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Sequential Minimally Invasive Fetal Interventions for Two Life-Threatening Conditions: A Novel Approach

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Established Facts

- Already known fact 1. Fetal therapy has the potential to improve postnatal outcomes of severe congenital anomalies with otherwise high morbidity/mortality.
- Already known fact 2. Fetal endoscopic tracheal occlusion and ultrasound-guided laser ablation of feeding vessels are established fetal interventions for isolated congenital diaphragmatic hernia and bronchopulmonary sequestration, respectively.

Novel Insights

- New information 1. Multiple comorbid congenital anomalies should not necessarily preclude prenatal therapy.
- New information 2. Individualized fetal care with sequential prenatal interventions may be a viable treatment model for fetuses with comorbid congenital anomalies.

Keywords
Congenital diaphragmatic hernia · Fetal lung mass · Bronchopulmonary sequestration fetoscopy · Fetal endoscopic tracheal occlusion

Abstract
Introduction: In utero interventions are performed in fetuses with "isolated" major congenital anomalies to improve neonatal outcomes and quality of life. Sequential in utero

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interventions to treat 2 anomalies in 1 fetus have not yet been described. ***Case Presentation:*** Here, we report a fetus with a large left-sided intralobar bronchopulmonary sequestration (BPS) causing mediastinal shift, a small extralobar BPS, and concomitant severe left-sided congenital diaphragmatic hernia (CDH). At 26-week gestation, the BPS was noted to be increasing in size with a significant reduction in right lung volume and progression to fetal hydrops. The fetus underwent ultrasound-guided ablation of the BPS feeding vessel leading to complete tumor regression. However, lung development remained poor (O/E-LHR: 0.22) due to the left-sided CDH, prompting fetal endoscopic tracheal occlusion therapy at 28-week gestation to allow increased lung growth. After vaginal delivery, the newborn underwent diaphragmatic repair with resection of the extralobar sequestration. He was discharged home with tracheostomy on room air at 9 months. ***Discussion/Conclusion:*** Sequential in utero interventions to treat 2 severe major anomalies in the same fetus have not been previously described. This approach may be a useful alternative in select cases with otherwise high morbidity/mortality. Further studies are required to confirm our hypothesis.

Introduction

Fetal therapy is indicated for severe congenital conditions that untreated are associated with extremely high morbidity and/or mortality. Congenital diaphragmatic hernia (CDH) is a defect in the fetal diaphragm that is associated with displacement of abdominal viscera into the fetal thorax and abnormal pulmonary parenchymal and vascular development; the resulting pulmonary hypoplasia and pulmonary arterial hypertension account for the majority of CDH morbidity and mortality [1, 2]. Fetal endoscopic tracheal occlusion (FETO) has been proposed for severe forms of CDH with observed-to-expected lung area to head circumference ratio (O/E-LHR) <0.25 [1, 3–6].

Bronchopulmonary sequestration (BPS) has been associated with CDH and is characterized by an unaerated but perfused mass of lung tissue. These masses receive direct blood supply from the aorta and may be intra- or extralobar [7–9]. Extremely large BPS may cause in utero mediastinal shift, cardiac dysfunction, hydrops fetalis, or fetal demise. Postnatal finding includes ventilation-perfusion mismatch that further complicates issues of pulmonary hypoplasia and hypertension seen in CDH patients. Ultrasound-guided laser ablation of abnormal feeding vessels has been proposed and performed successfully to decrease the chances of perinatal death in fetuses with isolated BPS [10–13].

Even with the promising advancements in fetal therapy, fetal comorbidities present a unique challenge due to the limited guidance on technical approach and outcome data, the compounded effects of multiple congenital anomalies, and the inherent risk to maternal health undertaken for potential but uncertain fetal benefit. In addition, the presence of multiple major congenital anomalies is typically considered an exclusion criterion for potential in utero treatment. The present article describes our experience with sequential in utero interventions to treat 2 severe major anomalies (severe left-sided CDH and giant intralobar BPS) over the course of gestation using a multidisciplinary approach as a model of individualized fetal care.

