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ORIGINAL ARTICLE

The prognostic factors and the outcome of primary isolated fetal ascites

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Abstract
Purpose The purpose of the present study was to evaluate the prognostic factors and review the outcome of primary isolated fetal ascites.
Methods A retrospective cohort study was conducted for fetuses with primary isolated ascites with a prenatal diagnosis between 1994 and 2009. The patients were divided into the favorable group (Group I) whose ascites were resolved by medical treatment alone and an unfavorable group (Group II) who required surgical intervention after birth due to refractory ascites.
Results There were seven patients in Group I and five patients in Group II. Six of seven patients who developed ascites after 30 weeks' gestation were categorized in Group I, and four of five infants who developed ascites before 30 weeks' gestation were categorized in Group II. There was a negative correlation between the gestational age at diagnosis and the severity of the fetal abdominal distention. In Group II, the ascites resolved in two cases and was reaccommodated in another two cases after surgery. An infant with trisomy 21 received continuous drainage and eventually died of infection.
Conclusions The prognosis of primary isolated fetal ascites can be predicted based on the gestational age at diagnosis and the severity of the fetal abdominal distention.

Keywords Etal ascites · Chylous ascites · Prenatal diagnosis · Fetal intervention · Prognosis

Introduction

Fetal ascites is frequently recognized as a symptom in non-immune fetal hydrops, which arise in response to numerous causes [1]. Fetal ascites also occurs independently without a fluid accumulation in any other serosal cavities or subcutaneous tissue due to various congenital abnormalities [2–4]. In contrast, the causes of primary isolated fetal ascites are unclear. Most of these fetuses develop chylous ascites after birth [5] which may be caused by either congenital lymphatic dysplasia or abnormal lymphatic drainage [6, 7]. Although the prognosis has been reported to usually be favorable for these infants [5], there are some unfavorable cases with severe chylous ascites that persists after various types of therapy including dietary treatment, total parenteral nutrition (TPN) and surgical intervention [8–10]. However, a few studies have reported the prognostic factors and proposed optimal management of primary isolated fetal ascites [6, 11, 12]. Therefore, a retrospective review of primary isolated fetal ascites was conducted to evaluate the prognostic factors and explore the optimal management both in utero and after birth.

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Materials and methods

Study population

A retrospective cohort study was performed for fetuses with primary isolated fetal ascites at the unit of pediatric surgery of Osaka university hospital and Osaka Medical Center and Research Institute for Maternal and Child Health from 1994 through 2009. Isolated ascites was defined as fluid collection in the abdominal cavity without involvement of fluid accumulation in other serosal cavities or subcutaneous tissue. Cases with secondary isolated fetal ascites caused by intrauterine infections, cardiovascular malformations, cardiac arrhythmia, and other fetal malformations such as genitourinary, pulmonary, or gastrointestinal anomalies were excluded from this study. This study was performed in accordance with the rules of both institutional review boards.

Medical and surgical treatment

Our medical treatment strategies and the surgical indications were as described below. Dietary treatment was started with a special diet using either an elemental diet or medium-chain-triglyceride diet in principle, except for the cases with mild ascites that could be started on regular milk. TPN with fasting was performed if the dietary treatment had either no effect or an increase the amount of ascites. TPN was considered from the first if the cases demonstrated severe ascites. Surgical treatment was indicated in order to identify the cause of either lymphatic leakage or abnormal lymphatic drainage at the site of mesenteric root including intestinal malrotation, when refractory ascites had accumulated even after treatment with TPN for more than 4 weeks. When the site of lymphatic leakage could not be identified in spite of Sudan black oral administration, then fibrin glue may be applied at the site that is responsible for the lymphatic leakage.

Collected data and analysis

The onset of fetal ascites was detected by routine ultrasound scans. Prenatal factors such as gestational age at diagnosis, duration of persisting fetal ascites, and the ultrasonographic measured values at third trimester of pregnancy, such as the abdominal circumference (AC), fetal trunk area (FTA), femur length (FL), and amniotic fluid index were reviewed from the medical records. The postnatal factors including sex, gestational age at birth, mode of delivery, Apgar scores at 1 and 5 min, body weight at birth, head circumference at birth, abdominal circumference at birth, need for TPN, need for surgical intervention, details of the surgical procedure, duration of hospitalization, duration of persisting ascites, and final outcome were also collected. Cytological count and chemical analysis of fluid were performed for the identification of chyle in the cases ascites was sampled transabdominally under ultrasound guidance either antenatally or postnatally. The patients were divided according to the clinical course into the favorable group (Group I) whose ascites were resolved by medical treatment alone, and unfavorable group (Group II) who required surgical intervention after birth due to refractory ascites. Prenatal and postnatal prognostic factors were compared between the two groups.

Statistical analyses

The mean and standard deviation or the median and range were used to describe continuous variables, and the frequency was used to describe the categorical data. Either the Wilcoxon rank sum test or Student's t test was used for comparison of continuous variables. The Fisher's exact test was used for analysis of categorical data. Values of $p < 0.05$ were considered significant. The statistical analysis was performed with the JMP software package (Version 8.02; SAS Institute, Inc., Cary, NC, USA).

Results

Twelve fetuses with primary isolated fetal ascites were enrolled in this study. There were six males and six females and the median gestational age at birth was 36.9 weeks' gestation. The treatments after birth and outcomes of these cases are summarized in Fig. 1. The ascites regressed spontaneously without TPN in six infants. TPN was conducted in the other six cases and one of the infants improved after the initiation of TPN. These seven cases were managed only by medical treatment (Group I). The remaining five infants required surgery or continuous drainage due to refractory ascites (Group II) (Fig. 1).

Prenatal and postnatal prognostic factors

The gestational age at diagnosis was significantly earlier in Group II than in Group I. There were no fetuses whose ascites resolved spontaneously prior to delivery. Therefore, the duration of persisting fetal ascites turned out to be longer in Group II in comparison to Group I. There were no differences in the amount of amniotic fluid and head size between the two groups. Both AC and FTA were standardized by dividing them with FL, which were indicators of abdominal distention, and were larger in Group II than in Group I (Table 1). As a result, the severity of abdominal distention or size was thus considered to be poor prognostic factors for primary isolated fetal ascites.

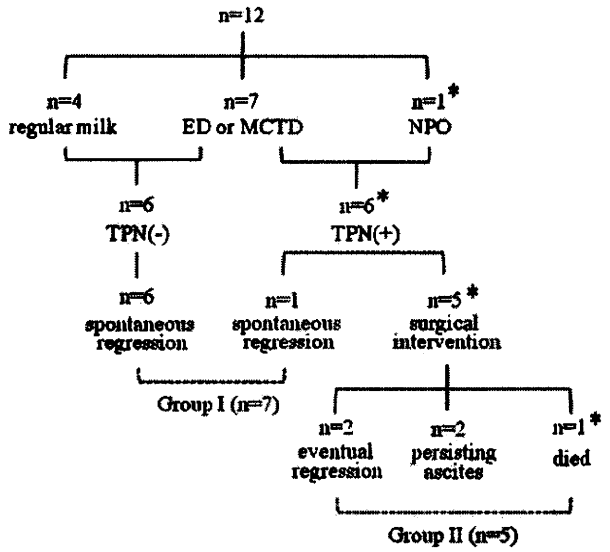

Fig. 1 Overview of the treatments and outcomes after birth for the infants with primary isolated fetal ascites. The *asterisk* indicates a case of continuous drainage alone. *ED* elemental diet, *MCTD* medium-chain-triglyceride diet, *NPO* non per oral, *TPN* total parenteral nutrition

There was a negative correlation between the gestational age at diagnosis and FTA divided by FL, with a correlation coefficient of −0.848. Four out of 5 (80%) infants who developed ascites before 30 weeks' gestation required surgical intervention and two of these, in which the ascites was detected before 20 weeks' gestation had persistent ascites for more than 10 months despite any treatment including repeated surgical procedures. The ascites resolved spontaneously without any surgical intervention in 6 of 7 (86%) patients who developed ascites after 30 weeks' gestation (Fig. 2). There were no significant differences between the two groups in the findings at birth such as sex, gestational age, Apgar scores, body weight, and the measured values of the body including the abdominal circumference (Table 2).

