

# Fetoscopic Endoluminal Tracheal Occlusion versus Expectant Management for Severe Congenital Diaphragmatic Hernia at a Single Center

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## Keywords

Congenital anomalies · Congenital diaphragmatic hernia · Fetal surgery · Fetoscopic endoluminal tracheal occlusion · Fetoscopy · Neonatal outcome · Pulmonary hypoplasia

## Abstract

**Introduction:** The TOTAL trial showed survival benefit in patients with severe congenital diaphragmatic hernia (CDH) who underwent fetoscopic endoluminal tracheal occlusion (FETO). We aim to add to the current literature by describing implementation, feasibility, and outcomes of patients treated with FETO compared to a contemporary cohort of expectantly managed maternal-child dyads. **Methods:** A single-center, retrospective cohort study evaluated patients with a

prenatal diagnosis of isolated left-CDH with an observed/expected lung-to-head ratio (O/E LHR) <30% referred to our center from September 2016 to January 2023. **Results:** Twelve patients who underwent FETO were compared to 35 expectantly managed patients. At initial evaluation, FETO patients had a lower O/E LHR value (21.7% versus 24.9%) compared to the expectant management patients. Chorioamniotic membrane separation occurred in half of the FETO patients (6/12) compared with 1 patient in the expectant management group and most FETO patients (75.0%) experienced preterm prelabor rupture of membranes compared to only 4 (11.4%) expectant management patients. FETO patients had a lower median gestational age at delivery compared to expectant management patients (35.0 vs. 38.9 weeks). Fewer FETO patients were treated with extracorporeal-membrane oxygenation (ECMO);

25.0% vs. 60.0% expectant management). FETO patients also had higher survival (91.7% vs. 71.4%) and longer duration of hospitalization (135 vs. 94.8 days). At time of discharge, no FETO patients required pulmonary hypertension (PH) medications while 28.0% of expectant management patients were on PH medications. **Conclusion:** FETO for severe CDH was feasible in our single center setting. FETO may increase risk of obstetric complications and prematurity, but improved ECMO use, PH, and survival of infants with severe CDH.

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## Introduction

Congenital diaphragmatic hernia (CDH) is a congenital anomaly that occurs in approximately 1 in 2,500 births, with left sided defects accounting for 85% of cases [1, 2]. Herniation of the abdominal viscera into the thoracic cavity impairs lung development, leading to increased risk of death due to pulmonary hypoplasia, pulmonary hypertension (PH), and cardiac dysfunction [3]. Prenatal liver herniation and observed to expected lung-to-head ratio (O/E LHR) measurements are validated predictors of disease severity, with an inverse relationship between O/E LHR and mortality [4–8]. The survival rate for all prenatally diagnosed CDH patients is approximately 70%, while severe cases have a reported survival less than 25% with traditional management [9]. Surviving patients often suffer from gastrointestinal problems, respiratory complications, and orthopedic deformations, and may also experience neurodevelopmental delay, necessitating multidisciplinary follow-up [10, 11]. While improved surgical management, standardized care guidelines, and specialized CDH programs have improved outcomes, no postnatal treatment modality can reverse the underlying pathogenesis of pulmonary hypoplasia [12–14]. Therefore, prenatal intervention was pursued with the goal to prevent or reverse pulmonary hypoplasia.

In utero tracheal occlusion as a treatment for CDH was developed from observations of excessive lung growth due to alveolar fluid secretions that accumulate in the lungs of fetuses with congenital high airway obstruction syndrome [12]. Early methods to achieve fetal tracheal occlusion for CDH included tracheal ligation during open fetal surgery. These treatments demonstrated remarkable lung growth; however, growth was inconsistent, and lungs did not function normally due to procedure-associated prematurity and decreased function in type II pneumocytes [13, 14]. The fetoscopic

endoluminal tracheal occlusion (FETO) technique was developed to address these limitations [15]. In patients with an isolated left-CDH and O/E LHR <25%, the Tracheal Occlusion to Accelerate Lung Growth (TO-TAL) trial demonstrated a survival rate of 40% in patients that received FETO compared to 15% among those treated with expectant management [16]. Results reported from centers in the USA also show increased survival among the FETO group and describe the long-term outcomes of patients that received FETO within single and multicenter retrospective reviews [17–20]. Within the USA, short- and long-term morbidity outcomes associated with FETO remain limited.

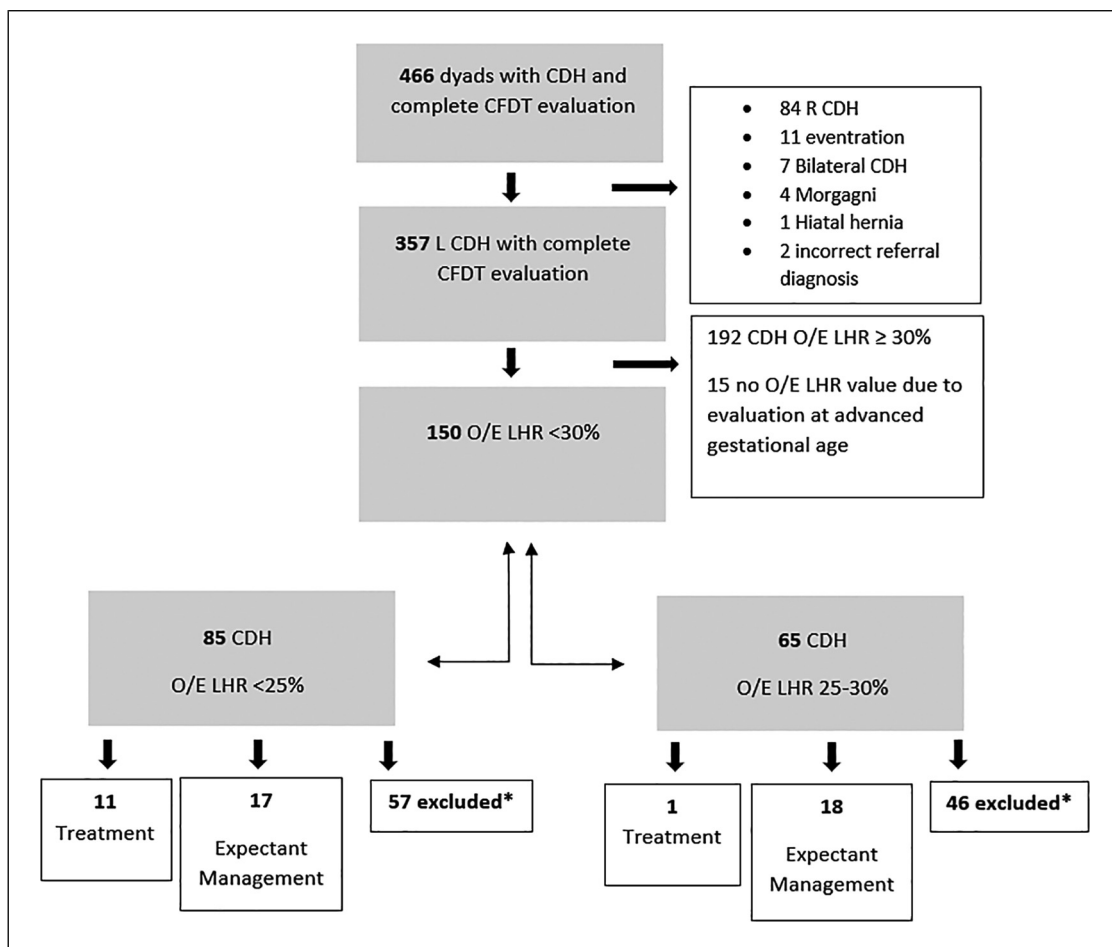
This study reports a single-center experience of FETO in severe left-CDH patients and describes the implementation and feasibility of FETO. We aim to add to the current literature by describing maternal and neonatal outcomes of patients treated with FETO compared to a contemporary cohort of expectantly managed maternal-child dyads.