Case Report/Case Presentation

A 36-year-old, gravida 4, para 1021, woman was referred to our fetal center with a preliminary diagnosis of CDH. Ultrasound evaluation at 22 weeks confirmed a left-sided CDH with suspected liver and stomach herniation into the left fetal chest in association with an extremely large posterior left intralobar BPS (3.7 × 2.6 × 5.2 cm) with abnormal feeding artery from the aorta and a small anterior left-sided extralobar BPS with a feeding artery from the chest wall (Fig. 1a). The Congenital Pulmonary Airway Malformation Volume Ratio (CVR) for the intralobar mass was 1.2 (CVR <1.6 suggests a low risk of fetal hydrops); O/E-LHR was 0.21 (severe CDH). Fetal MRI at 22 5/7 weeks of gestation confirmed ultrasound findings and identified no normal-appearing left fetal lung and reduced right lung volume (O/E total lung volume [TLV] was 0.24) (Fig. 1b). Three-dimensional ultrasonography confirmed the presence of a large abnormal artery feeding the intralobar BPS (Fig. 1c). Ultrasound-guided amniocentesis was performed, and a normal male fetal microarray was confirmed.

At 25 5/7 weeks, the BPS was noted to be increasing in size with CVR increasing to 1.9, but no evidence of hydrops. Betamethasone was administered for mass size reduction and fetal lung maturation [14]. Despite steroid therapy, follow-up scans demonstrated rapid growth of the BPS. The O/E-LHR was 0.19, and the CVR progressed to 2.8 (high risk of hydrops) at 26 2/7 weeks. Given the increasing size of the lesion with severe compression of the right lung and early signs of hydrops including a small pericardial effusion and scalp edema, fetal therapy was considered as an alternative to expectant prenatal management.

A multidisciplinary team was assembled to discuss treatment options and included maternal-fetal surgeons, pediatric surgeons, neonatologists, pediatric otolaryngologists, obstetric anesthesiologists, radiologists, palliative care, social workers, and ethicists. Options of open fetal surgery with resection of the BPS and possible diaphragm closure versus ultrasound-guided laser ablation with possible subsequent FETO procedure were considered. Given the poor fetal prognosis and known maternal risks associated with

