図 4　膀胱羊水腔シャント施行後の腎のマクロ所見

A．正常コントロール，B．腎盂，腎杯の拡張した水腎症所見，C．ネフロンの少ない
萎縮腎，D．尿細管の拡張を認める MCDK 様の囊胞腎。

尿路閉塞後，同じ時期にシャントを行ったが約半数は正常な腎組織を認めたが，半数
はネフロン形成の少ない腎，また半数は尿細管の拡張が続いていた。

機能を廃絶させるのではないかと考え，V-A シャントチューブの改良を試みた。

3．バルブ付きシャントチューブの使用

筆者らは，尿路閉塞後の胎仔に行う V-A シャントが胎児期の膀胱の収縮と拡張のサイクルを消失させることが問題ではないかと考えた。そこで，シャントチューブの先端に胎仔の排尿サイクルを調整し，生理的な膀胱運動が維持できる機能を備えることができないかと考えた。小さなシャントチューブの先端に複雑な機器を装着することは困難なため，脳外科で用いる脳室-腹腔シャントチューブ（vesico peritoneal shunt tube：V-P シャントチューブ）に着目し，これを胎仔期の膀胱内に挿入することを考えた（図 5）。当初はシャントチューブが埋没したり，周囲から尿が漏れたりしたが，最終的に，27 匹のヒツジのなかで 14 匹の胎仔に脳外科で用いる圧調整付きの V-P シャントを挿入し，13 匹に今までの通常の圧調整機能のないシャントチューブを挿入し比較検討した。その結果，V-P シャントチューブを挿入した膀胱容量は 57±41 ml，通常のシャントチューブでは
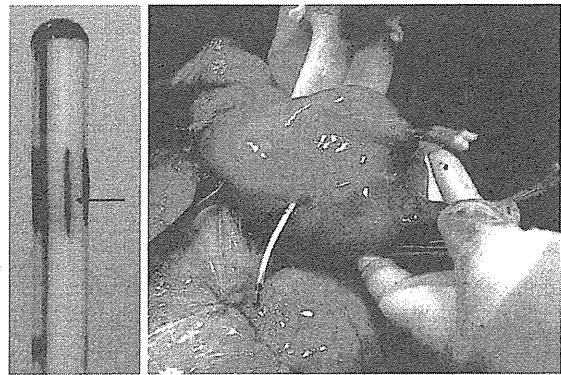

図 5　V-P shunt tube

側溝があいており，ここから流出する尿に対して圧がかかる仕組みになっている。胎仔にシャントチューブを挿入した図を示す。

8.8±4.7 ml と V-P シャントチューブを用いた膀胱は，病理組織の線維化を防げることが明らかとなった[11]（図 6）。
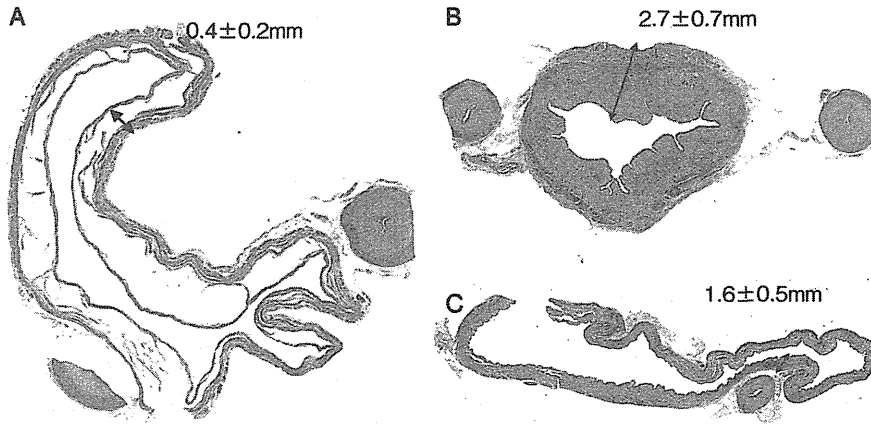
4．適正なシャントチューブ圧の検討

ヒツジを用いた尿路閉塞モデルで，V-A シャントにより膀胱壁の線維化が起こることが証明さ

図 6 低圧シャントチューブ挿入時の膀胱壁の厚さの比較 (HE)
A. control, B. 通常のシャントチューブ挿入後, C. 低圧シャントチューブ挿入後。
低圧シャントチューブ挿入時の膀胱壁の厚さは 1.6±0.5 mm, 通常のシャントチューブでは
2.7±0.7 mm (n=11) であった。また尿路閉塞を起こしていない正常コントロールは 0.4+
0.2 mm (n=5) であった (p=0.001)。

れ, V-A シャント時に膀胱に一定の圧をかけるこ
とで膀胱機能を温存できることがわかった[11]。し
かし, その適正圧がどれほどかが臨床応用するに
は必要となる。脳外科領域で用いるシャント
チューブに圧の調整機能がついていることに着目
し, 今まで用いた低圧用シャントチューブ (Inte-
gra Neuro Sciences, Pudenz Peritoneal Catheter,
Plainsboro, NJ, REF NL850-1380, low pressure
15〜54 mmH$_2$O) と高圧用シャントチューブ (Inte-
gra Neuro Sciences, Pudenz Peritoneal Catheter,
Plainsboro, NJ, REF NL850-1382, high pressure
95〜150 mmH$_2$O) を, それぞれ異なるヒツジの膀
胱に挿入し, 圧の相違による膀胱壁の変化につい
て検討した (図 7)。

まず, 胎仔尿路閉塞モデル (n=16) を作製し,
2 匹は体内死亡が確認され, 9 匹にシャント術を
行った。5 匹に低圧シャントチューブ (4 匹生存),
4 匹に高圧シャントチューブ (3 匹生存) を挿入
した。また, 5 匹はシャントせず, 尿路閉塞のま
ま妊娠を継続させた。今回は通常より 2 週間早い
胎生 130 日に帝王切開で胎仔を娩出させ, その時
点での剖検所見を正常コントロール (胎生 130
日) と比較した。その結果, 高圧シャントチュー
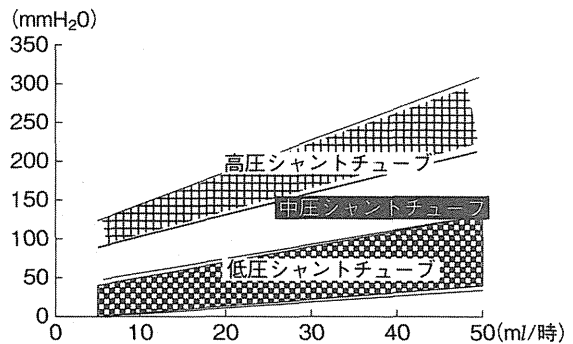ブでは全例に尿膜管の拡張, 尿腹水を認め, シャ

図 7 高圧用シャントチューブと低圧用シャント
チューブの圧, 流量曲線
低圧ではおおよそ尿産生が 9 ml/時のときにカテーテル
内は 15〜54 mmH$_2$O にて開く。高圧シャントチューブで
は 105〜140 mmH$_2$O で開くこととなる。

ントを行わなかった尿路閉塞モデルと同様の肉眼
所見を呈した (表)。また, 低圧群では水腎症様所
見は認めたが, ネフロン数の減少などの尿路閉塞
に認められる不可逆的腎の病理所見は認めなかっ
た (図 8)。また, 膀胱壁の厚さを測定すると, 壁
の厚さが正常対照群で 338±118 (μm), 尿路閉塞
群で 1,953±941 (μm), 高圧シャント群で 1,479±
505 (μm), 低圧シャント群で 1,018±230 (μm)
と, 尿路閉鎖ではもっとも線維化が著明であった

表　シャントチューブによる胎仔腎所見の比較

	尿膜管の拡張，尿腹水	水腎症	尿細管の拡張	ネフロン数の減少
低圧シャント（n＝4）	0	3（75%）	1（25%）	0
高圧シャント（n＝3）	3（100%）	0	1（33%）	0
閉塞モデル（n＝5）	5（100%）	0	2（40%）	2（40%）

低圧シャントでは尿膜管の拡張や尿腹水は認められず，高圧シャントでは尿路閉塞同様に尿膜管の拡張，尿腹水を全例に認めた。
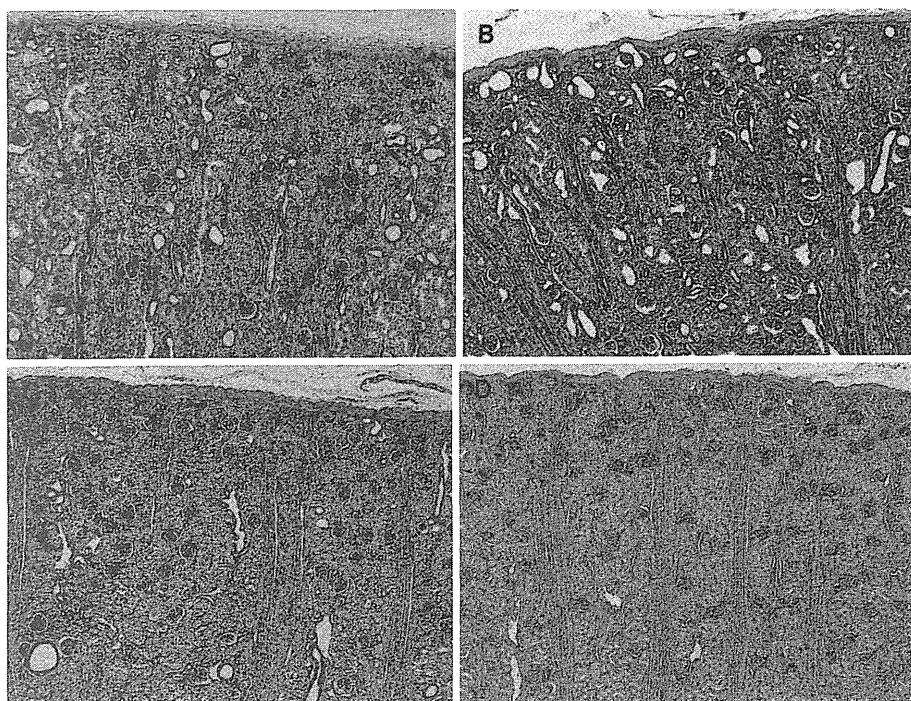