Treatment and outcome

Although six fetuses underwent intrauterine therapeutic paracentesis for an extremely enlarged abdomen, the ascites reaccumulated within a few days in all cases. A cesarean section was performed in five cases because the enlarged abdomen of the fetuses. Three of the six infants who underwent intrauterine therapeutic paracentesis could avoid cesarean section and were delivered transvaginally. The existence of chyle was confirmed in all cases in Group II and three cases in Group I, because abdominal paracentesis was not performed in 4 of 7 cases in Group I (Table 3). Three infants in Group I were started on an elemental diet due to moderate ascites, while the others were started on regular milk. Only one case in Group I needed TPN due to the ineffectiveness of the elemental diet and later showed a good outcome. Four infants in Group II started on either an elemental diet or medium-chain-triglyceride diet due to severe ascites, and all patients of this group, including other non per oral case subsequently needed TPN, and eventually underwent surgery (Fig. 1; Table 3). After Sudan black oral administration, laparotomy was performed to identify the presence of either lymphatic leakage or a lymphatic drainage abnormality in the retroperitoneum or at the site of mesenteric root including intestinal malrotation. However, neither the site of lymphatic leakage nor any abnormal lymphatic drainage was detected during the laparotomy in all surgical cases, Fibrin glue was used in region that were thought to be responsible for the lymphatic leakage in three cases of Group II. The ascites regressed after surgery in two patients in spite of the fact that the lymphatic leakage site could not be identified. Refractory ascites persisted in two patients even after undergoing more than two surgical procedures. An infant with trisomy 21 who received continuous drainage eventually died of infection (Fig. 1). Consequently, the duration of hospitalization and persistent ascites after birth became longer in Group II than in Group I. The morbidity was 60%, and the mortality was 20% in Group II (Table 3).

Discussion

Fetal ascites is generally a part of the symptoms in cases with nonimmune fetal hydrops, which refers to fluid collection in at least two body cavities or to fluid collection in

Table 1 Prenatal findings of the infants with primary isolated fetal ascites

BPD biparietal diameter, *FL* femur length, *HC* head circumference, *AC* abdominal circumference, *FTA* fetal trunk area

[a] Median with range

[b] Mean ± standard deviation

	Group I (n = 7)	Group II (n = 5)	p
Gestational age at diagnosis (days)[a]	225 (192–250)	196 (127–216)	0.016
Duration of persisting fetal ascites (days)[a]	36 (13–60)	60 (37–137)	0.016
Amniotic fluid index (cm)[b]	18.0 ± 7.89	22.1 ± 8.15	0.393
BPD/FL[b]	14.7 ± 0.79	15.4 ± 0.69	0.127
HC/FL[b]	4.9 ± 0.40	5.4 ± 0.48	0.108
AC/FL[b]	5.4 ± 0.53	6.4 ± 0.94	0.037
FTA/FL[b]	1.3 ± 0.25	1.8 ± 0.42	0.038

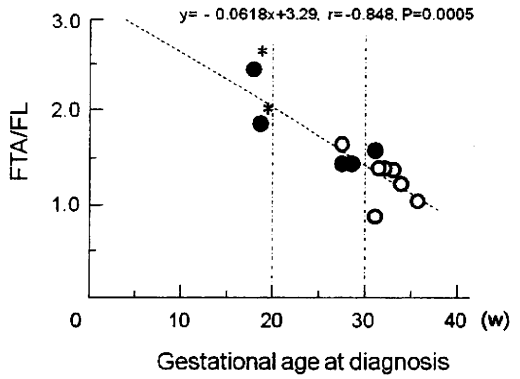

Fig. 2 The relationship between the gestational age at diagnosis and fetal trunk area (FTA) divided by femur length (FL) indicated a negative correlation with a correlation coefficient of −0.848. The *open circles* represent the infants in Group I and the *closed circles* represent the infants in Group II. The *asterisk* shows the cases persisting ascites after surgical intervention

one cavity plus diffuse subcutaneous edema. The etiology of nonimmune fetal hydrops include numerous causes such as chromosomal anomalies, intrauterine infections, cardiac failure, and structural anomalies of various organs [1]. Fetal ascites sometimes occur independently without a fluid accumulation in any other serosal cavities or subcutaneous tissue. Favre et al. [3] analyzed a large series, focusing on nonimmune fetal ascites, and reported that the fetal ascites accompanied by fetal hydrops had more unfavorable prognosis in comparison with isolated fetal ascites without an association of hydrops. Several investigators have reported that these isolated fetal ascites are often caused by cardiac [13], renal [14], gastrointestinal [15], pulmonary [16] and metabolic disorders [17]. The prognosis for these cases is mostly favorable, although the presence of isolated fetal ascites is a rare diagnosis and work-up should be followed to ensure a proper diagnosis as most of the cases are associated with other abnormalities [18].

In contrast, isolated fetal ascites occasionally occurs primarily without any evident underlying causes. Although the mechanisms of primary isolated fetal ascites is not fully understood, most of these fetuses result in chylous ascites after birth [5, 11]. The causes of congenital chylous ascites are congenital lymphatic dysplasia [7], obstruction of lymphatic vessels [10], and leakage from lymph ducts [6, 7]. Although the prognosis of these infants is usually favorable [5], there are some unfavorable cases with severe chylous ascites [19], and the prognostic factors of primary

Table 2 Findings of the infants with primary isolated fetal ascites at birth

	Group I (n = 7)	Group II (n = 5)	p
Sex (M/F)	3/4	3/2	1.000
Gestational age at birth (weeks)[a]	37.0 ± 0.98	36.6 ± 0.75	0.423
Apgar score at 1 min[a]	8.1 ± 0.69	7.8 ± 1.09	0.715
Apgar score at 5 min[a]	8.3 ± 0.76	9.0 ± 0.0	0.064
Body weight at birth (kg)[a]	2.92 ± 0.30	3.05 ± 0.34	0.504
Head circumference at birth (cm)[a]	33.6 ± 1.23	33.5 ± 0.96	0.860
Abdominal circumference at birth (cm)[a]	35.8 ± 5.84	38.4 ± 3.64	0.456
AC/HC[a]	1.1 ± 0.18	1.1 ± 0.09	0.508

HC head circumference, *AC* abdominal circumference

[a] Mean ± standard deviation

Table 3 Treatments and outcome for the fetuses with primary isolated ascites

	Group I (n = 7)	Group II (n = 5)	p
Fetal abdominal paracentesis	2	4	0.242
Cesarean section	1	4	0.072
Confirmation of chyle	3	5	0.080
Dietary treatment	3	4	0.198
Total parenteral nutrition	1	5	0.015
Surgical intervention	0	5	0.001
Duration of hospitalization (days)[a]	17 (4–40)	79 (18–95)	0.023
Duration of persisting ascites (days)[a]	25 (5–81)	238 (64–966)	0.005
Morbidity	0	3	0.046
Mortality	0	1	0.417

[a] Median with range

isolated fetal ascites have not been fully elucidated because of its small population.

Therefore, a retrospective review of primary isolated fetal ascites was conducted to evaluate the prognostic factors. The results demonstrated that the most important prognostic factor was the gestational age of onset for fetal ascites. In fact, 86% of the patients who had fetal ascites detected after 30 weeks' gestation regressed without surgical intervention. In contrast, 80% of the infants who developed fetal ascites before 30 weeks' gestation eventually required some kind of surgical intervention. In particular, two patients whose ascites were detected before 20 weeks' gestation experienced the chylous ascites more than 10 months after birth, despite treatment, including repeated surgery. In addition, there was a negative correlation between the gestational age at diagnosis and the severity of the fetal ascites, which was also a prognostic factor of primary isolated fetal ascites. These results indicated that the gestational age of the onset of fetal ascites may suggest the etiology or mechanism of fetal ascites, because congenital chylous ascites is caused by several types of lymphatic abnormalities [11, 20], and the type of lymphatic abnormalities determines the outcome [5, 7].

The development of the lymphatic system commences after 5 weeks' gestation and will be completed by 16 weeks' gestation [21]. Therefore, the appearance of fetal ascites before the complete formation of lymphatic system suggests the abnormal development of the lymphatic system, and the appearance after the formation of this system suggests an accidental abnormality in the lymphatic system. Ascites detected after 30 weeks' gestation in the current series were more likely to regress spontaneously with medical treatment alone. These facts implied that fetal ascites that appeared later in pregnancy may be caused by a localized occlusion or leakage of a lymphatic duct, and thus, often regresses spontaneously [5] or will respond to conservative therapy using a medium-chain-triglyceride diet or TPN [22]. The involvement of lymphatic abnormalities may be greater in the fetuses with ascites detected between 20 and 30 weeks' gestation than in the later onset cases. Even though conservative treatments may be ineffective in these cases [8], surgical intervention may be effective and indicated. An exploratory laparotomy may therefore improve ascites due to adhesion of the lymphatic leakage area [8, 23] and decrease the chyle flow [24], even if no responsible lesion is identified during the surgery.