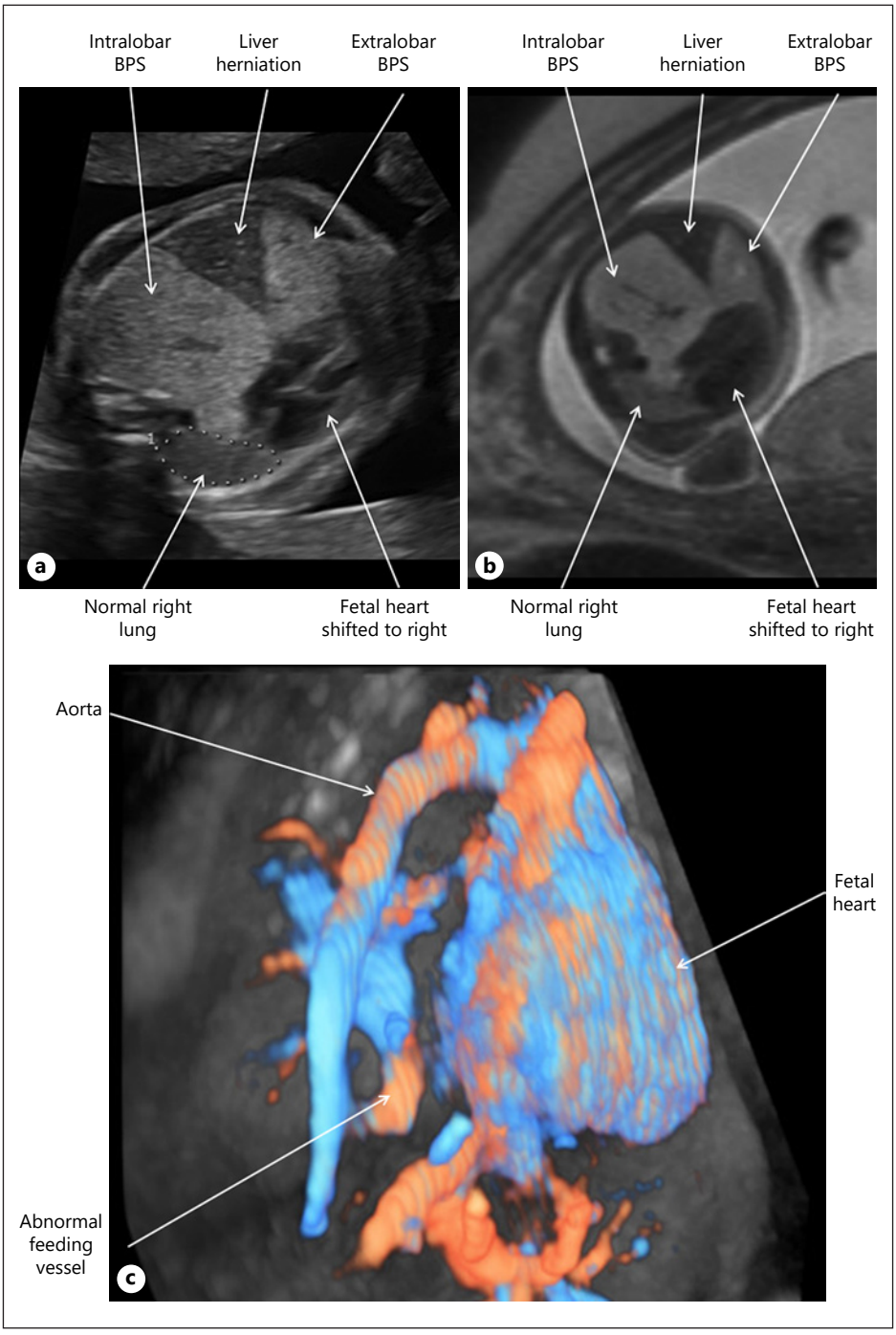

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Fig. 1. a Two-dimensional ultrasound imaging of a cross-sectional view of the fetal chest at the 4-level chamber view at 22 weeks of gestation showing a large posterior intralobar BPS, liver herniation caused by CDH in the middle, and a small anterior extralobar BPS associated with severe mediastinal shift in a fetus at 22 weeks of gestation. **b** Fetal magnetic resonance imaging of a cross-sectional view of the fetal chest at the 4-level chamber view at 22 weeks of gestation showing a large posterior intralobar BPS, liver herniation caused by CDH in the middle, and a small anterior extralobar BPS associated with severe mediastinal shift in a fetus at 22 weeks of gestation. **c** Three-dimensional color Doppler ultrasonography showing a large abnormal pulmonary sequestration feeding vessel from the aorta artery. BPS, bronchopulmonary sequestration; CDH, congenital diaphragmatic hernia.

open fetal surgeries, the team recommended a minimally invasive sequential approach. This was approved by our Fetal Ethical Advisory Board, and the management options were reviewed with the parents who consented for the procedures.

At 26 6/7 weeks, ultrasound-guided percutaneous laser ablation of the BPS feeding vessel [11, 12] was performed. The patient received preoperative tocolysis with intravenous magnesium sulfate. Local anesthesia was provided with 20 cc of 1% lidocaine in conjunction with midazolam (3 mg) and a propofol infusion (25–65 μg/kg/min) for intravenous sedation. Under ultrasound guidance, an 18-gauge needle was inserted into the amniotic cavity and advanced into the fetal leg where a combination of fentanyl (10 μg/kg), atropine (20 μg/kg), and vecuronium (0.2 mg/kg) was injected intramuscularly for fetal anesthesia. The needle was then directed into the abnormal feeding vessel of the large left BPS (vascular laser ablation) [12]. A 400-mc laser fiber was advanced through the nee-