図8　各シャントチューブ挿入後の腎組織所見
A．高圧シャント，B．尿路閉塞，C．低圧シャント，D．正常対照群（HE stain，×40）。
尿路閉塞モデルでは尿細管の拡張が認められるが正常対照群では認めない。低圧シャントでは高圧シャントと比較するとわずかな拡張を認める。腎のネフロン数をみても低圧シャントは正常対照群に近い像を呈した。

が，高圧シャントモデル，低圧シャントモデルで減少してくる傾向が得られた（図9）。これらのことから，胎児期の V-A シャントは，チューブの圧が膀胱の発達や腎の発達に影響を与えていることが明らかとなった。

II．考　察

胎児治療は双胎間輸血症候群（twin-twin transfusion syndrome：TTTS）などの一部の産科領域による治療は良好な結果が得られているが，横隔膜ヘルニア（CDH），先天性嚢胞状腺腫様奇形（congenital cystic adenomatoid malformation：CCAM）などの小児外科的疾患に関しては未だその適応，手術時期，手術術式に関して議論が絶えない。尿路閉塞に関しては，Harrison ら[1]がその治療法に V-A シャントを臨床応用した。しかし，Freedman ら[2]によりその長期予後が検討されるにつれ，術後の腎機能および膀胱機能に問題のあることが示されてきた。
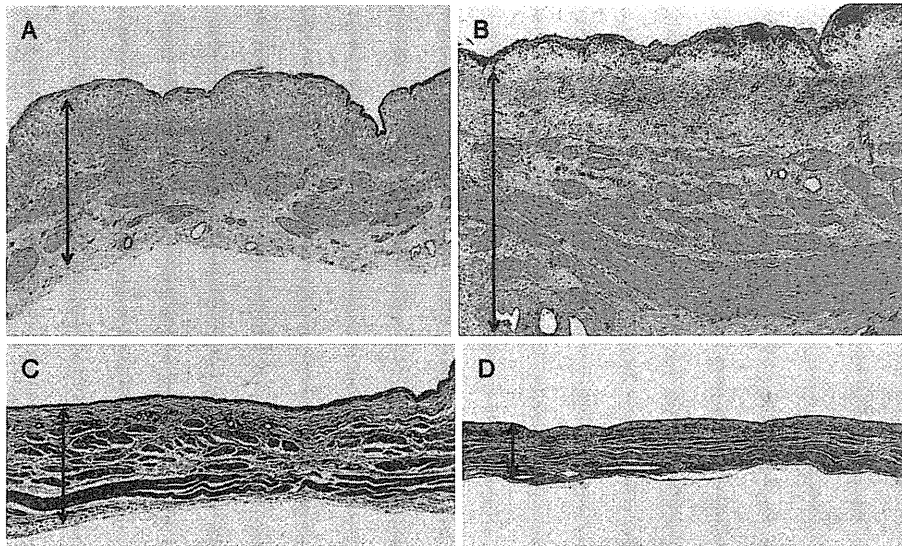
当該実験は，Pringle ら[12]により行われていたヒ

図 9　各シャントチューブ挿入後の膀胱壁の組織所見
A. 高圧シャント，B. 尿路閉塞，C. 低圧シャント，D. 正常対照群（HE stain，×40）。
尿路閉塞モデルでは筋層の肥厚および粘膜下層の線維化が認められる。高圧シャントでは尿路
閉塞より筋層の肥厚は少ないが低圧モデルと比較すると肥厚の程度は強い。

ツジ胎仔を用いた横隔膜ヘルニアの術式を応用し，ヒツジを側臥位で手術した。オスでは尿道と尿膜管を閉塞させ，メスでは膀胱頸部と尿膜管を結紮するモデルを確立した。1999 年に行われた胎生 60 日と 90 日のメス胎仔を用いた pilot study では，最終的に手術成功率は 70％に達し母体死亡はなかった[7,9]。当初はハロセン（fluothane）を用いてマスクで麻酔を導入したが，現在ではバルビタールの静脈内麻酔で導入し，その後，イソフルレン（isoflurane）の吸入麻酔で維持するように変更された。

　現在，臨床例における V-A シャントの最適と考えられる手術時期は胎生 20 週以前ともいわれている。可及的早期手術が望まれるが，当然実施時期には限界がある。筆者らの実験では，腎の発生において，胎生 90 日に作製した尿路閉塞では水腎症が認められネフロン形成に影響しなかった[6]。加えて 60 日の閉塞モデルでは，大小さまざまな尿細管の拡張を認め，肉眼的にも異なる 2 つのタイプの腎病変が発生した[9]。胎生 50 日というきわめて早期の尿路閉塞モデルにおける腎組織の特徴は萎縮腎の病態であった。この変化は，neph-

rogenic zone の胎生早期の消失が示唆され，不可逆的変化と考えられる所見であった[8]。すなわち胎児尿路閉塞に対するシャント実施はより早期であれば，より高い効果が期待できると思われる。実際，Szaflik ら[13]は，胎生 24 週以前に V-A シャントを行う必要性を述べており，Shimada ら[14]は，胎生 20 週以前に行った治療の有効性を示唆している。筆者らはそれよりさらに早期のシャント術の必要性を示唆したことになる。

　今回一連の胎児実験で，MCDK の発生時期と発生過程の様子を胎生早期から明らかにすることができた。これらの経過から胎児治療により，その腎機能を温存できる時期を推定できた[10]。しかし，膀胱機能に目を移すと，一度尿路閉塞で拡張した膀胱壁には筋線維の断裂，そのあとに起こる線維化により膀胱拡張が障害されていることが組織学的検討から明らかとなった[11,15]。しかし，一般的にいわれている後部尿道弁患者における排尿障害が，尿路閉塞により起こるものなのか，あるいは V-A シャントにより起こるものなのか疑問であったが，この疑問については正常胎仔の膀胱をシャントした場合の変化をみることで，胎児期の

膀胱はシャントにより排尿のサイクルを停止させ，胎児期に使用しないことで萎縮が助長されることが明らかとなった[16,17]。また，萎縮した筋層間に線維化が起こる可能性が示唆された。そこで，膀胱内に一定の圧がかかるバルブシャントチューブを挿入することで，この膀胱萎縮を停止させることができた[19]。この一定の圧とはどれほどかを検証した結果，胎児期の膀胱内には 15～54 mmH$_2$O 程度の圧があれば膀胱機能が保たれ，これ以上の圧では胎生 81 日の膀胱内の尿は排泄されず，尿路閉塞同様の所見を呈したことは興味深い。シャントチューブに圧をかけることは脳外科の V-P シャントチューブから得られた思いつきではあったが，発生段階の膀胱にとってわずかな圧の変化はシャントが機能せず，尿路閉塞同様の所見を呈したことは今後の臨床応用に大切な結果と思われた。

胎児期にこのような一定の圧のかかるシャントを挿入した研究は内外では認められず，新たな胎児治療に応用できる機器となりうると考えている。しかし，腎，膀胱両者の機能温存には，排尿サイクルを考慮した穿刺キットとシャントチューブの開発が必要であろう。

おわりに

胎児治療のなかでもっとも診断が容易で侵襲の少ない領域が胎児期の尿路閉塞と思いこの研究を開始し，直視下胎児手術，内視鏡手術，腹腔からの膀胱穿刺，膀胱羊水腔シャント留置など，さまざまな治療選択が施行された。筆者らのヒツジを用いた研究も 15 年の歳月が流れたが，その長いトンネルの出口の光がみえてきたのが現状である。これらが臨床応用されてから 25 年以上経過するが，患児の救命はできても QOL を考慮した予後を期待するには，さらなる進化が必要と思われた。現在わが国では使用頻度の少ない V-A シャントチューブの入手が難しい状況になりつつあるが，侵襲が少ない V-A シャントはぜひ，シャントチューブの改良を加えながら進化をさせていきたいと願っている。この領域においても今後遺伝子工学，再生医療技術の進歩により新たな治療法の展開も期待したい。

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ORIGINAL ARTICLE

The utility of muscle sparing axillar skin crease incision for pediatric thoracic surgery

Tomoaki Taguchi · Kouji Nagata · Yoshiaki Kinoshita · Satoshi Ieiri ·
Tatsuro Tajiri · Risa Teshiba · Genshiro Esumi · Yuji Karashima ·
Sumio Hoka · Kouji Masumoto

Abstract

Background Posterolateral or standard axillar incisions for the pediatric thoracic surgery are occasionally associated with poor motor as well as cosmetic results, including chest deformities and large surgical scars. A muscle sparing axillar skin crease incision (MSASCI) was initially proposed by Bianchi et al. (in J Pediatr Surg 33:1798–1800, 1998) followed by Kalman and Verebely (in Eur J Pediatr Surg 12:226–229, 2002) resulting in satisfactory cosmetics. However, they performed operations through the third or fourth intercostals space (ICS), therefore the target organs were restricted in the upper two-thirds of the thoracic cavity.

