head circumference in the standard biparietal view. Because lung and head sizes do not increase equally during pregnancy, lung size measurement of the index case is better expressed as a function of what is expected in a gestational age control using a formula specific for the measuring technique and the side of the lesion [15-17]. This method has been validated in 354 fetuses with unilateral isolated CDH evaluated between 18 and 38 weeks' gestation, both in terms of mortality and morbidity (Fig. 1) [18]. Volumetry of both lungs should intuitively increase accuracy. Three-dimensional ultrasound is now widely available, but accurate imaging of the smallest, ipsilateral lung is not possible in more than 40% of fetuses [19]. Fetal magnetic resonance imaging (MRI) does not have this limitation and hence will probably become the method of choice for anatomical lung assessment [20]. Several studies have demonstrated a correlation between total lung volume and survival, as well as the need for extracorporeal membrane oxygenation [21,22]. Liver herniation, which in several studies has been shown to be an independent predictor, is another marker. Although it is identifiable by ultrasound, the degree of liver herniation can be quantified by fetal MRI [23]. Interestingly, the amount of herniated liver may be independent of lung volume. Lung vascularization can be assessed by looking at the number of branches, vessel diameters, flow velocimetry or volume, and reactivity to maternal oxygen inhalation, as recently reviewed by Claus et al [13]. Several studies have shown that the latter techniques may improve predictive accuracy [24-26]. At this time, most studies come from centers where severe cases are overrepresented, with some undergoing fetal intervention. Future studies by other groups will enable a more thorough validation. In summary, there is increasing evidence that the prognosis of an individual fetus with isolated CDH can now be made in a timely manner, which raises the question about use of fetal therapy in the most severe cases.

Table 1 Recent series on postnatal outcome of isolated CDH

	No. of cases	TOP rate	Survival rate
Stege et al [6]	185	N.R.	70%
Gallot et al [3]	314	7%	63%
Hedrick et al [7]	89	N.R.	66%
Datin-Dorrière et al [8]	99	20%	63%
Postnatal series			
Sartoris et al [9]	244	N.R.	70%
Mettauer et al [10]	147	N.R.	77%
Grushka et al [5]	121	N.R.	81%

Some units report survival rates after transfer of the neonate. These series therefore do not include the hidden mortality. TOP indicates termination of pregnancy; N.R., not reported. This table was adapted from Deprest et al [11].

2. Fetal surgery for CDH

The initial approach to CDH was anatomical repair, as demonstrated experimentally [27]. Clinical application of anatomical fetal CDH repair was abandoned once it became clear that it was not possible in fetuses with liver herniation and that those without did not benefit from the intervention [28,29]. Lung growth can also be triggered by tracheal occlusion (TO), as evidenced by several experimental studies. In brief, lung fluid production and fetal breathing movements stimulate lung growth and maturation. Occlusion prevents egress of lung fluid, increasing airway pressure, causing proliferation, increased alveolar air space, and maturation of pulmonary vasculature [30]. When TO is sustained, it reduces the number of type II pneumocytes and hence surfactant expression, which can be alleviated by in utero release ("plug-unplug sequence") [31]. TO was first clinically achieved by maternal laparotomy, hysterotomy, and fetal neck dissection and tracheal clipping [32]. The Philadelphia group with Flake et al [32] described a variable, at times explosive lung response, even prompting earlier delivery. The survival rate in that study was 33%, with the majority having serious neurological morbidity. The San Francisco team of Harrison et al [33] moved to endoscopic

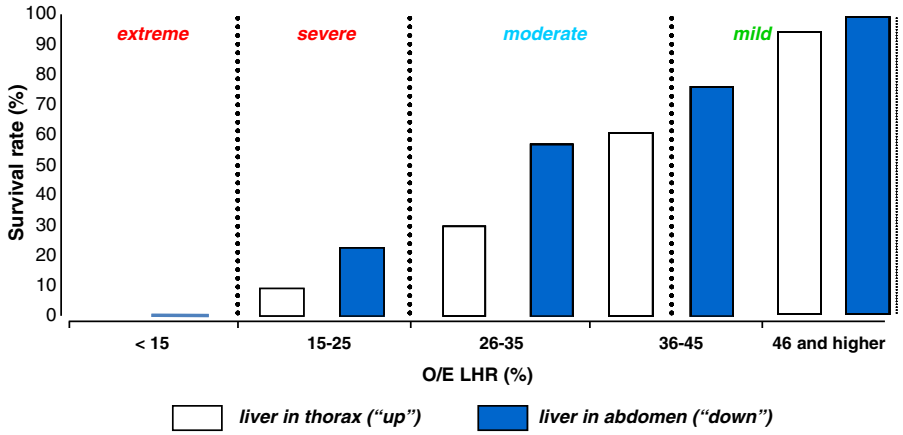

Fig. 1 Survival rates of fetuses with isolated left-sided CDH, depending on measurement of the O/E LHR and position of the liver as in the Antenatal CDH Registry. Adapted from: Jan A. Deprest et al., Antenatal prediction of lung volume and in-utero treatment by fetal endoscopic tracheal occlusion in severe isolated congenital diaphragmatic hernia, Seminars in Fetal & Neonatal Medicine (2008), doi:10.1016/j.siny.2008.08.010.