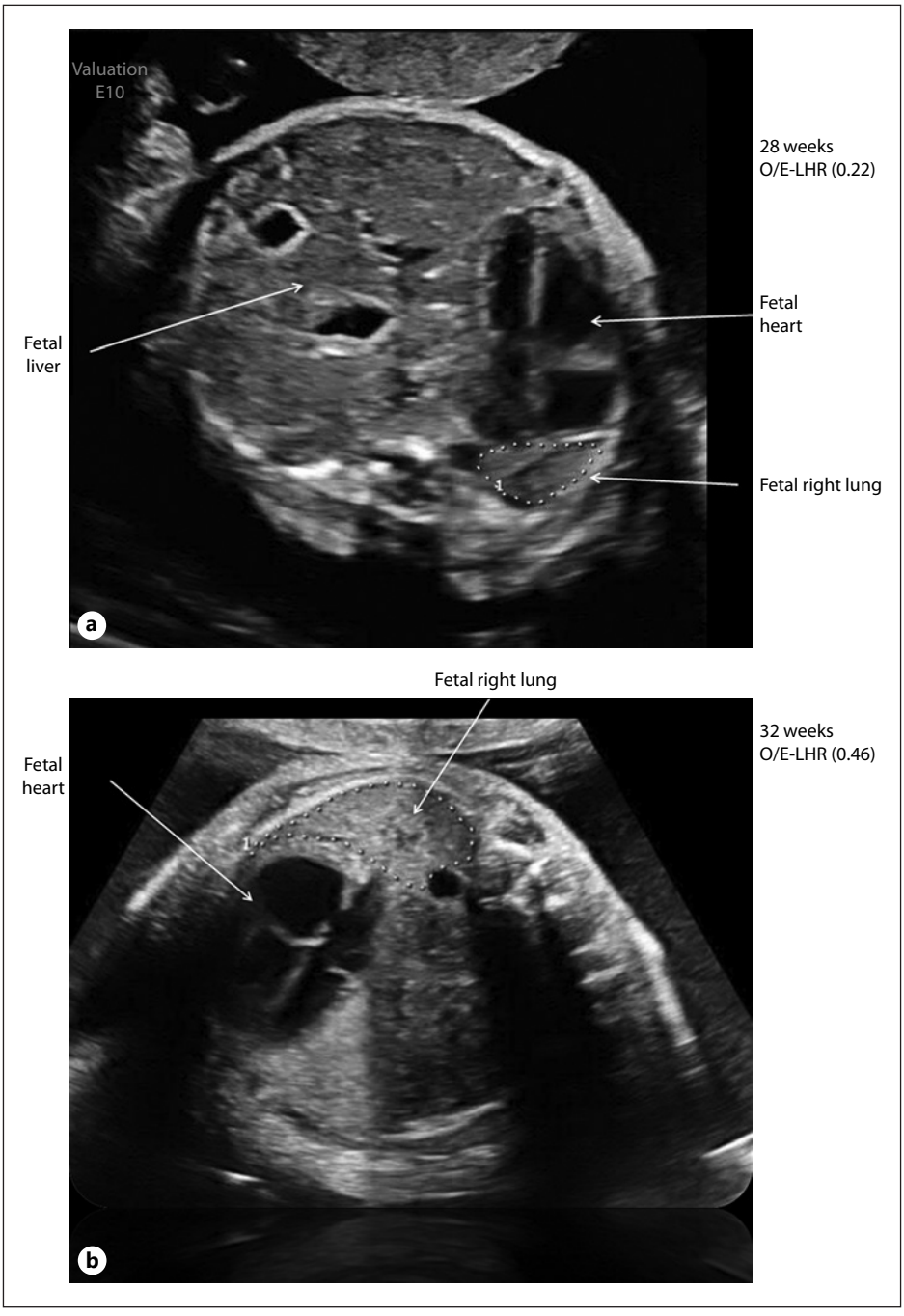

Fig. 2. a Two-dimensional ultrasound imaging of a cross-sectional view of the fetal chest at the 4-level chamber view at 28 weeks of gestation showing a severe left-sided CDH with the O/E-LHR of 0.22. **b** Two-dimensional ultrasound imaging of a cross-sectional view of the fetal chest at the 4-level chamber view at 32 weeks of gestation showing an increased O/E-LHR of 0.46. CDH, congenital diaphragmatic hernia; O/E-LHR, observed-to-expected contralateral lung area to head circumference ratio.

