



Fetal endoscopic tracheal occlusion for congenital diaphragmatic hernia: a narrative review of the history, current practice, and future directions

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Abstract: Fetal intervention for fetuses with congenital diaphragmatic hernia (CDH) has been investigated for over 30 years and is summarized in this manuscript. The review begins with a discussion of the history of fetal intervention for this severe congenital anomaly beginning with open fetal surgery with repair of the anatomical defect, shifting towards tracheal occlusion via open surgery techniques, and finally fetoscopic endoluminal balloon tracheal occlusion using a percutaneous approach. The current technique of fetal endoscopic tracheal occlusion (FETO) is described in detail with steps of the procedure and complementary figures. The main outcomes of single-institutional studies and multiple systematic reviews are examined and discussed. Despite these studies, the fetal community agrees that FETO remains investigational at this time as there is insufficient evidence to recommend it as the standard of care for CDH. A randomized controlled trial, The Tracheal Occlusion to Accelerate Lung Growth (TOTAL) trial, has been designed to attempt to answer this question in an elaborate, international, multi-institutional study and is described in the text. Finally, future directions of fetal intervention for antenatally diagnosed CDH are discussed, including options for non-isolated CDH, the Smart-TO balloon for nonoperative reversal of occlusion, and transplacental sildenafil for treatment of pulmonary hypertension prior to birth.

Keywords: Fetal endoscopic tracheal occlusion (FETO); congenital diaphragmatic hernia (CDH); fetal intervention

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Introduction

Congenital diaphragmatic hernia (CDH) is a defect in the fetal diaphragm that allows organs within the abdomen to migrate into the thorax which leads to a combination of pulmonary hypoplasia and pulmonary hypertension (1,2). The condition arises in the embryonic period, so

that lung development can already be impaired from early in pregnancy (2). It is diagnosed prenatally 68% of the time and in many series the outcome for these fetuses is associated with lower survival and less favorable long-term outcomes than those diagnosed postnatally, especially when diagnosed at an earlier gestational age (3-5). This coincides with larger defect sizes being diagnosed prenatally which

correlate to higher morbidity and mortality (3). Despite advances in neonatal care and resuscitation, survival rates as described by the CDH study group (CDHSG) are 71% when diagnosed prenatally and 83% when diagnosed postnatally (3). The CDHSG was developed in 1995 as a multi-center, international data collection initiative for live-born infants with CDH and used to advance knowledge and develop evidence-based solutions for clinical questions (6,7).

Prenatal ultrasound and fetal magnetic resonance imaging (MRI) are used to estimate lung volumes in the antenatal period and provide anticipatory counseling. Ultrasound utilizes the lung to head ratio (LHR), observed-to-expected lung to head ratio (o/e LHR), the position of the liver as “up” in the thorax versus “down” in the abdomen, and more recently stomach position (8-10). The LHR is calculated by measuring the area of the contralateral lung at the level of the four-chamber view of the heart divided by the head circumference (11). Since the gestational age affects the growth of the lung and head differently, LHR increases with gestational age. Therefore, the o/e LHR was developed based on the expected LHR for a given gestational age which has the advantage of remaining more constant throughout gestation (8). Currently, within the framework of a clinical trial, severe pulmonary hypoplasia is defined as corresponding with an o/e LHR <25% in isolated left-sided cases, correlating with a <20% survival rate (9). Fetal MRI is a useful adjunct in prenatal workup to measure fetal lung volumes with a variety of equations used to calculate “normal” lung volumes for gestational age (12). These are most commonly expressed as observed-to-expected total fetal lung volume (o/e TFLV) or percent predicted lung volume (PPLV) (13,14). An o/e TFLV with a value $\leq 25\%$ and a PPLV <15–25% are predictive of higher mortality (14-16).

There has been much interest and investigation into fetal treatment for CDH given its associated postnatal morbidity and mortality. The objective of this review is to provide the reader with information on the history of fetal intervention for CDH, current fetal endoscopic tracheal occlusion (FETO) practices with reported outcomes, and future directions. For the review of outcomes, we have included studies that were completed in humans with comparison groups and were available in English or with English-translation. We present the following article in accordance with the narrative review reporting checklist (available at <http://dx.doi.org/10.21037/tp-20-130>).

