Original Research

Single-Center Outcome of Fetoscopic Tracheal Balloon Occlusion for Severe Congenital Diaphragmatic Hernia

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OBJECTIVE: To assess feasibility and maternal and infant outcome after fetoscopic tracheal balloon occlusion in patients with severe congenital diaphragmatic hernia.

METHODS: We conducted a prospective cohort study of fetuses with congenital diaphragmatic hernia and observed/expected lung/head ratio less than 30%. Eligible women had planned fetoscopic tracheal balloon occlusion at 26 0/7–29 6/7 weeks of gestation and balloon removal 4–6 weeks later. Standardized prenatal and postnatal care was at a single institution. Fetoscopic tracheal balloon occlusion details, lung growth, obstetric complications, birth outcome, and infant outcome details until discharge were evaluated.

RESULTS: Of 57 women screened, 14 (25%) were enrolled between 2015 and 2019. The congenital diaphragmatic hernia was left in 12 (86%); the pre–fetoscopic tracheal balloon occlusion observed/expected lung/head ratio was 23.2% (range 15.8–29.0%). At a median gestational age of 28 5/7 weeks (range 27 3/7–29 6/7), fetoscopic tracheal balloon occlusion was successful in all cases, and balloons remained in situ. Removal was elective in 10 (71%) patients, by ultrasound-guided needle puncture in eight (57%), and occurred at a median of 33 4/7 weeks of gestation (range 32 1/7–34 4/7; median occlusion 34 days, range 17–44). The post–fetoscopic tracheal balloon occlusion observed/expected lung/head ratio increased to a median of 62.8% (44.0–108) and fell to a median of 46.6% (range 30–92) after balloon removal (all Mann Whitney U, $P<.003$). For prevention of preterm birth, all patients received vaginal progesterone; 11 (79%) required additional tocolytics, three (21%) had vaginal pessary placement for cervical shortening, and five (36%) had amnioreduction for polyhydramnios. Median gestational age at birth was 39 2/7 weeks (range 33 6/7–39 4/7), with term birth in eight (57%) patients. Twelve (86%) neonates required high-frequency ventilation, and seven (50%) required extracorporeal membrane oxygenation for a median of 7 days (range 3–19). All neonates needed patch repair. Neonatal survival was 93% (n=13, 95% CI 49–100%), and survival to hospital discharge was 86% (n=12, 95% CI 44–100%).

CONCLUSION: Fetoscopic tracheal balloon occlusion for severe congenital diaphragmatic hernia was feasible in our single-center setting, with few obstetric complications and favorable infant outcome.

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See related editorial on page 509.

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Each author has confirmed compliance with the journal's requirements for authorship.

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Congenital diaphragmatic hernia is the result of partial or complete absence of the diaphragm, which allows the prenatal herniation of abdominal contents into the chest cavity, leading to impaired fetal

lung growth and development.[1] Congenital diaphragmatic hernia complicates approximately 1 in 3,000 births and is associated with significant early neonatal mortality, primarily attributable to neonatal respiratory failure as a consequence of pulmonary hypoplasia and pulmonary hypertension.[2–4] The severity of pulmonary compromise and the associated postnatal risk profile is proportional to the degree of prenatal lung compression and can be estimated by prenatal ultrasound scan.[5] A prenatal ultrasound measurement of the observed/expected lung/head ratio derived from the traced outline measurement of the contralateral lung provides the most reliable assessment of contralateral lung compression.[6] A prenatally measured observed/expected lung/head ratio less than 25% and intrathoracic liver herniation identifies patients considered to have a severe congenital diaphragmatic hernia.[5] These patients have large defects requiring patch repair and are at highest risk for abnormal lung development, postnatal mortality, and feeding problems.[7,8] Standardized postnatal management strategies in congenital diaphragmatic hernia focus on gentle ventilation, including high-frequency oscillatory ventilation, pulmonary vasodilators, and extracorporeal membrane oxygenation (ECMO). Although this has improved outcomes overall, a severe congenital diaphragmatic hernia with an observed/expected lung/head ratio of less than 25% and intrathoracic liver herniation is expected to have a survival rate less than 20% with standard postnatal therapy irrespective of hernia laterality.[4,5,7–9] In more recent postnatal cohorts of severe congenital diaphragmatic hernia with diaphragmatic agenesis, survival of up to 60% has been reported but with little improvement in outcome in recent years when compared with milder forms of congenital diaphragmatic hernia.[10] Accordingly, there have been substantial efforts to develop antenatal interventions for these patients at highest risk of mortality and severe morbidity.[11]