In contrast, ascites noticed before 20 weeks' gestation were refractory and persisted despite various types of treatment. Surgical correction of the lymphatic system or adhesive therapy may be ineffective for these intractable ascites because these cases may be closely correlated with a congenital defect in the development of the lymphatic system [25]. More aggressive surgical therapy such as a peritoneovenous shunt may be required in such intractable cases, though this procedure has a higher incidence of serious complications, such as sepsis [26]. Intrauterine paracentesis had no effect on preventing an enlarged abdomen because of rapid reaccumulation of the ascites. However, intrauterine therapeutic paracentesis is useful for avoiding cesarean section by reducing the abdominal size over a short term and to ensure the safe delivery of the baby [26]. This procedure was performed in six fetuses and avoided cesarean section in two of them.

One major limitation of this study was that this retrospective study consisted of a small series of single institutions. However, primary fetal ascites is uncommon as a cause of isolated fetal ascites, which is rare in the fetal ascites diagnosed before birth [18], and thus, the study has generalizable information which is useful to practitioners for predicting the prognosis. In the present study, the prognosis of primary isolated fetal ascites can therefore be predicted by the gestational age at the time of diagnosis and it may be possible to estimate the optimal management for these fetuses both in utero and after birth based on these prognostic factors.

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The outcome and prognostic factors of twin–twin transfusion syndrome following fetoscopic laser surgery

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Objectives To evaluate the outcome and preoperative risks of twin–twin transfusion syndrome (TTTS) following fetoscopic laser surgery (FLS).

Methods A retrospective cohort study of a series of 181 consecutive cases of TTTS before 26 weeks' gestation subjected to FLS at four centers in Japan between July 2002 and December 2006.

Results The chances of survival of at least one twin at 28 days of age and 6 months of age were 91.2% and 90.1%, respectively. The rate of major neurological complications in survivors at 6 months of age was 4.7%. Preoperative findings that were significant risk factors for death were as follows: (1) being donor [odds ratio (OR): 3.01, 95% confidence interval (CI): 1.24–7.31, $P = 0.015$]; (2) reversed (OR: 11.78, CI: 3.05–45.55, $P < 0.001$) and absent (OR: 3.95, CI: 1.66–9.43, $P = 0.002$) end-diastolic velocity in the umbilical artery (EDV-UA) of the donor; and (3) reversed blood flow in the ductus venosus of the recipient (OR: 2.35, CI: 1.04–5.29, $P = 0.040$).

Conclusions FLS leads to high survival rates and low neurological morbidity for fetuses in TTTS. FLS is an effective therapeutic option for TTTS before 26 weeks of gestation. Preoperative Doppler findings of the umbilical artery and the ductus venosus are useful in predicting prognosis following FLS. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS: fetal therapy; fetoscopic laser surgery; odds ratio; prognostic factor; twins; twin-twin transfusion syndrome; ultrasound

INTRODUCTION

Twin–twin transfusion syndrome (TTTS), which occurs in 10% of monochorionic twin pregnancies, is associated with high perinatal morbidity and mortality (Mahony *et al.*, 1990; Saunders *et al.*, 1992). Blood flow imbalance between twins via placental vascular anastomoses is assumed to be responsible for TTTS (Diehl *et al.*, 2001; Bermúdez *et al.*, 2002). Fetoscopic laser coagulation of placental vascular anastomoses is believed to treat TTTS and improve the survival rate and neurological outcomes (De Lia *et al.*, 1990, 1995; Ville *et al.*, 1995). Retrospective studies have noted that fetoscopic laser surgery (FLS) resulted in higher survival rates and lower rates of neurological complications (Ville *et al.*, 1998; Hecher *et al.*, 1999; Quintero *et al.*, 2003). One prospective randomized trial by the Eurofoetus group has demonstrated that FLS is a superior and more effective first-line treatment compared to serial amnioreduction (Senat *et al.*, 2004). However, a prospective randomized trial performed in the United States failed to complete the study with unfavorable results (Crombleholme *et al.*, 2007). We began performing FLS for TTTS in Japan in 2002 (Ishii *et al.*, 2007; Murakoshi *et al.*, 2008). We evaluated the outcome of FLS with regard to its effectiveness as a treatment for TTTS.

The Quintero staging has been proposed to stratify cases of TTTS according to the degree of severity determined by sonographic findings (Quintero *et al.*, 1999). This widely used staging system has less prognostic significance in patients treated by FLS (Muratore *et al.*, 2009; Rossi and D'Addario, 2009). Doppler studies have been employed in an attempt to predict outcomes after FLS (Zikulnig *et al.*, 1999; Martínez *et al.*, 2003; Chang *et al.*, 2006; Ishii *et al.*, 2007; Murakoshi *et al.*, 2008). Although the association between reversed or absent end-diastolic velocity in the umbilical artery (EDV-UA) and intrauterine fetal death in the donor has been described (Martínez *et al.*, 2003; Chang *et al.*, 2006; Ishii *et al.*, 2007; Murakoshi *et al.*, 2008), little is known

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about preoperative predicting factors. The aims of this study were to validate the efficacy of FLS for TTTS performed in Japan and investigate preoperative findings that affect the survival of twin fetuses after FLS.

PATIENTS AND METHODS

A retrospective cohort study examined a series of 181 consecutive pregnant women affected by TTTS who underwent FLS at four centers in Japan between July 2002 and December 2006. The diagnosis of TTTS was based on a monochorionic twin pregnancy that was complicated by polyhydramnios with a maximum vertical pocket (MVP) ≥8.0 cm (with a distended bladder) in the recipient, and oligohydramnios with an MVP ≤2.0 cm (with a nondistended bladder) in the donor. Inclusion criteria for FLS were TTTS Quintero stages 1 through 4 and a gestational age between 16 and 26 weeks. Exclusion criteria were a major fetal anomaly, ruptured membranes, uncontrolled uterine contractions, and a maternal condition mandating delivery. All TTTS patients who qualified the above criteria were offered FLS. The protocol for the retrospective cohort study was approved by the institutional review board at each institute.

Routine preoperative ultrasound assessment including fetal biometry, fetal morphology, amniotic fluid volume, and placental location was performed followed by color and pulsed Doppler examination. The fetal weight was estimated by the Japanese Society of Ultrasound in Medicine (JSUM) formula using biparietal diameter, abdominal circumference, and femur length (Shinozuka *et al.*, 2000). In the Doppler studies, the occurrence of absent or reversed EDV-UA, reverse flow in the ductus venosus (RF-DV), and pulsatile flow in the umbilical vein (PF-UV) was recorded.

FLS for fetoscopic laser coagulation of placental vascular anastomoses was performed in a similar manner at each institute, based on previously described methods (Quintero *et al.*, 1998). Under adequate anesthesia (regional, local, or general in early cases), a 3.8-mm trocar was percutaneously inserted into the recipient sac. A 2-mm fetoscope with a 3-mm cannula (Karl Storz, Tuttlingen, Germany) was used through a trocar at two centers. A 3.5-mm diagnostic fetoscope and a 3-mm operating fetoscope (Richard Wolf, Vernon Hills, IL, USA) were used through a trocar at the other two centers. All communicating vessels between the twins on the chorionic plate of the placenta (including arteriovenous (AV), arterio-arterial (AA), and veno-venous (VV) anastomoses) were coagulated selectively using an output of 15 to 40 W with a 600-μm diameter Nd: YAG (neodymium: yttrium–aluminum–garnet) laser fiber and a nontouch technique. The amniotic fluid was subsequently drained through the cannula until the MVP reached less than 6 cm. All patients provided written consent to undergo FLS, and it was approved by the ethics committee of each institution.

Perioperative management with prophylactic tocolysis and antibiotics was provided by the four centers in which FLS was performed. Prenatal care with weekly ultrasound examination including pulsed Doppler assessment, and delivery and neonatal management was provided by the referring perinatal centers. Delivery was decided according to obstetrical indications by the treating perinatologist. Neonates were routinely examined by brain ultrasonography. Magnetic resonance imaging was performed when clinical examination or ultrasonography was suggestive of an abnormality. All infants were examined by trained pediatricians at 6 months of age at the referring perinatal centers.

The primary outcome measures were survival of at least one twin at 28 days of age, survival of at least one twin at 6 months of age, and the rate of major neurological complications in survivors at 6 months of age. Pregnancy loss was defined as delivery at less than 22 weeks of gestation. Major neurological complications were defined in all infants as severe intraventricular hemorrhage (grade 3 or 4), cystic periventricular leukomalacia, and other clinically significant abnormalities (cerebral palsy, hydrocephalus, ventriculomegaly, and multiple infarction).