access to the uterus, but the operation still required uterine exposure by laparotomy, and multiple cannulas to allow tracheal dissection and clipping, with an inherent risk for damage to the surrounding structures. We first described experimental foregut endoscopy [34], which was then used to position an endoluminal balloon into the trachea [35,36]. In experimental conditions, this has also been done under ultrasound guidance, but with a lower success rate [28,37]. Briefly after, the first clinical cases of endoluminal plugging were reported in active fetal surgery programs in the United States either by laparotomy or percutaneously [38,39]. In Europe, the Fetal Endoscopic Tracheal Occlusion (FETO) Task Force started the clinical program somewhat later but on severe cases only [40]. Technically, we also managed to move away from general anesthesia to locoregional anesthesia and eventually local anesthesia and from balloon removal on placental circulation at birth to elective in utero reversal, by either balloon puncture or fetoscopic retrieval. In utero "unplugging" was advocated mainly based on the experimental observation that it stimulates lung maturation [31]. We published our entire experience with 213 cases as of December 2008, and essential clinical results are summarized herein. We refer to the actual indications detailed in that report [41]. However, in this article, we detail the technical aspects of this procedure and some conclusions from a secondary analysis.

3. Technical requirements for fetoscopic balloon insertion as practiced today

3.1. Instruments

Severe CDH can be thought of as an orphan disease in this respect, that it is not commercially considered interesting enough to develop specially designed instruments or devices for. In addition, the potential medicolegal risks that devices for use in fetal medicine may pose to the manufacturer would make it unlikely that someone would invest heavily in technical developments for this purpose. The successive framework programs and the Marie Curie grants of the European Commission have facilitated industry-academic collaboration to develop and produce instruments that were designed for the exact purpose that clinicians had in mind. In addition to the EuroSTEC (www.eurostec.eu) project for the application of tissue engineering for congenital birth defects, there is also a research line for prenatal intervention for CDH. Engineers of Karl Storz Endoskope (Tuttlingen, Germany) designed instruments in collaboration with clinicians from the FETO Task Force, analogous to what happened earlier in the Eurofetus project [42-44]. Some instruments were borrowed from other fetoscopic procedures, but many others had to be purposely designed. Many of these have outgrown the prototype phase and were released for production, so that others can use them as well.

Table 2 displays these instruments and their properties. In essence, a fiber optic endoscope that is smaller than the one typically used for mid-trimester laser coagulation is used (2.0 mm). This reduces image quality and light transmission; however, one has to bear in mind that the visual requirements for this operation are less than those for laser surgery. The working space is restricted to the fetal mouth, nasopharynx, and trachea. The initial 1.2-mm fiber optic endoscope had only 10,000 pixels, but the new 1.3-mm version has 17,000 pixels. The fiber optic scope can be bent significantly, such that it adapts to the 30° curved sheath used for this procedure. It is however not proven that this curve is needed, as we have already performed tracheoscopy with a straight scope as well. The sheath is 3.3 mm in diameter, as it houses both the fiber optic endoscope (1.3 mm) and the catheter system loaded with the uninflated balloon (1.5 mm) used for occlusion. Thus far, we also passed another instrument (either a forceps or a stylet) through the sheath's additional connection, so that