Patients and methods Thoracic surgeries were performed using MSASCI in 27 patients (1-day to 9-year old). There were ten patients with esophageal atresia, seven with congenital cystic adenomatoid malformation, five with pulmonary sequestration, two with mediastinal neuroblastoma, two with right diaphragmatic hernia, and one with pulmonary hypertension. A thoracotomy was performed through the appropriate ICS (from third to eighth).

Results In all patients, the expected procedures, including pulmonary lower lobectomy, were successfully performed by MSASCI throughout the thoracic cavity. A good operational field was easily obtained in neonates and infants. Most of the patients achieved excellent motor and aesthetic outcomes.

Conclusions MSASCI may become the standard approach for the thoracic surgery for small children.

Keywords Axillar skin crease · Thoracotomy · Pulmonary lobectomy · Neonate · Infant

T. Taguchi · K. Nagata · Y. Kinoshita · S. Ieiri · T. Tajiri ·
R. Teshiba · G. Esumi
Department of Pediatric Surgery, Graduate School of Medical
Sciences, Kyushu University, Fukuoka, Japan

T. Taguchi (✉)
Department of Pediatric Surgery, Reproductive and
Developmental Medicine, Faculty of Medical Sciences,
Kyushu University, 3-1-1 Maidashi, Higashi-Ku,
Fukuoka 812-8582, Japan
e-mail: taguchi@pedsurg.med.kyushu-u.ac.jp

Y. Karashima · S. Hoka
Department of Anesthesiology and Critical Care Medicine,
Graduate School of Medical Sciences, Kyushu University,
Fukuoka, Japan

K. Masumoto
Department of Thoracic, Endocrine, and Pediatric Surgery,
Fukuoka University School of Medicine, Fukuoka, Japan

Introduction

Advances in antenatal diagnosis, surgical technique and perioperative care have improved survival rate for neonatal surgical diseases. The mortality rate has become less than 10% [1]. It is now important to consider the long-term good "quality of life" (QOL) in neonatal surgical disease. Therefore, surgeons have sought to establish procedures that leave no scars, using the natural skin crease such as axillar crease and umbilical crease [2–4].

Posterolateral or standard axillar incisions for the pediatric thoracic surgery sometimes cause poor functional as well as cosmetic results, including chest deformities (scoliosis, shoulder deformity, and winged scapula) and large surgical scars. Muscle sparing axillar skin crease incision (MSASCI) was initially proposed for neonates by Bianchi et al. [5] in 1998, and then Kalman and Verebely [6] extended this approach for children in 2002, thus resulting

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in a good postoperative cosmetic results. However, they performed surgery through the third or fourth intercostals space (ICS), therefore the performed operations were restricted in the upper two-thirds of the thoracic cavity.

Patients and methods

Thoracic surgeries were performed using MSASCI in 27 patients (1-day to 9-year old) from December 2006 to February 2011. There were ten patients with esophageal atresia, seven with congenital cystic adenomatoid malformation, five with pulmonary sequestration, two with mediastinal neuroblastoma, two with right diaphragmatic hernia, and one with pulmonary hypertension. The performed operations were 10 primary esophageal anastomoses, 12 pulmonary lobectomies (including lower lobectomies) or partial resections, 2 subtotal neuroblastoma resections, 1 diaphragmatic repair, 1 pulmonary biopsy, and 1 exploratory thoracotomy.

This study was performed, according to the Ethical Guidelines for Clinical Research published by the Ministry of Health, Labor, and Welfare of Japan on 30 July 2003 and complies with the Helsinki Declaration of 1975 (revised 1983). Regarding this retrospective study, properly informed consent was obtained from the parents.

The patient was placed in the lateral position. The uppermost arm was extended to about 130°, drawn forward, and placed on an arm-rest. A pulse-oxymeter was applied on hand of the extended arm.

A skin incision was made just on the axillar skin crease, and the pectoralis major and latissimus dorsi muscles were retracted superiorly and medially, respectively. Either of these muscles could be partially incised in case. The incision was deepened and the axillary fat pad and lymph nodes were pushed upward. The long thoracic nerve was preserved in the posterior part of the wound (Fig. 1). The anterior serratus muscle was split along its fibers just on the targeted costa. The thoracic cavity was entered through the appropriate ICS. The peripheral pulse was monitored by the pulse-oxymeter of the extended arm avoid a circulatory failure of the arm.

Thoracotomy for esophageal atresia was performed through the fourth ICS and the upper and lower esophagus was exposed via an extrapleural approach. After cutting The azygos vein was cut and the Tracheoesophageal fistula (TEF) was closed by 5-0 polydioxanon (PDS) transfixing sutures and cut. Esophageal end-to-end anastomosis was performed with one layer stitch sutures. Both lateral sides were approximated using 5-0 PDS, and a transanastomotic tube was inserted from the nose to the stomach through the anastomosis. The anterior and the posterior aspects were sutured with 6-0 PDS in stitch.

One-lung ventilation was attempted in order to obtain adequate operational field for pulmonary lower lobectomy [7]. Briefly, bronchial blockade with a 4Fr or 5Fr Fogarty embolectomy catheter was attempted in each case. Children were initially intubated with a Fogarty embolectomy catheter under direct laryngoscopy. Then, immediately, an endotracheal tube was placed alongside the catheter in the trachea. After securing the tube, a pediatric fiberoptic bronchoscope (2.2 mm in diameter) was passed through to set a Fogarty embolectomy catheter to the mainstem bronchus. And then, bronchial blockade was performed with its balloon inflated with an appropriate volume of normal saline. Thoracotomy was done through the fifth or sixth ICS, and then the lung was deflated. The pulmonary arteries were ligated and cut and then the bronchus was cut and closed with 5-0 PDS sutures. Finally, the pulmonary vein was doubly ligated and cut, and the pulmonary ligament was dissected.

One-lung ventilation was also performed for the pulmonary sequestration. Thoracotomy was performed via the seventh or eighth ICS in order to approach the abnormal artery in pulmonary ligament at first. One-lung ventilation allowed lower lobe to be easily lifted for the dissection of pulmonary ligament and the ligation of abnormal artery. This abnormal artery was ligated, before ligation of pulmonary vein in order to avoid lung volume expansion.

A rolled vicryl sheet was inserted between the costa during thoracic closure, in order to avoid bony adhesion in some cases. Both the thoracic and subcutaneous tubes were inserted through both ends of wound; therefore, no additional wounds were necessary for tubes.

Results

Thoracotomy was successfully done through from the third and eighth ICS using MSASCI. All of the expected procedures, including pulmonary lower lobectomies, were able to be performed adequately. A good operational field was easily obtained in neonates and infants in comparison to that in elder children. The incision was extended caudally, about 1 cm in only one infant with pulmonary sequestration. Two patients died due to the severe cardiopulmonary anomalies, and one patient with right diaphragmatic hernia showed recurrence and required reoperation using an abdominal approach. The other patient with a right diaphragmatic hernia showed no right lung; therefore, no procedure was performed (exploratory thoracotomy).

Surgical complications included wound disruption in the four cases and transient arm paralysis in the two cases. The wound disruptions were treated by vacuum therapy and healed about 1 week, and the transient arm paralysis

Fig. 1 Operation schema for MSASCI. *M.LD* lattismus dorssi muscle, *N.TL* long thoracic nerve, *M.PM* pectoralis major muscle, *M.SA* serratus anterior muscle, The *numbers* are labeling in the individual ribs.

M. LD

N.TL

M. PM

4

5

6

M. SA

Axillar skin crease incision
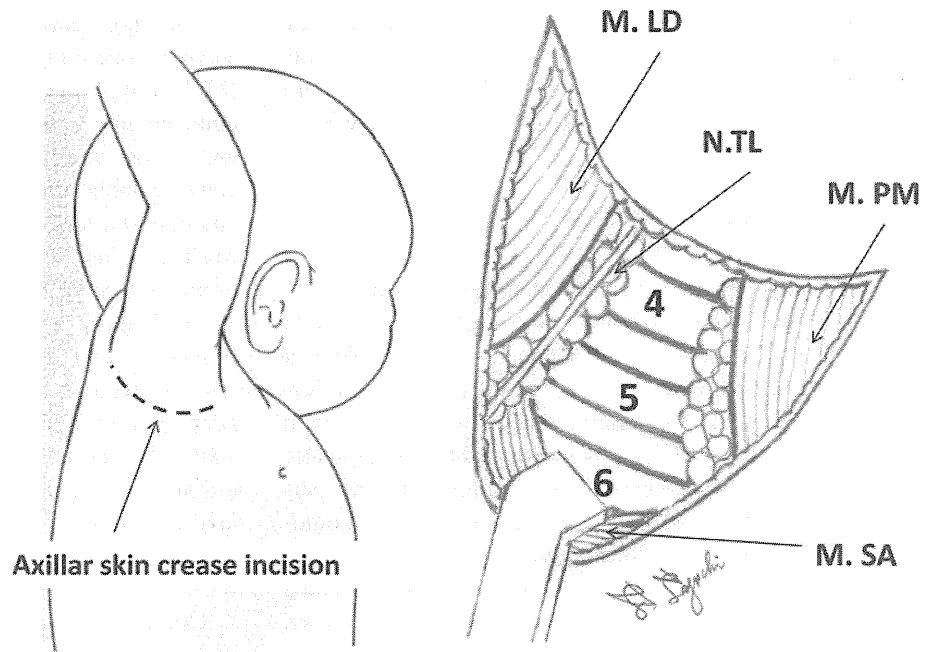
recovered spontaneously in a few weeks. All of the patients showed uneventful postoperative course and achieved excellent motor and aesthetic outcomes after 1 month. The surgical scar was almost hidden by the axillar skin crease in a year (Figs. 2, 3). So far, there have been no patients showing thoracic deformity, in a relatively short-term follow-up (no more than 4 years). The outcome of each patient is shown in Table 1.