Statistical analysis

The odds ratio (OR) was used to estimate the risk of fetal or neonatal death (all deaths up to 28 days), according to the risk factors of preoperative findings. We selected all deaths up to 28 days instead of those *in utero* as the outcome for prognostic factors because survival at 28 days was the primary outcome of this study. Univariate analyses were used to estimate the crude ORs and their 95% CIs of the preoperative risk factors. These factors included estimated fetal weight (EFW) [standardized using JSUM standardization formula (Table 5 footnotes) and categorized to be equal to or less than −2SD and more than −2SD], the MVP in the donor and in the recipient, nonvisualization of the donor's bladder, EDV-UA of the donor (categorized as reverse, absent, or normal), RF-DV of the donor, PF-UV in the donor, EDV-UA of the recipient, RF-DV of the recipient, PF-UV in the recipient, hydrops in the recipient, and gestational age at FLS. The gestational age at delivery, which was not a preoperative finding, was also used in univariate analysis for reference. Multiple logistic regression models were used to control for the possible confounding effects between the preoperative variables, which showed significant ORs in the univariate analysis. We used the generalized estimating equation (GEE) method for modeling the twins simultaneously, and included some interaction terms to estimate their risks separately. The reported P values were two-sided. $P \leq 0.05$ was considered to be statistically significant. Analyses were performed using SAS software version 9.1.2 (SAS/STAT software: user's guide, version 9.1. SAS Institute Inc.; 2004, Cary, NC, USA)

RESULTS

A total of 181 patients underwent laser surgery. The mean gestational age at the time of surgery was

21.2 weeks. Approximately 50% of the cases were found to have an anterior placental location. Most of the cases (75%) were at Quintero stage 3 or 4 (Table 1). In two cases, the procedure was not completed because of the difficulty in observing all communicating vessels in an anterior placental location and turbid amniotic fluid. There was no maternal death. One case of placental abruption and two cases of mirror syndrome (these cases were previously reported) were observed (Hayashi *et al.*, 2006; Matsubara *et al.*, 2008). There were six cases of treatment failure including one case of TTTS, which resulted in delivery at 26.6 weeks of gestation and five cases of twin anemia polycythemia sequence that were diagnosed by neonates' blood analyses followed by dye injection studies of placenta (Lopriore *et al.*, 2007). In these six cases, two donors and two recipients died. In addition, two donors and two recipients showed major neurological handicaps.

Pregnancy outcomes are presented in Table 2. The rate of premature rupture of membranes within 28 days after FLS was 7.7%. Delivery before 24 weeks, which was including pregnancy loss, occurred in 13 cases (7.2%).

Table 1—Baseline characteristics ($n = 181$)

Age (year)[a]	31.0 ± 4.5
Nulliparity: *n* (%)	100 (55%)
Gestational age at surgery (week)[a]	21.2 ± 2.5
Location of placenta: *n* (%)	
Anterior	89 (49%)
Posterior	92 (51%)
Quintero stage: *n* (%)	
Stage 1	14 (8%)
Stage 2	30 (17%)
Stage 3	113 (62%)
Stage 4	24 (13%)

[a] Mean ± standard deviation.

Table 2—Pregnancy outcomes ($n = 181$)

Pregnancy complications	
Pregnancy loss within 7 days after FLS: *n* (%)	4 (2.2%)
PROM within 7 days after FLS: *n* (%)	7 (3.9%)
PROM within 28 days after FLS: *n* (%)	14 (7.7%)
Gestational age at delivery (week)	
Median	32.9
Interquartile range	29.3–36.1
Gestational age at delivery: *n* (%)	
<24 weeks[a]	13 (7.2%)
24 to <28 weeks	20 (11.1%)
28 to <32 weeks	40 (22.1%)
32 to <34 weeks	36 (19.9%)
34 to <36 Weeks	19 (10.5%)
≥36weeks	53 (29.3%)
Birth weight (g)	
Donor ($n = 137$)	1471 ± 596
Recipient ($n = 157$)	1787 ± 613

FLS, fetoscopic laser surgery; PROM, premature rupture of membranes.
[a] Including pregnancy loss.

The mean gestational age at delivery was 32.9 weeks. A total of 72 cases (39.8%) were delivered at 34 weeks or later.

Survival rates are presented in Table 3. The rate of survival of at least one twin at 28 days of age was 91.2% (95% CI: 86.1–94.5%). The rate of survival of at least one twin at 6 months of age was 90.1% (95% CI: 84.8–93.6%). A minimal difference was found for both the survival of at least one twin and the survival of both twins at 6 months of age compared to those rates at 28 days of age. There were no differences in the survival rates of at least one twin at 28 days of age between Quintero stage 1 to 2 (90.9%) and stage 3 to 4 (91.2%). However, the rates of the two survivors at 28 days of age had decreased in Quintero stage 3 to 4 (59.1%) compared to those at stage 1 to 2 (81.8%). The survival rate of at least one twin at 6 months of age was less than 60% in cases that were delivered before 28 weeks of gestation.

Perinatal and neonatal outcomes, including neurological complications, are presented in Table 4. The percentage of fetuses that died *in utero* or by 6 months of age was 24%. The death rate of the donor (30.9%) was almost double of that of the recipient (17.1%). Following FLS, 52/87 (60%) of the deaths occurred *in utero*; of these deaths, 35/52 (67%) occurred within 7 days after FLS. The rate of major neurological complications in the survivors at 6 months of age was 4.7% (13/275). The rate of survivors at 6 months of age without major neurological complications was 72.4% (262[275–13]/362).

Univariate analysis showed that low EFW (equal to or less than −2SD) of the donor and reversed or absent EDV-UA of the donor strongly correlated with fetal or neonatal death of the donor; RF-DV of the recipient and hydrops of the recipient correlated with the outcome of the recipient (Table 5). Variables such as MVP, PF-UV, or gestational age at surgery did not affect the outcome. Although nonvisualization of the bladder was suspected as a favorable prognostic factor (OR: 0.56), it did not reach significance (Table 5). It became significant when the analysis was limited to the patients of Quintero stage 3 ($N = 113$; OR: 0.37; CI: 0.16–0.82; $P = 0.013$;

Table 3—Survival rates ($n = 181$)

Survival at 28 days	
0 survivors	16 (8.8%)
1 survivor	48 (26.5%)
2 survivors	117 (64.6%)
Quintero stage 1 or 2	36/44 (81.8%)
Quintero stage 3 or 4	81/137 (59.1%)
At least 1 survivor	165 (91.2%)
Quintero stage 1 or 2	40/44 (90.9%)
Quintero stage 3 or 4	125/137 (91.2%)
Survival at 6 months	
0 survivors	18 (9.9%)
1 survivor	51 (28.2%)
2 survivors	112 (61.9%)
At least 1 survivor	163 (90.1%)
At least 1 survivor at 6 months by gestational age at delivery	
<28 weeks	19/33 (57.6%)
28 to <32 weeks	37/40 (92.5%)
≥32weeks	107/108 (99.1%)

Table 4—Perinatal and infant outcomes

Outcome	Donor (n = 181)	Recipient (n = 181)	Total (n = 362)
All deaths at 6 months	56 (30.9%)	31 (17.1%)	87 (24.0%)
Pregnancy loss (<22 week)	6 (3.3%)	6 (3.3%)	12 (3.3%)
Fetal, neonatal, or infant death			
In utero	35 (19.3%)	17 (9.4%)	52 (14.4%)
Within 7 days after FLS	24/35 (68.6%)	11/17 (64.7%)	35/52 (67.3%)
0–7 Days after delivery	5 (2.8%)	5 (2.8%)	10 (2.8%)
8–28 Days after delivery	4 (2.2%)	2 (1.1%)	6 (1.7%)
1–6 Months after delivery	6 (3.3%)	1 (0.6%)	7 (1.9%)
Major neurological complications	12 (6.6%)	9 (5.0%)	21 (5.8%)
Intraventricular hemorrhage (grade 3 or 4)	7 (3.9%)	1 (0.6%)	8 (2.2%)
Cystic periventricular leukomalacia	3 (1.7%)	5 (2.8%)	8 (2.2%)
Others	2 (1.1%)	3 (1.7%)	5 (1.4%)
Alive at 6 months without major neurological complications	121 (66.9%)	141 (77.9%)	262 (72.4%)
Alive at 6 months with major neurological complications	4/125 (3.2%)	9/150 (6.0%)	13/275 (4.7%)

nonvisible bladder: number of dead/alive, 15/48; visible bladder: 23/27). The gestational age at delivery, the intermediate variable, had a significant influence on the outcome (Table 5). The results of multivariate GEE analysis of preoperative factors are shown in Table 6. There was a great risk involved in being a donor. Reverse or absent EDV-UA was a significant risk factor for the death of the donor; in these cases, the OR of reverse EDV-UA was about three times higher than that for cases with absent EDV-UA. RF-DV of the recipient was a significant risk factor for the death of the recipient. The effect of gestational age at FLS, EFW, and hydrops was not statistically significant.