## Materials and Methods

### Study Cohort

This single-center, retrospective cohort study evaluated all patients with a prenatal diagnosis of CDH referred to the Richard D. Wood Jr. Center for Fetal Diagnosis and Treatment (CFDT) at the Children's Hospital of Philadelphia (CHOP) with an evaluation from September 2016 to January 2023 (Fig. 1). Comprehensive 2-day prenatal evaluation includes a detailed fetal ultrasound, fetal magnetic resonance imaging (MRI), and fetal echocardiogram, as well as extensive maternal history and physical examination. Following diagnostic imaging, patients are counseled by a team of maternal-fetal medicine specialists, pediatric surgeons, neonatologists, genetic counselors, psychologists, social workers, and other relevant specialties [21–23]. The multidisciplinary team collaborates to determine maternal and fetal eligibility for FETO.

In December 2014, the Food and Drug Administration (FDA) approved the use of the Goldbal2<sup>®</sup> balloon and catheter for FETO at our institution under investigational device exemption (IDE) status. CHOP's Institutional Review Board (IRB) approved the feasibility trial in July 2015, and the first case was performed in December 2016. The criteria for FETO enrollment are outlined by the FDA IDE submission (G140236) and IRB approved protocol (IRB 15-011714). A multidisciplinary



**Fig. 1.** Flow diagram of determination of FETO and expectant patients. \*Excluded due to maternal factors including pregnancy termination, delivery at another hospital, cervical length, and psycho/social limitations or fetal factors including IUGR, IUFD, cardiac anomalies (VSD, TOF), genetic syndromes, lung lesions, and multiple gestations.

group, independent of the procedure team, comprises the Fetal Oversight Committee that approves each case and annually reviews maternal and child outcomes.

Enrollment criteria varied over the study period. The initial FDA investigational device exemption restricted FETO to patients diagnosed with an isolated left-CDH, intrathoracic liver, and O/E LHR of less than 25%. In March 2017, based on internal survival analysis, a second arm of the study was added to include patients with an O/E LHR between 25 and 30%. In May 2019, TOTAL trial investigators notified the institution of study that interim analysis of their moderate arm failed to demonstrate benefit for those with O/E LHR 25–34.9% and urged centers to no longer offer the inventions in patients with O/E LHR >25% [24]. Therefore, out of an abundance of caution, those with an O/E LHR greater

than 25% and less than 30% were no longer offered FETO at our institution after May 2021.

Additional inclusion criteria were consistent throughout the study period: maternal age over 18 years carrying a singleton pregnancy, normal fetal karyotype, and gestational age between 27 and 29 weeks 6 days at balloon placement. Patients were not considered candidates for FETO if there were maternal contraindications to fetoscopic surgery including maternal medical conditions, technical limitations precluding fetoscopic surgery, history of latex allergy, history of preterm delivery or current preterm labor, short cervix (<15 mm at enrollment), psychosocial ineligibility, inability to remain at the FETO site through delivery, or declined participation in long-term follow-up. Patients that met all eligibility criteria but did not receive FETO compose the expectant management group.

