Intrauterine Ultrasound-Guided Laser Coagulation as a First Step for Treatment of Prenatally Complicated Bronchopulmonary Sequestration: Our Experience and Literature Review

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Abstract

Introduction  Prenatal ultrasound-guided laser coagulation (USLC) for complicated bronchopulmonary sequestrations has been described but a consensus on the procedure and on the following management is still lacking. We present our experience and provide a literature review.

Methods  Retrospective review of patients treated in our center. Literature review and combined analysis of perinatal data were performed.

Results  Five cases were treated at our center, all presenting with severe hydrothorax. Four met the criteria for fetal hydrops. Four cases underwent postnatal computed tomography (CT) scan: in one case, there was no evidence of persistent bronchopulmonary sequestration. The other three underwent thoracoscopic resection, in two, a viable sequestration was found. Including our series, 57 cases have been reported, with no mortality and a success rate of 94.7%. Mean gestational age (GA) at the procedure was 28 ± 3.4 weeks and mean GA at birth and birth weight (BW) were 38.6 ± 2.3 weeks and 3,276 ± 519.8 g, respectively. In 80.6% of the cases investigated postnatally, a residual mass was found, 50% of cases who showed prenatal arterial flow cessation had a persistent sequestration postnatally, and 26.3% of cases underwent postnatal sequestrectomy. Both patients in our series had pathology examination confirming a viable bronchopulmonary sequestration.

Conclusion  Prenatal USLC seems to be a valid option for bronchopulmonary sequestration complicated by severe hydrothorax and/or fetal hydrops. Authors believe that this procedure should aim to reverse fetal distress and allow pregnancy continuation, and it should not be considered a definitive treatment. The currently available data do not support changes of the common postnatal management.

Keywords  ► fetal surgery  ► prenatal laser  ► bronchopulmonary sequestration  ► congenital lung malformation  ► thoracoscopy

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Introduction

Bronchopulmonary sequestration (BPS) is a rare congenital malformation of the respiratory tract in which nonfunctional tissue is supplied by one or multiple feeding arteries (FA), usually arising from the aorta. This is the main sonographic feature that allows to distinguish between microcystic Congenital Pulmonary Airway Malformation (CPAM) and BPS. Although the vast majority of fetuses with BPS has an uneventful prenatal course, a small percentage can undergo potential fatal complications. In BPS, these are more commonly due to hydrothorax rather than direct mass effect, as it is commonly observed in CPAM.

Hydrothorax is a potential lethal complication, being associated to an overall mortality of up to 68%. It may cause mediastinal shift, decreased venous return, and increased central venous pressure leading to fetal hydrops which is associated with a high mortality. Possible causes of hydrothorax in the context of BPS include obstruction of the venous drainage due to kinking or twisting of the vascular pedicle and fetal hyperdynamic circulation due to blood sequestration by the lesion which may lead to development of signs of fetal anemia.

Thoracoamniotic shunt (TAS) proved to be effective in treating fetal hydrothorax and preventing fetal hydrops, however, a considerable rate of mechanical complications such as occlusion or displacement has been reported. Moreover, TAS is a symptomatic treatment and it does not affect the underlying condition.

In 2007, Oepkes et al reported the first case of complicated fetal BPS, successfully treated with intrauterine ultrasound-guided laser coagulation (USLC) of the feeding artery. Since then, few reports of laser coagulation for fetal BPS have been published providing preliminary evidence of a potential benefit for fetal survival. However, a general consensus on this procedure is lacking, and the optimal postnatal management of such cases is still unclear.

The aim of this study is to present our experience on prenatal USLC of the feeding artery for complicated BPS, as well as the postnatal management of these cases and to review the currently available literature focusing on prenatal and postnatal management and outcomes.

Materials and Methods

Our Case Series

A retrospective review of all patients treated with USLC for complicated BPS at our institution was conducted. According to the institutional protocol approved in 2016, the indications for prenatal surgery in BPS were hydrothorax with mediastinal shift, hydrops, and/or other sonographic signs of fetal hemodynamic compromise, such as increased peak of systolic velocity in the fetal middle cerebral artery with polyhydramnios. All cases meeting the indication criteria for the procedure underwent a detailed fetal anatomical survey, fetal echocardiography, and karyotype analysis. Exclusion criteria were the presence of other congenital anomalies or chromosomal abnormalities. The procedure was discussed with the parents explaining other options: expectant management with a likely deterioration toward fetal hydrops and intrauterine death or pregnancy termination before 22 weeks of gestational age.