Table 2 Instrument specifications for the FETO procedure

Instrument	Physical properties	Other specific features
Insertion instruments		
Fetal tracheoscope, 11540AA, Karl Storz	Outer diameter = 1.3 mm Working length = 30.6 cm Opening angle = 70° Angle of view = 0° 17,000 pixels	Deported eye piece (lighter weight) Autoclavable Fiber optic endoscope (allows bending)
Tracheoscopic sheath with 3 side ports, 11540KE, Karl Storz	Outer diameter = 3.3 mm With 2 connections for instruments Working length = 30.6 cm Precurved 30°	Sandblasted tip for increased echogenicity Autoclavable Blunted tip to avoid direct trauma
Balloon removal instruments		
Inner sheath for postnatal tracheoscope, 26161CN, Karl Storz	Outer diameter = 4.3 mm Working channel = 1.7 mm, with stopcock and Luer lock connection	Together with outer sheath, it forms a continuous-flow sheath. Tip is blunted as to avoid trauma.
Continuous-flow fetoscope sheath, 26161CD, Karl Storz	Outer diameter = 5 mm With Luer lock connection	
Third-trimester tracheoscope, 26008FUA, Karl Storz	Outer diameter = 2.0 mm Opening angle = 60° Angle of view = 12° Working length = 26 cm	Autoclavable Rod lens telescope (comes also as 0° [26008AA] or 30° [26008BUA]
Retrieval forceps, 11510C, Karl Storz	Outer diameter = 1.0 mm Length = 35 cm	Semirigid Double-action jaws
Adjustable puncture stylet, 11506P, Karl Storz	Length = 50 cm Outer diameter = 0.4 mm Single use	Movable torquer allows adjustment of length to avoid overintroduction
Other instruments that are generic to fetoscopy		
Trocar, 11650TG	Pyramidal trocar, for introduction of cannula Length = 170 mm	For introduction of cannula
Cannula RCF-10.0, Check-Flo Performer Set, Cook	Outer diameter flexible cannula = 10 Fr Working length = 13 cm	
Single-use balloon and catheter systems (as used by the FETO consortium)		
GVB 16 detachable balloon, Nfocus Neuromedical (Palo Alto, CA) (off-label use)	Latex balloon, with radiopaque inclusion Outer diameter * = 1.5/8.0 mm Length * = 6.5/21 mm	Earlier marketed by Cathnet Science, and before by Nycomed. Recommended filling volume = 0.8 mL
Goldbal 2 detachable balloon, Balt (Montmorency, France) (off-label use)	Latex balloon, with radiopaque inclusion Outer diameter * = 1.5/7.0 mm Length * = 5.0/20.0 mm	Recommended filling volume = 0.6 mL
CIFN Mini-Torquer catheter, Nfocus Neuromedical (off-label use)	Length = 130 cm, tapered microcatheter supple section 20 cm Outer diameter = maximum, 0.X mm Tapered to ward the tip Guiding catheter inner diameter = 0.066"	Comes with mandrel and Toohy-Borst connection. Different lengths available
BALTACCI-BDPE catheter, Balt (off-label use)	Length = 160 cm, tapered microcatheter Outer diameter = maximum, 0.9 mm; minimum, 0.4 mm (tapered toward the tip) with guiding catheter	Comes with mandrel. Toohy-Borst (11510V, Karl Storz) Y- connection can be added. A coaxial double catheter system can be used as well.

* The first value refers to uninflated state; second value, inflated state. Conversion: 3 Fr = 1 mm.

we could immediately remove the balloon if malpositioned. There is sufficient space in the sheath to permit effective irrigation through a third connection to the sheath. The tip of the sheath was blunted, to avoid fetal trauma, and sandblasted, to increase its echogenicity.

3.2. Balloon and catheter systems

Many groups have been seeking the perfect way to occlude the trachea [45]. We have chosen an inflatable balloon as an occlusion device. The rationale is that a balloon can accommodate increasing diameter related to tracheal growth during pregnancy. The dimensions of the balloon were chosen such that it slightly oversizes the anticipated tracheal diameter at the anticipated time of release (Table 2). The biometry of the trachea has been well studied [46]. Experimental work has documented the local pressure it can generate, as well as the local side effects on the fetal trachea [47,48]. In essence, the balloon induces flattening of the epithelium and widens the tracheal diameter but without apparent damage to the cartilage. We therefore were confident in using the device clinically. Furthermore, the balloon appears obvious on ultrasound examination as a fluid-filled structure, so that it eventually can be punctured either percutaneously or in its absence at the time of fetoscopy.

Obviously, the balloons are clinically used off-label, as they are borrowed from the field of invasive radiology. For that indication, they function as vascular occlusive devices and are inserted via a long catheter system. Even when unfilled, the balloon is radiopaque, thanks to the included ball, which marks the most frontal tip of the balloon. Filling is typically done with an MRI isotonic contrast agent. For fetal use, this is not necessary. Contrast agents are in reality toxic, and, more importantly, the typically sausage-shaped fluid-filled structure is easily identified on ultrasound or MRI even without contrast. We have clinically used only balloons made from latex natural rubber, which would have better retention properties than silicone. Silicone devices were used earlier by the San Francisco group of Harrison et al [38], but they are no longer on the market. The market of balloon vascular occlusion devices has shrunk significantly owing to the introduction of coils. For this reason, we had to move during the course of our program from balloons made by Cathnet (Paris, France; later acquired by Nfocus, Palo Alto, CA) to the current ones produced and being modified wherever possible by Balt (Montmorency, France). Both balloons have an integrated one-way valve for filling. These are handmade devices such that the balloon needs testing prior to insertion. A Luer lock syringe is connected to a blunt needle that is advanced beyond the valve. The balloon is filled with normal saline at the preset volume (Table 2). The filled balloon is then guided over the mandrel and the catheter tip, which has already been inserted through the fetoscopic sheath. It will then empty into the catheter, filling its dead space. The microcatheter has a certain degree of stiffness to allow manipulation and steering. When one uses a Y-connection (Toohy-Borst), the mandrel can be kept in place, which allows easier manipulation. These catheters have also changed over time to end up with a purpose-designed one produced by Balt (Table 2). The catheter tip must then be advanced beyond the valve of the filled balloon, and the catheter will start filling the dead space of the catheter backwards. Once in its correct position, the balloon is inflated and released by simple withdrawal of the catheter out of the valve. We use our scope tip to give counterpressure and keep it in place, although that may not be essential. Alternatively, one can use a coaxial catheter (COAX, Balt), which basically has an outer catheter pushing the balloon off the tip of the withdrawing inner catheter tip.