dle, and a 25-W laser was fired. Immediately following ablation of the vessel, the fetus acutely developed pleural effusions and ascites associated with fetal tachycardia to 180 beats per minute. The pediatric cardiologist performing fetal echocardiography identified the ventricles were underfilled supporting our teams' hypothesis that there was an acute sequestration of blood within the lung mass resulting in hypovolemia as no signs of bleeding were identified. Blood transfusion was performed by removing the 18-gauge needle and directing a 22-gauge needle into the right ventricle because of a rapid deterioration of the fetal cardiac function. Ten milliliters of concentrated O negative, leukocyte-reduced blood was transfused, which resulted in normalization of the cardiac rate. No significant pericardial effusion was noted, and the 22-gauge needle was removed. Reassessment of the BPS demonstrated a persistent flow in the feeding vessel. The 18-gauge needle was replaced into the mass, and repeat laser ablation was performed by targeting the feeding vessel. The procedure was at this point considered successful with no blood flow seen in the abnormal feeding vessel. The

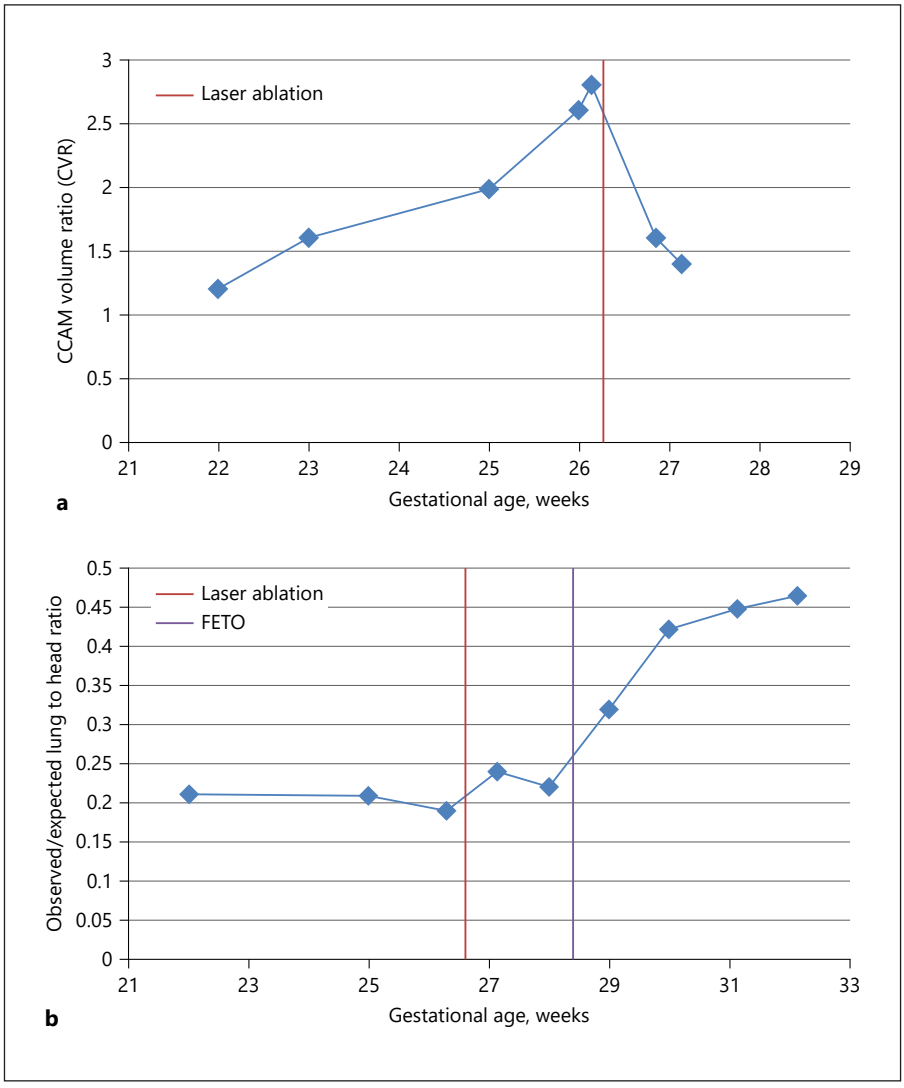

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Fig. 3. a Longitudinal measurements of the CVR (volume of the large extralobar BPS by head circumference) according to gestational age in the present fetus. The red line indicates the gestational age at the ultrasound-guided laser ablation of the abnormal feeding vessel (first fetal intervention). **b** Longitudinal measurements of the O/E-LHR according to gestational age in the present fetus. The red line indicates the gestational age at the ultrasound-guided laser ablation of the abnormal feeding vessel (first fetal intervention).The purple line indicates the gestational age at FETO (second procedure in the fetus). CVR, Congenital Pulmonary Airway Malformation Volume Ratio; O/E-LHR, observed-to-expected contralateral lung area to head circumference ratio; FETO, fetal endoscopic tracheal occlusion.

remainder of her surgical course was uncomplicated. There were no sonographic signs of fetal brain injury at the end of the procedure.