The prenatal procedure was performed by a fully trained obstetrician (N.P.) with extensive experience in intrauterine interventions, such as fetoscopic tracheal occlusion for congenital diaphragmatic hernia, fetoscopic laser for twin-to-twin transfusion syndrome, fetal-amniotic shunt placement, and fetoscopic repair of myelomeningocele, with another obstetrician assistant. The feasibility of the procedure was previously evaluated, identifying the safest access to the amniotic cavity based on the position of the placenta, target, and presence of myometrium vessels.

The intervention was performed under maternal local anesthesia. Fetal anesthesia was given with percutaneous US-guided intramuscular injection of a combination of fentanyl, rocuronium, and atropine. Rectal indomethacin was used for tocolysis and intravenous cefazolin for antibiotic prophylaxis. Under US guidance, a 17-G needle was inserted and positioned close to the feeding artery at few millimeters from its origin from the aorta. Then a 600-μm diameter diode laser fiber (Dornier MedTech GmbH, Westling, Germany) was advanced through the sheath of the needle. Laser energy with a power of 15 to 20 Watts was applied for 5 seconds, then blood flow in the artery was reassessed. Laser coagulation was repeated until no blood flow in the feeding artery could be demonstrated. Patients were discharged after a few days and underwent close weekly follow up until birth.

The procedure was considered successful in the absence of residual blood flow within the BPS and by demonstrating an improvement of sonographic signs of hemodynamic imbalance.

The parents are then advised to give birth in a tertiary level hospital with available and experienced neonatal intensive care unit (NICU) and pediatric surgery. No absolute indication for cesarean section was given.

Postnatally, our protocol for asymptomatic BPS includes a chest X-ray followed by a “feed&wrap” magnetic resonance imaging (MRI) of the chest and cardiological evaluation in the first month of life. In case of pathological MRI, a preoperative chest computed tomography (CT) followed by thorascopic resection is performed between 4 and 6 months of age. Symptomatic BPSs undergo open emergency resection.

Obstetric data, such as gestational age at procedure, preoperative, and postoperative fetal ultrasound findings, and delivery details were retrospectively collected. Postnatal management, radiologic and pathology results, and outcome were retrospectively reviewed and collected in case of inborn patients. For patients treated prenatally at our institutions but born and managed in other centers, telephonic information was collected from the parents.

The following postnatal data were collected: gestational age (GA) at birth and birth weight (BW), presence and type of symptoms, imaging performed (CT and/or MRI), timing and relative findings, whether an operation was done and, if so, the surgical approach (open or minimally invasive), as well as...
operative and pathology findings, and the available follow-up.

**Literature Review**

A review of the English Literature was conducted on PubMed using the following research query: “((antenatal)OR(fetal)) AND((laser)OR(ablation))AND((sequestration)OR(lung malformation)).” All papers were screened based on title and abstract. All papers reporting at least one case of BPS treated with prenatal laser coagulation were reviewed. Reviews reporting previously published data were not included in our review. Papers reporting only original data were therefore included in our review. In case of papers published by same authors or centers, results were cross-analyzed to eliminate duplicates of reported cases.

Data regarding all the cases of BPS treated with USLC were collected and summarized. BPS treated with other kind of prenatal intervention such as sclerotherapy, radio ablation, or TAS alone were not included. For each case, if available, the following information was collected: GA at the time of the procedure, side of the BPS, indications, presence of hydrothorax, presence of hydrops, and any associated procedures such as TAS or thoracentesis, need for repeat procedure, resolutions of fetal pathological signs, reported complete disappearance of BPS, complications, overall survival, GA at birth and BW, postnatal imaging and/or surgery, and radiological surgical and pathologic findings.

Postnatal management was assessed, specifically whether the patients underwent second level imaging, surgery, and collecting intraoperative and pathological findings, if mentioned.