In our clinical experience, we could no longer visualize a balloon during follow-up in 8.1% of cases, and this was at a median of 28 days (range, 1-63 days). In a few cases, we had all reasons to assume that this was a result of dislodgment of an intact balloon, but spontaneous deflation was probably more frequently the cause. When used as an endovascular occlusion device, this is without further consequences, because the vessel is clotted by then. For this off-label indication, deflation obviously leads to a loss of the biologic effect of the procedure. One should consider reinsertion if the pulmonary response seems insufficient. Recently, we have witnessed a higher and nearly immediate failure rate, which was probably a result of a poor-quality batch of balloons (data not published). This problem has since been solved, and we are currently working with the manufacturer on further improvements.

3.3. Uterine access

This is not different from the technique used for fetoscopic laser surgery on the placenta. We use a disposable, thin-walled flexible cannula loaded with a trocar for introduction under ultrasound guidance in the area of interest. The target of the operation is an area between the base of the fetal nose and the mouth. Occasionally, one may have to do an external version to enable a safe and effective entry. When the fetus is in vertex with the head deep in the pelvis, it may help to push the head up vaginally. Along the same lines, an occiput anterior position may also be pushed backwards by external pressure. Obviously, the placenta is avoided at all times. Anterior placenta is not a contraindication as a placenta free window could so far always be identified. When working under local anesthesia, infiltration with lidocaine is similar as for laser surgery. In our experience, the mean operative time was 10 minutes (range, 3-93 minutes) (Table 4). Longer operative times are typically associated with a less-than-ideal position of the fetus. This can be primary or occur during the operation. Polyhydramnios is associated with fetal mobility and may benefit from drainage first. In total, we failed to position a balloon during the first procedure in 4%; some patients may accept a second attempt. Although it is difficult to substantiate with hard numbers, it might be wise to delay

the procedure if it seems that it will not be possible to position the trocar in an acceptable position: longer operation times are directly linked to a higher risk for rupture of the membranes.

4. Reestablishment of the airways

There are 2 clinical scenarios: One is that the postoperative course is uneventful, and the patient can be scheduled for planned elective in utero *reversal* of the occlusion, which is now typically set at 34 weeks. This can be accomplished either by ultrasound-guided puncture or, more frequently, by fetoscopy. That time point is based on experimental findings, but clinical data also show at this moment no further increase in survival in fetuses being reversed beyond 34 weeks. Patients presenting with amniorrhexis without labor or infection can be managed similarly. Oligohydramnios may make it more difficult, but amnioinfusion can be considered prior to fetoscopic release. The second intervention may be followed by preterm delivery: spontaneous onset of labor within 7 days after elective removal was approximately 18%.

The other scenario is that the patient presents earlier than planned, with threatening delivery, with or without ruptured membranes. In the published experience, this occurred prior to 34 weeks in 3 of 10 cases. Whenever clinically possible, we try to remove the balloon in utero. If not considered possible or safe, this can also be done at the time of delivery, either when still connected to the placenta or, in the worst scenario, on the resuscitation table. Although we initially performed an ex utero intrapartum treatment procedure, we have moved to balloon extraction while still on the umbilical