**Table 1.** Patient characteristics by treatment group

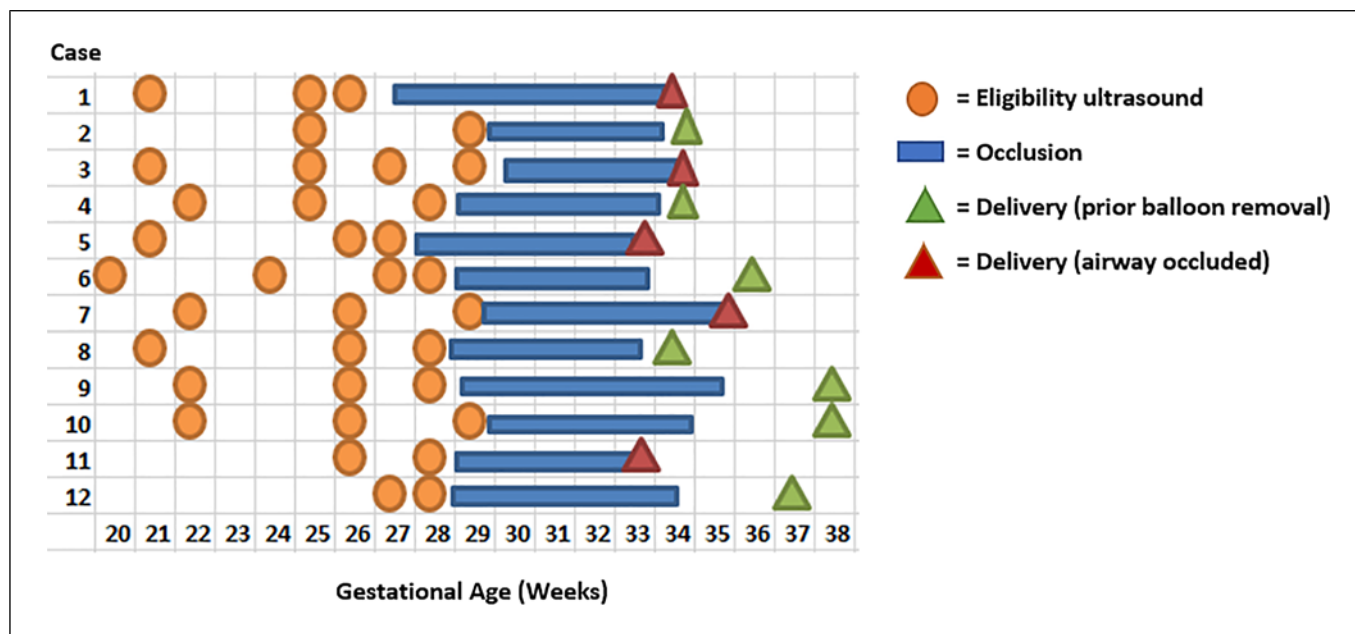
	FETO (N = 12)	Expectant management (N = 35)	Overall (N = 47)
Race/ethnicity			
Non-Hispanic White	10 (83.3)	16 (45.7)	26 (55.3)
Non-Hispanic Black	0 (0)	7 (20.0)	7 (14.9)
Multi-racial/other	1 (8.3)	4 (11.4)	5 (10.6)
Hispanic/Latino	1 (8.3)	8 (22.9)	9 (19.1)
Health insurance at birth, n (%)			
Commercial	11 (91.7)	20 (57.1)	31 (66.0)
Government	0 (0)	12 (34.3)	12 (25.5)
Self pay	1 (8.3)	3 (8.6)	4 (8.5)
Maternal age at child's birth			
Median [Q1, Q3]	31.0 [29.9, 33.6]	28.7 [24.7, 34.1]	30.6 [25.3, 34.1]
Total number of pregnancies, including current, n (%)			
1	3 (25.0)	9 (25.7)	12 (25.5)
2	4 (33.3)	14 (40.0)	18 (38.3)
3+	5 (41.7)	12 (34.3)	17 (36.2)
Total number of live births, including current, n (%)			
Nulliparous	8 (66.7)	13 (37.1)	21 (44.7)
1	1 (8.3)	14 (40.0)	15 (31.9)
2+	3 (25.0)	8 (22.9)	11 (23.4)
Maternal BMI at first visit			
Median [Q1, Q3]	28.4 [27.1, 32.6]	28.8 [26.4, 34.8]	28.8 [26.6, 34.4]
Gestational age at initial evaluation (weeks)	22.5 [22.2, 23.4]	23.6 [22.3, 25.0]	23.3 [22.2, 25.0]
O/E LHR: trace or AP			
Median [Q1, Q3]	21.7 [21.4, 23.6]	24.9 [22.9, 27.8]	24.5 [21.7, 27.2]
MRI O/E TLV			
Median [Q1, Q3]	29.8 [23.9, 34.5]	24.0 [21.5, 32.0]	26.0 [21.5, 32.0]
Year of delivery, n (%)			
2017	5 (41.7)	2 (5.7)	7 (14.9)
2018	0 (0)	6 (17.1)	6 (12.8)
2019	1 (8.3)	5 (14.3)	6 (12.8)
2020	2 (16.7)	11 (31.4)	13 (27.7)
2021	2 (16.7)	4 (11.4)	6 (12.8)
2022	1 (8.3)	4 (11.4)	5 (10.6)
2023	1 (8.3)	3 (8.6)	4 (8.5)

BMI, body mass index; O/E LHR, observed to expected lung-to-head ratio; O/R TLV, observed to expected total lung volume.

O/E LHR was measured by a fetal radiologist, independent of the procedural team. The trace method was preferred for the O/E LHR ultrasound measurement [25]. If the trace method was not conducted, the AP method was used for eligibility [6]. MRI O/E total lung volumes were calculated using the Meyers standards [26]. Polyhydramnios was defined using the Society for Maternal-Fetal Medicine guideline [27]. Prenatal and neonatal clinical management of both FETO and expectant management patients have been previously described by Wild et al. [28].

### Statistical Methods

Data were collected and validated using the Clinical Outcomes Data Archive [29]. This retrospective study was approved by the Institutional Review Board at the Children's Hospital of Philadelphia (IRB 21-018553). Continuous variables were summarized as mean (standard deviation) or as median (interquartile range) based on the distribution of the data, and categorical data were summarized as frequencies. Due to the small sample size and the descriptive nature of this study, all comparisons



**Fig. 2.** Prenatal timeline of FETO patients.

between groups were based on observational frequency differences and no formal statistical comparisons were conducted.

## Results

### Demographics

Within the study period, 12 patients underwent FETO, and 35 were expectantly managed. Patient characteristics are displayed in Table 1. Both FETO and expectant management patients were predominantly White race, non-Hispanic ethnicity, and had commercial insurance. The median maternal age at delivery was slightly older for FETO versus expectant management patients (31.0 and 28.7 years, respectively). At first evaluation, FETO patients had a lower median O/E LHR (21.7% versus 24.9%), but higher MRI O/E total lung volume (29.8% versus 24.0%) than expectant management patients.