Descriptive statistics regarding total number of cases, prevalent indications, success and complication rate, prevalence of prematurity and low BW, and type of postnatal management were obtained and presented.

**Results**

**Our Case Series**

During the study period (2017–2019), five cases have been treated with LC at our institution, two of which have been already previously reported. Details of our cases are reported in Table 1. All five cases presented with left BPS with severe hydrothorax with mediastinal shift, two of them also had associated ascites, and one had associated subcutaneous edema; hence, a total of four presented with fetal hydrops. The fifth case had associated polyhydramnios.

Mean GA at presentation was 25.6 (range: 20.1–31) weeks. Mean GA at the time of the procedure was 26.6 (range: 24–31) weeks. Mean duration of the procedure was 10 to 15 minutes.

In all cases, it was possible to successfully achieve complete coagulation of the feeding artery. No maternal or fetal intraoperative complications have been recorded.

The first case underwent concomitant placement of a TAS, while in the remaining cases, thoracocentesis was performed at the end of laser treatment. Amnioreduction was performed in the case with polyhydramnios. In all five cases, there was progressive improvement of preoperative fetal

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of the five patients treated at our center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient no.</td>
<td>GA at laser (wk)</td>
</tr>
<tr>
<td>1</td>
<td>31±7</td>
</tr>
<tr>
<td>2</td>
<td>26±7</td>
</tr>
<tr>
<td>3</td>
<td>24±7</td>
</tr>
<tr>
<td>4</td>
<td>28±7</td>
</tr>
<tr>
<td>5</td>
<td>24±7</td>
</tr>
</tbody>
</table>

Abbreviations: BPS, bronchopulmonary sequestration; CT, computed tomography; GA, gestational age; NA, not available.
sonographic findings, neither case of reperfusion of the feeding artery was documented nor was hydrothorax recurrence occurred at US follow-up. In all cases, the size of the BPS remained stable throughout follow-up.

One case was lost to follow-up 3 weeks after the procedure. The other four cases were born at a mean GA of 38.3 (range: 38–39) weeks after an uneventful postprocedure pregnancy. Mean BW was 3,396 (range: 2,820–4,070) g. No cases of neonatal distress were reported. Two patients were delivered at our institution, while the remaining two were delivered at other tertiary hospitals. Both patients delivered at our Institution were asymptomatic at birth. Therefore, the institutional standard protocol for BPS was applied. The MRI confirmed the presence of a lower left BPS in both cases, apparently extralobar. Chest CT scan showed persistence of the mass. In one case, there was no sign of perfusion while in the other, the BPS showed mild contrast enhancement.

Both patients were operated on thoracoscopically. In both cases, a macroscopically viable and perfused mass was found. The feeding artery was recognizable in its proximal part arising from the aorta. Extensive adhesions among the BPS, lung, and chest wall were present. Dissection of these adhesions was challenging with moderate bleeding, although not requiring transfusion. Pathological analysis confirmed the diagnosis of BPS. In one case, signs of necrosis were described but together with neoangiogenesis.

Of the two cases delivered elsewhere, one had a postnatal CT that demonstrated a nonperfused small left lower BPS. Decision was made to proceed with thoracoscopic exploration and a small mass was found. No intra- nor postoperative complications were reported. The last case underwent a postnatal CT scan that did not show any residual mass, and conservative management was chosen. All four patients are doing well at follow-up (mean = 2.6; range: 1–4 years).

**Literature Review**

Review of the literature identified 11 studies with original data of at least one case of BPS treated prenatally with USLC. Data on a total of 57 patients, including the five cases reported in the present series, were extrapolated and analyzed.

The side of the BPS was specified in 49 cases, 42 were left (85.7%) and 7 were right (14.2%).

Regarding indications, Table 2 summarizes perioperative and pregnancy characteristics of reported cases and details on postnatal management. A total of 56 cases (98.2%) presented with hydrothorax. In eight cases, no information was given on associated fluids collection. Among the others, in 12 (24.5%) cases, the hydrothorax was reported as isolated, in 19 (38.8%), it was associated with polyhydramnios, and in 19 (38.8%) cases, fetal hydrops were present.

