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Antenatal Management of Bronchopulmonary Sequestration by Intrafetal Vascular Laser Ablation under Ultrasound Control: Narrative Review of the Literature and Report of Three Cases

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Keywords
Fetal pulmonary malformation · Bronchopulmonary sequestration · Laser coagulation · Hydrops

Abstract
Objective: The objective of this study is to assess the effectiveness and safety of intrafetal vascular laser ablation (VLA) for fetuses with bronchopulmonary sequestration (BPS) with hydrops. ***Methods:*** First, we present 3 cases of fetuses with BPS and hydrops treated by VLA. Second, we aimed to conduct a narrative review to identify all reported cases of fetuses with BPS treated by intrafetal VLA. ***Results:*** The review of the literature identified 41 fetuses treated by VLA for BPS with hydrops. The median gestational age of the VLA was 27^{+0} weeks' gestation [25^{+0}–31^{+0}] with an associated procedure at the same time in 43% of the cases (pleuroamniotic shunt, thoracentesis, and amniodrainage). A second procedure was required in 25% of cases for residual flow in the feeding vessel. No stillbirth or neonatal death was reported. The complications reported were a fetal thoracic hematoma complicated by fetal anemia and 4 preterm deliveries with a rate of 9%. ***Conclusion:*** VLA of the feeding vessel can be an effective treatment but is not without complications. In cases demonstrating cardiac output failure, intrafetal VLA should be considered as a treatment for BPS.

Introduction

Fetal pulmonary malformations are rare, representing approximately 1/15,000 live births [1]. The most common are congenital pulmonary airway malformation

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(CPAM) and bronchopulmonary sequestration (BPS). BPS is an abnormal mass of lung tissue without bronchial communication and with vascularization from an aberrant systemic vessel [2]. BPS is called intralobar when located in the pulmonary lobe and extralobar otherwise. Ultrasound shows a hyperechoic mass, most often posterior basal and triangular, with a feeding vessel from the systemic circulation [3]. BPS can be hybrid lesions, which are a combination between BPS and CPAM [4, 5]. When stable in size over the pregnancy, BPS is associated with favorable perinatal outcome with spontaneous regression in 50% of cases [6, 7]. However, in rare cases, rapid and significant growth of BPS can lead to mediastinal compression, eversion of diaphragm, pleural effusion, cardiac output failure, and hydrops with a perinatal mortality close to 100% [5, 8, 9]. Different therapeutic options with heterogeneous results have been described for the management of fetuses with complicated BPS, including symptomatic treatments (thoracentesis and pleuroamniotic shunting) and ablation of the feeding artery of the BPS (sclerotherapy, radiofrequency, and open fetal surgery) [7, 9–12]. Laser coagulation of the feeding vessel under ultrasound guidance was described for the first time by Oepkes et al. [13]. Although only short case series and case reports have been reported, by occluding the feeding vessel this technique seems to improve the survival of fetuses with BPS complicated by hydrops. There is now a 10-year set of data from published case series and case reports. Our aims were to describe the surgical technique, to report the outcomes of the cases in our center, and to carry out a narrative review to assess the effectiveness and risks of laser coagulation of the feeding vessel under ultrasound guidance in cases of BPS.

Materials and Methods

Case Reports

We report 3 cases of fetuses treated in our center for complicated BPS by vascular laser ablation (VLA). Patients gave their consent for the case reports. We describe the surgical technique.

Surgical Technique

The procedure is performed under local maternal anesthesia with 1% xylocaine. Fetal anesthesia is performed by fetal intramuscular injection of sufentanil, curare, and atropine using a 20-gauge needle. A 17-gauge needle is inserted adjacent to the feeding vessel inside the BPS under ultrasound guidance. The diode laser 600 μ fiber is introduced into the needle, and the feeding vessel is coagulated with a power of 30 Watts under continuous ultrasound guidance until complete cessation of the blood flow.