DISCUSSION

We report the initial comprehensive results of FLS for TTTS in Japan. The rate of survival of at least one twin at 28 days of age was above 90% regardless of the stage. The rate of premature rupture of membranes within 28 days after FLS was less than 8%. The rate of treatment failure was 3% (6/181). The rate of major neurological complications in the survivors at 6 months of age was less than 5%. In the reliable outcomes of FLS published between 1997 and 2007, the rate of survival of at least one twin was 75% to 87% and the rate of cerebral anomalies was 2% to 33% (Rossi and D'Addario, 2008). This meta-analysis found that FLS was associated with better outcomes than serial amnioreduction. Our results support the premise that FLS is an effective treatment option for TTTS before 26 weeks of gestation.

The preoperative findings of the donor or recipient only contributed to the death of that fetus. Reversed or absent EDV-UA of the donor, which related to the death of the donor, was a major predictor; RF-DV of the recipient, which related to the death of the recipient, was a secondary predictor. The association between reversed or absent EDV-UA and intrauterine fetal death in the donor has been reported (Martínez *et al.*, 2003; Chang *et al.*, 2006; Ishii *et al.*, 2007; Murakoshi *et al.*, 2008). Our results confirm this association and demonstrate that reversed EDV-UA has a threefold risk of death compared to absent EDV-UA. A correlation between RF-DV and mortality is suspected; however, only one study has reported a lack of association between reversed or absent EDV-UA and mortality (Zikulnig *et al.*, 1999). Our results demonstrate this correlation of RF-DV in the recipient with strong association of EDV-UA in the donor.

There were no differences in the survival of at least one twin at 28 days of age between Quintero stages 1 to 2 and 3 to 4; however, the number of cases with two survivors decreased in Quintero stage 3 to 4 compared to that in stage 1 to 2. This finding is understandable because significant risk factors for one death (such as reversed or absent EDV-UA and RF-DV) are the findings for Quintero stage 3. Nonvisualization of the bladder, which is the finding for Quintero stage 2, also has no adverse effect. It has been suggested that the commonly used Quintero staging does not accurately reflect post-FLS mortality risk (Muratore *et al.*, 2009; Rossi and D'Addario, 2009). It has been reported that the highest mortality of TTTS after FLS has been recognized in Quintero stage 3 (Muratore *et al.*, 2009). We suspected that there is a considerable range of potential outcomes of Quintero stage 3; therefore, we tried to validate the Quintero stage 3 subclassification based on the visibility of the bladder of the donor (Murakoshi *et al.*, 2008). Quintero stage 3 atypical, which is defined as abnormal Doppler findings with bladder visualization, was associated with a high donor mortality after FLS (Murakoshi *et al.*, 2008). Our study has confirmed this finding to demonstrate that nonvisualization of the bladder is a favorable prognostic factor in Quintero stage 3.

Risk factors for post-FLS mortality may not accurately represent the severity of TTTS. They may instead reflect an adverse effect of FLS or the status of monochorionic twins after ablation of placental communicating vessels. The cause of absent or reversed EDV-UA in TTTS is suspected to be linked to a small placental territory, placental vascular anastomoses, or both (Martínez *et al.*, 2003; Chang *et al.*, 2006). Resolution of an absent or reversed EDV-UA after FLS implies the presence of an adequate individual placental territory and removal of donor hypotension caused by vascular anastomoses

Table 5—Crude OR of baseline risk factors for fetal or neonatal death

	Donor			Recipient		
Variables	OR (95% CI)	*P* value	No. of dead/alive	OR (95% CI)	*P* value	No. of dead/alive
Gestational age at surgery (+1 week)	0.92 (0.81–1.06)	0.246		0.93 (0.79–1.09)	0.381	
Gestational age at birth (+1 week)	0.54 (0.38–0.76)	<0.001	$N = 140$	0.59 (0.44–0.80)	<0.001	$N = 158$
Estimated fetal weight (≤−2SD/>−2SD)[a]	2.76 (1.39–5.49)	0.004	≤−2SD: 34/57, −2SD<: 16/74	—[b]	—	≤−2SD: 0/0, −2SD<: 30/151
MVP (+5 mm) (donor)	1.08 (0.85–1.38)	0.523		0.77 (0.56–1.06)	0.105	
MVP (+5 mm) (recipient)	0.97 (0.90–1.05)	0.502		0.97 (0.88–1.07)	0.488	
Nonvisible bladder (donor)	0.56(0.29–1.08)	0.084	Nonvisible: 25/84, visible: 25/47	2.02(0.85–4.83)	0.113	Nonvisible: 22/87, visible: 8/64
Reverse EDV-UA (donor)[c]	10.24 (3.21–32.63)	<0.001	Reverse: 10/6, absent: 26/39, normal: 14/86	0.28(0.04–2.29)	0.237	Reverse 1/15, absent: 10/55, normal: 19/81
Absent EDV-UA (donor)[c]	4.09 (1.93–8.69)	<0.001		0.78(0.34–1.79)	0.552	
RF-DV (donor)	2.65 (0.16–43.25)	0.493	Reverse: 1/1, normal: 49/130	0	1.000	Reverse: 0/2, normal: 30/149
PF-UV (donor)	0.79 (0.24–2.55)	0.692	Pulse: 4/13, normal: 46/118	0	1.000	Pulse: 0/17, normal: 30/134
Reverse EDV-UA (recipient)[c]	0	1.000	Reverse: 0/1, absent: 1/9, normal: 49/121	0	1.000	Reverse 0/1, absent: 3/7, normal: 27/143
Absent EDV-UA (recipient)[c]	0.27 (0.03–2.22)	0.226		2.27 (0.55–9.33)	0.256	
RF-DV (recipient)	1.07 (0.51–2.21)	0.862	Reverse: 14/35, normal: 36/96	2.90 (1.29–6.52)	0.010	Reverse: 14/35, normal: 16/116
PF-UV (recipient)	1.37 (0.71–2.65)	0.342	Pulse: 28/63, normal: 22/68	0.99 (0.45–2.16)	0.974	Pulse: 15/76, normal: 15/75
Hydrops (recipient)	0.86 (0.32–2.30)	0.758	Hydrops: 6/18, normal: 44/113	3.07 (1.17–8.02)	0.022	Hydrops: 8/16, normal: 22/135

CI, confidence interval; EDV-UA, end-diastolic velocity in the umbilical artery; MVP, maximum vertical pocket; OR, odds ratio; PF-UV, pulsatile flow in the umbilical vein; RF-DV, reverse flow in the ductus venosus.

[a] Estimated fetal weight were standardized with mean = $-2891 + 70.737 \times$ gestational age $- 0.67477 \times$ gestational age$^2 + 0.0029753 \times$ gestational age$^3 - 0.00000426311 \times$ gestational age^4 and SD = $0.2089 \times$ gestational age $+ 0.0049 \times$ gestational age$^2 - 74$.

[b] No cases ≤−2SD.

[c] Reference = Normal.

Table 6—Multivariate-adjusted OR of preoperative factors for fetal or neonatal deaths after laser surgery

Prognostic factors	OR	95% CI	*P* value
Donor/recipient	3.01	1.24–7.31	0.015
Gestational age at FLS (+1 week)	0.93	0.83–1.04	0.195
Estimated fetal weight (≤−2SD/−2SD<)	1.33	0.62–2.87	0.469
Reverse EDV-UA[a]			
For donor death	11.78	3.05–45.55	<0.001
For recipient death	0.41	0.06–2.71	0.352
Absent EDV-UA[a]			
For donor death	3.95	1.66–9.43	0.002
For recipient death	0.85	0.35–2.07	0.717
RF-DV[a]			
For donor death	1.29	0.54–3.04	0.567
For recipient death	2.35	1.04–5.29	0.040
Recipient hydrops	1.51	0.64–3.57	0.346

CI, confidence interval; EDV-UA, end-diastolic velocity in the umbilical artery; FLS, fetoscopic laser surgery; OR, odds ratio; RF-DV, reverse flow in the ductus venosus.

[a] The interaction terms were used to estimate ORs of the donor and recipient separately.

(Chang *et al.*, 2006). A small placental territory or vascular anastomoses-induced donor hypotension is suspected to be a cause of deaths of donors after FLS. To prevent donor hypotension caused by vascular anastomoses after FLS, the surgical technique of sequential selective laser photocoagulation of communicating vessels has been introduced, and the initial results are promising (Quintero *et al.*, 2007; Nakata *et al.*, 2009). Being a donor that has smaller placental territory than the recipient is a significant risk factor. Placental insufficiency caused by a small placental territory may be a major prognostic factor for the donor after FLS (Habli *et al.*, 2008).