The procedure was performed at a mean GA of 28 ± 3.4 (range: 19–34) weeks. In four cases, a concomitant TAS was placed. Two papers mentioned the diameter of the feeding artery that was coagulated. Mean diameter was 4.01 mm, ranging from 2 to 7.2 mm. A total of 17 cases (29.8%) showed evidence of reperfusion of the mass. Of these, 16 patients underwent at least a second procedure (28%). Two patients underwent a third laser procedure. No case of antenatal death has been reported. One case of intrathoracic fetal bleeding requiring a subsequent fetal transfusion has been reported (morbidity: 1.8%). In three (5.3%) cases, while the procedure succeeded in terminating BPS perfusion, it did not succeed in reversing fetal hydrothorax/hydrops. Therefore, among the total of 57 reported cases, USLC was effective in reversing fetal hemodynamic compromise in 54 (94.7%) cases.

Excluding three cases in whom no information was given, post-USLC ultrasound demonstrated a complete regression of the BPS in 15 of 54 cases (27.8%) and a partial regression of BPS size in 41 (71.9%) cases. Among the 15 cases documented to have completely regressed antenatally, 5 underwent either MRI or CT, in 2 cases, a persistent BPS was found, and 1 was operated on with no imaging and a persistent BPS was found. Two patients did not receive imaging while for the other seven, no postnatal information is available.

The mean GA at birth was 38.6 ± 2.3 (range: 30–42) weeks and the mean birth weight 3,276 ± 519.8 (range: 2,450–4,585) g. Prematurity rate was 12.2% (7/57).

Regarding the postnatal management, in 18 cases, no information about postnatal radiological investigation was available, 6 received an MRI, and 24 underwent chest CT. Out of the 31 cases investigated, in a total of 25 cases (80.6%), a persistent mass was found. One patient, in our series, who had a CT showing evidence of residual perfusion of the BPS. Among the 25 patients in whom a persistent BPS was found at postnatal imaging, five were operated on. Three patients were operated on without second-level imaging investigation.

Postnatal sequestrectomy was performed in a total of 15 patients (26.3%). Surgical approach was open in three cases, thoracoscopic in two, and not specified in the others. In one case, significant adhesions were reported, another case was described having a good size of feeding artery, and in another one, the BPS was assessed as a hybrid lesion in fact. Pathological examination findings are not reported for any case other than the two of our series, described above.

**Discussion**

Since Oepkes et al published the first report of a fetal complicated BPS treated with prenatal USLC in 2007, only 11 papers have been published about this technique, mostly case report or case series. The largest case series has been published by Cruz-Martínez et al in 2018, encountering 15 patients. Together with our five cases, a total of 57 cases of complicated BPS treated with USLC have been reported to date.

In terms of indications, all but one cases presented with hydrothorax, associated either with mediastinal shift (severe hydrothorax) and/or fluid collection in one or more other compartment (fetal hydrops). Therefore, there seem to be a general consensus in offering this treatment in those BPS who develop either severe hydrothorax or fetal hydrops.
The success of the procedure, in terms of reversing fetal hemodynamic compromise, was achieved in 94.8% of patients with USLC. A second procedure was performed in 27.6% of patients. However, in all these cases, the reported indication for the second procedure was the reappearance of blood flow in the feeding artery and it was not specified whether the hydrothorax had recurred.

Since fetal surgery is still associated with potential severe complications, we believe that a repeat procedure should be indicated only in those cases in which recurrence of pleural effusion is noted in addition to reperfusion of the mass. Cases in which blood flow in the feeding artery has recurred without signs of fetal hemodynamic compromise should be treated, in our opinion, as noncomplicated BPS in which the definitive treatment can be safely performed postnatally.