Review

We aimed to conduct a narrative review to identify all reported cases of fetuses with BPS or hybrid lesions treated with vascular laser coagulation, in order to assess the efficacy, feasibility, and safety of this treatment. We searched the PubMed and Medline databases with the following search criteria: "bronchopulmonary sequestration," "prenatal treatment," and "laser ablation" until August 2018. Included articles were case series and case reports of fetuses with BPS complicated by hydrops. Articles about CPAM treated by interstitial laser coagulation were excluded. Included articles were reviewed by 2 reviewers, and the data were extracted according to a preestablished protocol. Only the articles in English were included to make a detailed analysis. For each selected fetus, we recorded for analysis information about (1) the diagnosis: the type of lesion suspected (hybrid lesion or BPS), gestational age at diagnosis, and the presence of associated signs (pleural effusion, hydrops defined by either a subcutaneous edema associated with the effusion of a serosa or by the effusion of 2 serous membranes), (2) the management: the gestational age at the time of procedure, the emitted laser power, the need for a second procedure, and complications, and (3) the outcomes: presence of residual blood flow in the feeding vessel, progression of the pleural effusion, change in the size of the BPS, gestational age at birth, perinatal survival, and the need for postnatal surgery. Data obtained from the literature and the 3 new cases were analyzed.

Results

Case 1

Case 1 was a patient gravida 2 para 2, with no medical history. The first-trimester screening result was 1/10,000. A left lower BPS was suspected on the second-trimester ultrasound exam. At 28^{+0} weeks' gestation (WG), the patient was referred to our center because of signs of hydrops (hydrothorax, a low-volume ascites, and hydrocele) without mediastinal deviation (Fig. 1a). The feeding vessel of the BPS highlighted by color Doppler was from the systemic circulation (Fig. 1b). Because of the hydrops, an intrauterine treatment by laser ablation of the feeding vessel was indicated. Antenatal corticosteroid therapy for fetal pulmonary maturation was performed at 28^{+0} WG. Amniocentesis showed a normal karyotype 46, XX. The procedure was performed at 28^{+2} WG as previously described. Figure 2 shows the complete cessation of the blood flow in the feeding vessel of the BPS at the ultrasound exam. After 15 min, there was no visualization of Doppler flow with a 0.9 Hz pulse radio frequency in the feeding vessel. At 30^{+0} WG, there was a complete resolution of the hydrops (Fig. 2). At 34^{+0} WG, the size of the BPS had decreased by 35%, with a change in the echogenicity (hypoechoic) and no residual flow in the feeding artery. At 38^{+0} WG, a 2,870 g male child was delivered vaginally

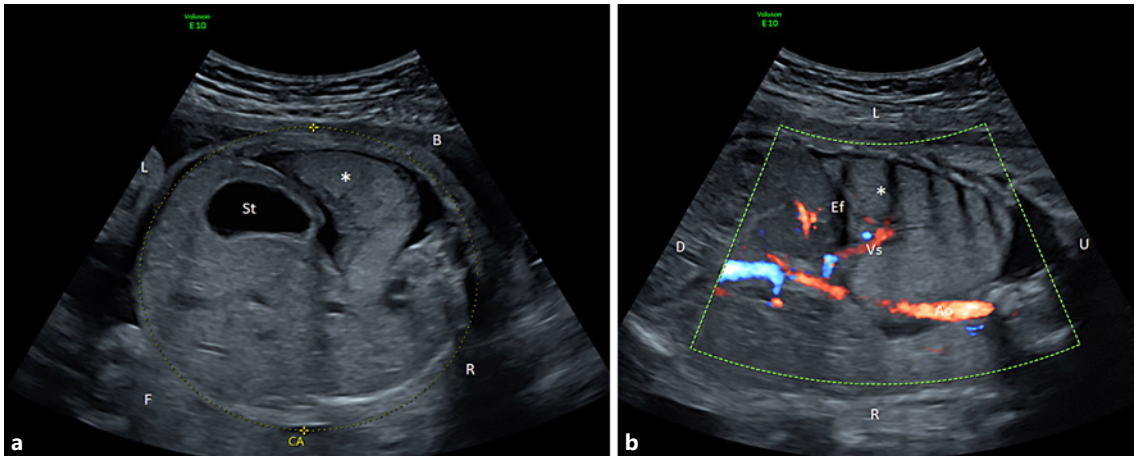

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Fig. 1. a Preoperative ultrasound exam. **b** Axial view: left isoechoic BPS (*) surrounded by pleural Ef. Preoperative ultrasonography exam, frontal view, Doppler: visualization of the feeding vessel (Vs) of systemic origin vascularizing BPS (*) which is a posterior left basal triangular isoechoic image, surrounded by pleural Ef. U, up; D, down; Ef, effusion; St, stomach; R, right; L, left; BPS, bronchopulmonary sequestration.