### Procedure

FETO patients underwent several ultrasounds prior to enrollment to confirm inclusion criteria (Fig. 2). The median O/E LHR prior to balloon insertion was 20.6%, at median gestational age of 29.6 weeks. In six (50.0%) procedures, the trocar was inserted into the lower uterine segment, 3 (25.0%) in a mid-uterine location, and 3

(25.0%) in an upper uterine quadrant. The median total time that the trocar remained inserted was 22 min, with 6 (50.0%) patients have a trocar insertion time between 11 and 20 min, 2 (16.7%) between 21 and 30 min, and 4 (33.3%) >30 min. An amnioinfusion occurred during 8 (66.7%) of the procedures, and an amnioreduction occurred in 5 (41.7%) procedures. All balloons were successfully removed from the trachea. Ultrasound guided needle puncture was attempted in 3 cases, but successful in only 1. Six (50.0%) patients underwent fetoscopic balloon removal before delivery. Two patients underwent balloon removal by bronchoscopy at Ex-utero intrapartum treatment (EXIT), and 3 underwent balloon removal by bronchoscopy during delayed cord clamping at cesarean delivery (modified C-section) (Table 2). Fetoscopic balloon removal was completed at a median of 35 days after insertion and most fetuses (91.7%) were in vertex position at balloon removal. The trocar remained in utero for a median of 13 min, and the median duration from balloon removal to birth was 10.5 days. As reported in Figure 3a and b, O/E LHR values of the fetuses improved substantially in all but 1 of the FETO patients.

### Maternal Outcomes

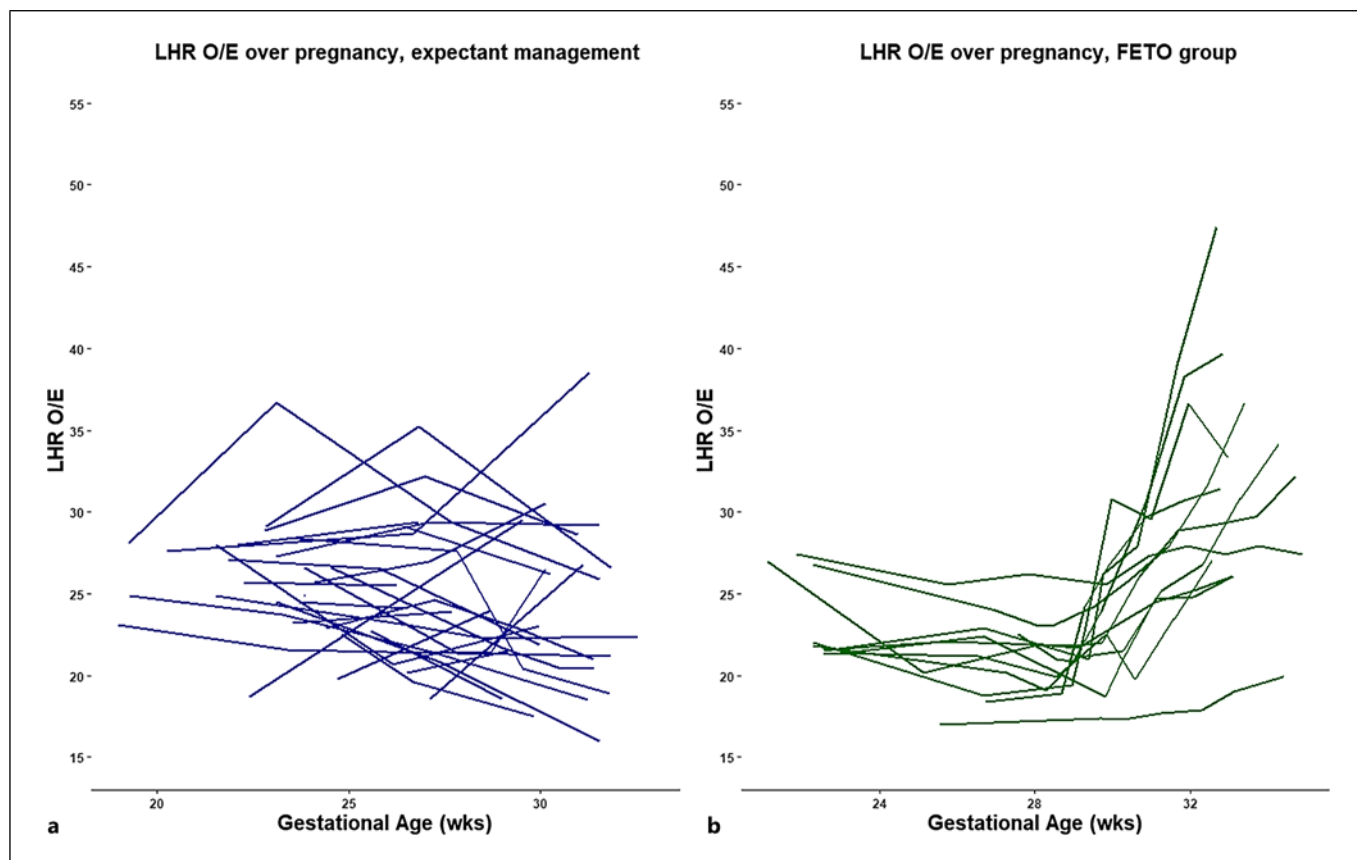
All FETO patients had an antepartum hospitalization, with a median cumulative duration of 10.5 days. Expectant management patients had a lower

**Table 2.** FETO procedure characteristics

	Overall (N = 12)
<i>Balloon insertion</i>	
LHR O/E: trace or AP prior to FETO insertion	
Median [Q1, Q3]	20.6 [19.3, 21.8]
GA at insertion, weeks	
Median [Q1, Q3]	29.6 [29.0, 30.1]
Prenatal position at balloon insertion, n (%)	
Breech	7 (58.3)
Vertex	4 (33.3)
Transverse	1 (8.3)
Trocar location, n (%)	
Lower uterine segment	6 (50.0)
Mid	3 (25.0)
Upper uterine quadrant	3 (25.0)
Total time trocar remained in utero during insertion, min	
Median [Q1, Q3]	22.0 [18.8, 47.3]
11–20 min	6 (50.0%)
21–30 min	2 (16.7%)
>30 min	4 (33.3%)
Amnioinfusion performed during insertion, n (%)	8 (66.7)
Amnioreduction performed during insertion, n (%)	5 (41.7)
Amnioinfusion volume, mL	
Median [Q1, Q3]	650 [525, 1,010]
Amnioreduction volume, mL	
Median [Q1, Q3]	500 [400, 1,750]
<i>Balloon removal</i>	
Balloon removal route: successful attempt, n (%)	
Bronchoscopy	5 (41.7)
Fetoscopic	6 (50.0)
Ultrasound guided needle puncture	1 (8.3)
Fetal position at successful balloon removal, n (%)	
Breech	1 (8.3)
Vertex	11 (91.7)
Among fetoscopic balloon removals	n = 6
Total time of occlusion, days	
Median [Q1, Q3]	35.0 [31.3, 35.8]
Time from removal to delivery, days	
Median [Q1, Q3]	10.5 [4.25, 18.3]
Total time trocar remained in utero during successful balloon removal, min	
Median [Q1, Q3]	13.0 [12.3, 20.5]