Temporary fetoscopic tracheal occlusion (FETO) is an experimental prenatal treatment strategy for patients with congenital diaphragmatic hernia that evolved from clinical observations that fetal laryngeal atresia results in larger lungs and from animal experiments that confirmed that prenatal tracheal occlusion experimentally reverses pulmonary hypoplasia.[12] The lung stretch that is the consequence of lung fluid accumulating in the bronchial tree, activates a pathway of proliferation and increased growth in the airways and lung vasculature.[13] Once this process has been initiated, reversal of tracheal occlusion before birth is required to avoid excessive type II pneumocyte loss and to produce an optimal balance between type I and II pneumocytes.[14] In fetuses with severe congenital diaphragmatic hernia, FETO is typically performed between 27 and 29 weeks of gestation, and balloon removal is scheduled at 34 weeks of gestation based on experimental evidence.[15] Feasibility studies have demonstrated that, compared with historic controls, FETO increases survival rate from 24% to 49% in left congenital diaphragmatic hernia with an observed/expected lung/head ratio of less than 25% and from 17% to 42% in right congenital diaphragmatic hernia with an observed/expected lung/head ratio of less than 45%.[10,16] The benefits of FETO are partly offset by the risks of preterm prelabor rupture of membranes (PROM) in 47% of cases, preterm birth before 34 weeks of gestation in 31% of cases, an average delivery gestational age of 35 weeks of gestation and the need for emergent peripartum balloon removal in 30% of cases.[10] A randomized controlled trial of FETO treatment for severe congenital diaphragmatic hernia is currently enrolling in European and U.S. centers (NCT01240057). For U.S. centers to participate in this trial, feasibility of FETO was required to be evaluated under a U.S. Food and Drug Administration (FDA) investigational device exemption. The goal of this study was to determine feasibility of FETO in a severe congenital diaphragmatic hernia cohort managed in a single center. Our hypothesis was that FETO would result in higher-than-expected survival and significant prenatal lung growth without an increase in procedure-related complication rates over those reported in the literature.

METHODS

This is a prospective cohort study that evaluated all patients with a suspected diagnosis of congenital diaphragmatic hernia for eligibility to undergo FETO between May 2015 and June 2019. Evaluation included detailed fetal ultrasound examination and fetal echocardiography using a high-resolution ultrasound system (4–8 MHz transducers; Voluson E10). Gestational age was determined by last menstrual period or an early ultrasound examination. Estimated fetal weight was calculated based on measurement of the fetal head circumference, abdominal circumference, and femur length.[17] All patients with a confirmed diagnosis of congenital diaphragmatic hernia had ultrasound measurement of the traced contralateral lung outline in millimeters using at the level of the cardiac four-chamber view.[18] Based on the paired measurements of fetal head circumference and the contralateral lung area, the observed/expected lung/head ratio was calculated using the open access online

TOTAL trial calculator (https://totaltrial.eu). In addition, contents of the ipsilateral chest were determined including the presence or absence of intrathoracic liver herniation. All patients that considered study participation were informed that a normal fetal karyotype was an inclusion criterion with the option to undergo fetal cytogenetic testing with their referring providers or at our center. Those meeting eligibility requirements received information about the trial and were offered participation.

Enrollment criteria changed over the study period. The primary FDA investigational device exemption and study protocols were restricted to patients with left-sided congenital diaphragmatic hernia that had an observed/expected lung/head ratio less than 25% and intrathoracic liver herniation. In March 2017, a second arm was added for less severe left congenital diaphragmatic hernia cases with an observed/expected lung/head ratio between 25% and less than 30% and intrathoracic liver herniation. In June 2017, a third arm was added for right congenital diaphragmatic hernia with an observed/expected lung/head ratio of less than 30%. Patients with severe congenital diaphragmatic hernia who had any modifying circumstances required an individual compassionate use application to the Institutional Review Board and the FDA. The additional eligibility criteria were: 1) patient older than 18 years of age with a singleton pregnancy; 2) absence of major additional fetal anomaly; 3) normal fetal karyotype by invasive testing; 4) absence of maternal contraindication to fetoscopic surgery, including the absence of adequate intrauterine access; and 5) maternal agreement to comply with the care path for FETO, that is, specifically to remain within a 30-minute access radius to the Center for Fetal Therapy while the balloon was in place and willingness to deliver at our institution and receive neonatal care until discharge. Exclusion criteria were: 1) severe maternal medical condition, 2) uterine anomaly strongly predisposing to preterm labor, 3) placenta previa, 4) preterm labor or cervical shortening less than 15 mm within 24 hours before FETO, 5) risk of emotional interference of maternal depression in the consent process as measured by a Beck Inventory score of 17 or higher, or 6) maternal latex allergy.

All patients signed informed written consents for FETO and subsequent neonatal follow-up. For women residing further than 30 minutes from the Center for Fetal Therapy, the study social worker facilitated the identification and procurement of appropriate accommodations throughout the maternal and neonatal treatment period as dictated by individual family needs.

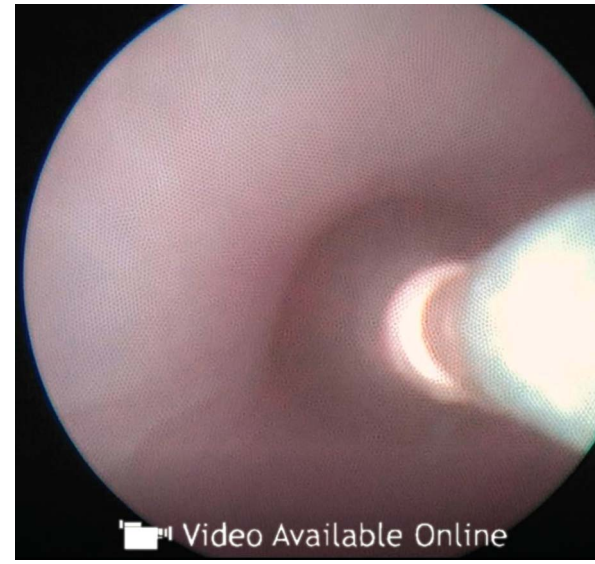
Before study initiation, the primary investigator (A.A.B.) underwent training at European FETO feasibility study sites and also participated in a dedicated training course at Center for Surgical Technologies at the Catholic University Leuven. In preparation for individual cases, the team performed simulation training on a purpose-developed model to maintain competency.[19] The fetal therapy team (A.A.B., M.R., J.L.M) performed the FETO procedure, prenatal care, and obstetric management. Before enrollment, parents received multidisciplinary consultation with a Neonatologist, Pediatric Surgeon, and Pediatric Intensivist, and were provided with written information about the pathophysiology and health effects of congenital diaphragmatic hernia. Once enrolled, patient progress throughout the pregnancy, including any anticipated postnatal care considerations, were communicated to the multidisciplinary team in regular or ad hoc meetings. From the time of balloon insertion, a multidisciplinary team of fetal therapists, neonatologists, pediatric surgeons, pediatric otorhinolaryngology, and obstetric and pediatric anesthesiologists was available for emergent balloon removal or securing patency of the neonatal airway.[20] In addition, all patients were provided with a laminated fetal alert card with all pertinent information to present anytime they were seeking medical evaluation.