Historical perspective

Due to the severity of the disease and high mortality, Dr. Michael Harrison and his team at the University of San Francisco (UCSF) began the study into fetal treatment of diaphragmatic hernia in the 1990s (17,18). Fetal anatomical repair through maternal laparotomy and hysterotomy, although operatively successful in liver-down CDH, led to increased rates of premature birth and no difference in survival when compared to postnatal repair (19). Open fetal surgery for liver-up CDH, the more severe cohort, was abandoned as it had a high risk of fetal death during the operation due to kinking of the umbilical vein when the liver was returned to the abdomen (18). Due to these outcomes, this strategy was stopped as other strategies for prenatal intervention were explored. It was known that fetuses with congenital high airway obstruction syndrome (CHAOS) had hyperplastic lungs at birth and fetal rabbit studies from 1965 showed that tracheal ligation led to increased lung size (20). Later studies confirmed that tracheal occlusion could lead to improved lung volume as well as functional improvement in the lung in the fetal CDH lamb model (21-25). Animal models also showed a benefit to removing the balloon prior to delivery (plug-unplug sequence) as this normalizes the number of type II pneumocytes in the alveoli which are decreased if tracheal ligation remains until birth (26,27). Therefore, techniques for tracheal occlusion in humans were subsequently developed, including those that were endoscopic and amenable to easy reversal of occlusion, since temporary occlusion is associated with improved lung maturation (26,28,29).

Clinically, sustained tracheal occlusion was originally performed via open hysterotomy. In the first series of eight patients, an external tracheal clip (n=6) or internal foam plug (n=2) was used for occlusion. In this series from UCSF, four fetuses showed dramatic in-utero lung growth despite only a single survivor (30). Interestingly, tracheal damage was most significant with the internal plug as they required tracheotomy for removal while the external clips produced minimal tracheal damage (30). These cases all required an ex utero intrapartum treatment (EXIT) procedure in order to remove the plug or clip on placental bypass prior to full Cesarean delivery (31). Tracheal occlusion was also done via open hysterotomy, neck dissection, and external clip application in 15 patients at the Children’s Hospital of Philadelphia (CHOP) with a survival rate of 33%

(5/15) (32). Although this clinical experience demonstrated that tracheal occlusion induces lung growth, open hysterotomy techniques were plagued with premature birth and therefore fetoscopic tracheal occlusion was investigated (30,33,34). Simultaneously, endoluminal tracheal occlusion was being studied in animal models with a variety of different devices utilized including foam plugs, magnetic valves, a self-expanding umbrella, and, finally, vascular occlusion balloons, all with the purpose to make reversal easy (29,35,36).

Human trials shifted to endoscopic tracheal occlusion after maternal laparotomy, or the Fetendo Clip, as it was originally named (34), and had impressive results in the first 8 patients at the UCSF. This group had a 75% survival rate compared with 15% in the open tracheal occlusion group ($n=13$) and 38% in the postnatal treatment group (33). Given these promising findings, a randomized trial was initiated and recruited pregnant mothers carrying fetuses with liver-up CDH who had isolated CDH and were on the moderate to severe spectrum (LHR <1.4 between 22 and 27 weeks) (37). For this trial, the technique evolved from external metallic clips to the detachable endoluminal balloon following maternal laparotomy using a single port of 4.5mm diameter into the exposed uterus (38). Despite initial excitement, the trial was stopped by the data safety monitoring board after 24 patients due to a higher than expected survival at 90 days of age in the expectantly managed group (8/11, 73%) and no better in the tracheal occlusion group (10/13, 77%) (37). The improved survival in the untreated group was thought to be due to improved perinatal care during the study period and inclusion of fetuses with moderate hypoplasia (LHR 1.0–1.4) (37).