frequency of antepartum hospitalizations (22.9%) with a shorter median duration (1 day). Chorioamniotic membrane separation occurred in half of the FETO patients (6/12) compared with 1 patient in the expectant management group. Most FETO patients (75.0%) experienced preterm prelabor rupture of membranes (PPROM) compared to only 4 (11.4%)

expectant management patients. Polyhydramnios was present in both FETO (66.7%) and expectant management patients (74.3%). Ten (83.3%) FETO patients delivered by cesarean, and 2 (16.7%) by EXIT compared to 13 (37.1%) cesarean and 22 (62.9%) vaginal deliveries in the expectantly managed patients (Table 3).



**Fig. 3.** Prenatal O/E LHR over pregnancy duration for expectant management group (a) and FETO group (b).

Among FETO patients, cesarean delivery was indicated in 5 cases due to tracheal occlusion, 4 for non-reassuring fetal status, prior history of cesarean delivery in 2, and 1 failed trial of labor. Cesarean delivery was performed in the expectant management group in 6 cases for non-reassuring fetal status, 5 due to history of prior cesarean delivery, 1 for arrest of dilation, and 1 for malpresentation. Surgical delivery complications such as uterine atony and blood transfusion occurred in 41.6% and 2.9% of FETO and expectant management patients, respectively. In FETO patients with uterine atony, 1 case occurred during modified cesarean delivery using delayed cord clamping to facilitate balloon removal. The additional 3 cases occurred in routine cesarean deliveries status post fetoscopic balloon removal. One patient received a blood transfusion during modified cesarean delivery using placental bypass to facilitate emergency balloon removal and the other for postpartum hemorrhage in cesarean delivery status post fetoscopic balloon removal. No surgical delivery complications were observed in patients that delivered via EXIT (Table 3).

#### Neonatal Outcomes

Fewer FETO patients were treated with extracorporeal-membrane oxygenation (ECMO) (25.0% vs. 60.0% expectant management). FETO patients had higher survival (91.7%) at the time of NICU discharge than those with expectant management (71.4%). For those that survived to NICU discharge, the median duration of invasive ventilation (79 vs. 40 days), noninvasive ventilation (62 vs. 25.5 days), and hospitalization (135 vs. 94.8 days) was longer among FETO patients than those expectantly managed, respectively. At time of discharge, no FETO patients required PH medications while 28.0% of expectant management patients were on PH medications. All FETO patients were discharged on reflux medications and a feeding tube. Seventy-two and 88.0% of expectant management patients were discharged with reflux medications and a feeding tube, respectively. A higher percentage of FETO patients were discharged with respiratory support; however, only 1 patient required supplemental oxygen therapy greater than 2L nasal cannula while 5 expectant

**Table 3.** Maternal outcomes by treatment group

	FETO (N = 12)	Expectant management (N = 35)	Overall (N = 47)
Mode of delivery, n (%)			
Cesarean section	10 (83.3)	13 (37.1)	23 (48.9)
EXIT	2 (16.7)	0 (0)	2 (4.3)
Vaginal	0 (0)	22 (62.9)	22 (46.8)
Chorioamniotic membrane separation, n (%)	6 (50.0)	1 (2.9)	7 (14.9)
Premature prelabor rupture of membranes, n (%)	9 (75.0)	4 (11.4)	13 (27.7)
Antepartum admission, n (%)	12 (100)	8 (22.9)	20 (42.6)
Total duration of antepartum admission, days			
Median [Q1, Q3]	10.5 [4.75, 21.5]	1.00 [0.25, 2.00]	1.00 [1.00, 3.50]
GA at delivery			
Median [Q1, Q3]	35.0 [34.3, 36.8]	38.9 [38.3, 39.5]	38.5 [35.4, 39.3]
Polyhydramnios, n (%)	8 (66.7)	26 (74.3)	34 (72.3)
Maximum AFI, cm			
Median [Q1, Q3]	24.0 [22.4, 30.7]	27.5 [23.5, 29.7]	27.0 [23.0, 30.2]
Indication for surgical delivery, n (%) <sup>a</sup>			
Failed induction of labor	1 (8.3)	0 (0)	1 (2.1)
Non-reassuring fetal status	4 (33.3)	6 (17.1)	10 (21.3)
Obstructed airway	5 (41.7)	0 (0)	5 (10.6)
Repeat cesarean	2 (16.7)	5 (14.3)	7 (14.9)
Arrest of dilation	0 (0)	1 (2.9)	1 (2.1)
Fetal position	0 (0)	1 (2.9)	1 (2.1)
Surgical delivery complications, n (%) <sup>a</sup>			
None	7 (58.3)	12 (34.3)	19 (40.4)
Blood transfusion	1 (8.3)	0 (0)	1 (2.1)
Blood transfusion and uterine atony	1 (8.3)	0 (0)	1 (2.1)
Uterine atony	3 (25.0)	1 (2.9)	4 (8.5)

<sup>a</sup>Values less than total due to vaginal delivery.

management patients required continuous positive airway pressure (CPAP/BiPAP), and one required a tracheostomy (Table 4).

## Discussion

This single-center study demonstrates the successful incorporation of FETO into our management of severe CDH patients. Although a higher proportion of patients in the FETO group had a premature birth and Cesarean section, critical outcomes of neonatal survival and successful CDH repair were high for all patients and more frequent among the FETO group. Additionally, ECMO utilization and PH medication at discharge were lower in FETO patients than a contemporary cohort of expectant management patients.