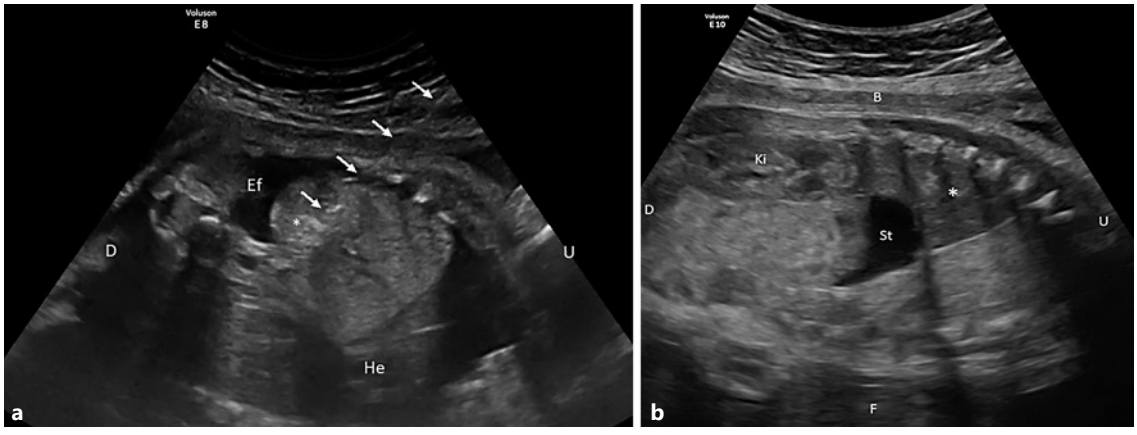

Fig. 2. a Perioperative ultrasound, frontal view: (→) visualization of the 17-gauge needle adjacent to the vessel. (*) BPS. **b** Postoperative ultrasound exam, parasagittal view: The sequestration (*) becomes hypoechoic and decreases in size. Complete regression of pleural effusion. St, stomach; Ki, kidney; U, up; D, down; BPS, bronchopulmonary sequestration; He, heart, Ef, effusion; U, up, D, down.

with normal Apgar scores and normal acid-base balance in cord blood. At 15 min of life, the child was transferred to the neonatal intensive care unit for 12 h because of respiratory distress. The ultrasound exam at day 1 showed the persistence of a 10 mm left BPS. A computerized tomography scan performed at 2 months of age showed a 15 mm BPS in the left costodiaphragmatic recess. The child is now in good health at the age of 18 months, and no surgery has been performed.

Case 2

Case 2 was a patient gravida 3 para 2, with a medical history of 1 vaginal delivery and 1 cesarean section. The first-trimester screening result was 1/1,194. At 22^{+0} WG, the ultrasound exam showed a left BPS associated with CPAM. There was an isolated mediastinal deviation without hydrops. The ultrasound follow-up showed at 28^{+0} WG signs of fetal hydrops with left pleural effusion, eversion of the diaphragm, ascites, hydrocele, and polyhy-

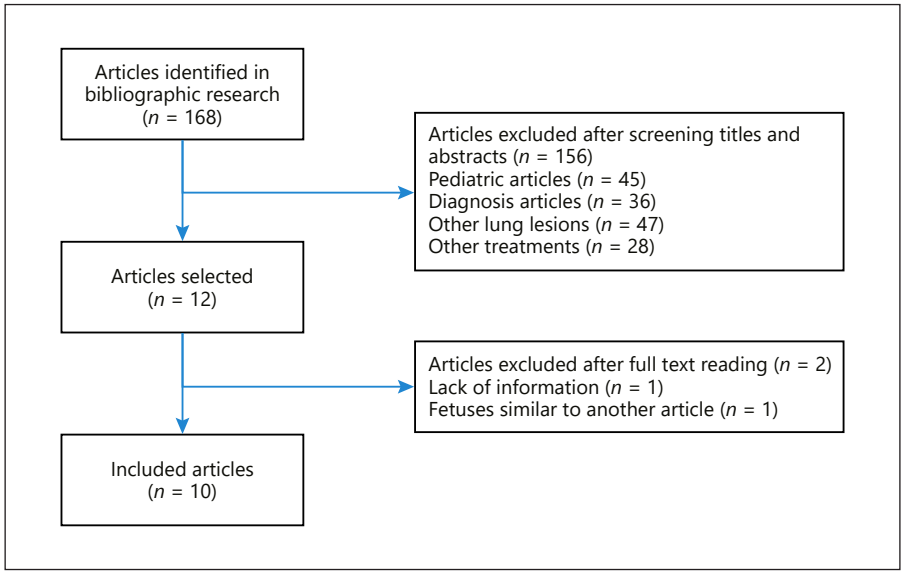

Fig. 3. Flow chart of the review of the literature.