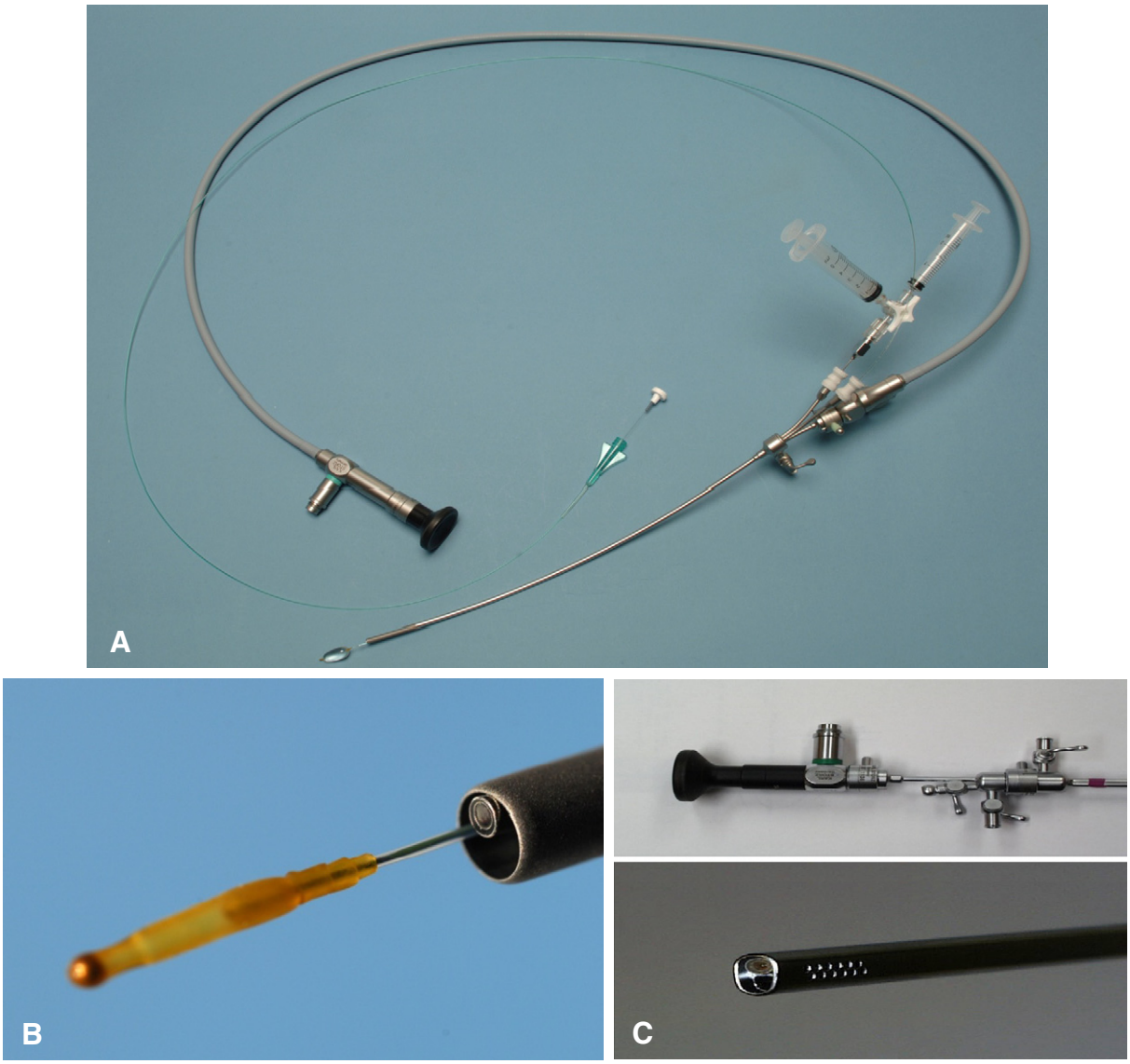

Fig. 2 Instruments used for the FETO procedure and postnatal extraction of the balloon under vision. (A) Curved sheath loaded with 1.3-mm fiber optic fetoscope with deported eye piece and loaded balloon catheter. (B) Detail of balloon catheter with deflated balloon. (C) Postnatal tracheoscope. Partly reproduced from Beck et al [43], with permission from the publisher.

cord during conventional cesarean section under locoregional anesthesia [49]. The conditions are different from when one wants to ensure appropriate and long-lasting placental circulation. The latter should be done under deep inhalational anesthesia, and several additional measures that allow a formal ex utero intrapartum treatment procedure are required [50]. Following FETO, the nature and location of the obstruction and the technique to reverse it are all well identified, such that balloon reversal should take only a matter of seconds. In reality, this is indeed the case if done by a well-prepared team, expecting the situation and having the appropriate instruments. We have also done a limited number of ex utero postnatal extractions, with the purpose-designed tracheoscope (Fig. 2) and some by direct puncture through the neck. Although the latter can be done in a true emergency by physicians unfamiliar with the procedure, it is definitely not recommended. At present, we are working on a new bronchoscope for balloon retrieval. It is a smaller-diameter version of a conventional bronchoscope (which has aspiration and ventilation side openings), with additional working channels for irrigation, forceps, and stylet insertion. It is now being evaluated in animal experiments.

Overall, the most used technique for reversal of occlusion was fetoscopy (50%) (Table 3). For this purpose, the same fetoscope and sheath were used. The balloon can be punctured with a sharp stylet. Inadvertent overintroduction of the stylet (eg, beyond the carina) is avoided by sizing the instrument prior to its use by a Mini-Torquer. Holding the it's tail with a forceps allows later withdrawal of the latex balloon. Ultrasound-guided puncture accounted for 19% of cases. The balloon can then be washed out by the fluid coming from the lungs. This means that a third of patients were managed around the time of delivery. In 21% of cases, this was while still on the umbilical cord; in 7%, it was postnatal. It is important to note that in the published experience, there were several patients who were not managed at one of the FETO centers after balloon insertion.