Multicenter European and US FETO studies reported PPROM rates of 48% and 54%, respectively, while our study reported PPROM in 9 of 12 (75%) cases [16, 19]. Compared to the TOTAL trial, our patients also experienced chorioamniotic membrane separation more frequently. Our higher incidence of PPROM and membrane separation may be attributable to operative duration. Four cases had operative times >30 min, which has been associated with higher PPROM rates following FETO [30].

Despite higher rates of PPROM and chorioamniotic membrane separation, the same median gestational age at delivery (35 weeks) was observed as both USA and international multicenter studies [16, 19]. Emergent balloon removal was required in 42% of our reported cases. Similarly, 52% of infants in the original clinical trial of FETO required emergent balloon removal [30].

**Table 4.** Neonatal outcomes by treatment group

	FETO (N = 12)	Expectant management (N = 35)	Overall (N = 47)
ECMO, n (%)	3 (25.0)	21 (60.0)	24 (51.1)
CDH repair, n (%)	12 (100)	31 (88.6)	43 (91.5)
Survival to NICU discharge, n (%)	11 (91.7)	25 (71.4)	36 (76.6)
<i>Among survivors</i>			
Duration of invasive ventilation, days Median [Q1, Q3]	49.0 [40.5, 64.0]	40.0 [32.0, 46.0]	41.0 [30.5, 49.0]
Duration of noninvasive ventilation, days Median [Q1, Q3]	64.0 [27.5, 97.0]	26.5 [20.0, 62.5]	32.0 [21.0, 92.0]
Length of hospitalization, days Median [Q1, Q3]	135 [103, 166]	94.8 [75.8, 150]	109 [76.9, 162]
Discharge on PH medications, n (%)			
No	11 (100)	18 (72.0)	29 (80.6%)
Yes	0 (0)	7 (28.0)	7 (19.4%)
Discharge on reflux medications, n (%)			
Yes	11 (100)	18 (72.0)	29 (80.6%)
No	0 (0)	7 (28.0)	7 (19.4%)
Discharge route of feeding, n (%)			
PO	0 (0)	3 (12.0)	3 (8.3%)
NG tube	4 (36.4)	12 (48.0)	16 (44.4%)
G tube	4 (36.4)	7 (28.0)	11 (30.6%)
GJ tube	2 (18.2)	3 (12.0)	5 (13.9%)
NJ tube	1 (9.1)	0 (0)	1 (2.8%)
Discharge respiratory support, n (%)			
None	5 (45.5)	18 (72.0)	23 (63.9%)
<2 L nasal cannula	5 (45.5)	1 (4.0)	6 (16.7%)
CPAP/BiPAP	1 (9.1)	5 (20.0)	6 (16.7%)
Tracheostomy	0 (0)	1 (4.0)	1 (2.8%)

For infants requiring emergent balloon removal at the time of delivery, EXIT procedure is generally preferred. However, delivery and balloon removal plans are individualized based on the method deemed safest for each maternal-fetal dyad. Emergent balloon removal requires an experienced multidisciplinary team, including the presence of maternal-fetal medicine specialists, pediatric surgeons, otolaryngologists, neonatologists, and anesthesiologists [31]. Our institution has implemented ongoing emergent balloon removal simulation exercises to maintain skills and aid in communication.

Consistent with prior reports, mothers experience more obstetric complications after undergoing FETO compared to expectant management. Reducing obstetric complications and prematurity remain an area for improvement. Minimizing in utero instrumentation time has been associated with reduced compli-

cations in fetal surgery [30]. Team experience and proficiency in fetoscopic surgery may impact operative time, however, given the rarity of CDH and strict eligibility criteria, most high-volume centers perform only a handful of cases per year. Regardless of surgeon experience, fetal positioning also largely dictates the method and duration of both balloon insertion and removal. Even with the assistance of expert maternal-fetal medicine specialists and perfect alignment of a placental-free window, the fetal airway may be difficult to access, resulting in several insertion/removal attempts. Ultrasound guided needle puncture and development of novel tracheal occlusion devices (such as the Smart-TO balloon) hold the greatest potential to reduce obstetrical complications and prematurity associated with FETO by eliminating the need for invasive balloon removal [32].

This study demonstrated that despite the increased obstetrical complications and prematurity, neonates that underwent FETO realized benefits that include a reduced use of ECMO and discharge without medications for PH. These findings are consistent with a previous multicenter US-based study which reported a reduction in ECMO use from 52% in expectant management to 36% amongst FETO patients [19]. In our study, FETO patients demonstrated an increase in survival compared to expectant management patients (91.7% versus 71.4%). However, the scale of increased survival (40% versus 15%) demonstrated by patients in the treatment versus expectant management arm of the TOTAL trial was not appreciated. This is likely attributable to a difference in neonatal management at our center. Specifically, ECMO was used more frequently in this study compared with the TOTAL trial (25% vs. 5% FETO; 60% vs. 29% expectant management). Additionally, 91.5% of patients in our study underwent defect repair compared to only 44% of patients in TOTAL regardless of treatment arm [16]. These findings, and those supported by other US studies, suggest that the benefits of FETO in North American institutions are primarily related to the reduction in morbidity associated with ECMO and PH, with a smaller decrement in mortality [18, 19, 33].

This study describes the initiation of FETO and maternal-child outcomes from a single high-volume North American fetal center. Study strengths include its ability to compare granular data of patients treated with FETO in the USA to a robust contemporary expectant management group. However, given the limited sample size, the study was not powered to conduct formal statistical analysis or control for potential confounding variables such as race or insurance status. Additional limitations include its retrospective single-center nature and change in FETO enrollment criteria over the study period restricting generalizability. Additionally, despite the extensive inclusion criteria, severe CDH still appears to be a heterogeneous diagnosis as not all patients responds to tracheal occlusion. Further research should focus on identifying biological characteristics of FETO “non-responders.” Longer term follow-up of neurodevelopmental outcomes will also be important to assess the impact of prenatal interventions and prematurity [34].

## Conclusion

FETO for severe CDH was feasible in our single-center setting. Given the attendant increased risk of obstetric complications and prematurity, we recom-

mend that FETO be offered in high-volume centers with experience in fetal surgery, the capacity to remove the balloon emergently, and familiarity with the complex medical needs of neonates with CDH. Multidisciplinary teamwork is essential in caring for the complex medical and psychosocial needs of patients undergoing FETO both before and after delivery.