Follow-up ultrasound scans showed evidence of BPS shrinkage with a considerable decline in CVR from 2.8 presurgery to 1.4, 2 days postsurgery (Fig. 3a). After this initial evaluation, it became difficult to measure the treated BPS as the borders could not be distinguished from the surrounding tissue. Serial ultrasounds, however, demonstrated a slight but unremarkable increase in O/E-LHR (0.22) with the liver persistently up at 28-week gestation (Fig. 2a). Because of the absence of improvement of the contralateral (right) lung size, FETO was offered and performed at 28 6/7 weeks with no perioperative complications, using the technique previously described [1, 15]. In brief, under ultrasound guidance, a 10F catheter (Cook Medical) was inserted through the maternal abdomen into the uterus and amniotic cavity. A 1.3-mm fetoscope was placed into the sheath and advanced toward the fetal mouth. The tongue was identified, and the fetoscope was manipulated to identify and advance through the vocal cords into the trachea. The balloon (GOLDBAL2; Balt Extrusion, Montmorency, France) was advanced into position above the carina to be inflated with 0.8-mL saline. The balloon placed did not inflate fully; therefore, a second balloon was deployed without any issues.

The patient was followed by weekly ultrasound examinations at our fetal center. Following the FETO procedure, the O/E-LHR improved over the course of gestation (0.46 prior to delivery, Fig. 2b) until spontaneous preterm labor at 32 weeks and 5 days of gestation (Fig. 3b). In utero fetoscopic endotracheal balloon retrieval was performed. Both balloons were punctured and removed. The initial balloon was partially deflated. No fetal trachea abnormality was seen during fetal laryngoscopy. The patient delivered a male neonate vaginally 2 h after balloon retrieval. The birth weight was 2,600 g, and APGARS were 2 and 5 at 1 and 10 min, respectively. The neonate was intubated and transferred to the neonatal intensive care unit for further management. The patient was adequately supported after delivery on a conventional ventilator initially without the need for nitric oxide or milrinone therapy. By day of life (DOF) 2, he was transitioned to high-frequency jet ventilation to minimize

lung injury given an increasing respiratory acidosis. He was also started on nitric oxide therapy for increasing oxygen requirements. After these interventions, minimal ventilator changes were required with a stable oxygenation index of 5–8 until surgical intervention. A computed tomography scan performed on DOL 4 demonstrated a significant reduction in the intralobar sequestration size with a small amount of blood flow in the pulmonary vein, persistent anterior extralobar sequestration, and CDH with herniation of the stomach, spleen, pancreas, and bowel into the left chest. He began milrinone on DOL 6 and did transition to the oscillator with 12-rib expansion noted on preop X-ray.

During central line placement on DOL 7, a through-and-through venous puncture occurred. Because high pressures were required to ventilate him, this injury resulted in intrathoracic bleeding. The vein was repaired with a single suture, and he was placed on central extracorporeal life support (ECLS) via median sternotomy. On DOL 10, the type D diaphragmatic hernia was repaired with a Gor-Tex mesh and the extralobar sequestration was resected. Of note, the omentum was adherent to the previously ablated sequestration and carefully dissected free. The spleen and stomach were then able to be reduced. No attempt was made to resect the residual intralobar sequestration due to the response to the ablation.

His postnatal course was complicated by severe posterior tracheobronchomalacia comprising much of the tracheal length. To allow for healing, ECMO was continued until DOL 22. He then underwent tracheostomy and laparoscopic gastric tube placement on DOL 130. He was noted to have severe anterior collapse at the tracheostomy site. The neonate accordingly underwent slide tracheoplasty on DOL 252 in anticipation of eventual decannulation. He was weaned completely off of the ventilator DOL 276 to tracheostomy collar at night and Passy Muir valve during the day. The remainder of his hospitalization was uncomplicated, but prolonged while waiting for in-home nursing support. He was discharged home on DOL 296 (9 months). There is no evidence for hernia recurrence at 1 year of life.