dramnios. A treatment by laser ablation of the feeding vessel was indicated. The procedure was performed at 28^{+5} WG as described in the section below. A 1,250 mL amniodrainage was performed. The karyotype was normal 46, XY. Two days after the procedure, there was a complete regression of pleural effusion, ascites, and hydrocele. The amniotic fluid volume was normal. Three days after the procedure, a residual flow persisted in the feeding vessel. The flow was minimal and, therefore, a second procedure was not performed considering the high risk of premature rupture of membranes with repeated invasive procedures. At 30^{+4} WG, the size of the BPS had decreased by 25%, with a very slow residual flow in the feeding artery (pulse radio frequency 0.6 Hz) and a persistent moderate mediastinal deviation. At 38^{+0} WG, a 2,780 g male child was delivered by cesarean section because of fetal distress. He was put into therapeutic hypothermia for peripartum anoxia whose course was favorable after 8 days. The ultrasound exam at 5 days of life showed a BPS of 23 mm. At the age of 1 year, the child had a respiratory infection that resolved after antibiotic treatment. The child did not undergo sequestrectomy and is in good health at the age of 7.

Case 3

Case 3 was a nulliparous patient. The first-trimester screening result was 1/2,134. At 25^{+0} WG, the ultrasound exam showed a left BPS associated with mild pleural effusion and moderate heart deviation. At 30^{+0} WG, the ultrasound follow-up showed the growth of the BPS measuring 41 mm long-axis with an increased left pleural effusion, heart deviation, and eversion of the diaphragm. Antenatal corticosteroid therapy for fetal pulmonary maturation was performed at 30^{+2} WG. At 30^{+6} WG, the patient was referred to our center because of the important growth of the BPS. A treatment by laser ablation of the feeding vessel was indicated. The procedure was performed at 30^{+6} WG as described in the section. The karyotype was normal 46, XY. Two days after the procedure, there was a residual flow persistent in the feeding vessel. Therefore, a second procedure was performed at 31^{+2} WG and was successful with cessation of the blood flow. At 33^{+1} WG, the size of the BPS was stable with a change in the echogenicity (hypoechoic) and no residual flow in the feeding artery. MRI performed at 33^{+3} WG showed stability in BPS size with the appearance of signal changes consistent with ischemic-hemorrhagic changes. At 38^{+2} WG, a 3,030 g male child was delivered vaginally with normal Apgar scores and normal acid-base balance in cord blood. The neonate remained asymptomatic and was discharged with her mother in good condition.

Review

General Data

The literature search yielded 168 articles. After screening the titles and abstracts, we identified 12 articles related to intrafetal VLA under ultrasound control. One article was excluded because the study population was similar to that of another article (5 similar patients) [14]. In total, including our case reports, 44 fetuses were studied in 10 articles (Fig. 3). We present here a narrative summary of the articles that we found on the topic.

Table 1. Diagnosis, management, and complications of fetuses with complicated BPS managed by VLA: Review of the 44 cases reported in the literature and our 3 cases [22–24]

Series	Cases, *n*	Lesion type	Gestational age at diagnosis, WG	Pleural effusion or hydrops	Mediastinal deviation	Associated procedure at the same time	Gestational age at procedure, WG	Power, W	Second-line treatment	Complications
Oepkes et al. [13]	1	BPS	23	1	1	0	23	20–50	0	0
Ruano et al. [3]	1	BPS	28	1	1	Amniodrainage	29	35	0	0
Cavoretto et al. [7]	8	BPS	21^{+0}	8	8	0	29	30–50	0	3 preterm deliveries 34–34–35 WG
Witlox et al. [20]	1	BPS	23	1	1	Amniodrainage 1 Thoracentesis 1	23	35	0	0
Rammos et al. [22]	2	BPS	29^{+4}	2	2	Pleuroamniotic shunt 2	30^{+4}	na	VLA 1	0
Ruano et al. [1]	2	BPS	na	2	na	0	26^{+0}	30	VLA 1	0
Baud et al. [10]	1	Hybrid	18^{+0}	1	1	Pleuroamniotic shunt 1	18^{+0}	50	0	0
Cruz Martinez et al. [23]	8	BPS	na	8	na	0	27^{+0}	25	VLA 2	0
Gottschalk et al. [15]	12	BPS	29	12	12	Thoracentesis 12	31^{+0}	50	VLA 4	Anemia $n = 1$ PPROM $n = 1$
Cruz Martinez et al. [24]	5	Hybrid	na	5	5	0	25^{+0}	25	VLA 2	0
Our study, 2020	3	2 BPS/ Hybrid	23^{+0}	3	3	Thoracentesis 1	29^{+2}	30	VLA 1	0
Median/total	44	BPS 84% Hybrid 16%	25^{+0} [21^{+0}–29^{+0}]	100%	34/34 (100%)	19/44 (43%)	27^{+0} [25^{+0}–31^{+0}]		11/44 (25%)	5 (11.4%)