Given the importance of gestational age at birth and the paucity of clinical trials to inform the best obstetric management practices for women undergoing fetal intervention, we made several pragmatic decisions regarding the prenatal management of preterm birth risks. All patients were initiated on vaginal progesterone 200 mg daily before FETO. After exclusion of preterm labor, cervical shortening less than 25 mm was treated by insertion of a cervical pessary based on the potential for pregnancy prolongation in patients undergoing operative fetoscopy.[21] Symptomatic preterm contractions were treated with nifedipine or indomethacin tocolysis. To avoid unnecessary invasive procedures, the need for amnioreduction for polyhydramnios was not based on a maximal fluid pocked cutoff,[14] but rather on the presence of associated uterine activity or cervical shortening. Two courses of betamethasone were planned for all patients coincident with FETO and balloon removal.

Fetoscopic tracheal occlusion was performed between 26 0/7 and 29 6/7 weeks of gestation by either of two operators with the other assisting (A.A.B. or J.L.M.). After administration of maternal neuraxial or local analgesia, fetal anesthesia was administered

by ultrasound-guided percutaneous or intravenous injection. Medication doses were based on estimated fetal weight and included fentanyl 3 micrograms/kg, atropine 40 micrograms/kg and rocuronium 0.7 mg/kg. After paralysis was verified by ultrasound examination, the fetus was externally manipulated to position the face toward a placenta-free window in the fundus of the uterus to allow fetoscopic access to the oropharynx. If there was no placenta-free window near the fundus, the port was inserted in the lower uterine segment. The optimal insertion site was for the fetoscope to point at the tip of the fetal nose.[14] Standard obstetric external version maneuvers were used to manipulate the fetus into a position that allowed this through an upper uterine insertion. A sterile, thin-walled, flexible, nonstick cannula (10 French or 3.3 mm), loaded with a pyramidal trocar (11650TG) was inserted percutaneously into the amniotic cavity using ultrasound guidance. After withdrawal of the trocar, a curved fetoscopic sheath (3.3 mm outer diameter, 11540 KE), preloaded with a 1.3 mm, 0° fetoscope (17,000 pixels, 11540 AA) and the delivery catheter loaded with a 1.5 mm detachable latex balloon was inserted. The sheath was advanced into the fetal mouth under direct visualization. Once in the mouth, the fetoscope was guided into the trachea following the landmarks of the midline raphe of the pharynx, the uvula and epiglottis, the arytenoid folds and the vocal cords. Once the trachea was entered, the main bronchi were visualized, and the balloon was inflated with 0.8 mL of normal saline halfway between the carina and the vocal cords and detached from the delivery catheter (Video 1). Before withdrawal of the nonstick sheath, amnioreduction was performed if polyhydramnios was present. After FETO, the magnesium dose was titrated to achieve fewer than six contractions per hour, and the patient remained on bed rest until the next day. Indomethacin 25–50 mg every 6 hours was administered for breakthrough contractions. Follow-up ultrasound examination was performed the next day to verify balloon placement, evaluate for chorioamniotic separation, and measure cervical length.

After FETO, participants were instructed to remain on reduced activity for 2 weeks, after which time they could gradually increase to normal activity in the absence of symptomatic uterine activity. Weekly examinations were performed until delivery for ultrasound verification of intratracheal balloon placement, measurement of the observed/expected lung/head ratio, assessment of amniotic fluid volume and membrane status, fetal biometry, and cervical length measurement. Participants were clinically assessed for evidence of preterm labor at each visit, and weekly nonstress testing surveillance was initiated at 32 weeks of gestation. Preterm contractions were treated with nifedipine 10 mg orally every 6–8 hours. Indomethacin 25 mg every 6–8 hours was used up until 34 weeks of gestation for breakthrough contractions in patients on Nifedipine in whom further dose escalation was not possible owing to maternal hypotension.



Video 1 Fetoscopic tracheal balloon occlusion. The video shows the oropharynx and trachea of a fetus at 28 weeks of gestation undergoing fetoscopic tracheal balloon occlusion for a severe congenital diaphragmatic hernia. The fetoscope is advanced from the mouth into the trachea guided by the anatomic landmarks as shown in the video. Video created by Ahmet Baschat, MD. Used with permission.