(Skin incision)   (Lt. Upper lobectomy)   (6 months after operation)
The 5ᵗʰ ICS
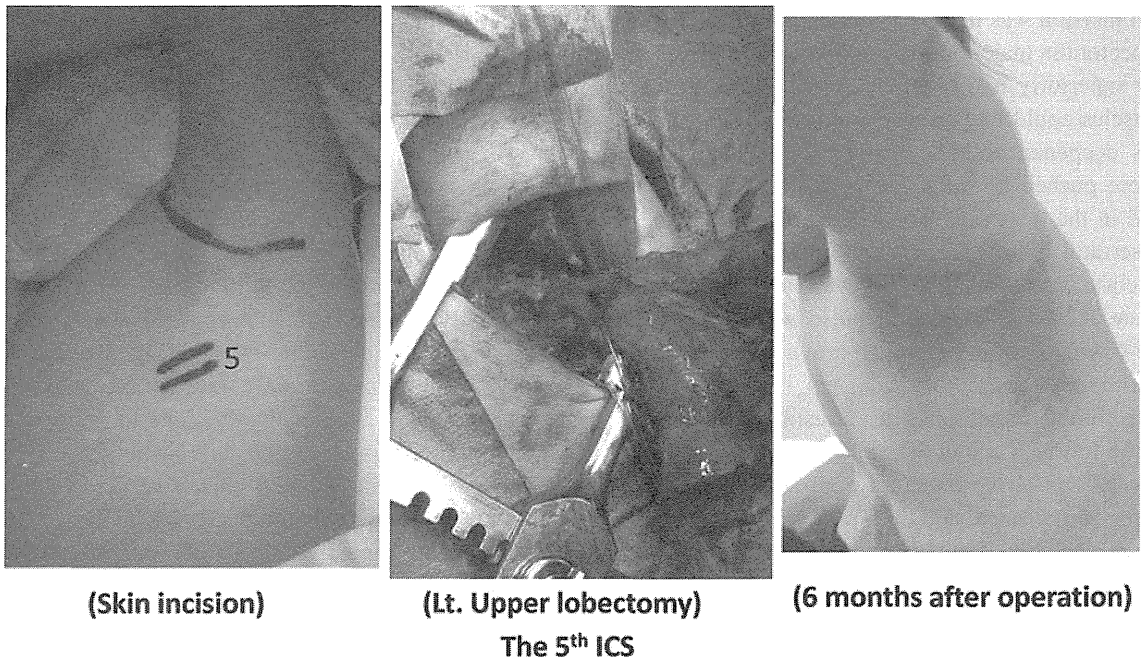
Fig. 2 Pre, intra, and postoperative appearance of Case 15. Congenital cystic adenomatoid malformation in Lt. upper lobe. *Left* skin incision on the axillar crease. *Middle* Lt. upper lobectomy of lung was performed through the fifth ICS at 1-month old. *Right* operative wound was almost hidden 6 months after operation

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(Skin incision)   (Rt. Lower lobectomy)   (8 months after operation)

The 6th ICS
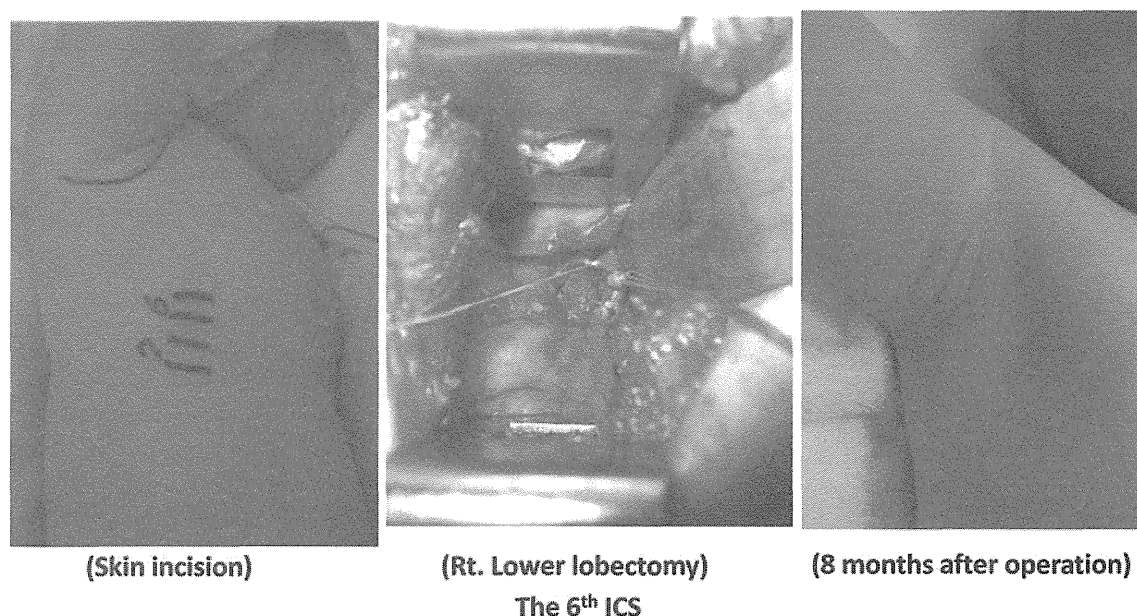
Fig. 3 Pre, intra, and post operative appearance of Case 17. Intralober lung pulmonary sequestration in Rt. lower lobe. *Left* skin incision on the axillar crease. *Middle* Rt. lower lobectomy of lung was performed through the sixth ICS at 3-month old. *Right* operative wound was almost hidden 8 months after operation

Discussion

Axillary skin crease incision for thoracic surgery was initially reported by Atkinson as "peraxillary approach" for dissection of the upper thoracic and stellate ganglia through the second ICS in adult in 1949 [8]. Bianchi et al. [5] reported using "high axillary skin crease, muscle-sparing to right lateral thoracotomy" for children in 1998. They operated on 29 neonates including 27 esophageal atresia and two patent ductus arteriosus (PDA) through the third or fourth ICS. Kalman and Verebely [6] also reported this approach as "axillary skin crease incision" for thoracotomy of neonates and children in 2002. They performed 17 operations in neonates (8 esophageal atresia, 8 PDA, 1 CCAM) and 9 operations in children (3 neuroblastoma, 1 teratoma, 5 pulmonary operations including lobectomies) through the third or fourth ICS. The oldest patient of this report was a 15-year-old girl with a large teratoma from the anterior mediastinum. They performed five pulmonary operations including one biopsy for histiocytosis, one marsupialization of an inflammatory cyst, one cystectomy of a congenital cyst and two pulmonary resections for bronchiectasia (one S2-3-4 trisegmentectomy on the left side and one middle lobe lobectomy). They concluded that it ensured unrestricted access to the upper two-thirds of the thoracic cavity through the third or fourth ICS. They did not perform any pulmonary lower lobectomies.

These reports indicate that the term MSASCI is appropriate. The approach was extended downward up to the eighth ICS in the current series to perform the expected procedures in all cases, including pulmonary lower lobectomy and intralobular pulmonary sequestration. This technique is feasible for almost all kinds of pediatric thoracic surgery from third to eighth ICS. The appropriate ICS for thoracotomy depends on the target organ. For example, the fourth ICS is used for esophageal atresia, the fifth ICS is for standard pulmonary lobectomy, and the seventh or eighth ICS for pulmonary sequestration. We experienced technical difficulties in patch closure of right diaphragmatic hernia in one case. The medial margin of diaphragmatic defect was difficult to be exposed for suturing, because liver and intestine interfered to the operation field. Right diaphragmatic hernia might not be indication for MSASCI from our restricted experience.