## Statement of Ethics

FETO protocol was reviewed and approved by The Children’s Hospital of Philadelphia Institutional Review Board (IRB 15-011714) and Fetal Oversight Committee. Written informed consent obtained was obtained from all FETO participants. The retrospective review of expectant management patients was granted exemption from written informed consent under CHOP IRB 21-018553.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

All authors contributed to the design and implementation of this study. S.L. conducted literature review, collected data, completed data analysis, and drafted the manuscript. S.F. and L.M. co-created the methods, assisted in data collection and analysis, and aided in drafting manuscript. T.A.R. assisted in study design and supplied manuscript revisions. A.M.A., B.G.C., J.S.G., J.S.M., O.N., E.R.O., E.A.P., W.H.P., N.E.R., K.T., and K.T.W. contributed clinical expertise essential to methods implementation and manuscript revisions. H.L.H. devised the study design, led implementation, and provided critical clinical expertise, support, mentorship, and revision of manuscript. All authors approved the final version of the manuscript prior to publication.

## Data Availability Statement

The data outlined in this study is not publicly available due to containing sensitive information that could compromise the privacy of research participants but are available from the corresponding author upon reasonable request.

## References

- Langham MR, Kays DW, Ledbetter DJ, Frentzen B, Sanford LL, Richards DS. Congenital diaphragmatic hernia. *Clin Perinatol*. 1996;23(4):671–88. [https://doi.org/10.1016/S0095-5108\(18\)30201-x](https://doi.org/10.1016/S0095-5108(18)30201-x)
- Shanmugam H, Brunelli L, Botto LD, Krikov S, Feldkamp ML. Epidemiology and prognosis of congenital diaphragmatic hernia: a population-based cohort study in Utah. *Birth Defects Res*. 2017;109(18):1451–9. <https://doi.org/10.1002/bdr2.1106>
- Keijzer R, Liu J, Deimling J, Tibboel D, Post M. Dual-hit hypothesis explains pulmonary hypoplasia in the nitrofen model of congenital diaphragmatic hernia. *Am J Pathol*. 2000;156(4):1299–306. [https://doi.org/10.1016/S0002-9440\(10\)65000-6](https://doi.org/10.1016/S0002-9440(10)65000-6)
- Bebington M, Victoria T, Danzer E, Moldenhauer J, Khalek N, Johnson M, et al. Comparison of ultrasound and magnetic resonance imaging parameters in predicting survival in isolated left-sided congenital diaphragmatic hernia. *Ultrasound Obstet Gynecol*. 2014;43(6):670–4. <https://doi.org/10.1002/uog.13271>
- Jani J, Nicolaides KH, Keller RL, Benachi A, Peralta CFA, Favre R, et al. Observed to expected lung area to head circumference ratio in the prediction of survival in fetuses with isolated diaphragmatic hernia. *Ultrasound Obstet Gynecol*. 2007;30(1):67–71. <https://doi.org/10.1002/uog.4052>
- Metkus AP, Filly RA, Stringer MD, Harrison MR, Adzick NS. Sonographic predictors of survival in fetal diaphragmatic hernia. *J Pediatr Surg*. 1996;31(1):148–52. [https://doi.org/10.1016/S0022-3468\(96\)90338-3](https://doi.org/10.1016/S0022-3468(96)90338-3)
- Senat MV, Bouchghoul H, Stirnemann J, Vaast P, Boubnova J, Begue L, et al. Prognosis of isolated congenital diaphragmatic hernia using lung-area-to-head-circumference ratio: variability across centers in a national perinatal network. *Ultrasound Obstet Gynecol*. 2018;51(2):208–13. <https://doi.org/10.1002/uog.17463>
- Alfaraj MA, Shah PS, Bohn D, Pantazi S, O'Brien K, Chiu PP, et al. Congenital diaphragmatic hernia: lung-to-head ratio and lung volume for prediction of outcome. *Am J Obstet Gynecol*. 2011;205(1):43.e1–438. <https://doi.org/10.1016/j.ajog.2011.02.050>
- Chock VY, Danzer E, Chung S, Noh CY, Ebanks AH, Harting MT, et al. In-hospital morbidities for neonates with congenital diaphragmatic hernia: the impact of defect size and laterality. *J Pediatr*. 2022;240:94–101.e6. <https://doi.org/10.1016/j.jpeds.2021.09.001>
- Harting MT, Lally KP. The congenital diaphragmatic hernia study group registry update. *Semin Fetal Neonatal Med*. 2014;19(6):370–5. <https://doi.org/10.1016/j.siny.2014.09.004>
- Idelson A, Tenenbaum-Gavish K, Danon D, Duvdevani NR, Bromiker R, Klinger G, et al. Fetal surgery using fetoscopic endoluminal tracheal occlusion for severe congenital diaphragmatic hernia: a single-center experience. *Arch Gynecol Obstet*. 2024;310(1):345–51. <https://doi.org/10.1007/s00404-023-07215-1>
- Mong A, Johnson AM, Kramer SS, Coleman BG, Hedrick HL, Kreiger P, et al. Congenital high airway obstruction syndrome: MR/US findings, effect on management, and outcome. *Pediatr Radiol*. 2008;38(11):1171–9. <https://doi.org/10.1007/s00247-008-0962-2>
- Flake AW, Crombleholme TM, Johnson MP, Howell LJ, Adzick NS. Treatment of severe congenital diaphragmatic hernia by fetal tracheal occlusion: clinical experience with fifteen cases. *Am J Obstet Gynecol*. 2000;183(5):1059–66. <https://doi.org/10.1067/mob.2000.108871>
- Perrone EE, Deprest JA. Fetal endoscopic tracheal occlusion for congenital diaphragmatic hernia: a narrative review of the history, current practice, and future directions. *Transl Pediatr*. 2021;10(5):1448–60. <https://doi.org/10.21037/tp-20-130>
- Deprest J, Gratacos E, Nicolaides KH, FETO Task Group. Fetoscopic tracheal occlusion (FETO) for severe congenital diaphragmatic hernia: evolution of a technique and preliminary results. *Ultrasound Obstet Gynecol*. 2004;24(2):121–6. <https://doi.org/10.1002/uog.1711>
- Deprest JA, Nicolaides KH, Benachi A, Gratacos E, Ryan G, Persico N, et al. Randomized trial of fetal surgery for severe left diaphragmatic hernia. *N Engl J Med*. 2021;385(2):107–18. <https://doi.org/10.1056/NEJMoa2027030>
- Sferra SR, Nies MK, Miller JL, Garcia AV, Hodgman EL, Penikis AB, et al. Morbidity in children after fetoscopic endoluminal tracheal occlusion for severe congenital diaphragmatic hernia: results from a multidisciplinary clinic. *J Pediatr Surg*. 2023;58(1):14–9. <https://doi.org/10.1016/j.jpedsurg.2022.09.042>
- Baschat AA, Rosner M, Millard SE, Murphy JD, Blakemore KJ, Keiser AM, et al. Single-center outcome of fetoscopic tracheal balloon occlusion for severe congenital diaphragmatic hernia. *Obstet Gynecol*. 2020;135(3):511–21. <https://doi.org/10.1097/AOG.0000000000003692>
- Bergh E, Baschat AA, Cortes MS, Hedrick HL, Ryan G, Lim FY, et al. Fetoscopic endoluminal tracheal occlusion for severe, left-sided congenital diaphragmatic hernia: the North American fetal therapy network fetoscopic endoluminal tracheal occlusion consortium experience. *Obstet Gynecol*. 2024;143(3):440–8. <https://doi.org/10.1097/AOG.0000000000005491>
- Tsao K, Johnson A. Fetal tracheal occlusion for congenital diaphragmatic hernia. *Semin Perinatol*. 2020;44(1):151164. <https://doi.org/10.1053/j.semperi.2019.07.003>
- Howell LJ, Adzick NS. The essentials of a fetal therapy center. *Semin Perinatol*. 1999;23(6):535–40. [https://doi.org/10.1016/S0146-0005\(99\)80032-9](https://doi.org/10.1016/S0146-0005(99)80032-9)
- Cole JCM. Mental health screening, treatment, and referral during the perinatal period. *J Obstet Gynecol Neonatal Nurs*. 2017;46(6):891–4. <https://doi.org/10.1016/j.jogn.2017.08.004>
- Dempsey AG, Chavis L, Willis T, Zuk J, Cole JCM. Addressing perinatal mental health risk within a fetal care center. *J Clin Psychol Med Settings*. 2021;28(1):125–36. <https://doi.org/10.1007/s10880-020-09728-2>
- Deprest JA, Benachi A, Gratacos E, Nicolaides KH, Berg C, Persico N, et al. Randomized trial of fetal surgery for moderate left diaphragmatic hernia. *N Engl J Med*. 2021;385(2):119–29. <https://doi.org/10.1056/NEJMoa2026983>
- Abbasi N, Cortes MS, Ruano R, Johnson A, Morgan T, Coleman B, et al. Variability in antenatal prognostication of fetal diaphragmatic hernia across the North American Fetal Therapy Network (NAFTNet). *Prenat Diagn*. 2020;40(3):342–50. <https://doi.org/10.1002/pd.5560>
- Meyers ML, Garcia JR, Blough KL, Zhang W, Cassady CI, Mehollin-Ray AR. Fetal lung volumes by MRI: normal weekly values from 18 through 38 Weeks' gestation. *AJR Am J Roentgenol*. 2018;211(2):432–8. <https://doi.org/10.2214/AJR.17.19469>
- Society for Maternal-Fetal Medicine SMFM EL, electronic address pubs@smfm.org, Dashe JS, Pressman EK, Hibbard JU. SMFM consult series #46: evaluation and management of polyhydramnios. *Am J Obstet Gynecol*. 2018;219(4):B2–8. <https://doi.org/10.1016/j.ajog.2018.07.016>
- Wild KT, Hedrick HL, Ades AM, Fraga MV, Avitabile CM, Gebb JS, et al. Update on management and outcomes of congenital diaphragmatic hernia. *J Intensive Care Med*. 2023;8850666231212874.
- Reynolds TA, Goldshore MA, Flohr S, Land S, Mathew L, Gebb JS, et al. A clinical outcomes data archive for a comprehensive fetal diagnosis and treatment center. *Fetal Diagn Ther*. 2024;1–9. <https://doi.org/10.1159/000541877>
- Jani JC, Nicolaides KH, Gratacos E, Valencia CM, Doné E, Martinez JM, et al. Severe diaphragmatic hernia treated by fetal endoscopic tracheal occlusion. *Ultrasound Obstet Gynecol*. 2009;34(3):304–10. <https://doi.org/10.1002/uog.6450>