BPS, bronchopulmonary sequestration; na, not available; WG, weeks of gestation; PPROM, premature preterm rupture of membranes; VLA, vascular laser ablation.

Pulmonary lesions were BPS in 84% of cases and hybrid lesion with macrocysts in 16% of cases (Table 1). A feeding artery for pulmonary lesions was identified at the ultrasound exam. All lesions were complicated by hydrops or pleural effusion. The diagnosis of BPS associated with hydrops was made at the second trimester of the pregnancy at a median gestational age of 25^{+0} WG [IQR 21^{+0}–29^{+0}]. Those cases of BPS with hydrops were not associated with other malformations.

The median gestational age at the VLA of the feeding artery was 27^{+0} WG [IQR 25^{+0}–31^{+0}]. The procedure was performed under local anesthesia except in 1 case where general anesthesia was performed. At the same time as the VLA, an associated procedure was performed in 43% (19/44) of the fetuses: 2 amniodrainages (5%), 3 pleuroamniotic shunts (7%), and 14 thoracenteses (32%) (Table 1). A second VLA was required for 25% (11/44) of the fetuses because of recurrence of blood flow in the feeding vessel on the ultrasound exam. This situation occurred about 1 week after the first vascular laser coagulation.

Two complications were reported. First, fetal thoracic hematoma leading to fetal anemia complicated the procedure performed at 34 WG [15]. The fetus required postoperative blood transfusion. The outcome was favorable, with complete regression of BPS and no postnatal surgery. The second complication reported was a preterm premature rupture of membranes with a preterm delivery at 29^{+0} WG in a woman with a BMI of 34 kg/m^2[16]. There was a recurrence of blood flow in the feeding vessel. Because of the maternal obesity and the fetal position, a second intervention could not be performed. Neonatal surgery was performed and the neonate survived at discharge. In the present series, they were 4 preterm deliveries including 1 case with premature rupture of membranes at 29^{+4}, 2 at 34^{+0} WG, and 1 at 35^{+0} WG. No fetal death was reported.

Residual vascularization was reported for 3 fetuses (i.e., in 7% of the cases) (Table 2). However, regression of pleural effusion or hydrops was observed in 41/44 (i.e., 93%). Postnatal sequestrectomy was performed in 13/42 fetuses (i.e., 31%). Figure 4 shows the clinical course according to the size of the BPS after the intervention.

Figure 4 shows the postnatal need for surgery according to how the size of the BPS changed antenatally. After the procedure (Fig. 4), the BPS completely regressed at prenatal ultrasound in 16/41 fetuses (i.e., 39.0% of cases), only 2 of which (i.e., 12.5%) had a residual lesion found postnatally and underwent subsequent sequestrectomy. In 24/41 fetuses (i.e., 58.5% of cases), the size of the BPS decreased progressively but not completely antenatally

Table 2. Outcomes of fetuses with complicated BPS managed by VLA: Review of the 44 cases reported in literature including our 3 cases