There were initially several complications, such as wound disruption and transient arm paralysis. In 18 out of the 27 patient, thoracotomy was performed below the fourth ICS. The wound disruption occurred in four cases (Cases 5, 7, 9 and 26). These four were operated through fifth, fourth, sixth, and fifth ICS, respectively. Three out of four cases underwent thoracotomy below the fourth ICS. Therefore, downward hyperextension of skin by metal retractor may cause wound disruption. In addition, the case five was extremely premature infant and the modified gestational age at operation was 40 weeks. Cases 7, 9 and 26 were operated in their neonatal period. And the three out of these four cases showed cyanosis in perioperative period due to their congenital heart disease and the subsequent pulmonary hypertension. Therefore, hyperextension of the skin as well as vulnerable factors of each child may cause

Table 1 Summary of 27 pediatric patients performed thoracotomies with MSASCI

Case	Sex	Diagnosis	Type or site	Age at op.	Operation	Intercostal space	Complication	Prognosis
1	M	EA	Gross type A	1 year 3 month	Esophageal EEA	Rt. 4th intercostal	Minor leakage	Alive
2	F	EA	Gross type C	2 days	Esophageal EEA	Rt. 4th intercostal	Stenosis	Alive
3	M	EA, AA, TAC	Gross type C	1 day	Esophageal EEA	Rt. 4th intercostal	None	Alive
4	F	EA	Gross type C	2 days	Esophageal EEA	Rt. 4th intercostal	None	Alive
5	F	EA, ELBWIPA stenosis	Gross type C	3 months	Esophageal EEA	Rt. 5th intercostal	TEF recurrence wound disruption	Died[b]
6	F	EA	Gross type D	1 day	Esophageal EEA	Rt. 4th intercostal	None	Alive
7	M	EA, TA	Gross type D	1 day	Esophageal EEA	Rt. 4th intercostal	Wound disruption transient paralysis	Died[c]
8	F	EA	Gross type C	1 day	Esophageal EEA	Rt. 5th intercostal	Stenosis	Alive
9	F	EA	Gross type C	1 day	Esophageal EEA	Rt. 6th intercostal	Wound disruption	Alive
10	F	EA	Gross type C	1 day	Esophageal EEA	Rt. 4th intercostal	None	Alive
11	M	CCAM	Rt. middle lobe	8 months	Partial resection	Rt. 5th intercostal	None	Alive
12	M	LPS	Rt. lower lobe	4 days	LPS resection	Rt. 5th intercostal	None	Alive
13	F	CCAM	Lt. upper lobe	1 month	Partial resection	Lt. 5th intercostal	None	Alive
14	F[a]	LPS	Lt. lower lobe	8 months	LPS resection	Lt. 8th intercostal	None	Alive
15	M	CCAM	Lt. upper lobe	1 month	Lt. upper lobectomy	Lt. 5th intercostal	Pneumothorax	Alive
16	F	CCAM	Lt. lower lobe	4 months	Lt. lower lobectomy	Lt. 5th intercostal	None	Alive
17	M	LPS	Rt. lower lobe	3 months	Rt. lower lobectomy	Rt. 6th intercostal	None	Alive
18	F	CTA with LPS	Lt. lower lobe	4 months	Rt. lower lobectomy	Rt. 6th intercostal	Transient paralysis	Alive
19	M	CCAM	Lt. lower lobe	3 months	Lt. lower lobectomy	Lt. 6th intercostal	None	Alive
20	M	CCAM	Rt. lower lobe	4 months	Rt. lower lobectomy	Rt. 5th intercostal	None	Alive
21	M	LPS	Lt. lower lobe	7 months	LPS resection	Lt. 7th intercostal	None	Alive
22	F	CCAM	Rt. lower lobe	4 months	Rt. lower lobectomy	Lt. 5th intercostal	None	Alive
23	M	Mediastinal NB	Lt. upper lobe	6 years 1 month	Subtotal excision	Lt. 4th intercostal	None	Alive
24	F	Mediastinal NB	Lt. upper lobe	9 years 4 months	Subtotal excision	Lt. 3th Intercostal	None	Alive
25	M	Pulmonary HT	Lt. upper lobe	5 years 11 months	Biopsy	Lt. 6th intercostal	None	Alive
26	M	Rt. CDH		5 days	Repair	Rt. 5th intercostal	Wound disruption CDH recurrence	Alive
27	F	Rt. CDH Rt. lung agenesis		5 days	Exploratory thoracotomy	Rt. 7th intercostal	None	Alive

EA esophageal atresia, *AA* anal atresia, *TAC* truncus arteriosus communis, *ELBW* extremely low birth weight infant, *PA* pulmonary artery, *TA* tricuspid atresia, *CCAM* congenital cystic adenomatoid malformation, *LPS* lung pulmonary sequestration, *CTA* congenital tracheal atresia, *NB* neuroblastoma, *CDH* congenital diaphragmatic hernia, *HT* hypertension, *EEA* end to end anastomosis, *TEF* tracheoesophageal fistula

[a] Incision was extended caudally about 1 cm

[b, c] Two patients died due to the severe cardio-pulmonary anomalies

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the wound disruption. In order to prevent this complication, a wound retractor XS has been currently applied to protect the surgical wound. This instrument can prohibit skin and subcutaneous tissue damage during surgery. Postoperative subcutaneous negative-pressure drainage is also an effective for avoiding or treating wound disruption.

The transient arm paralysis occurred in the case 7 and 18. They were operated through the fourth ICS and the sixth ICS, respectively. Therefore, the transient paralysis is not considered to be related to the level of thoracotomy. Actually, there were no complications in the patients operated from the seventh to eighth ICS. Currently, a pulse-oxymeter has been applied, on the hand, of the extended arm for monitoring peripheral blood pulse and saturation of oxygen. During operation blood pulse and saturation of oxygen has been kept in normal range. Since then, no patient has experienced transient arm paralysis. Therefore, transient arm paralysis is considered to be vascular origin caused by the hyperextension of arm or the hyperextension of wound.

The surgical field is relatively small; therefore, there are a few technical methods in order to overcome this disadvantage. One-lung ventilation is required for pulmonary lower lobectomy during the dissection of the pulmonary ligament and pulmonary vein. Furthermore, one-lung ventilation provides adequate operative field in ligation of the abnormal artery during surgery of pulmonary sequestration. One-lung ventilation has been technically feasible in infant, using Fogarty embolectomy catheter [7]. Hemoclips facilitate the ligation of pulmonary arteries. The proximal site is ligated by 3-0 or 4-0 silk suture and the distal site is closed by a hemoclip, to provide sufficient distance for a safe cut. A long and fine-tip needle holder and forceps are required for dissection of the TEF and anastomosis of the esophagus in esophageal atresia. Fine monofilament absorbable 5-0 or 6-0 PDS with the two needles in both ends are useful for full thickness stitch suture using an inside-to-outside and inside-to-outside manner.

In conclusions, MSASCI for pediatric thoracic surgery resulted in excellent motor and aesthetic outcomes. MSASCI may become the standard approach for thoracic surgery for the small children, especially for neonates and infants.

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SHORT REPORT

Persistent pulmonary hypertension of the newborn in twin–twin transfusion syndrome following fetoscopic laser surgery

Hironori Takahashi, Shigehiro Takahashi, Keiko Tsukamoto, Yushi Ito, Tomoo Nakamura, Satoshi Hayashi & Haruhiko Sago

Department of Maternal-Fetal and Neonatal Medicine, National Center for Child Health and Development, Tokyo, Japan

Objective: We investigated persistent pulmonary hypertension of the newborn (PPHN) among monochorionic-diamniotic (MD) twins. *Methods*: A retrospective cohort study examined MD twins from 195 deliveries and 373 live-born neonates at our center. *Results*: PPHN occurred in three cases (3/373: 0.8%), all of which were recipients of twin–twin transfusion syndrome (TTTS), after fetoscopic laser surgery (FLS) (3/117: 2.6%). Although the clinical course of the three cases differed, all cardiothoracic area ratios exceeded 40%, and other cardiac parameters also worsened after FLS. *Conclusions*: The occurrence of PPHN in TTTS recipients should be noted, particularly when fetal cardiac function declines following FLS.

Keywords: Cardiac enlargement, monochorionic-diamniotic twin, persistent pulmonary hypertension of the newborn, recipient, twin–twin transfusion syndrome

Introduction

Persistent pulmonary hypertension of the newborn (PPHN), presents as systemic cyanosis, due to right-to-left shunting in the patent ductus arteriosus or patent foramen ovale, without structural abnormalities. PPHN is observed in 0.19% of live-birth neonates [1]. Most PPHN cases result from hypoxemia, hypothermia, hypoglycemia, and meconium aspiration. Early closure of the ductus arteriosus, which increases pulmonary flow before birth, can also cause PPHN [2]. Monochorionic-diamniotic (MD) twins share one placenta; thus, a flow imbalance can easily occur between the twins. The most unbalanced condition is twin–twin transfusion syndrome (TTTS), which occurs in 10% of MD twins. Although an MD twin has a risk of PPHN derived from the circulating overflow, the association between MD twins and PPHN has been little discussed. Here, we retrospectively reviewed MD twins at our center and examined the correlation between MD twins and PPHN.

Methods

We reviewed the medical records of 195 MD twin pregnancies and 373 live-born neonates that were managed at our center between April 2002 and March 2008. The inclusion criterion was the establishment of chorionicity on transvaginal ultrasound in the first trimester. We routinely monitored the MD twins by a minimum of biweekly fetal ultrasounds, by which we determined the estimated fetal body weight, maximum vertical pocket, and cardiothoracic

area ratio (CTAR). CTAR was defined as the ratio of the cardiac area to the thoracic area in the four-chamber view of the heart in diastole. Less than 35% CTAR is normal regardless of gestational age [3]. The grade of TTTS complied with Quintero staging [4]. Fetoscopic laser surgery (FLS) was performed in TTTS stages 1–4 at a gestational age of 16–26 weeks [4]. After FLS, we performed fetal ultrasound weekly. Termination of pregnancy was based on ordinary obstetric management. PPHN was documented by severe hypoxemia necessitating inhaled nitric oxide (iNO), in addition to right-to-left shunting at the level of the patent ductus arteriosus and/or patent foramen ovale without structural heart abnormalities, as noted using echocardiography. Cases of PPHN were investigated in detail both prenatally and postnatally. A small number of TTTS cases that involved FLS were transferred to regional hospitals after the surgery; for these cases, we collected perinatal information by documents and telephone.

Results

Of 195 deliveries and 373 neonates, 66 deliveries and 117 neonates were derived from MD and TTTS, respectively. Of the 66 deliveries with TTTS, FLS was performed in 49 cases (49/66: 74.2%). Three cases of PPHN were observed (3/373: 0.8%), all of which resulted from TTTS (3/117: 2.6%).