Elective balloon removal was scheduled for 6 weeks after occlusion or by 34 6/7 weeks of gestation. Balloon removal was performed either by ultrasound-guided balloon puncture using a 20-gauge needle if considered feasible by the operator, or by repeat fetoscopy using the same approach as balloon placement. Needle puncture was attempted when there was

Scan this image to view Video 1 on your smartphone.

no vital structure in the path of the needle to the balloon and when this path could be continuously imaged by ultrasound scan. After balloon removal, patients could return to their home residence, regardless of distance from our facility, with the expectation that they would return to deliver at our facility. The timing and mode of delivery was based on obstetric indications. In the absence of spontaneous labor, induction of labor was scheduled by 40 weeks of gestation to prevent spontaneous delivery outside the treatment center.

All neonates were managed and treated at our facility by a prospectively defined congenital diaphragmatic hernia management protocol (Appendix 1, available online at http://links.lww.com/AOG/B719). This protocol prioritized gentle ventilator management strategies to avoid barotrauma, including limiting the peak inspiratory pressure delivered using a conventional ventilator, use of high frequency oscillatory, permissive hypercapnia, and lower PaO_2 targets. We optimized the treatment of pulmonary hypertension using multiple agents, including pulmonary vasodilators (inhaled nitric oxide, sildenafil, epoprostenol sodium [Flolan], sedatives, analgesics, and inotropes). Paralytic agents were avoided when possible. For hypoxic respiratory failure refractory to medical management alone, we used standardized criteria to facilitate the coordinated transition to ECMO for ongoing cardiopulmonary support. Timing of surgical repair was at the discretion of the managing pediatric surgeon. At surgery, defect size was classified according to Tsao and Lally.[22]

We defined the enrollment and study criteria prospectively in a protocol that was approved for the investigational device exemption by the FDA and the Institutional Review Board of the Johns Hopkins University. The inclusion criteria were extended to an observed/expected lung/head ratio of less than 30% based on unpublished communication between several U.S. congenital diaphragmatic hernia centers with the FDA that, in a contemporaneous congenital diaphragmatic hernia cohort, survival significantly drops below this threshold. The trial was registered at clinicaltrials.gov (NCT02710968).

After enrollment, all study data points and their source documentation were ascertained by the primary investigator or dedicated research personnel in the center and entered into a dedicated REDCap database.

The primary study endpoint was successful insertion and removal of the tracheal occlusion balloon before birth. The secondary study endpoints were neonatal survival at 28 days of life and percentage of contralateral lung size increase after tracheal occlusion (clinicaltrials.gov; NCT02710968). To assess the primary study endpoint, we recorded the procedural details at balloon insertion and removal including number of attempts, specifics of the technique, and procedure-related complications. To assess lung growth, the pre-FETO observed/expected lung/head ratio, highest observed/expected lung/head ratio during occlusion (post-FETO observed/expected lung/head ratio) and after balloon removal (postremoval of the observed/expected lung/head ratio) were compared. To assess survival, we recorded the number of neonates alive on day 28 as well as the number of infants alive at discharge or at 6 months (whichever was sooner). Additional variables evaluated included the need for obstetric interventions, incidence of preterm labor, preterm PROM, chorioamnionitis, abnormal amniotic fluid indices, preterm birth, and delivery gestational age. After birth, we recorded the defect size, day of surgery, type of repair, presence of severe pulmonary hypertension diagnosed by transthoracic echocardiography, need for and number of days on ECMO support, days on ventilator support, and mode of ventilation. Descriptive statistics included absolute numbers and frequencies for categorical variables and median and ranges for continuous variables. The FDA recommended enrollment of at least 10 patients with left congenital diaphragmatic hernia for the feasibility with the option to enroll an additional five patients under a compassionate request. Lung growth was analyzed using the Mann Whitney U test with a significance level set at <0.05. Comparison of the rank scores was conducted to analyze for ties. SPSS 24.0 was used for analysis.

RESULTS

During the study period, 57 patients were evaluated and 14 (25%) were enrolled in the study (11 under the primary investigational device exemption and three with an individual compassionate use application [cases 1, 2, and 14]; Table 1 and Fig. 1). Participants were predominantly Caucasian and nulliparous, had a median age of 33 years and a body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) of 26, respectively (Table 2). None had a history of prior preterm birth. All fetuses had an observed/expected lung/head ratio less than 30% (median 23.2, range 15.8–29.0) and intrathoracic liver herniation ("liver up"). Fetoscopic tracheal occlusion was performed at a median gestational age of 28 5/7 (27 3/7–29 6/7) weeks of gestation and successful in all cases. Three procedures (21.4%) required a second tracheal entry for balloon insertion. The median procedure length for balloon insertion was 11 minutes.

Table 1. Individual Case Characteristics of Patients Undergoing Fetoscopic Tracheal Occlusion