The OR of low EFW of the donor in univariate analysis (OR: 2.76; $P = 0.004$) was reduced in multivariate logistic analysis (OR: 1.33; $P = 0.469$). This implies that low EFW affects mortality via a high correlation with reversed or absent EDV-UA of the donor. Similarly, the reduction of the OR of hydrops of the recipient in multivariate logistic analysis (OR: 1.51; $P = 0.346$) compared to that in univariate analysis (OR: 3.07; $P = 0.022$) implies that hydrops affects mortality via a high correlation with RF-DV of the recipient. RF-DV of the recipient, which is an abnormal venous flow, is a sign of significant right cardiac overload of the recipient (Hecher *et al.*, 1995). Hydrops of the recipient is a sign of cardiac failure caused by cardiac overload of the recipient. Cardiac overload caused by a blood flow imbalance may be a major prognostic factor for the recipient after FLS.

Gestational age at delivery had a strong effect on the outcome of survival. This is not surprising because gestational age at delivery has a strong influence on the survival of neonates in general. Gestational age at delivery, an event after FLS, was the intermediate variable for relationship between preoperative findings and the outcome of survival after FLS. Gestational age at delivery was not used as a variable for multivariate analysis because it was not appropriate to use the intermediate variable in multivariate analysis to examine the effects of preoperative factors on the outcome. It is interesting to investigate the preoperative variables that are associated with gestational age at delivery. Further research is required to examine the analysis using gestational age at delivery as the outcome.

Our study has strengths and limitations. The strength of this study is its evaluation of a large cohort of patients that underwent FLS in Japan under the same protocol. Although this is a retrospective study, there is no lack of data with regard to survival, major neurological complications, or preoperative ultrasound findings. The limitations of this study are lack of data on long-term follow-up and further parameters such as a cardiovascular profile (Shah *et al.*, 2008). Neurological morbidity was assessed at 6 months of age; however, long-term follow-up is necessary to evaluate the incidence of neurological morbidity (Graef *et al.*, 2006). We assessed the predictive factors using preoperative ultrasound findings mainly described in Quintero staging. Further parameters will give further insight into prognostic factors.

CONCLUSION

This study demonstrated a high survival rate and low neurological morbidity for TTTS treated by FLS. Our findings suggest that FLS has been successful in Japan, and that FLS is an effective treatment option for TTTS before 26 weeks of gestation. Significant preoperative risk factors for post-FLS mortality are being a donor (OR: 3.01), reversed or absent EDV-UA of the donor (ORs for donor death: 11.78, 3.95, respectively), and RF-DV of the recipient (OR for recipient death: 2.35). Prognostic factors for the donor, such as reversed or absent EDV-UA, imply placental insufficiency. Prognostic factors for the recipient such as RF-DV imply cardiac overload.

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Successful management of a large fetal mediastinal teratoma complicated by hydrops fetalis

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Abstract This report describes a case of fetal mediastinal teratoma complicated by hydrops fetalis managed successfully by aspiration of the tumor cyst fluid. Fetal mediastinal teratomas are rare tumors that cause hydrops fetalis or fetal demise in the prenatal period and respiratory distress in the neonatal period. The patient presented with a large cystic mass in the thoracic cavity complicated by hydrops fetalis. The hydrops resolved after fetal aspiration of the tumor cyst fluid. The infant was born without respiratory distress, and tumor resection was performed at the age of 30 days. The postoperative course was uneventful, and the patient was in good health 6 months postoperatively.

Mediastinal teratomas (MTs) represent approximately 20% of all mediastinal masses and 10% of all teratomas in childhood. They usually occur in the anterior mediastinum [1-4]. This entity is rarely diagnosed prenatally and often results in the development of hydrops and fetal demise [4-7]. Mediastinal teratomas are rare in neonates and present with severe respiratory distress immediately after birth [1,2,8-10]. Previous reports emphasize that despite early and uncomplicated surgical excision of the tumor, it is difficult to salvage an infant with MT because of poor heart development and lung hypoplasia resulting from intrauterine compression [2,8,10]. The following report illustrates a rare case of fetal MT with hydrops fetalis treated by prenatal aspiration of the tumor cyst fluid and subsequent postnatal resection.

1. Case report

A 37-year-old gravida 1 para 0 woman was referred to our hospital for evaluation of a cystic mass in the fetal thorax associated with hydrops fetalis at 29 weeks of gestation. The initial ultrasound examination at 23 weeks of gestation showed a structurally normal fetus with the exception of a large cyst in the right anterior mediastinum. Magnetic resonance imaging demonstrated a large cystic and solid

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mass occupying the thoracic cavity bilaterally without pericardial effusion, and a presumptive diagnosis of mediastinal teratoma was made. Serial ultrasound examinations were performed. There was no evidence of heart failure on fetal echocardiography. At 29 weeks of gestation, the size of the lesion had increased and fetal hydrops was present characterized by edema and ascites (Fig. 1A).

Magnetic resonance imaging at the time of referral showed a large cystic mass in the fetal thorax with hydrops fetalis and polyhydroamnios (Fig. 1B). Three days after referral, aspiration of the fetal tumor cyst fluid and an amniocentesis were simultaneously performed. The amount of the fluid aspirated from the mass was 75 mL. After the procedure, the hydrops fetalis subsided within a week (Fig. 2A). The size of the cystic lesion in the thorax decreased; however, the solid component increased in size (Fig. 2B). The fetus appeared to do well with continued growth after aspiration of the tumor cyst fluid.

A male infant weighing 3070 g was born by assisted breech delivery at 39 weeks of gestation. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively, and there was no respiratory distress noted. Human chorionic gonadotropin, serum alpha-fetoprotein, and CA125 levels were within normal limits for a newborn; however, the CA 19-9 level was slightly elevated (89.8 U/mL). Chest computed tomography

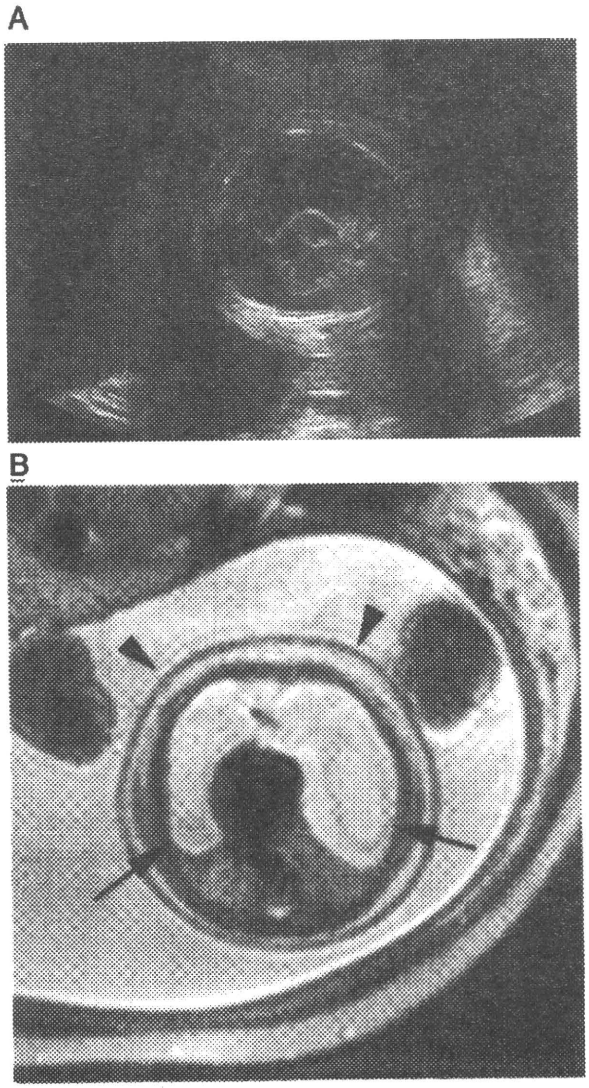

Fig. 1 A, Fetal ultrasound at 29 weeks of gestation shows a large cystic mass and compressed heart and lung. B, Fetal magnetic resonance imaging (single-shot turbo spin echo sequence: repetition time, 900 milliseconds; echo time, 84 milliseconds) obtained in an axial plane at 29 weeks gestation. Axial views revealed a large cystic lesion in the fetal thorax (arrow) compressing the lungs and the heart. Skin edema was present (arrowhead).