Survival following USLC is currently 100%, while perinatal survival with TAS has been reported as high as 87.8%. However, the currently available data on TAS are based on heterogeneous populations and not only on BPSs which have a favorable prognosis. Therefore, it is not possible to compare the overall mortality rate reported for TAS with the mortality rate of USLC found in our literature review. The only study which compared TAS and USLC for the treatment of complicated BPS was published by Mallmann et al. in 2014. Authors stated that USLC seemed to be more effective than TAS with fewer complications. However, in the group treated with USLC, only 20% of patients presented with fetal hydrops compared with 57% in the TAS group. Therefore, we believe that the superior effectiveness cannot be attributed for sure to the different procedure in their study. However, in the absence of a randomized control trial, addressing the superiority of one of the treatments, the currently available data seem to identify USLC as a promising and potentially better alternative to TAS which is only a symptomatic treatment. We therefore believe that in fetuses with BPS complicated by severe hydrothorax and/or fetal hydrops USLC can now be considered a valid treatment option, and it has become the first choice in our institution for these cases. Given the rarity of the disease, the learning curve for this procedure benefits from the expertise gained with different surgical indications such as twin reversed arterial perfusion (TRAP) sequence, twin-twin transfusion, chorioangioma, and other neonatal tumors.

Few of the published studies focus also on the postnatal management. Postnatal imaging of these cases seems controversial. Symptomatic neonates at birth were reported in two cases and underwent open resection without previous imaging. Some cases underwent CT scan and/or MRI. The postnatal imaging varied from case to case and was not always performed. It was not always clear whether the postnatal imaging had any impact on the decision to perform a postnatal sequestrectomy.

Table 2: Perioperative and pregnancy characteristics and postnatal management of fetuses with BPS undergoing prenatal USLC

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>n</th>
<th>GA at laser (wk)</th>
<th>Additional procedures</th>
<th>Success: n cases (% rate)</th>
<th>Repeated laser</th>
<th>GA at birth (mean)</th>
<th>Postnatal sequestrectomy: n cases (% of total)</th>
<th>Postnatal imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oepkes et al2 (2007)</td>
<td>1</td>
<td>23</td>
<td>No</td>
<td>1 (100)</td>
<td>0</td>
<td>0</td>
<td>1 (100)</td>
<td>0 CT</td>
</tr>
<tr>
<td>Cavoretto et al3 (2008)</td>
<td>8</td>
<td>29</td>
<td>No</td>
<td>8 (100)</td>
<td>No</td>
<td>39</td>
<td>5 (63)</td>
<td>CT</td>
</tr>
<tr>
<td>Witlox et al4 (2009)</td>
<td>1</td>
<td>23</td>
<td>Thoracocentesis</td>
<td>1 (100)</td>
<td>41</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rammos et al5 (2010)</td>
<td>2</td>
<td>30</td>
<td>TAS</td>
<td>2 (100)</td>
<td>1 (50)</td>
<td>NA</td>
<td>2 (100)</td>
<td>NA</td>
</tr>
<tr>
<td>Ruano et al6 (2012)</td>
<td>2</td>
<td>27</td>
<td>No</td>
<td>2 (66.7)</td>
<td>1 (50)</td>
<td>37</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Baud et al7 (2013)</td>
<td>1</td>
<td>18</td>
<td>TAS</td>
<td>1 (100)</td>
<td>No</td>
<td>29</td>
<td>1 (100)</td>
<td>NA</td>
</tr>
<tr>
<td>Mallmann et al8 (2014)</td>
<td>5</td>
<td>30</td>
<td>No</td>
<td>5 (100)</td>
<td>2 (40)</td>
<td>39</td>
<td>1 (20)</td>
<td>NA</td>
</tr>
<tr>
<td>Gottschalk et al9 (2018)</td>
<td>12</td>
<td>29</td>
<td>TAS, thoracocentesis</td>
<td>11 (85)</td>
<td>4 (33)</td>
<td>39</td>
<td>3 (25)</td>
<td>US, MRI, CT</td>
</tr>
<tr>
<td>Kosinski et al10 (2017)</td>
<td>2</td>
<td>25</td>
<td>Thoracocentesis</td>
<td>2 (100)</td>
<td>No</td>
<td>41</td>
<td>0</td>
<td>US, X-ray</td>
</tr>
<tr>
<td>Cruz-Martinez et al11 (2018)</td>
<td>15</td>
<td>27</td>
<td>Thoracocentesis</td>
<td>9 (60)</td>
<td>6 (40)</td>
<td>39</td>
<td>0</td>
<td>CT</td>
</tr>
<tr>
<td>Grozdeva et al12 (2021)</td>
<td>3</td>
<td>29</td>
<td>Thoracocentesis</td>
<td>3 (100)</td>
<td>1 (33)</td>
<td>38</td>
<td>0</td>
<td>US, CT</td>
</tr>
<tr>
<td>Our study</td>
<td>5</td>
<td>27</td>
<td>TAS, thoracocentesis</td>
<td>3 (100)</td>
<td>No</td>
<td>38</td>
<td>3 of 4 a (75)</td>
<td>MRI, CT</td>
</tr>
</tbody>
</table>