Case No.	CDH Side	Anomalies	Pre-FETO O/E LHR	Pre-FETO CL (mm)	GA at FETO (wk)	GA at Balloon Removal (wk)	Obstetric Complication	GA at Delivery (wk)	Delivery Indication and Route	1- and 5-Min Apgar Score	Cord Artery pH	Infant Outcome
1	Right		29	37.0	29 6/7	34 3/7		38 5/7	IOL, CD	1.4	7.34	Alive at D/C
2	Left	Left CPAM	22.6	25.9	29 3/7	33 1/7	PTL	35 3/7	PTL, SVB	2.5	7.34	Alive at D/C
3	Left	TOF	21.2	42.1	28 6/7	33 4/7	Preterm PROM, PTL	36 4/7	PTL, SVB	1.5	7.31	Alive at D/C
4	Left		18.7	37.3	29 2/7	33 3/7	PTL	34 0/7	PTL, SVB	3.6	7.27	Alive at D/C
5	Left		24.8	39.8	28 5/7	33 5/7		39 4/7	IOL, SVB	6.7	7.38	Alive at D/C
6	Left		24.9	32.8	27 5/7	33 3/7		39 3/7	IOL, CD	4.9	7.38	Alive at D/C
7	Left		24.8	44.0	28 5/7	34 5/7		39 0/7	IOL, SVB	7.8	7.35	Death, day 70
8	Left		23.6	48.7	27 5/7	33 5/7		39 2/7	IOL, CD	5.9	7.27	Alive at D/C
9	Right		27.2	49.0	28 3/7	33 6/7	Preterm PROM, PTL	33 6/7	PTL, CD	2.5	7.25	Alive at D/C
10	Left		22.3	38.4	28 4/7	32 1/7		39 3/7	IOL, SVB	3.6	7.28	Death, day 14
11	Left		15.8	30.0	29 0/7	32 4/7	Preterm PROM, PTL	34 2/7	IOL, SVB	3.6	7.32	Alive at D/C
12	Left		22.6	33.0	27 0/7	33 2/7		39 2/7	IOL, SVB	4.8	7.28	Alive at D/C
13	Left		23.1	43.0	28 5/7	32 4/7	Preterm PROM	36 4/7	IOL, SVB	6.8	7.29	Alive at D/C
14	Left	Left CPAM	23.2	27.3	29 5/7	34 5/7		39 3/7	IOL, FAVB	5.8	7.34	Alive at D/C

CDH, congenital diaphragmatic hernia; FETO, fetoscopic tracheal occlusion; O/E LHR, observed/expected lung/head ratio; CL, cervical length; GA, gestational age; IOL, induction of labor; CD, cesarean delivery; D/C, hospital discharge; CPAM, congenital pulmonary airway malformation; PTL, preterm labor; SVB, spontaneous vaginal birth; TOF, tetralogy of Fallot; PROM, prelabor rupture of membranes; FAVB, forceps-assisted vaginal birth.

There were no procedure-related maternal complications such as uterine wall bleeding or chorioamnionitis.

None of the patients experienced spontaneous balloon deflation. In one case, tetralogy of Fallot was diagnosed after balloon placement (case 3).[23] There were two cases with concomitantly diagnosed congenital pulmonary airway malformation lesion who received FETO under the compassionate use

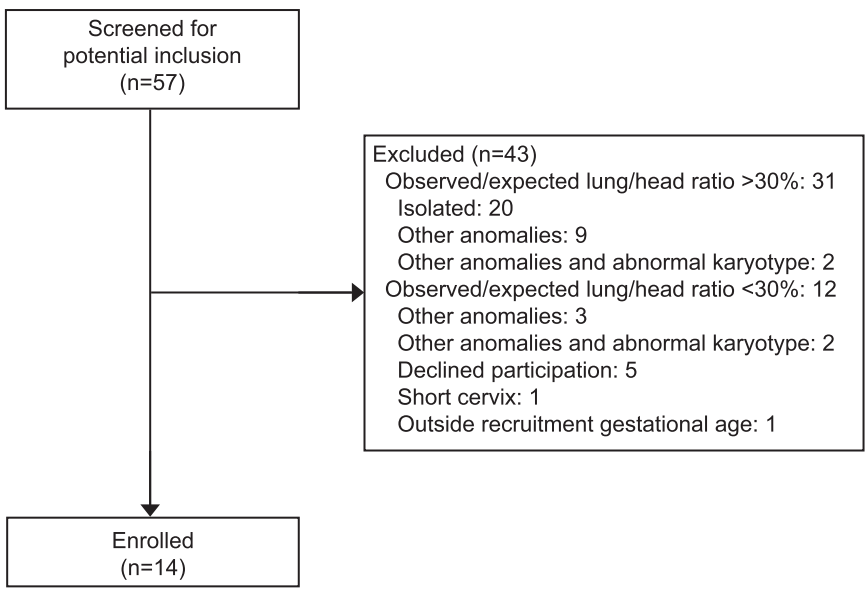


Fig. 1. The figure displays the numbers of screened and enrolled patients as well as the characteristics of women excluded from participation.
Baschat. Fetoscopic Tracheal Occlusion for Congenital Diaphragmatic Hernia. Obstet Gynecol 2020.

Table 2. Prenatal Characteristics and Occlusion Details for Women Undergoing Fetoscopic Tracheal Occlusion for Severe Congenital Diaphragmatic Hernia