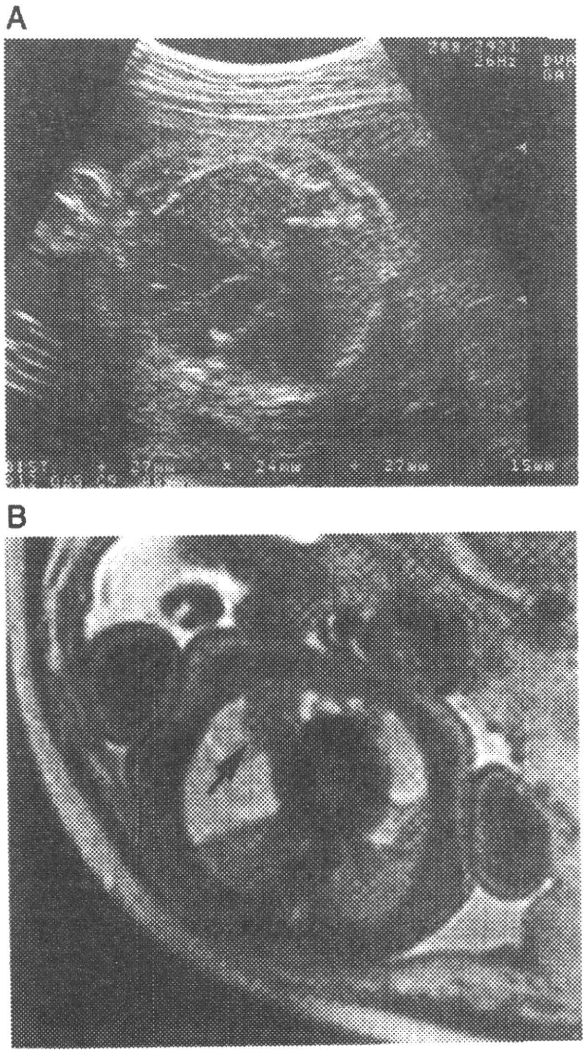

Fig. 2 A, Fetal ultrasound performed 3 days after the aspiration of the tumor cyst fluid. The cystic lesion decreased in size dramatically and the size of the lung increased. B, Fetal magnetic resonance imaging (single-shot turbo spin echo sequence: repetition time, 900 milliseconds; echo time, 84 milliseconds) obtained in an axial plane at 36 weeks of gestation (after thoracocentesis). The solid component of the tumor increased in size (arrow in A).

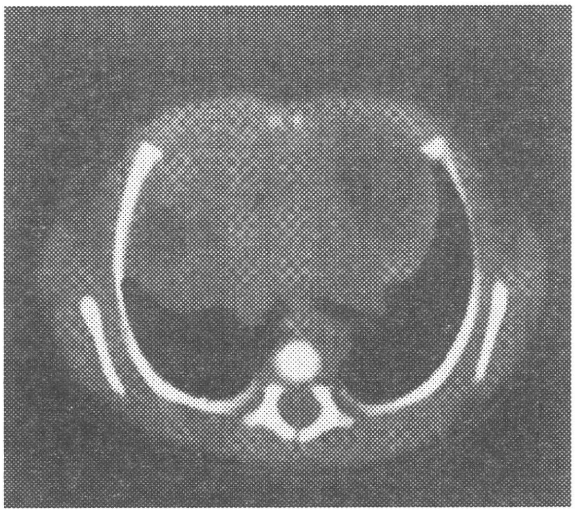

Fig. 3 Precontrast chest CT scan at 27 days after birth. The fat attenuation and calcification (arrowhead) became more obvious in the mass.

(CT) 3 days after birth showed a bilateral heterogeneous mass containing soft tissue, fluid, and a minute amount of fat and calcium attenuation. The fat and calcium attenuation in the mass became more apparent in the chest CT obtained 27 days after birth (Fig. 3). At 30 days of age, tumor resection was performed via a median sternotomy incision. The resected tumor was 9 × 7.5 × 3.5 cm. The cut surface revealed a solid component and a mutilocular cyst containing serous liquid and hair. Histopathology demonstrated a mature teratoma containing elements of pancreatic, intestinal, cartilaginous, fat, and thymic tissue. The patient had an uneventful postoperative course. Six months postoperatively, the infant was in good health with no respiratory problems or evidence of recurrence.

2. Discussion

Mediastinal teratomas represent approximately 10% of congenital teratomas in children [1,3,4], and are rarely reported prenatally or neonatally. To date, few prenatal cases have been reported [4-7,10-13]. Typical findings are a cystic and solid mass in the chest, polyhydramnios, and hydrops fetalis [10-13]. The mechanisms of polyhydramnios and hydrops have been explained by several previous authors. Polyhydramnios is caused by esophageal compression and decreased swallowing of amniotic fluid; hydrops is because of obstruction of venous return from the placenta by the tumor [5-7,10]. Once fetal hydrops develops, fetal demise rapidly ensues [4-7]. In the present case, we performed fetal echocardiography and did not detect any evidence of heart failure of the fetus. Fortunately, hydrops resolved immediately after the aspiration of the tumor cyst fluid. An early intervention at the onset of hydrops may have been effective and sufficient for reversal of this condition [12].

There are few reports of MTs in newborns. Almost all neonates with MTs require urgent surgery because of severe respiratory distress [2,8,9]. In some cases, severe morbidity and mortality have been reported even after complete resection of the tumor [8,10]. In one case [8], a newborn with MT died of hypoplastic heart despite successful removal of the mass. Although the case had no evidence of hydrops in the prenatal period, the compression of the heart by MT was the probable cause of the hypoplastic heart.

In the present case, aspiration of the tumor cyst fluid was effective in halting the progression of hydrops. In addition, relief of the thoracic pressure by the aspiration of the tumor cyst fluid may have prevented the development of hypoplasia of the lungs and heart. Fortunately, neonatal MTs are almost always benign [1,2]. Spillage of malignant cells is unlikely even if the thoracic cavity is contaminated by fluid in the cysts during the fluid aspiration. Malignant cells were not detected in the fluid aspirated in this case. The present case suggests that aspirating tumor cyst fluid resolves the hydrops fetalis associated with fetal MTs.

Merchant et al [13] reported 2 cases of MTs treated by fetal surgery and an ex utero intrapartum procedure. One fetus with hydrops underwent in utero resection of the mass at 23 weeks of gestation and the other underwent an ex utero intrapartum procedure for establishment of an airway and tumor resection at 36 weeks of gestation [13]. The authors recommend an in utero resection of the tumor for cases with fetal hydrops found before 30 weeks of gestation. From our experience with the present case, we recommend aspiration of the tumor cyst fluid as first-line therapy when the tumor is cystic in nature. When fluid aspiration is ineffective and/or the tumor is solid, in utero resection should be considered. Ultrasonography and echocardiography of the fetus are useful to evaluate and follow the status of the fetus.

Interestingly, the imaging features of the lesion changed significantly in the postnatal period. After the aspiration of the tumor cyst fluid, the solid portion of the lesion became more dominant. After birth, fat attenuation and calcification became obvious (Fig. 3). Similar "maturation" on imaging has been reported in an ovarian teratoma [14]. To the best of our knowledge, this is the first report describing the evolution of imaging features of an MT diagnosed prenatally.

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Current status of negative treatment decision-making for fetuses with a prenatal diagnosis of neonatal surgical disease at a single Japanese institution

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Prenatal diagnosis;
Decision-making;
Neonatal surgery;
Congenital anomaly;
Termination of pregnancy;
Fetal palliative care

Abstract

Background/Purpose: The termination of pregnancy because of fetal abnormalities in Japan has not been described. The aim of the present study was to analyze the current status and to evaluate the medical and ethical relevance in our institution for negative treatment decision-making for fetuses demonstrating neonatal surgical disease with a prenatal diagnosis.

Materials and methods: The medical records of 209 fetuses with a prenatal diagnosis from 1999 to 2008 were retrospectively reviewed. The cases with a negative treatment policy were analyzed according to the potential for survival. The negative treatment policies were defined as those in which the pregnancy was not actively continued, including elective termination of pregnancy and palliative or limited treatment that are primarily provided after birth.

Results: The selected treatment policies were active in 162 cases and negative in 46 cases. Thirty-three cases with negative policies were in the second-half period of pregnancy. The potential for survival was high in 5 cases, moderate in 11 cases, and nonviable in 30 cases. Eight of the nonviable cases underwent either limited or palliative treatment, whereas the remaining 38 fetuses were aborted.

Conclusions: The negative treatment policies in the nonviable fetuses were considered to be medically and ethically relevant. However, the number of cases with negative policies increased over the last 5 years and is therefore associated with complex ethical issues.

The mortality rate of neonatal surgical disease has been in continuous decline in Japan [1], with the exception of several diseases. It is believed that the potential causes of this decline include the effects of increased rates of prenatal diagnoses, which have advanced and are now widely conducted in Japan [2,3], as well as advancements in postnatal treatment, including perioperative management. The prenatal diagnosis may contribute to the improvement in outcomes by maternal transport, fetal intervention, and perinatal management. However, these reasons may not be the only explanations for the improvement in the prognoses of neonatal surgical diseases.