The clinical percutaneous approach to tracheal occlusion was first reported as a single case report by Quintero *et al.* but the infant did not survive due to device failure (39). In Europe, the FETO Task Force developed a percutaneous technique using a 3.3 mm diameter uterine access, initially under general anesthesia and evolving to loco-regional and later local anesthesia (40,41). Their first-in-woman trial used this percutaneous approach and recruited patients with LHR <1.0 between 25 and 29 weeks gestation (42,43). Selection criteria were later modified to correct for gestational age in outcome prediction, hence using the o/e LHR rather than the LHR, which is gestational age dependent (9). In 2009 this consortium reported survival rates increasing from 24.1% (expected) to 49.1% (FETO) in left-sided CDH and from 0% (expected) to 35.3% (FETO) in right-sided CDH (42). A later study confirmed better outcomes in cases of right-sided CDH (44). There is also

some evidence that FETO reduces early neonatal morbidity (45,46). Results from this trial have been criticized, however, as the comparison group was historical rather than contemporaneous and the expected percentages for survival were therefore low. In Brazil, a randomized control trial of FETO versus control for LHR <1.0 showed significant improvement in survival with FETO (10/19, 52.6%) versus controls (1/19, 5.3%) (47). This trial was even more criticized as it merged left and right-sided cases, the balloon was left until delivery, there was an unexplainable difference in the numbers in the treatment group, and the extremely low survival rate in the expectantly managed group (48).

Due to these varying results, the fetal community has agreed that currently there is insufficient evidence to recommend fetal intervention as the standard of care (49,50). The Tracheal Occlusion to Accelerate Lung Growth (TOTAL) trial (www.totaltrial.eu; ClinicalTrials.gov, NCT01240057 and NCT00763737) is a randomized control trial of FETO *vs.* expectant postnatal management followed by standardized postnatal care initiated in Europe, and meanwhile extended to Australia, the United States, and Japan (51). At this time, the severe arm of the trial continues to enroll patients while the moderate arm is completed with enrollment and awaiting final analysis of endpoints.

Procedure description

The current procedure utilizes a fetoscopic approach with a detachable balloon that is placed midgestation and removed around 34 weeks (see *Figure 1*) (41,52,53). Inclusion criteria vary slightly at different centers but typically include singleton pregnancy and isolated CDH with normal chromosomal and no other associated anomalies. The GOLDBAL2 (Balt Extrusion, Montmorency, France) is a latex balloon with a one-way valve that was originally designed for endovascular use. It is used off-label and it measures 7.0×20 mm² when inflated (see *Figures 2,3*) (53,54). The procedure can be performed under local anesthesia with or without maternal sedation and fetal anesthesia (e.g., fentanyl, atropine, and vecuronium, or equivalent neuromuscular blocking agent) to ensure minimal fetal movement. Balloon placement is typically done between weeks 27–29 weeks in severe cases and later (30–32 weeks) for moderate cases (53). A 3.3 mm cannula is placed percutaneously (i.e., through the maternal skin, abdominal wall, and uterus) and directed towards the fetal mouth, taking care to avoid the placenta to gain fetoscopic access. The deflated balloon on the delivery microcatheter