Characteristic	Cases (N=14)
Maternal age (y)	33 (20–39)
Maternal ethnicity	
Caucasian	12 (86)
Asian	2 (14)
Parity	
0	9 (64)
1	3 (21)
2 or more	2 (14)
BMI (kg/m^2)	26 (18.5–44.8)
CDH side	
Left	12 (86)
Right	2 (14)
Pre-FETO O/E LHR (%)	23.2 (15.8–29.0)
Associated anomalies	
Congenital lung lesion	2 (14)
Tetralogy of Fallot	1 (7)
Placental location	
Anterior	7 (50)
Posterior	6 (43)
Lateral	1 (7)
Gestational age at FETO (wk)	28 5/7 (27 3/7–29 6/7)
AFI at FETO	23.4 (15.8–38.3)
Length of FETO procedure (min)	11 (4–110)
Post-FETO O/E LHR (%)	62.8 (44–108)
% increase in lung size	178 (80.5–330)
Length of occlusion (d)	34 (17–44)
Balloon removal	
Elective	10 (71)
Emergency	4 (29)
Removal technique	
Fetoscopy	6 (43)
Needle puncture	8 (57)
Trocar insertion site at fetoscopy (n=20)	
Upper uterine quadrant	18 (90)
Lower uterine segment	2 (10)
Length of balloon-removal procedure (min)	12 (5–25)
Gestational age at balloon removal	33 4/7 (32 1/7–34 4/7)
Post-removal O/E LHR (%)	46.6 (30–92)
Removal-to-delivery interval (d)	30 (0–59)

BMI, body mass index; CDH, congenital diaphragmatic hernia; FETO, fetoscopic tracheal occlusion; O/E LHR, observed/expected lung/head ratio; AFI, amniotic fluid index.
Data are median (range) or n (%).

application; in both instances, the size of the lesion decreased with advancing gestation (cases 2 and 14).[10,17]

Balloon removal was performed at a median gestational age of 33 4/7 weeks after a median of 34 days of occlusion. The removal was scheduled electively in 10 (71%) cases and was performed by percutaneous ultrasound-guided balloon puncture with a 20-gauge needle in more than half of cases. In one case, cesarean delivery occurred at 33 6/7 weeks of gestation after emergent successful balloon removal and required activation of the emergency airway team to be on standby as a safety measure if prenatal removal could not be accomplished. Overall, the median interval between balloon removal and birth was 30 days (Table 2). Serial observed/expected lung/head ratio measurements showed lung size increase from pre-FETO (median observed/expected lung/head ratio 23.2%, 15.8–29.0), to post-FETO in all cases (median observed/expected lung/head ratio 62.8%, 44.0–108, Mann-Whitney U, $P<.001$) and a postremoval size decrease (median 46.6%, range 30–92, Mann-Whitney U $P<.003$). However, the lung size remained higher than before FETO in all patients (Mann-Whitney U, $P<.001$; Fig. 2).

All patients received vaginal progesterone and two complete betamethasone courses. The majority (11, 79%) received additional tocolytic treatment for preterm contractions or labor (Table 3). Two patients required amnioreduction at the time of FETO for

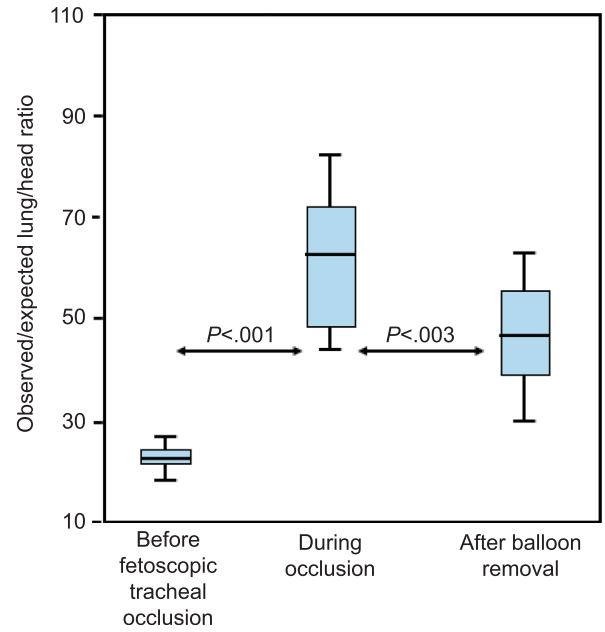


Fig. 2. Lung dimensions before and after tracheal occlusion. The figure displays the median, interquartile range, and 95% CI of the largest measurements of the observed/expected lung/head ratio. The measurements were obtained immediately before fetoscopic tracheal occlusion, at weekly intervals during intratracheal balloon placement, and at weekly intervals from balloon removal to delivery. *P*-values are based on the Mann-Whitney U test, with no ties observed between measurements.

Baschat. Fetoscopic Tracheal Occlusion for Congenital Diaphragmatic Hernia. Obstet Gynecol 2020.

symptomatic polyhydramnios and three patients required multiple procedures. Three patients had cervical pessary placement for cervical shortening, and five patients received multiple treatment modalities for preterm labor. During the prenatal course, four participants (29%) experienced preterm PROM (median gestational age 33 5/7, range 33 2/7–36 3/7), five developed spontaneous preterm labor without premature rupture of membranes (36%). All patients delivered at our facility at a median and mean gestational age of 39 2/7 weeks and 37 2/7 (range 33 6/7–39 4/7), respectively. Eight (57%) of the patients delivered at term (37 weeks of gestation or more) after scheduled term induction (Table 1). The majority of patients (71%) were delivered vaginally (Table 1), and all neonates were intubated in the delivery room per the postnatal management guidelines. The 5-minute Apgar score was less than 7 in seven (50%) neonates, but cord arterial blood gases were all within the normal range (Tables 1 and 3).