Abbreviations: BPS, bronchopulmonary sequestration; CT, computed tomography; GA, gestational age; MRI, magnetic resonance imaging; NA, not available; TAS, thoracoamniotic shunt; USLC, ultrasound-guided laser coagulation.

Note: Data are presented as n (%).

aOne case was lost to follow-up.
Intrauterine Ultrasound-Guided Laser Coagulation  Zanini et al.

found either on imaging or intraoperatively. Considering that 80% of patients treated with USLC still had a persistent mass after birth and that prenatal ultrasound disappearance of BPS was mistaken in 50% of cases, we believe that the currently available data do not support a change in the postnatal common management which includes radiological investigation with either CT or MRI in all prenatally diagnosed BPSs.

Once the persistence or disappearance of the BPS has been assessed, decision has to be made regarding conservative versus operative management. Only 26.3% of patients underwent postnatal surgery. Some Authors reported that surgery was not indicated because of the prenatal disappearance of the BPS. However, those patients were not investigated postnatally and therefore, it can be estimated a 50% possibility that a persistent BPS was missed. Cruz-Martinez et al reported that their 15 cases were not operated on the basis of a postnatal chest CT scan that showed a nonperfused residual mass in asymptomatic patients. However, one of the patients in our series, in whom cessation of blood flow in the feeding artery was achieved prenatally, showed a reperfused BPS on the CT chest performed at 4 months of age. Although we are comparing two different studies, we believe that the feeding artery might have recanalized over a 4 months’ postnatal time. Moreover, a nonenhancing mass on CT scan does not automatically mean necrosis. Another case in our series had a chest CT performed at 4 months of age that showed a residual nonenhancing BPS. Author’s decision was to proceed with surgical exploration anyway, which found a viable BPS, confirmed at histology. We realize that our experience may be anecdotal, but until a bigger study will be available, we believe that CT findings of a nonperfused residual BPS should not be considered an indication for nonoperative management. This is confirmed by the case reported by Baud et al in which the lung malformation turned out to be a hybrid lesion instead of an extralobar BPS. Hybrid lesions are connected with the airways, thus predisposing to recurrent infections, and they also contain tissue proper of CPAMs, therefore carrying a higher risk of neoplasms. CT scan usually allows to distinguish between extralobar BPS and hybrid lesions. However, in such cases, the multiple adhesions secondary to the USLC may cause subversion of the normal anatomy, making the radiological differential diagnosis extremely difficult. Furthermore, it has been described that CPAM tissue can be present even in the extralobar BPS, and malignancies arising from BPS have also been reported in literature. We therefore believe that surgical exploration and resection of the residual mass should be routinely performed in case of positive CT or MRI findings.

It may be argued that open thoracotomy is a significantly invasive approach and it may be considered not justified for excision of an asymptomatic mass supposedly already devascularized. However, we reported the first cases of prenatal laser ablated BPS who have been operated postnatally with a minimally invasive approach without complications.

Hence, considering the potential risks of leaving a residual BPS in situ and since postnatal thoracoscopic resection can be safely performed, we believe that the benefit-to-risk ratio of minimally invasive surgical management overcomes those conservative management.

Conclusion
We believe that prenatal USLC is a valid treatment for fetuses with BPS complicated by severe hydrothorax and/or fetal hydrops before the 33rd week of GA. The aim of USLC should not be to definitely treat the BPS but rather to improve the fetal complications, such as hydrothorax, ascites, and hydrops, preventing fetal death and allowing the fetus to reach an acceptable GA. To date, there is no evidence that routine postnatal management protocols of BPSs should be altered, regardless of prenatal USLC and postprocedure prenatal US findings.

Conflict of Interest
None declared.

References