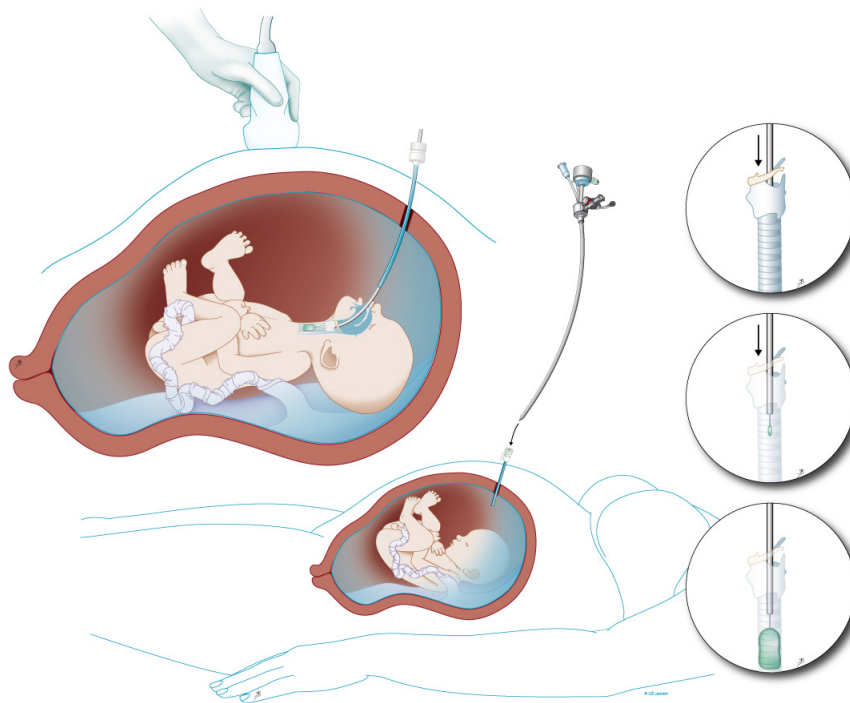


Figure 1 Illustration of fetal endoscopic tracheal occlusion (FETO) procedure with fetoscopic balloon placement. The inset pictures (in circles) represent the fetoscope going into the trachea (top), the advancement of the microcatheter with deflated balloon (middle), and the inflated balloon placed above the carina upon completion (bottom). *Reprinted with permission from “UZ Leuven, Belgium”.*

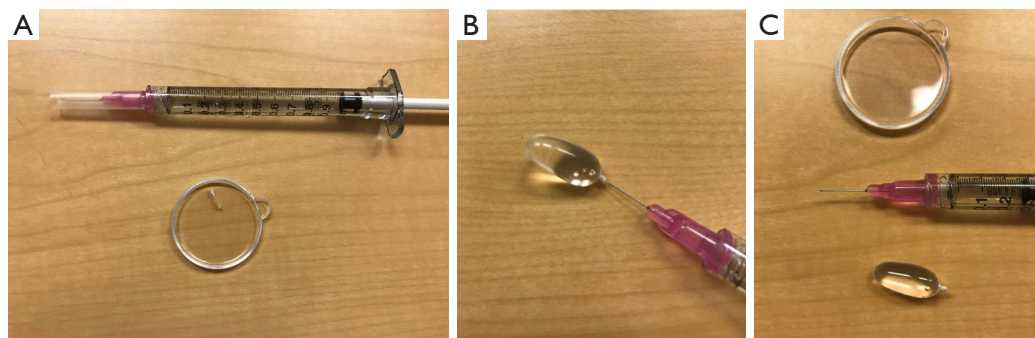


Figure 2 GOLDBAL2 balloon appears the size of a small grain of rice when deflated (A) and is 7×20 mm² when inflated with 0.6 mL of saline (B and C). *Printed with permission from “University of Michigan, Fetal Diagnosis and Treatment Center”.*

(BALTACCI-BDPE100) is preloaded into the fetal tracheoscopic sheath (11540KE; Karl Storz) (see *Figure 3A*). This sheath was designed specifically for FETO and has 3 side ports to allow all necessary equipment to be available for placement and retrieval: camera (11540AA; Karl Storz), balloon with microcatheter, adjustable puncture needle (11506P; Karl Storz), and forceps (11510C; Karl Storz)

(see *Figure 4*). Adequate alignment to the fetal mouth is required and guided with ultrasound (see *Figure 1*). The fetoscope is placed into the fetal mouth and the operator carefully visualizes the tongue, uvula, epiglottis, and vocal cords (see *Figure 5*). Once past the vocal cords, the balloon is positioned above the carina and 0.6 mL of saline is used for inflation. The inflated balloon is detached from



Figure 3 GOLDBAL2 detachable deflated balloon is pulled back into the sheath on the microcatheter (BALTACCI-BDPE100) to begin the operation (A), and the inflated balloon is grasped by its tail (B, ex-vivo balloon grasped) and then punctured with the needle (C, no balloon visualized but needle and grasper seen out the end of the fetoscope). *Printed with permission from “University of Michigan, Fetal Diagnosis and Treatment Center”.*



Figure 4 Equipment needed for the procedure from top to bottom: camera (11540AA; Karl Storz), fetal tracheoscopic sheath with 3 side ports (11540KE; Karl Storz), retrieval forceps (11510C; Karl Storz), and adjustable puncture needle (11506P; Karl Storz), from top to bottom. *Reprinted with permission from “©2020 KARL STORZ Endoscopy-America, Inc.”*

the microcatheter and verification of correct position is completed with ultrasound (53,55).