After stabilization in the delivery room, all neonates were transferred to the intensive care unit. At initial evaluation, all neonates had a patent airway irrespective of the type of balloon removal that was performed. In the one neonate in whom balloon puncture occurred just before birth, the deflated balloon was removed by suction through the endotracheal tube. The majority of neonates required high-frequency oscillatory ventilation, and, ultimately, 50% required ECMO (median duration 7 days [range 3–19 days]). All neonates were treated for pulmonary hypertension, predominantly with inhaled nitric oxide and sildenafil (Table 4). All but one of the neonates had complete unilateral diaphragmatic agenesis (1 type C, 13 type D defects). Patch repair was required for all neonates and was performed within the first week of life. The primary postoperative complication was recurrence of diaphragmatic herniation owing to patch dehiscence (5/14, 36%, Table 4). The average time to extubation was 45 days; two infants required prolonged intubation, ultimately necessitating tracheostomy tube placement. Neonatal survival on day 28 was 93% (95% CI 49–100%), and the overall survival to 6 months or hospital discharge was 86% (95% CI

Table 3. Obstetric Interventions for Preterm Birth Risk Management After Fetoscopic Tracheal Occlusion

Intervention	Cases (N=14)
Vaginal progesterone—200 mg	14 (100)
Cervical pessary insertion for cervical shortening	3 (21)
Amnioreduction for polyhydramnios	5 (36)
At the time of FETO only	2 (14)
Multiple amnioreductions	3 (21)
No. of amnioreductions/patient	2 (1–3)
Additional tocolytic use (total)	11 (79)
Nifedipine for preterm contractions	5 (36)
Indomethacin for preterm contractions	3 (21)
Indomethacin for preterm contractions & polyhydramnios	3 (21)
Use of multiple treatment modalities for suspected preterm labor	5 (36)

FETO, fetoscopic tracheal occlusion.
Data are n (%) or median range.

Table 4. Postnatal Outcomes After Fetoscopic Tracheal Occlusion

Variable	Cases (N=14)
Gestational age at delivery (wk)	39 2/7 (33 6/7–39 4/7)
Delivery route	
Spontaneous vaginal birth	9 (64)
Forceps	1 (7)
Cesarean delivery	4 (29)
Sex	
Female	6 (43)
Male	8 (57)
Birth weight (g)	3,055 (1,920–3,710)
Cord arterial pH at birth	7.31 (7.25–7.38)
Arterial pH at 1 h of life	7.16 (6.56–7.29)
HFOV	12 (86)
Mechanical ventilation (d)	45 (14–252)
Reintubation	7 (50)
Tracheotomy	2 (14)
Pulmonary hypertension treatments	
Inhaled nitric oxide	14 (100)
Sildenafil	11 (79)
Inhaled epoprostenol	9 (64)
Treprostinil	6 (43)
Bosentan	4 (29)
Milrinone	3 (21)
ECMO	7 (50)
Day of life at surgery	6 (2–15)
Defect type	
C	1 (7.1)
D	13 (92.9)
Postoperative complications	
Operation for re-herniation	5 (36)
Abdominal compartment syndrome	1 (7)
Cardiac arrest	2 (14)
Supplemental oxygen at discharge	7 (50)
Pulmonary hypertension at discharge	7 (50)
Neonatal survival	13 (93)
Survival until discharge	12 (86)
Days in intensive care	82 (14–455)
Days until discharge	114 (14–456)

HFOV, high-frequency oscillatory ventilation; ECMO, extracorporeal membrane oxygenation.
Data are median (range) or n (%).

44–100%, Table 4). There was significant improvement in respiratory function over the course of the admission, and 50% of infants required supplemental oxygen or treatment of pulmonary hypertension at discharge (Table 4).

DISCUSSION

We report the feasibility and outcomes of FETO performed in a single center with standardized prenatal and postnatal management strategies in a cohort of pregnancies complicated by severe congenital diaphragmatic hernia. Fetoscopic tracheal occlusion was feasible in all cases and removal of the balloon was successful in all patients before delivery in our center. After FETO, 86% of infants survived until hospital discharge despite significant respiratory acuity and intensive care requirements. The measurable prenatal effect of FETO was a significant and sustained increase in prenatal lung size even after balloon removal. In this small sample size, outcome was better than expected with a low rate of emergency balloon removals, low prematurity rate, and a higher survival rate than previously reported. Prenatal ultrasound criteria captured a patient population with diaphragmatic agenesis that is at high risk for mortality and severe morbidity.

Fetoscopic endotracheal balloon occlusion has been studied in one randomized trial,[24] a large feasibility study[10] and several smaller cohorts both outside[10,25–28] and within the United States.[29] The procedure related details for FETO such as technique, gestational age, procedure length, and the anticipated effects on subsequent prenatal lung growth were comparable with our study. Although the overall approach to FETO was modelled on the severe congenital diaphragmatic hernia TOTAL randomized controlled trial, we employed a deliberate strategy to minimize potential contributors to preterm birth at every step in recognizing the effect of delivery gestational age on outcome. This included the pre-FETO initiation of vaginal progesterone, transplacental fetal analgesia administration into the umbilical vein in anterior placentation to minimize the number of amniotic punctures, avoidance of the lower uterine segment for fetoscopy, aggressive treatment of preterm contractions and symptomatic polyhydramnios, and using needle puncture as the primary balloon removal technique with a deliberate effort to minimize reliance on the ex-utero intrapartum treatment to avoid associated maternal risks.[19] The preferred use of percutaneous ultrasound-guided needle puncture for balloon removal, even in the setting of emergent balloon removal, differs from other studies. Our approach was based on the intention to minimize the high risk of preterm PROM due to a second fetoscopy[10,23,25] and the maternal surgical risks associated with emergency ex-utero intrapartum treatment.[14,15] Additionally, our 29% incidence of preterm PROM may be attributable to avoiding the lower uterine segment for fetoscopic entry.[30]