Table 3 Airway establishment following FETO in 210 consecutive cases

In utero		~70%
Fetoscopy	106	50.5%
Puncture under ultrasound	40	19%
Around the time of delivery		~20%
On placental circulation	14	6.6%
Postnatal puncture	13	6%
Postnatal tracheoscopy	21	10%
Others		
Removal unneeded	16	7.6%
Total	210	

The need for removal may have been obviated typically because of release or because of other reasons, such as in utero fetal death and termination, among others.

We are aware that this is less than ideal. This was because many patients cannot or want not to stay on campus or in town. It might also be because referring institutions engaged themselves for management of the airways around the time of birth. In retrospect, this led to dramatic situations in 10 cases, in which difficulties with balloon removal resulted in or may have contributed to neonatal death. Although we cannot completely estimate what happened in all these individual cases, we believe this adverse outcome may have occurred as frequently as 1 in 5 *unplanned* balloon removals. Therefore, unplanned emergency balloon (this means either its location or the time point) removal should be avoided. Both patients and physicians need to take their responsibilities seriously. At-risk patients (with shortened cervix, ruptured membranes, or preterm contractions) should be identified and stay at the FETO center, or in an institution that can truly offer service for management of the fetal airways 24 h/d 7 d/wk. Since rupture or labor can actually set off at any time, it would be better if all patients are at or close to such an institution. It is our opinion that patients should be encouraged at all costs to stay as close as possible to the FETO center during the occlusion period because the center is experienced with regard to case volume and its engagement to the program and is organized such that there is always a team that can manage fetal airways available. In our center, there are 4 trained individuals available for emergency balloon retrieval, such that failed removal should not occur. To keep the length of stay away from home reasonable, we now propose to remove the balloon at 34 weeks, because there seems to be no measurable increase in survival beyond 34 weeks (Fig. 3). Waiting longer must eventually leads to the sudden need for emergency balloon extraction.

5. Summary of outcomes

The European FETO consortium reported fetal intervention in 210 fetuses with liver herniation and an observed/expected lung-to-head ratio (O/E LHR) <27%-28% (corresponding to an LHR <1.0 in the early third trimester). Preterm premature rupture of the membranes (PPROM) within 3 weeks occurred in 16.7% of cases, which is less than the earlier experience in the trial reported by Harrison et al [51]. Nevertheless, membrane rupture remains the Achilles' heel of fetoscopy [52]. Delivery took place at a median of 35.3 weeks, with 30.9% of patients delivering prior to 34 weeks. Survival rates for left-sided cases only were equal between those delivering at 32-33 weeks and those delivering beyond (approximately 60%; Fig. 3). On the basis of stratified data from the Antenatal CDH Registry, FETO therefore increased survival in severe cases with left-sided CDH from 24.1% to 49.1% and with right-sided CDH from 0% to 35.3% ($P < .001$). The strongest predictors of survival were O/E LHR *prior* to the procedure (odds ratio = 1.490, $P = .019$) and gestational age at delivery (odds ratio = 1.024, $P = .007$).

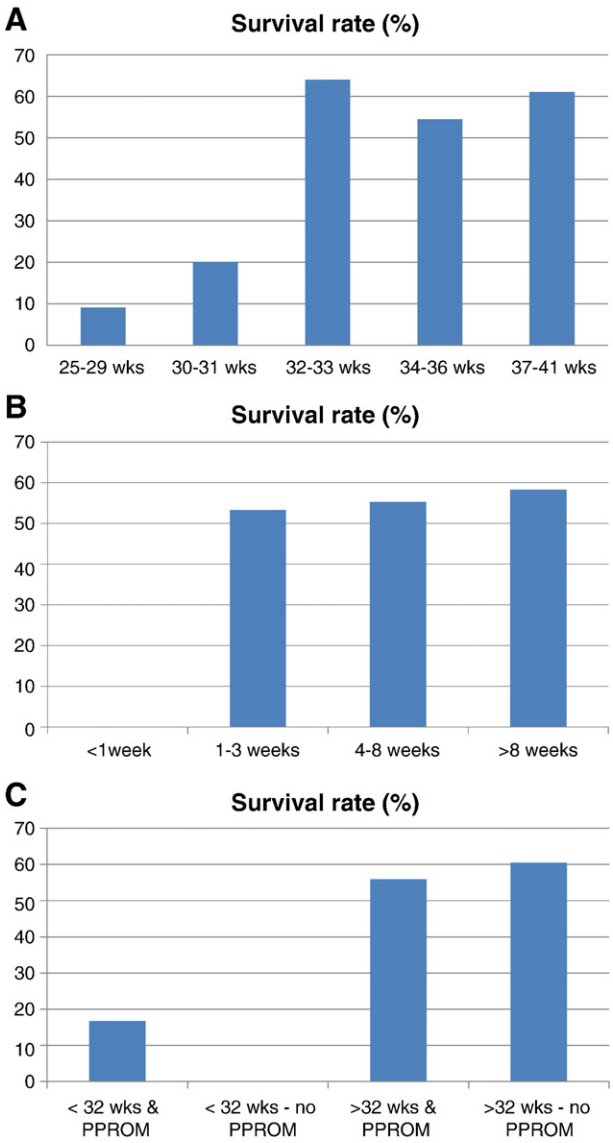

Fig. 3 Graphical displays of effects of (A) gestation at delivery, (B) duration of occlusion on survival rate, and (C) preterm delivery rate with and that without PPROM (n = 161 left-sided CDHs).