Ideally, the balloon remains in place until 34 weeks with weekly maternal follow up to monitor for potential deflation of the balloon and complications, most commonly polyhydramnios, chorioamniotic membrane separation, preterm rupture of membranes, chorioamnionitis, or other signs of preterm labor (53). Balloon removal is performed via fetoscopic retrieval, percutaneous puncture using ultrasound-guidance, or tracheoscopic removal on

placental circulation during standard cesarean section or, at last resort, in the immediate neonatal period (56). The method of balloon removal depends upon the expertise at each center, the accessibility of the balloon for ultrasound guided puncture, and the stability of the mother and fetus at the time of removal. The fetus is anesthetized and, for fetoscopic removal, a forceps and an adjustable puncture needle is utilized (*Figure 3B,C*). Once the balloon is removed, the pregnancy can be managed expectantly and women can deliver vaginally.

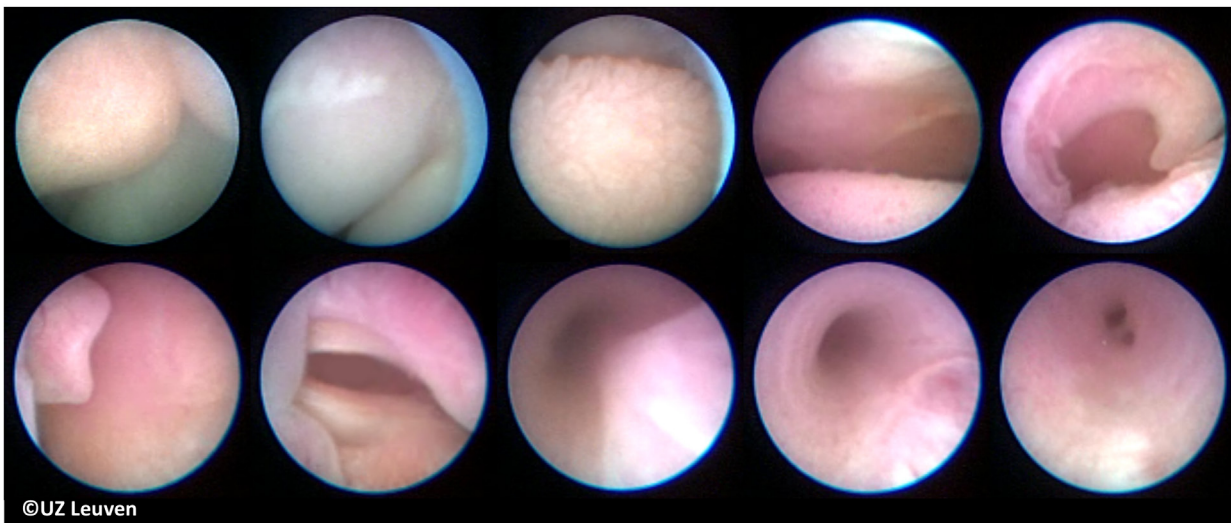


Figure 5 Fetal landmarks visualized during the procedure. Upper images from left to right: tip of nose, upper lip, tongue, raphe palate, and uvula. Lower images from left to right: epiglottis, vocal cords, trachea with bulging pars membrane, more expanded tracheal view, and carina with visible tracheal rings. *Reprinted with permission from “UZ Leuven, Belgium”.*

Outcomes

Despite our current inability to recommend FETO as standard of care as described above, much has been learned from the patients that have undergone this fetal intervention. Lung size increases in a majority of patients and echogenic changes are visualized within 48 hours of balloon placement (40,57). The increase in lung size is dependent on initial o/e LHR and the timing of the occlusion and balloon removal (58,59). The tracheal balloon has local side effects, both on the epithelium and causes widening of the trachea, which decreases with increasing age (52,60). In some patients, a temporary barking cough on effort has been described (61). The gestational age at insertion is also related to the degree of tracheomegaly, and early insertions may cause more clinical problems (62,63).

The most commonly reported neonatal outcomes are survival and gestational age (GA) at delivery with comparative studies consistently reporting earlier GA at delivery for FETO and mixed results around survival (see *Table 1*) (37,40,42,47,57,64-71). A few studies report rates of extracorporeal membrane oxygenation (ECMO) utilization and severe pulmonary hypertension and that neonates who received FETO have lower rates of both (47,65,67,68,71). Other neonatal outcomes (including need for respiratory support and length of stay) are even more scarce but

included in *Table 1* when available.