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The termination of pregnancy specifically because of fetal congenital abnormalities is not permitted in Japan. However, in fact, such terminations of pregnancy do occur by extending the interpretation of indications, which allows the termination of pregnancy before 22 weeks of gestation when the maternal health may be significantly compromised. In recent years, Japanese pediatric surgeons have noticed a decrease in the number of extremely severe neonatal surgical cases. We hypothesized that this was because of the choice of "negative treatments," including elective termination of pregnancy, in severe cases [4,5] that have been increasing in Japan because of earlier prenatal diagnoses. The purpose of the present study were to clarify the current status of negative treatment decision-making for fetuses with prenatal diagnoses of neonatal surgical disease in our institution, and to evaluate the medical and ethical relevance of these cases by an analysis of the potential for fetal survival.

1. Materials and methods

A retrospective analysis was conducted to examine the outcomes of fetuses with neonatal surgical diseases who underwent a prenatal diagnosis and were managed by the Department of Obstetrics or Department of Pediatric Surgery in our institution between January 1999 and December 2008. After obtaining approval from the institutional review board (no. 09274), a total of 209 medical records were reviewed. The cases in which the main diagnosis was an anomaly of the central nervous system, congenital heart disease, or primary immune and nonimmune fetal hydrops were excluded from the present series because these cases could not be assessed and treated by pediatric surgeons. However, the cases with fluid collections in the serosal cavities accompanied by secondary fetal hydrops were included because these conditions could be managed by pediatric surgeons. The medical records were reviewed to examine the gestational age at the time of diagnosis, chromosomal abnormalities, associated malformations, the severity of the disease, the final outcome, the macroscopic findings at the time of the abortion, the anatomical findings at the autopsy, and the treatment policy selected after counseling the parents, with respect to both the first and the second half of the study periods. According to the potential for survival when active treatment was provided, the cases were classified into the following 3 groups: the high-potential group, in which the potential for survival appeared to be greater than 50% even with conventional treatments; the moderate-potential group, which appeared to have less than 50% probability for survival with conventional treatments but indicated a potential for survival if fetal intervention [6] or ex utero intrapartum treatment (EXIT) [7] was performed, or had a high risk for physical disabilities with a reduced quality of life; and the nonviable group, which appeared to have no potential for long-term survival with current medical and surgical technology or was associated with a fatal chromosomal abnormality such as trisomy 13 or trisomy 18.

We counseled the parents by providing detailed explanations regarding the expected prognosis and the potential for physical or neurologic disabilities before the parents were asked to make a decision. The selected treatment policies were divided into active policies and negative policies. The active policies were defined as those in which the pregnancy was continued after the diagnosis, treatment was provided for healthy fetuses in cases of fetal distress, and surgical treatment was performed whenever indicated after birth. The negative policies were defined as those in which the pregnancy was not actively continued, including elective termination of pregnancy, and in which the fetus was not actively resuscitated in cases with fetal distress, and palliative or limited treatment were primarily provided after birth. The gestational age was expressed as the mean ± SD. A statistical analysis was performed using the χ^2 test for the gestational age and an analysis of variance was performed to analyze the other factors. P values of less than .05 were considered to be statistically significant.

2. Results

Two hundred nine fetuses with neonatal surgical diseases were diagnosed prenatally during the study period. Thirty-two cases were managed by obstetricians alone, 3 cases were seen only by pediatric surgeons, and 172 cases were managed by both types of physicians. The selected policies were active in 162 cases and negative in 46 cases. One fetus died in utero before a policy was selected. The fetuses undergoing a prenatal diagnosis ranged from 15 to 30 cases per year, and there was a tendency toward an increasing number of negative policy cases in recent years (Fig. 1). The total number of the cases, the distribution of the cases according to the potential for survival, the gestational age at diagnosis, the mortality rate in the cases with positive policies, the termination rate in the cases with negative

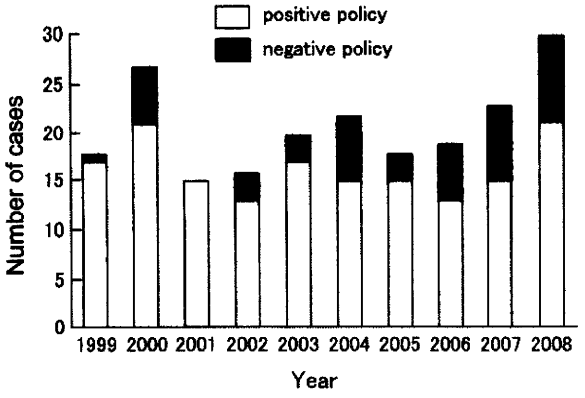

Fig. 1 The number of cases that underwent a prenatal diagnosis of neonatal surgical disease.

policies and the number of intrauterine fetal deaths were statistically compared between the first- and the second-half periods (Table 1). There were no differences in the mean gestational age at the time of diagnosis, but the number of cases that were diagnosed before 22 weeks of gestational age increased in the second-half period. The number of cases with active policies decreased, but there were no significant changes in the gestational age at the time of diagnosis and in the mortality rate. The number of cases with negative policies increased to approximately 2.5 times in the second-half period compared to the first-half period.

One hundred sixty-six cases were live births, and 5 fetuses died in utero. Termination of pregnancy was selected in 38 cases as negative treatment policies, and the number of cases undergoing a termination of pregnancy in the second-half period reached approximately 3 times the number during the first half-period. Thirty-four of 38 cases were performed in our institution, which was equivalent to 13.1% of the cases of termination of pregnancy performed in the same period. Among the 43 fetuses that were not live births, consent for autopsy was obtained in 23 cases and declined in 20 cases. The accuracy of the prenatal diagnosis, including the potential for survival, was pathologically verified during the autopsy in 23 cases and macroscopically confirmed in 15 cases. The potential for survival was assessed only by a prenatal fetal ultrasonography in 5 cases.

The cases demonstrating neonatal surgical diseases with active policies included congenital diaphragmatic hernia (n = 23), cystic lung disease (n = 16), intestinal atresia (n = 14), meconium peritonitis (n = 13), omphalocele (n = 11), duodenal atresia (10), ovarian cyst (10), sacrococcygeal teratoma (8), and others (n = 57). Among the 162 cases with active policies, 3 fetuses died in utero and 16 fetuses died after birth. The overall survival rate was 88.3% in this group. The mortality rate was high, at 30%, in the cases of both congenital diaphragmatic hernia and duodenal atresia.

The fetuses of neonatal surgical diseases with negative policies were arranged based on the potential for survival in Table 2. Five cases were classified in the high-potential group, 11 cases in the moderate-potential group, and 30 cases in the nonviable group. A termination of pregnancy was performed in all 5 cases of the high-potential group. Although the pulmonary hypoplasia of the 2 cases of isolated congenital diaphragmatic hernia were predicted to be severe based on the fetal ultrasonography findings [8], the potential for long-term survival in these cases appeared to be relatively high [8]. A fetus with congenital cystic adenomatoid malformation would be more likely to survive based on the contralateral lung size [9]. The case with fetal ascites, diagnosed as chylous ascites by fetal abdominal centesis, did not develop a hydrops and had a higher chance of survival [10]. In a case of giant cervical lymphangioma, which had spread into the mediastinum, survival would still be possible with a combined treatment using both surgery and sclerotherapy.

Termination of pregnancy was performed in the 11 cases of the moderate-potential group. All 4 cases of bilateral pleural effusions that were not associated with other malformations involved nuchal translucency, and autopsies revealed an odd-looking face in 2 cases. The case of fetal ascites involved skin edema and nuchal translucency, although fatal chromosomal abnormalities and fetal viral

Table 1 Fetuses with a prenatal diagnosis of neonatal surgical diseases

	First-half period (1999-2003)	Second-half period (2004-2008)	*P*
Total no. of cases	96	113	
Gestational age at diagnosis (range)	27.3 ± 6.1 (11-39)	26.4 ± 7.8 (11-40)	.347
diagnosed before 22 wk of gestation	18 (19%)	39 (35%)	.020
Potential for survival			
High	83	84	.057
Moderate	2	9	
Nonviable	11	20	
Cases with positive policy	83 (86%)	79 (70%)	.004
Gestational age at diagnosis (range)	28.4 ± 5.5 (15-39)	30.0 ± 5.9 (14-40)	.063
Mortality	10 (12%)	7 (8.8%)	.342
Intrauterine fetal death	1 (1.2%)	2 (2.5%)	.531
Cases with negative policy	13 (14%)	33 (29%)	.007
Gestational age at diagnosis (range)	20.7 ± 6.0 (11-31)	18.0 ± 4.3 (11-32)	.096
Termination of pregnancy	9 (69%)	29 (88%)	.133
Intrauterine fetal death	1 (8%)	0 (0%)	.107
Potential for survival			
High	0	5	.168
Moderate	2	9	
Nonviable	11	19	

The gestational age is expressed as mean ± SD (range). One fetus died in utero before the treatment policy was selected.