- 31 Wild KT, Rintoul NE, Ades AM, Gebb JS, Moldenhauer JS, Mathew L, et al. The delivery room resuscitation of infants with congenital diaphragmatic hernia treated with fetoscopic endoluminal tracheal occlusion: beyond the balloon. *Fetal Diagn Ther.* 2024; 51(2):184–90. <https://doi.org/10.1159/000536209>
- 32 Sananès N, Basurto D, Cordier AG, Elie C, Russo FM, Benachi A, et al. Fetoscopic endoluminal tracheal occlusion with Smart-TO balloon: study protocol to evaluate effectiveness and safety of non-invasive removal. *PLoS One.* 2023;18(3):e0273878. <https://doi.org/10.1371/journal.pone.0273878>
- 33 Style CC, Olutoye OO, Belfort MA, Ayres NA, Cruz SM, Lau PE, et al. Fetal endoscopic tracheal occlusion reduces pulmonary hypertension in severe congenital diaphragmatic hernia. *Ultrasound Obstet Gynecol.* 2019;54(6):752–8. <https://doi.org/10.1002/uog.20216>
- 34 Sferra SR, Penikis AB, Guo M, Baschat AA, Mogayzel PJ, Burton VJ, et al. Neurodevelopmental outcomes in children after fetoscopic endoluminal tracheal occlusion for severe congenital diaphragmatic hernia: results from a multidisciplinary clinic. *J Pediatr Surg.* 2024; S0022346824001957.