Series	Cases, *n*	Residual vascularization	Regression of effusion	Regression of BPS size	Gestational age at birth, WG	Survival	Sequestrectomy
Oepkes et al. [13]	1	0	1	Partial	39^{+0}	1	0
Ruano et al. [3]	1	1	1	Partial	38^{+0}	1	1
Cavoretto et al. [7]	8	0	8	Partial 5 Total 3	38^{+0}	8	5
Witlox et al. [20]	1	0	1	Total	41^{+0}	1	0
Rammos et al. [22]	2	1	0	Partial 1 NA 1)	NA	2	2
Ruano et al. [1]	2	0	2	NA	37^{+4}	2	NA
Baud et al. [10]	1	0	1	Partial 1	39^{+0}	1	1
Cruz Martinez et al. [23]	8	0	8	Partial 8	38^{+0}	8	0
Gottschalk et al. [15]	12	1	12	Total 8 Partial 3 NA 1	39^{+1}	12	2
Cruz Martinez et al. [24]	5	0	5	Total 3 Partial 2	39^{+0}	5	2
Our study 2020	3	1	3	Total 1 Partial 2	38^{+0}	3	0
Median/total	44	3/44 (7%)	41/44 (93%)	Partial 23/39 (59%) Total 16/39 (41%)	39^{+0} [38^{+0}–39^{+0}]	44 (100%)	13/42 (31%)

BPS, bronchopulmonary sequestration; na, not available; WG, weeks of gestation; VLA, vascular laser ablation.

(Fig. 4). Almost half of them had postnatal sequestrectomy. In 1 fetus, VLA did not reduce the size of the BPS (Fig. 4), and this child had sequestrectomy at birth. Neither fetal death nor neonatal death was reported. The perinatal survival rate was 100% (Table 2).

Discussion

We report 3 fetuses with BPS complicated by hydrops treated successfully by VLA. Review of the literature shows a real benefit of antenatal treatment by VLA in the case of complicated BPS, with an overall perinatal survival rate of 100%. The procedure was complicated in 6.8% of cases by preterm deliveries above 34 WG and in 2.3% by preterm rupture of membranes with preterm delivery at 30 WG.

Other therapeutic procedures have been proposed for treatment of BPS complicated by hydrops. In 2010, Adzick et al. [9] reported a series of 24 fetuses with pulmonary lung lesions treated by open fetal surgery with fetal thoracotomy and lobectomy. One fetus with BPS in this series did not survive after antenatal surgery. This invasive procedure was associated with greater maternal and fetal morbidity (bradycardia, chorioamnionitis, severe prematurity, and failure of the technique, acute maternal pulmonary edema, mirror syndrome, secondary uterine rupture, and risks associated with conventional laparotomy). Radiofrequency ablation of BPS in utero was described in 1 case. The procedure was complicated by a diaphragmatic hernia associated with a parietal hernia. The newborn died of severe sepsis in neonatal intensive care [10]. The technique of sclerotherapy was described in 3 cases and consists in injecting a sclerosing polidocanol agent into the feeding vessel under ultrasound control. Survival rate was 100% with resolution of hydrops and a decrease in lesion size. Transient bradycardia was described in 1 case [11]. A similar procedure was

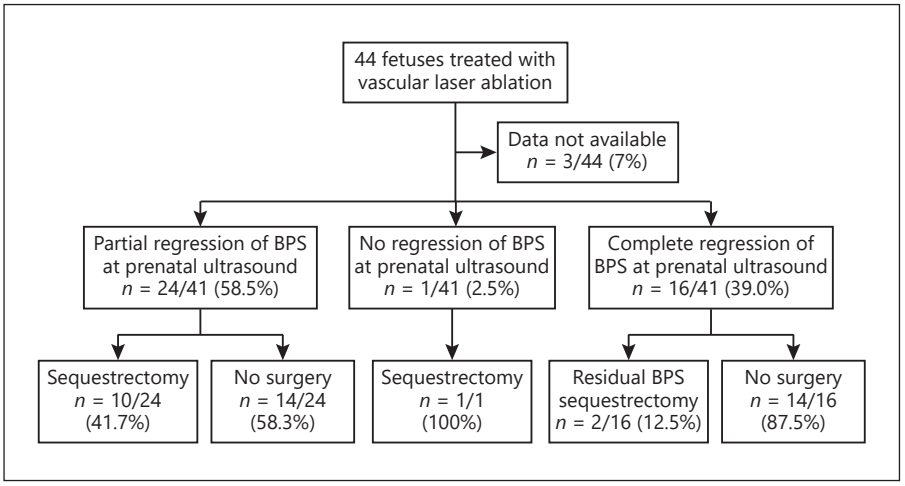

Fig. 4. Postnatal outcomes after VLA for BPS complicated by hydrops as a function of the change in size of the BPS. Review of the 44 cases reported in the literature, including our 3 cases. BPS, bronchopulmonary sequestration; VLA, vascular laser ablation.

described with alcohol injection [12], though very few cases were reported.