Case 1

A 38-year-old primigravida was referred to our center for TTTS stage III. Reversed blood flow in the ductus venosus was noted in the recipient. Mild tricuspid valve regurgitation (TR) and mild mitral valve regurgitation (MR) were also seen. FLS was performed at 19 weeks plus 2 days. Amniotic fluid discordance and reversed blood flow in the ductus venosus disappeared after FLS. However, CTAR increased to 45% from 32 weeks of gestation onward; the cause of this increase was unknown (Table I). Furthermore, ventricular wall hypertrophy appeared. Cesarean section was performed at 36 weeks plus 1 day. The recipient weighed 2,278 g. Apgar scores were 8 and 9 at 1 and 5 min, respectively. The hemoglobin (Hb) value of the recipient was 15.6 g/dL. Desaturation of the infant was observed on day one. Chest radiography did not show respiratory distress syndrome or any other lung diseases. Echocardiography revealed right-to-left ductal shunting and moderate tricuspid regurgitation without structural abnormalities. Under intermittent mandatory ventilation, iNO (20 ppm), prostaglandin E1, and milrinone were administered. Subsequently, oxygenation improved, and weaning off iNO was

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Table I. Changes in parameters after FLS.

	MVP	Fetal growth	Ventricular hypertrophy	CTAR	TR	MR	RVOT obstruction	Reverse flow in DV
Case 1	Normal (improved)	Good	Mild (worsened)	Enlarged up to 45%	Mild (no change)	Mild (no change)	None (no change)	None (improved)
Case 2	Normal (improved)	Good	Severe (worsened)	Enlarged up to 43%	Severe (worsened)	Mild (worsened)	Present (worsened)	Present (worsened)
Case 3	>80 mm (no change)	Good	Severe (worsened)	Enlarged up to 48%	Mild (no change)	Mild (worsened)	Present (worsened)	Present (no change)

CTAR, cardiothoracic area ratio; DV, ductus venosus; FLS, fetoscopic laser surgery; MR, mitral valve regurgitation; MVP, maximum vertical pocket; RVOT, right ventricular outflow tract; TR, tricuspid valve regurgitation.

initiated on day five. Echocardiography showed a regression of PPHN on the same day. Extubation was performed 19 days after birth. The infant was discharged on day 44 and developed uneventfully up to four years of age.

Case 2

A 29-year-old primigravida was referred to our center for TTTS stage III. Mild TR and ventricular hypertrophy were noted in the recipient before surgery. FLS was performed at 20 weeks plus 3 days. The donor died on postoperative day two (small occupied area of the placenta). Subsequently, the quantity of amniotic fluid and recipient well-being stabilized. However, cardiac enlargement of the recipient was noted as the pregnancy progressed, although the cause was unknown (Table I). CTAR increased up to 43%, and tricuspid regurgitation worsened. Eventually, right ventricular outflow tract (RVOT) obstruction was observed. Emergent cesarean section was performed at 33 weeks plus 3 days because of the non-reassuring fetal status on a cardiotocogram. The recipient twin weighed 2,484 g. Apgar scores were 7 and 8 at 1 and 5 min, respectively. The heart structure was normal, and chest radiography revealed no abnormalities. RVOT obstruction was not seen. The Hb value was 14.8 g/dL. However, mechanical ventilation was needed on day one, because of severe hypoxia. Echocardiography showed right-to-left shunting at the level of the patent foramen ovale. After PPHN was diagnosed, iNO and milrinone were administered. The PPHN symptoms subsequently improved. However, a methicillin-resistant *Staphylococcus aureus* infection worsened the patient's condition from day eight onward, and death occurred from sepsis on day thirteen.

Case 3

A 29-year-old primigravida was admitted to our center for TTTS. The recipient was hydropic and at TTTS stage IV. Mild TR and ventricular hypertrophy were seen. FLS was performed at 25 weeks plus 6 days. However, hydrops and amniotic discordance did not improve despite the surgery. Peak systolic velocity of the middle cerebral artery did not increase in either twin. Cardiac function of the recipient worsened gradually (Table I). RVOT obstruction also appeared. Cesarean section was performed at 31 weeks plus 6 days because of non-reassuring fetal status. The recipient—a severely edematous male infant—weighed 2,864 g. Apgar scores were 2 and 3 at 1 and 5 min, respectively. He had severe birth asphyxia requiring resuscitation. Massive desaturation was observed. The Hb value of the recipient was 10.0 g/dL at birth (donor: 13.6 g/dL). RVOT obstruction was not observed postnatally. Chest X-ray showed respiratory distress syndrome and a 63% increase in cardiothoracic ratio. On echocardiography, the ejection fraction was found to be 45%, with right-to-left shunting at the level of the foramen ovale. Although respiratory distress syndrome and left cardiac failure improved within a week, PPHN persisted. In addition to iNO, prostaglandin I_2 and bosentan were administered. The infant stabilized very slowly, and iNO was withdrawn at 51

days after birth. Extubation was performed at postnatal day 55. At five months of age, the infant continues to receive home oxygen therapy. One surviving placental arteriovenous anastomosis from the recipient to the donor was noted on histologic examination. In addition, an artery-artery anastomosis also persisted.

Discussion

In our study, infants with TTTS had a higher risk of PPHN, compared with the general incidence of the condition. This finding supports the only previous case series addressing the association between TTTS and PPHN (Table II) [5]. Interestingly, each of our cases differed in terms of clinical course. One case resulted in two survivors delivered at 36 weeks of gestation. Another case had one survivor from a preterm birth. The final case had prolonged TTTS associated with a residual communicating vessel despite FLS.

However, the three cases had a few common characteristics. In all three cases, PPHN occurred in the recipients of TTTS. The main reason why PPHN occurs in the recipient may be a chronic increase in circulating blood volume through placental anastomoses from the donor. A previous report showed that an increase in circulating blood volume in utero induces PPHN; in sheep, PPHN occurred when pulmonary flow was increased using surgical placements [6]. Also, the systemic circulating volume is known to be parallel to the pulmonary circulating volume in utero [7]. Patients with pulmonary hypertension have shown extension of muscle into small pulmonary arteries. Alveolar ducts and wall arteries, which are normally nonmuscular, have been found to be fully muscularized in infants with pulmonary hypertension [8]. Extracellular matrix deposition in the vessel wall increases simultaneously. Subsequently, vessels become stiff with increased pulmonary vascular resistance. Because of such remodeling, the alveoli cannot expand appropriately, inducing severe hypoxia after birth.

In addition, in our study, all three cases of PPHN were related to FLS. Notably, cardiac function did not improve after surgery in any of the three cases. CTAR, which is the most easily assessable parameter of fetal cardiac function, increased after FLS and exceeded 40% in all three cases. In addition, other cardiac parameters, including TR, MR, and ventricular hypertrophy, also worsened. Thus, cardiac dysfunction was associated with TTTS. In TTTS, the cardiac function of the recipient in particular tends to be affected. When cardiac function is severely impaired, RVOT obstruction occurs, which can also induce PPHN. FLS drastically changes the hemodynamic status of TTTS fetuses, and cardiac function in the recipient improves within a few weeks in most cases. However, the cardiac burden is prolonged for up to one month after FLS in some cases [9]. Although it remains unknown, why such variability in FLS response occurs, residual anastomoses may be involved in this pathologic state. A few studies have demonstrated that residual anastomoses were detected in about 30% of lasered placentas [10]. The majority of residual anastomoses were

Table II. PPHN cases associated with TTTS.

Case	TTTS stage	Donor/ Recipient	FLS course	Delivery (wk)	Birth weight (g)	Sex	Cardiac echo	Therapy for PPHN	iNO cessation (days)	Extubation (days)	Prognosis
Delsing[5] (Case 1)	II	Recipient	Good	28	1,122	M	PDA (RL)	iNO	2	Impossible	Death at 3 wk (sepsis)
Delsing[5] (Case 2)	IV	Recipient	Good	33	1,820	F	PDA (RL), TR	iNO	2	4	Good
Delsing[5] (Case 3)	III	Recipient	Good	28	1,213	F	PDA (RL)	iNO	2	5	Good
Delsing[5] (Case 4)	II	Donor	Recipient IUFD	30	1,477	F	PDA/PFO (RL)	iNO	2	5	Good
Case 1	III	Recipient	Decreased cardiac function in recipient	36	2,278	F	PDA (RL), TR	iNO, milrinone	13	19	Good
Case 2	III	Recipient	Donor IUFD, decreased cardiac function in recipient	33	2,474	M	PFO (RL), TR	iNO, milrinone, PGE_1	Impossible	Impossible	Death at 2 w (sepsis)
Case 3	IV	Recipient	Prolonged TTTS	31	2,864	M	PFO (RL)	iNO, PGI_2, bosentan	51	55	Home oxygen

FLS, fetoscopic laser surgery; IUFD, intrauterine fetal death; iNO, inhaled nitric oxide; PDA, patent ductus arteriosus; PG, prostaglandin; PPHN, persistent pulmonary hypertension of the newborn; TR, tricuspid regurgitation; TTTS, twin-twin transfusion syndrome.

very small and located near the placental margin. Further, 44% of cases with residual anastomoses demonstrated a twin anemia-polycythemia sequence (TAPS) [10]. An interesting finding of our study is that cardiac function worsened after FLS in *cases 1 and 2*, although residual communication vessels were not detected by ordinary histologic examination. However, considering the discrepancy between cardiac dysfunction in FLS-treated TTTS cases and such identifiable residual vessels [10], the cardiac dysfunction in *cases 1 and 2* in our study may have been due to the existence of very small, difficult-to-identify anastomoses, although these patients did not develop TAPS.