PPROM itself, without earlier delivery, did not predict outcome, but it was indeed a predictor of preterm delivery. For right-sided cases, there was no predictor of outcomes identified with the few cases available for analysis. Short-term morbidity in survivors is better than expected: it is close to that of case patients with *moderate* pulmonary hypoplasia who were managed expectantly during pregnancy [53].

Early clinical experience has shown few demonstrable clinical side effects of the balloon on the developing trachea, perhaps except in very early occlusions and complications arising at the time of removal [54]. However, the neonates and infants do have tracheomegaly that does not seem to have an obvious clinical impact, except for a barking cough on effort [54,55]. Over time, the widening seems to become less important [55]. Most newborns require surgical patching of the diaphragm, indicating the rather large size of the defect in this selected group.

6. Membrane rupture and correlogram

Outcome is predicted by lung size and gestational age at delivery. To further study the relationship of predictive factors of outcome, some of which may be controlled or influenced prenatally, we reanalyzed our data set (Table 4) [41]. The results are displayed in the correlogram in Fig. 4. A correlogram is a graphic representation of the statistically significant bivariate relations between all relevant combinations of independent and dependent variables [56]. The strength of a relationship is expressed by means of the R^2 value (%), obtained from linear or logistic regression, displayed along the line. The R^2 value is an approximate measure of the amount of information contained in the dependent variable that is explained by the independent one. The direction of the relation (increasing or decreasing) is obtained from the sign of the slope coefficient of the dependent variable. In all regressions, the individual "fetal surgery center" was included as a covariate in order to control for differences between them. The correlogram is consistent when all paths leading from one variable to another have the same sign, taking into account that plus followed by plus yields plus, minus followed by minus yields plus, and plus followed by minus (or vice versa) yields minus. The level of significance P was set at .01 in order to reduce the chance of obtaining false-positive results.

This way, one can anticipate the nature and the magnitude of an effect to be expected, if one would be able to control selected variables. The strongest effect (52%) in the upper correlogram A, displaying all cases (Fig. 4), is that of gestational age at removal of the balloon on the time point of delivery. Apparently, this second intervention, so to speak, triggers delivery. Later balloon removal, and hence later delivery, has a positive effect on survival (8%). That effect remains when one analyzes the data in cases without PPROM (the Correlogram B, at the bottom). In other words, if there is an option to wait for balloon removal, it might be wise to do so, although removal of the balloon more than 24 hours prior to birth is also a predictor of outcome. Because we did not

Table 4 Relationship with operation time (column 2) and spontaneous rupture (column 3) in 204 consecutive cases of diaphragmatic hernia

n (%)	Duration of FETO (min)	Rupture of the membranes within 3 wk of FETO [n (%)]
111 (54.4)	1-10	12 (10.8)
49 (24.0)	11-20	9 (18.4)
18 (8.8)	21-30	4 (22.2)
26 (12.8)	>30	9 (34.6)

Data from Jani et al [41].