A couple of recent systematic reviews have attempted to answer questions regarding outcomes (72-75). A 2016 systematic review (total of 5 studies; n=110 FETO and n=101 control) concluded that FETO favored increased survival [OR 13.32 (5.40–32.87)] and associated preterm birth with a mean gestational age of 35.6 weeks (72). A 2017 systematic review including expanded studies (18 studies; n=854 FETO cases) and concluded that preterm birth is a significant complication of FETO with 72% of patients delivering <37 weeks and nearly 18% delivering <32 weeks (73). Premature rupture of membranes has been seen in nearly 47% of cases while chorioamnionitis and placental abruption was recorded in 2.6% and 1.2% of cases, respectively (73). The authors also concluded that FETO increased neonatal survival at 30 days [RR 5.8 (1.5–22.9) days] and 6 months [RR 10.5 (1.5–74.7) months] but led to a higher rate of premature rupture of membranes [RR 1.7 (0.8–2.4)] and decreased gestational age at delivery by nearly 2 weeks (73). In a 2019 systematic review on maternal complications of fetoscopic surgery (122 studies; n=9,403 patients), the rate of complications was 6.15% (4.93–7.49%), including abruption as the most common severe complication (1.29%) with most being minor complications (4.33%) (74). Despite these reviews, critics question the validity given that data is coming

Table 1 List of consecutive FETO studies with outcomes of intervention (FETO) versus control (CTR)

Author/study type	Patient inclusion criteria	FETO timing	Control (CTR)	Neonatal outcomes
Harrison 2003 (37), Randomized control trial	LCDH: LHR <1.4, Liver up	22–27 weeks (n=11)	Contemporary, matched (n=13)	Survival at 90 days: FETO (77%) = CTR (73%); P=1.0 GA at Delivery: FETO (30.8 wks) < CTR (37.0 wks); P<0.001
Deprest 2004 (40), Case-control	LCDH and RCDH: LHR <1, Liver up	25–33 weeks (n=21)	Contemporary, not matched (n=12)	Survival at discharge: FETO (48%) > CTR (8%); No P value
Deprest 2006 (64), Case-control	LCDH: LHR <1, Liver up	26–28 weeks (n=24)	Contemporary, not matched (n=37)	Survival at discharge: FETO (50%) > CTR (9%); No P value
Jani 2009 (42), Case-control	Any CDH: LHR <1, Liver up	23–33 weeks (n=210)	Predicted survival of expectantly managed fetuses based on regression equation	Survival at discharge: LCDH: FETO (49%) > CTR (24%); P<0.001 RCDH: FETO (35%) > CTR (0%); P<0.001
Peralta 2011 (57), Case-control	LCDH: LHR <1, Liver up	(n=28)	Contemporary, matched (n=13)	Survival at discharge: FETO (36%) > CTR (0%); P=0.012
Ruano 2011 (65), Case-control	LCDH and RCDH: LHR <1, Liver up	26–30 weeks (n=17)	Contemporary, matched (n=18)	Survival at 28 days: FETO (53%) > CTR (6%); P<0.01 GA at delivery: FETO (35.6wks) = CTR (37.5wks); P=0.18 Severe pulmonary hypertension: FETO (47%) < CTR (89%); P=0.01
Ruano 2012 (47), Randomized control trial	LCDH and RCDH: LHR <1, Liver up	26–30 weeks (n=20)	Contemporary, matched (n=21)	Survival at 6 months: FETO (50%) > CTR (5%); P<0.01 GA at Delivery: FETO (35.6 wks) < CTR (37.4 wks); P<0.01 Severe pulmonary hypertension: FETO (50%) < CTR (86%); P=0.02
Ali 2016 (66), Case-control	L CDH: LHR <1 R CDH: Liver up	23–32 weeks (n=43)	Contemporary, not matched (n=35) Note: higher LHR at referral despite similar LHR at birth	Survival: FETO (44%) = CTR (63%); P=0.30 GA at Delivery: FETO (34 wks) < CTR (38 wks); P<0.001
Belfort 2017 (67)*, Case-control	L CDH: LHR <1, liver up	25–29 weeks (n=11)	Historic, matched (n=34)	Survival at 2yrs: FETO (67%) > CTR (11%); P=0.04 ECMO utilization: FETO (30%) < CTR (70%); P=0.05
Dhillon 2018 (68)*, Case-control	L CDH: o/eTFLV <32%, %LH >21	26–29 weeks (n=12)	Contemporary, matched (n=28)	Survival: FETO (67%) = CTR (61%); P=1.00 GA at Delivery: FETO (35.6 wks) < CTR (38.2 wks); P<0.01