In cases of TTTS without FLS, urgent delivery would be needed because of fetal distress, labor onset, or premature membrane rupture. In other words, the condition of overload in pulmonary vessels does not continue prenatally for a long period without FLS.

Our study had certain limitations. Laser surgery is available in only a few hospitals in Japan. Therefore, the rate of TTTS was relatively high in this report, compared to the actual incidence in the general population. Also, we limited our report to severe PPHN cases, such as those requiring iNO. Moreover, the diagnosis of PPHN—including the criteria for oxygenation—is ambiguous. A prospective study of PPHN after TTTS using proper PPHN diagnostic criteria would be desirable. FLS is a momentous procedure, and its use is expected to become widespread in the future. The occurrence of PPHN in TTTS recipients following FLS should be noted, especially when cardiac function does not improve despite surgery.

Declaration of interest: The authors declare no conflicts of interest.

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Original contribution

Squamous metaplasia in the cyst epithelium of type 1 congenital pulmonary airway malformation after thoracoamniotic shunt placement

Kentaro Matsuoka MD, PhD[a,*], Satoshi Hayashi MD, PhD[b],
Fumihiko Urano MD, PhD[a,c], Lihua J. Zhu PhD[c], Hajime Okita MD, PhD[a],
Haruhiko Sago MD, PhD[b], Atsuko Nakazawa MD, PhD[a]

[a]Department of Pathology, National Center for Child Health and Development, Tokyo 157-8535, Japan
[b]Center for Maternal-Fetal and Neonatal Medicine, National Center for Child Health and Development,
Tokyo 157-8535, Japan
[c]Department of Molecular Medicine, University of Massachusetts Medical School, Worcester, MA 01655, USA

Summary Thoracoamniotic shunting is the treatment of choice for management of the fetus with type 1 congenital pulmonary airway malformation. Thoracoamniotic shunting has been performed to reduce life-threatening risks such as fetal hydrops. However, caution is needed because of possible complications. Here, we report that thoracoamniotic shunting can cause histologic changes in the cyst epithelia. In 5 of 8 patients treated prenatally with thoracoamniotic shunting, squamous metaplasia in the cyst epithelia was seen; whereas squamous metaplasia was not found in 6 patients who were not treated with this procedure. Our results reveal that long-term exposure to the intrauterine environment could possibly lead to the change in the nature of cyst epithelium and consequent squamous metaplasia.
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1. Introduction

Congenital pulmonary airway malformation (CPAM), formerly known as *cystic adenomatoid malformation*, of the lung is a rare lung disorder characterized by an increased proliferation and cystic dilation of terminal respiratory bronchioles [1-3]. Although the etiology of CPAM is not clear, it has been suggested that it may be caused by a maturation defect in bronchopulmonary development [4,5].

It has been also shown that the presence of bronchial atresia is strongly associated with CPAM, which supports this concept [6].

Congenital pulmonary airway malformation (ie, cystic adenomatoid malformation) was originally classified into 3 groups based on the relative size of the cysts [3]. Currently, CPAM is classified into 5 types based on the presumed site of development of the malformation. Among these 5 types, type 1 CPAM is the most prevalent one, accounting for approximately 60% to 70% of all CPAM lesions [2,3]. Type 1 CPAM consists of 1 or more air- or air/fluid-filled large cysts. The cyst sizes range from 1 to 10 cm. These cysts are often surrounded by underdeveloped alveolar parenchyma and varying number of smaller cysts. Microscopically, the

cysts are lined by epithelium that varies from a low cuboidal epithelium to a ciliated pseudostratified columnar epithelium [2,7]. The cyst walls also consist of connective tissue similar to those of bronchi of the patient's uninvolved lung. Cartilage islands may be seen in some cases. It has been reported that tufts of mucigenic cells exist on the surface on large cysts or within the smaller bronchiolar-like structures adjacent to the larger cysts in about 35% of type 1 CPAM cases [2]. Past reports indicate that these cells are involved with the occurrence of bronchioloalveolar carcinoma in both older patients with type 1 CPAM and patients who have had a type 1 CPAM removed in infancy [8-13].

Type 1 CPAM usually causes respiratory distress in the newborn period. Thus, surgical removal of the involved lobe is often required to prevent respiratory distress and allow the other lobes to expand normally. Recent advances in antenatal diagnosis and prenatal ultrasound have allowed us to correctly diagnose and monitor fetuses with type 1 CPAM [14,15]. Fetal interventions are applied to fetuses with life-threatening conditions such as hydrops fetalis or polyhydramnios. Thoracoamniotic (TA) shunting is the treatment of choice for management of the fetus with type 1 CPAM and involves shunt insertion under ultrasound guidance [16-18]. Thoracoamniotic shunting has been performed to reduce life-threatening risks such as poly-hydramnios, mediastinal shift, and fetal hydrops [17-19]. However, caution is needed because of possible complica-tions. It has been reported that displacement of the catheter into the amniotic or thoracic cavity, catheter occlusion, premature delivery, and fetal demise can occur [19]. Here, we report that TA shunting can cause histologic changes in the cyst epithelia. In 5 of 8 patients treated prenatally with TA shunting, squamous metaplasia in the cyst epithelia was seen; whereas squamous metaplasia was not found in 6

patients who were not treated with TA shunting. These findings suggest that TA shunting could change the nature of the cyst epithelium as a consequence of long-term exposure to the intrauterine environment.

2. Materials and methods

2.1. Indications for TA shunting in fetal CPAM type 1

In the Department of Maternal-Fetal and Neonatal Medicine at the National Center for Child Health and Development, Tokyo, Japan, the indications for TA shunting in fetal CPAM type 1 include the following:

1. Macrocystic CPAM with large cysts
2. CPAM volume ratio greater than 1.6 [20] or hydrops fetalis
3. Before 34 weeks of gestation

We did not perform TA shunting on patient 1 with hydrop fetalis (Table 1). Instead, we performed thoracocentesis because the cysts were separated by the septum, which implied ineffectiveness of TA shunting.

2.2. Case selection

Between 2004 and 2011, TA shunts were used on 8 of 14 fetuses diagnosed as having type 1 CPAM in the Center for Maternal-Fetal and Neonatal Medicine at the National Center for Child Health and Development, Tokyo, Japan. Shunts were offered in pregnancies complicated by hydrops fetalis, polyhydramnios, or at a significant risk for pulmonary

Table 1 Clinical and microscopic data for type 1 CPAM

	TA shunt	Sex	Age (wk)	Weight (g)	Apgar score	Surgical removal (d)	Follow-up	Additional features
1	(−)	M	35	2800	2.2	0	Death at 2 mo, 17 d	Hydrops fetalis
2	(−)	F	37	2410	8.9	24	Free of disease at 1 y, 3 mo	
3	(−)	M	38	2800	8.9	23	Free of disease at 1 y, 1 mo	
4	(−)	F	39	3250	7.7	0	Free of disease at 7 y and 1 mo; rib deformity	
5	(−)	M	40	3400	7.8	12	Free of disease at 6 y, 8 mo	
6	(−)	M	39	3368	8.9	14	Free of disease at 2 mo	
7	(+)	F	28	1490	ND	0	Death at 1 d	Hydrops fetalis
8	(+)	F	33	3544	1.5	0	Free of disease at 7 mo, 25 d	Hydrops fetalis
9	(+)	F	37	3282	7.9	0	Free of disease at 1 y, 9 mo	Polyhydramnios
10	(+)	F	38	2858	8.9	0	Free of disease at 2 mo, 15 d	Hydrops fetalis
11	(+)	M	38	2722	8.8	0	Free of disease at 1 y, 5 mo; rib deformity	
12	(+)	F	38	2790	8.9	0	Free of disease at 4 y, 9 mo; rib deformity	Hydrops fetalis
13	(+)	F	37	2775	8.8	0	Free of disease at 1 mo	Hydrops fetalis
14	(+)	M	38	3032	8.9	0	Free of disease at 1 mo	Hydrops fetalis

Abbreviations: M, male; F, female; ND, no data.

hypoplasia. All patients underwent surgical resection within 1 month after birth. Patients treated with TA shunting underwent surgical resection at the time of delivery.

2.3. Pathologic examination

All cysts were examined macroscopically and microscopically by pathologists in the Department of Pathology at the National Center for Child Health and Development.

3. Results

Of the 14 fetuses antenatally diagnosed as having type 1 CPAM, 8 were female and 6 were male. Clinical, macroscopic, and histologic data for these 14 cases are summarized in Table 1. Thoracoamniotic shunting was used in 8 cases because of hydrops fetalis, polyhydramnios, or an increased risk of pulmonary hypoplasia (Table 1). Six cases did not undergo TA shunting. Extensive microscopic examination revealed that there existed squamous metaplasia of the cyst epithelia in 5 of 8 patients who underwent TA shunting. In contrast, squamous metaplasia was not found in patients who did not undergo TA shunting (Table 1). We did not find overt inflammation in the cases presented in this study. In some patients who underwent TA shunting, we found slight inflammation at the insertion site.

In case 8, a large complex fetal lung mass was found in the left lower lobe. Because of an increased risk of lung hypoplasia, TA shunt was placed at 26 weeks of gestation. At 1 day of life, the infant underwent lobular resection. The overall size of the mass was 7 × 5 × 1.7 cm. The mass contained several predominant macrocysts (Fig. 1A). Microscopically, the cysts were mainly lined by cuboidal, columnar, and ciliated columnar epithelia, which was consistent with the histology of type 1 CPAM (Fig. 1B). Mucinous epithelium and mucinous hyperplasia were also seen. Further examination revealed that the cyst wall was also lined by squamous metaplastic epithelium (Fig. 1C).