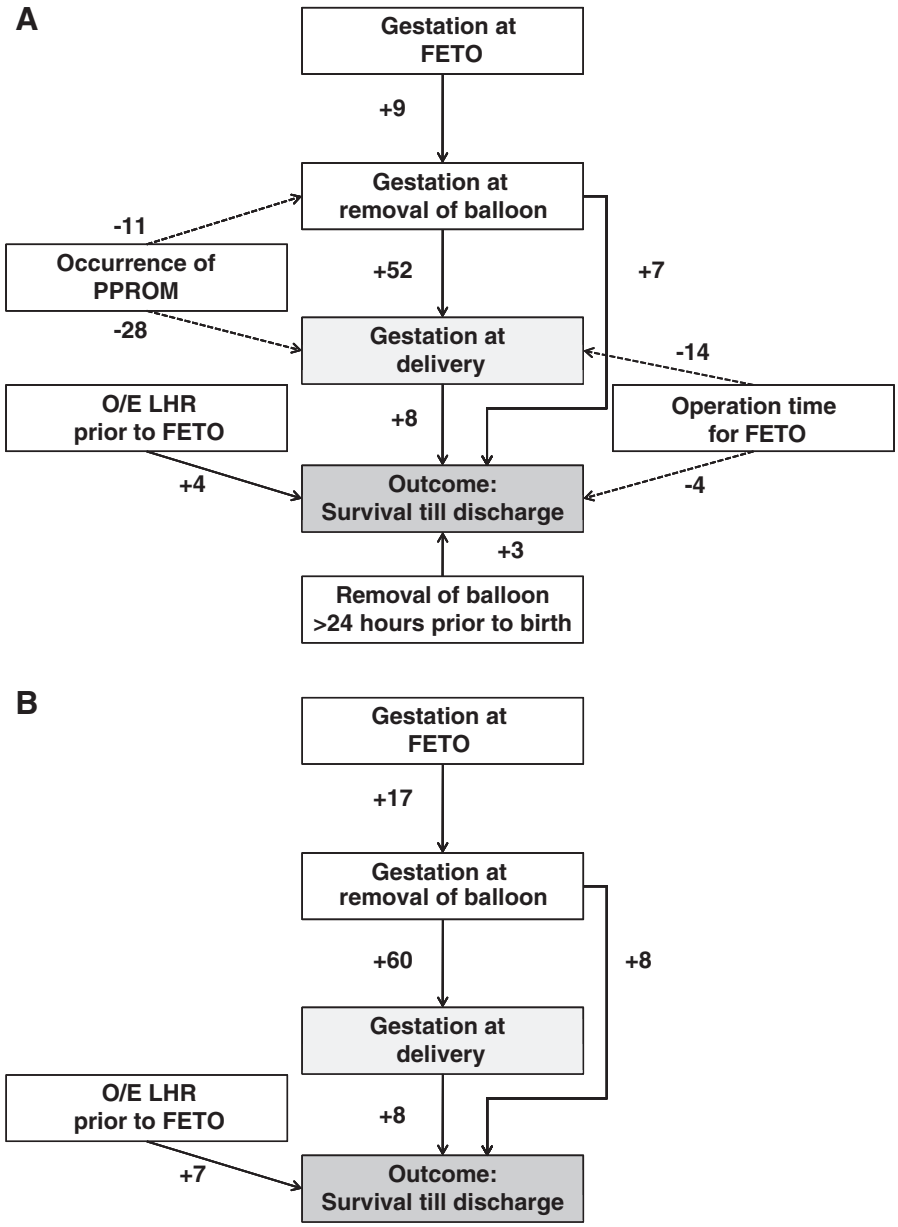

Fig. 4 Correlogram of the interaction between factors that may influence outcome, controlled for the fetal surgery center. (A) Including all data. (B) In case PPROM does not occur. Arrows point from independent to dependent variables. The signs (−, +) indicate the nature of the influence, and the numbers represent R^2 values (%) from linear and logistic regression analyses.

observe a further increase in survival between those born beyond 32 weeks and the likelihood that one may be surprised by an urgent need for removal if waiting until term (mean gestation at birth following FETO is 35 weeks), we ended up with a pragmatic approach of removing the balloon at 34 weeks whenever clinically possible. At that time, the neonate also has a reasonable weight.

Later gestation at balloon insertion has a positive effect on outcome, but there is also an upper limit here. Our experience has also shown that FETO beyond 30 weeks leads to lung a increase in long volume that is less than if FETO would have been done prior to that point [57]. Another observation one can make is that it seems wise to try to reduce operative time as much as possible as it has a negative effect on outcome, probably because it is related to PPROM. Through this, it has an effect on gestational age at delivery and hence survival. Shorter operation times are achievable by having surgeons with experience doing this intervention. Furthermore, one might refrain from attempting the procedure in case of unfavorable fetal position and rather wait for a better opportunity later on.

7. Trials on FETO vs expectant management

FETO has the potential of increasing survival and reducing morbidity. This will now be investigated in formal

trials. Because FETO beyond 30 weeks leads to less demonstrable lung volume increase, we reserve late occlusions to moderate cases, in which less lung volume needs to be gained to allow survival. We have started a trial that tests the hypothesis that FETO will lead to less bronchopulmonary dysplasia in survivors. It compares expectant management during pregnancy with late (30-32 weeks) FETO. For the more conventional indication (ie, fetuses with severe pulmonary hypoplasia), we will compare FETO at 27-30 weeks with expectant management. In all cases, the balloon is removed at 34 weeks' gestation. Postnatal management of this multicenter trial is standardized by a consensus protocol (www.totaltrial.eu). Power calculations have demonstrated that such a study is realistic such that all now depends on the disciplined attitude of the fetal medical community not to offer FETO outside these trials to allow sufficient patient recruitment. Although far from ideal, the multicenter setting accounts for a European reality, with limitations of national boundaries for certain patients or insurance companies, as well as the availability of consistent experience in fetoscopy. The trial in moderate cases has been approved in Leuven, Barcelona and Paris; the trial in severe cases is currently also under investigation by the review boards in London, Paris, Toronto (Canada) and selected US centers, all having an active fetoscopy programme, and (being) trained in the procedure, are investigating potential participation.

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