Discussion/Conclusion

The present report describes the successful management of 2 major fetal anomalies (CDH and BPS), affecting the development of normal lung tissue, with sequential therapies. Our case highlights the importance of a multidisciplinary approach with adequate family counseling. The BPS was targeted first due to its increasing size which significantly impeded right lung growth, along with ongoing progression to fetal hydrops. We hypothesized that reduction in the BPS size could result in right lung expansion. However, lung response after ultrasound-guided laser ablation was minimal, despite the remarkable tumor reduction, likely due to concomitant large CDH. FETO was subsequently performed to improve the lung response.

Fetal microcystic lung lesions including BPS have an overall favorable prognosis in the absence of hydrops. However, perinatal mortality can be as high as 100% if fetal hydrops develops [16]. Therefore, fetal interventions were proposed for this subset of patients to improve perinatal survival. Open fetal surgery is associated with higher maternal morbidity due to procedural complications and is associated with a 50% infant survival rate [12, 17, 18]. Conversely, a less invasive approach with percutaneous vascular laser ablation of BPS is associated with lower maternal morbidity and improved survival rates of up to 88% [12]. In our case, after the laser ablation reduced the mass, the fetus had regression of hydrops.

Severe CDH, defined as O/E-LHR <0.25, is associated with poor postnatal outcomes due to complications of pulmonary hypoplasia and pulmonary arterial hypertension [19]. Prognosis is further compounded by the presence of additional anomalies, including fetal thoracic lesions which impede lung growth. FETO has been proposed for severe CDH to promote regrowth of fetal lung tissue [1, 15, 20–22]. Early reports of the outcomes of FETO have demonstrated improved lung response and survival in fetuses with isolated severe (LHR <1.0 with liver herniation or O/E-LHR <0.25) [1, 23] and extremely severe (LHR <0.7 or O/E-LHR <0.17) [21] CDH. While our patient demonstrated improved lung growth prenatally and had adequate volume for ventilation postnatally, he suffered from tracheomalacia, which has been described as a complication of FETO [24–26]. However, the extent of tracheomalacia noted in our patient may have been due to abnormal development associated with 2 such severe anomalies since he had a stoma-level obstruction that needed tracheoplasty. A large multicenter randomized controlled trial (Tracheal Occlusion to Accelerate Lung Growth) is currently underway to further define the potential benefits and complications of FETO (ClinicalTrials.gov Identifier: NCT01240057 and NCT02875860).

Fetal interventions aim to primarily reduce neonatal morbidity and mortality associated with congenital anomalies. While multiple fetal anomalies may compound risks for postnatal complications, our innovative approach proposes that it should not automatically preclude fetal therapy depending on the anomalies. Hamrick et al. [27] reported a similar case of CDH with BPS, managed prenatally with concurrent FETO and open fetal thoracotomy for BPS resection at 27-week gestation. The patient delivered via ex utero intrapartum treatment following preterm contractions at 32-week gestation. Early neonatal course was further complicated by a postnatally diagnosed d-transposition of great arteries, which the authors attributed to poor postnatal outcomes and eventual death of the infant. We believe our sequential management with 2 less invasive approaches may have contrib-

uted to better outcomes observed in our patient and importantly decreases the maternal morbidity associated with open surgical procedures.

In conclusion, sequential minimally invasive fetal interventions can be performed successfully and may be useful in particular situations as described here. This approach however requires further studies to confirm our hypothesis.

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Statement of Ethics

The patient described in this case has provided a written informed consent for research purposes (including the use of select images).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Rodrigo Ruano: study conception and design and manuscript writing and review. Eniola R. Ibirogba and Michelle A. Wyatt: manuscript writing and review and approval of the final draft. Karthik Balakrishnan, M. Yasir Qureshi, Amy B. Kolbe, Joseph A. Dearani, R. Paul Boesch, Katherine W. Arendt, Ellen Bendel-Stenzel, Leal Segura, and Shana S. Salik: manuscript review and approval of the final draft. Denise B. Klinkner: manuscript outline and drafting and review.

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