In case 14, a large multilocular cyst of the lung was found in the right middle lobe. The size of the resected lung lobe was 6.5 × 5 × 1.5 cm (Fig. 2A). In this case, the insertion site of the shunt tube could be identified macroscopically. Microscopically, the vernix caseosa was found at the insertion site (Fig. 2B). At the distant area from the insertion site, focal squamous metaplasia was found, suggesting that squamous metaplasia was induced by the cyst content, not by the direct contact with a shunt tube (Fig. 2C).

4. Discussion

Recent improvements in antenatal diagnosis, prenatal ultrasound, and fetal surgery have allowed us to treat fetuses
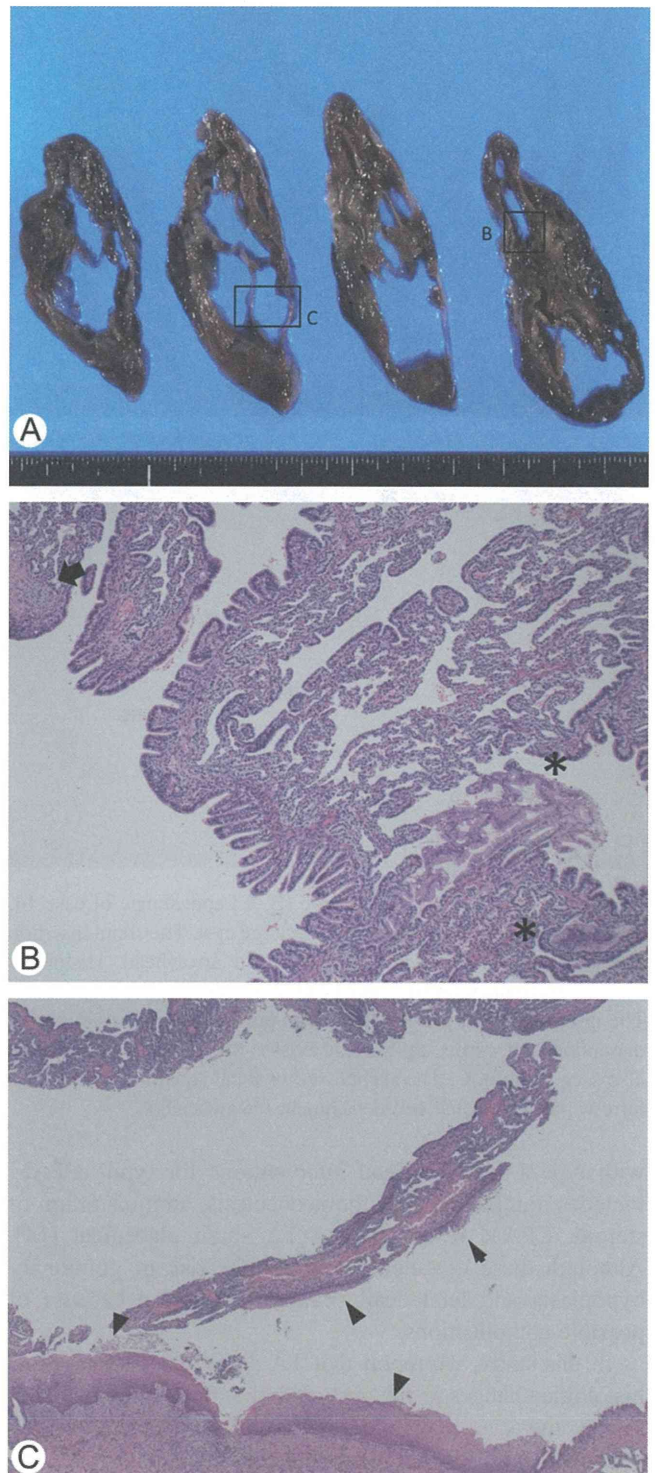
Fig. 1 Gross (A) and microscopic (B, C) appearance of case 8. A, The specimen displays several predominant macrocysts. Histologic sections were made from 2 areas and shown in images B and C. B, The cysts are lined by columnar to pseudostratified columnar epithelia. Mucinous epithelia are seen in the right lower area (asterisks). A small cartilaginous tissue can be found in the left upper area (arrow). C, A histologic section shows focal squamous metaplasia (arrow heads).
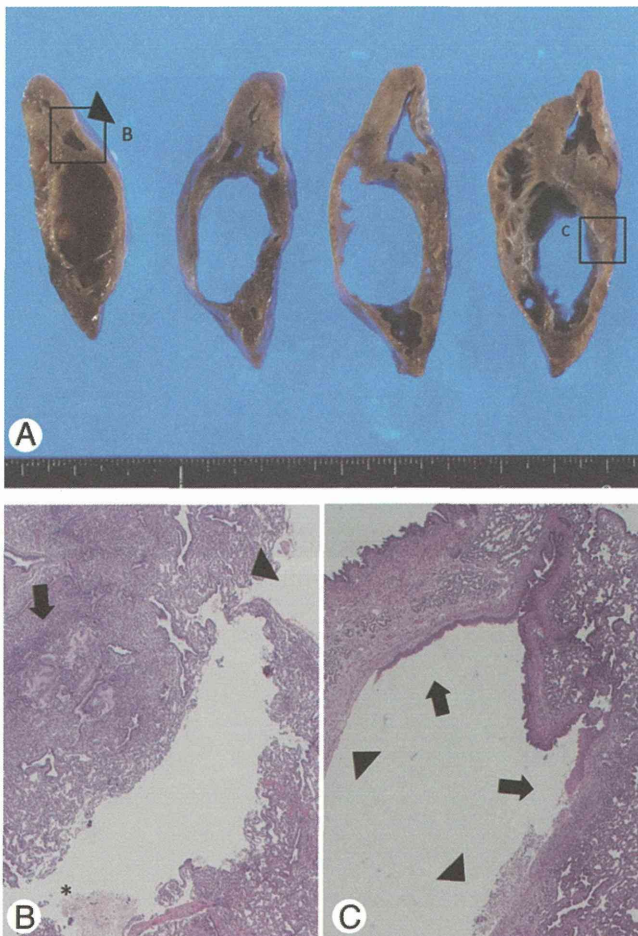
Fig. 2 Gross (A) and microscopic (B, C) appearance of case 14. A, The specimen shows a multilocular large cyst. The shunt insertion site can be identified and pointed by an arrowhead. Histologic sections were made from 2 areas and shown in images B and C. B, The insertion site of the TA shunt tube (arrowhead) shows cyst wall disruption and vernix caseosa (asterisk). Mucinous hyperplasia is also seen (arrow). C, The section shows focal squamous metaplasia (arrows) and epithelial cell detachment (arrowheads).

with type 1 CPAM. Fetal interventions for type1 CPAM includes amnioreduction, thoracocentesis, administration of steroid, CPAM resection, and TA shunt placement [14]. Although these treatments decrease the risk of pulmonary hypoplasia and fetal death, caution is needed because of possible complications.

In this study, we report that TA shunt placement causes histologic changes in the cyst epithelia. Squamous metaplasia in the cyst epithelia was found in fetuses treated prenatally with TA shunting, but not in untreated fetuses, suggesting that TA shunting may change the nature of the cyst epithelium as a consequence of long-term exposure to the intrauterine environment. Supporting this idea is our finding that the increase in mucinous hyperplasia seen in TA shunt population was statistically significant. The Mann-Whitney U test was used to test if there was a difference in mucinous hyperplasia between TA shunt population and non–TA shunt population (P =.073). This raises the

possibility that residual lung parenchyma could be also affected by the intrauterine environment. Because mucinous hyperplasia has been implicated in the occurrence of bronchioloalveolar carcinoma, this also raises the possibility that there is potential for seeding the thoracic cavity and amniotic cavity with malignant cells through TA shunting. Collectively, squamous metaplasia in the cyst epithelia may be a useful "biomarker" for predicting potential complications and occurrence of bronchioloalveolar carcinoma.

Although TA shunting has lower risks to the fetus and mother as compared to lobectomy, it has been recently reported that fetuses treated with TA shunting could develop postnatal chest wall deformities, suggesting that TA shunt may affect the rib development of patients [21]. Other known risks and complications for TA shunting include catheter displacement, improper function of the catheter, catheter occlusion from thrombus or effusion material, fatal fetal hemorrhage, procedure-related placental abruption, premature rupture of membrane, and preterm labor. These procedure-related complications should be carefully taken into consideration before TA shunting is chosen as a treatment option. In this study, we discovered that TA shunting causes squamous metaplasia of the cyst epithelium. Our findings suggest that histologic changes also should be carefully examined to identify other procedure-related complications.

The cause of squamous metaplasia seen in the cyst epithelium is not clear. It is also possible that long-term exposure to the intrauterine environment led to the change in the nature of cyst epithelium and squamous metaplasia. It has been shown that proinflammatory mediators and meconium in amniotic fluid can cause local inflammation and apoptosis of the lung epithelial cells [22-24]. It has been also reported that the nature of fetal tissue can be changed when it is exposed to the intrauterine environment in long term [25]. Collectively, it is possible that long-term exposure to the intrauterine environment led to the change in the nature of cyst epithelium and consequent columnar to squamous metaplasia.

Our findings raise the possibility that TA shunt placement could cause unexpected changes in the cyst environment, leading to histologic changes in the cyst epithelium. Careful pathologic examination of the cyst is crucial for further understanding of the possible biological effects of TA shunting and prevention of unexpected complications.

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