Table 1 (continued)

Table 1 (continued)

Author/study type	Patient inclusion criteria	FETO timing	Control (CTR)	Neonatal outcomes
				ECMO utilization: FETO (33%) < CTR (89%); P<0.01
Rodó 2018 (69), Case-control	L CDH: LHR<1, o/eLHR <45%, liver up	<32 weeks (n=20)	Contemporary, not matched (n=38) Note: only 35% with liver up	Survival: FETO (60%) < CTR (87%); P=0.02 GA at Delivery: FETO (34.7 wks) < CTR (38.7 wks); P<0.01
Morandi 2019 (70), Case-control	L CDH: o/eLHR <25% R CDH: o/eLHR <35%	26–31 weeks (n=30)	Contemporary, not matched (n=41) Note: higher initial LHR despite similar final LHR	Survival at Follow-up (mean 34.2 months): FETO (43%) < CTR (83%); P=0.008 GA at Delivery: FETO (35.5wks) < CTR (38.2wks); P<0.001 Respiratory Support (Total Invasive + Non-invasive): FETO (39.8 days) = CTR (27.8 days); P=0.14 LOS: FETO (80.4 days) > CTR (45.5 days); P=0.007
Style 2019* (71), Case-control	L CDH or RCDH: o/eTFLV<32% %LH >21%	22–30 weeks (n=16)	Contemporary, matched (n=25)	Survival at discharge: FETO (81%) = CTR (60%); P=0.454 GA at Delivery: FETO (35.3wks) < CTR (38.0wks); P=0.001 ECMO Utilization: FETO (44%) < CTR (84%); P=0.011 Severe pulmonary hypertension (need for iNO): FETO (88%) = CTR (92%); P=0.968 LOS: FETO (78 days) = CTR (79 days); P=0.338 Resolution of pulmonary hypertension at 1 year: FETO (69%) > CTR (28%); P=0.017

*, partially overlapping. GA, gestational age; wks, weeks; LOS, length of stay; %LH, percent liver herniation; ECMO, extracorporeal membrane oxygenation; iNO, inhaled nitric oxide.

from the same groups and were not properly controlled.

The TOTAL trial results are expected in the near future and many are anxiously awaiting the results. However, there have been concerns regarding the slow enrollment and leakage of patient's out of the trial (76). Despite these limitations, this will be the largest randomized control trial of fetal therapy to date and includes contemporary, matched controls. Together with standardization of CDH management and improvement of postnatal resuscitation, fetal intervention remains an exciting adjunct of care for this complex disease (40,52,57–63).

Future directions

Currently FETO is being offered for cases of isolated CDH, i.e., without associated fetal anomalies, due to the experimental nature of the procedure. Some have argued for expansion to include other anomalies as 25% of fetuses have other organ anomalies, most commonly cardiac defects or congenital lung lesions (77). A single institution demonstrated favorable outcomes when including selective non-isolated cases of severe CDH utilizing a compassionate use exemption, including a single case of Tetralogy of Fallot

identified post-balloon and congenital lung lesion identified prior to procedure (77). If the TOTAL trial demonstrates efficacy for FETO in isolated CDH, there may be rationale for expanding inclusion criteria to patients with certain additional anomalies.

A new “Smart-TO” balloon is in development that would avoid the need for a second procedure for puncture and retrieval of the balloon. This balloon utilizes a magnetic valve that can be activated in the fringe magnetic field of an MRI machine (78). The tracheal effects are similar to those of the currently used BALT balloon (79).

Although data suggests that tracheal occlusion stimulates lung growth, there is no convincing evidence that there is also concomitant vascular growth and remodeling, that might ameliorate pulmonary hypertension. Pulmonary hypertension is the second most important cause of death for these patients. Transplacental sildenafil, a phosphodiesterase-5 inhibitor, has been shown effective in several animal models (80,81). It is currently being tested in a phase I trial and may work synergistically with tracheal occlusion (82,83). Obviously, a pharmacologic approach would make prenatal therapy much more widely accessible (55).

Conclusions

There has been much work done within the past 40 years to study fetal intervention for CDH. This review focuses on what is known to date with reported outcomes of human trials and includes a look into future directions.

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