Other symptomatic treatments as thoracentesis and pleuroamniotic shunting have been proposed, but the results were poor, with reconstitution of the pleural effusion after thoracentesis [7]. Pleuroamniotic shunting allows in most fetuses avoidance of the reappearance of pleural effusion. However, these symptomatic treatments did not reduce the size of the sequestration or the pulmonary compression at birth. Only one case of regression of pulmonary sequestration after pleuroamniotic shunting has been reported [16]. In 2014, a study compared 7 fetuses with hydrops treated with pleuroamniotic shunting to 5 fetuses with hydrops treated with VLA. There was no complete regression in any case of BPS in the pleuroamniotic shunting group. This study showed that VLA was more effective than pleuroamniotic shunting [14].

Hyperechogenic lung lesions are known to decrease in size resulting in some cases in apparent disappearance after 28 weeks. So, 1 can argue that the 2 lesions might have decreased spontaneously. In both our cases, the worsening of hydrops made it difficult to wait and see [17]. In the third case, a significant growth of the BPS and increased pleural effusion were observed later in the third trimester at almost 31 WG suggesting that the lesion would not decrease. Considering the literature and the different therapeutic options described, intrafetal VLA is the main fetal therapy reported in the literature for the treatment of BPS complicated by hydrops. To date, very few isolated case reports on alternative treatments have been reported, especially cases of sclerotherapy with alcohol which consists of complete obliteration of the blood flow of the mass under ultrasound guidance [11, 12, 18], thrombogenic coil embolization [10], and radiofrequency ablation [10].

Intrafetal VLA is a standardized, minimally invasive procedure. Some clinicians perform pleuroamniotic shunting or thoracentesis in the case of massive pleural effusion, with no difference in the postnatal outcome. In our review, a second intervention was required for 25% of the fetuses because of recurrence of blood flow in the feeding vessel. The risk of recurrence of blood flow could be correlated with gestational age at the intervention, with a higher risk when performed after 28^{+0} WG, probably due to the greater size of the feeding vessel. The complication rate in our cohort was low. The main obstetrical risks are preterm delivery, with a rate of 9.1 versus 7.3% in the common population, and preterm premature rupture of membranes, with a rate of 2.3%. Only one fetal complication due to the procedure was reported: thoracic hematoma complicated by anemia. No case of perinatal death has been reported in the literature. The procedure was always performed in expert centers familiar with antenatal invasive procedures. The strength of our study is the exhaustive review of all reported cases of treatment by VLA for fetuses with complicated BPS. VLA is the most frequently reported procedure.

One limitation of our study is the retrospective design of the review that includes cases from different centers with various prenatal and postnatal practices, although all were expert centers. Another bias is the fact that the studies published (case series/case reports with very small numbers) probably include the cases with better outcomes, whereas cases that end poorly are unlikely to be written up for publication. As none of these articles had comparator groups and contain high risk of publication

bias, the results cannot be interpreted as sufficient evidence for laser as a first-line therapy. In many studies, the success of the procedure is assessed by the reduction of postnatal interventions. However, this is questionable because the postnatal management of BPS differs according to centers. Some consider that only symptomatic children should undergo surgery, whereas in other centers surgery is performed systematically to prevent the risk of complications of BPS, such as infection, pneumothorax, and secondary malignant degeneration. Few data are available on the long-term outcome of fetuses with antenatal intervention by VLA [19, 20]. Thanks to the prenatal reduction of the size of the sequestration, these fetuses could have decreased morbidity as less respiratory failure and fewer infections. Fetuses with chest masses and additional structural abnormalities were reported to have abnormal karyotype [21]. Even if no other malformation was associated at ultrasound exam, a karyotype was systematically realized at the time of laser.

VLA performed in fetal surgery centers is associated with a good perinatal survival rate. Further studies of long-term respiratory morbidity (pulmonary infections, oxygen dependence, and reintervention) are necessary.

Conclusion

Intrafetal VLA is an appropriate treatment for fetuses presenting BPS complicated by hydrops. It is associated with a good perinatal survival rate and with an obstetrical complication rate of less than 10%. Patients should be referred to prenatal surgery centers to be counseled about the procedure.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

H.B. designed the study. L.G. and H.B. reviewed and analyzed the relevant information in the literature and wrote the initial draft. A.B. and M.V.S. participated in the data analysis and revised the draft manuscript. V.C., V.F., G.L.B., and N.W. revised the draft manuscript for intellectual content.

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