We recognize that our findings have to be interpreted with the caveat of a small sample size and the lack of randomized interventions. Cumulative data from several hundred participants undergoing FETO have demonstrated 42–50% survival rates in severe right or left congenital diaphragmatic hernia and an associated risk of preterm PROM, need for emergency peripartum balloon removal in more than 30%, respectively.[8,10,14,15,17,23,26] The predominantly reported delivery gestational age after FETO is 35 weeks; 10–18% of women deliver before 32 weeks, 18–36% before 34 weeks, and 38–100% before 37 weeks.[10,14,15,23–25,27,28] With the caveat of our small sample size in mind, a striking difference in our study was the average gestational age of 37 weeks of gestation, with no deliveries before 32 weeks, 7% of deliveries before 34 weeks, and 43% of deliveries before 37 weeks of gestation. This allowed for all of the neonates to be considered as candidates for ECMO based on their size at birth and may have been an important contributor to neonatal survival.[31] The postnatal incidence and severity of respiratory morbidity, intensive care needs, nature of the diaphragmatic defect, and surgical management was comparable with other studies using the same prenatal observed/expected lung/head ratio cutoffs. Our survival rate at discharge of more than 80% is consistent with the only other U.S. FETO study[24] but higher than all other feasibility reports, in which expected survival for this patient population post-FETO is just less than 50%.[10,18–23] Although these numbers seem to support FETO treatment in severe congenital diaphragmatic hernia, survival rates with standard postnatal care of up to 60% have been reported even for infants with unilateral diaphragmatic agenesis.[4,10] These variations may in part be due to the care setting, including the standardized application of prenatal and postnatal care paths (Baschat AA, Jelin EB, Miller JL. Survival after fetoscopic tracheal occlusion for diaphragmatic hernia: the importance of the care setting [abstract]. Am J Obstet Gynecol 2019;220:S134.).[4] This stresses the need for a carefully constructed, randomized intervention trial to determine the benefit of FETO with consideration of factors that could affect the generalizability of study findings across different care settings. Although our study is in overall agreement

with prior feasibility reports, it differs in prenatal patient management, obstetric outcome, and neonatal and infant survival. It is plausible that our lower preterm PROM incidence, and possibly our overall obstetric management approach, contributed to the low prematurity rate, which in turn can significantly improve survival.[30]

Limitations of our study include the small sample size and the associated limitations on generalizability and the ability to evaluate potential confounders. The study was planned as a feasibility cohort study and therefore lacks a control group. Although it would be possible to compare the observed survival to expectations based on including the observed/expected lung/head ratio, such an estimate is based on historical controls and is unlikely to reflect the effects of current postnatal management strategies.[3,4,7,10] Belfort et al used a historical control group in which the survival was only 11%, which is significantly lower than expected in a more contemporary group of severe congenital diaphragmatic hernia patients managed without FETO.[3,4] Another limitation to the interpretation of our results is that our prenatal care strategies, with a strong emphasis on avoidance of preterm birth, were pragmatically based, and were not delineated in previous trials. We are therefore unable to determine the contribution of our prenatal management components to the differences observed in our study. Our strategy to minimize adverse obstetric outcomes and potentially prolong pregnancy drove several decisions. These included trocar insertion in the upper uterine quadrants and FETO reversal by guided needle balloon puncture, which was successfully accomplished in 90% and 57.1% of cases, respectively. Additionally, we universally prescribed vaginal progesterone and aggressively managed uterine contractions even irrespective of cervical change. Although we were not able to evaluate independent contributions of these management decisions, they raise the important point that there is a lack of high-quality evidence to guide the management of obstetric complications in the context of fetal interventions. For congenital diaphragmatic hernia in particular, postnatal outcomes are directly affected by birth weight and maturity.[4,26] In the case of FETO, where potential benefits of fetal therapy are substantially offset by the obstetric risks, especially preterm birth,[10,18,19] evidence-based approaches to mitigate these risks effectively need to be pursued as they may be critical to shift the risk to benefit ratio in favor of fetal intervention.

In summary, our results support feasibility of FETO in patients with severe unilateral congenital diaphragmatic hernia to improve postnatal infant survival. Standardized prenatal and postnatal care appear to be complementary in achieving survival in these infants. Standardized prenatal management with anticipatory and prompt reactive treatment of obstetric complications may improve the chance for patients to deliver at term. Once a randomized trial has confirmed the benefit of FETO in congenital diaphragmatic hernia, further research needs to determine how obstetric outcomes can be optimized to apply these management strategies in a harmonized approach across FETO centers.

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Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *Individual participant data will be available in deidentified format to collaborators with active data sharing agreements with the primary investigator. The data will include all data points captured in the clinical research forms as well as the data dictionaries.*

What data in particular will be shared? *Cumulative data that describe the primary and secondary study endpoints as well as individual data points if a data-sharing agreement exists.*

What other documents will be available? *Protocol details and the standardized management protocols used at the study site.*

When will data be available (start and end dates)? *On peer-reviewed publication of the study findings.*

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *Access to the primary study data requires an active data-sharing agreement. At the present time, this exists only for centers that collaborate on fetoscopic tracheal occlusion research under the umbrella of the North American Fetal Therapy Network.*

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