Ⅲ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Koshiishi T, Osada H, Hata A, Furugen Y, Murakoshi T, Mitsuhashi	Prenatal rupture of right ventricular diverticulum: a case report and review of the literature.	Prenatal Diagnosis	27	1154-1157	2007
Ishii K, Murakoshi T, Hayashi S, Matsuoka K, Sago H, Matsushita M, Shinno T, Naruse H, Torii Y.	Anemia in a recipient twin unrelated to twin anemia-polycythemia sequence subsequent to sequential selective laser photocoagulation of communicating vessels for twin-twin transfusion syndrome.	Prenatal Diagnosis	28	262-263	2008
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Ultrasound Assessment prior to Laser Photocoagulation for Twin-Twin Transfusion Syndrome for Predicting Intrauterine Fetal Demise after Surgery in Japanese Patients

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Key Words
Twin-twin transfusion syndrome · Ultrasound · Doppler velocimetry · Fetal therapy · Laser therapy · SLPCV

Abstract
Objective: To evaluate the use of ultrasound before selective laser photocoagulation of communicating vessels (SLPCV) for twin–twin transfusion syndrome in predicting intrauterine fetal demise (IUFD). ***Methods:*** Fifty-five patients underwent SLPCV in Japan. Fetal biometry and Doppler studies of the umbilical artery, ductus venosus, and umbilical vein were performed prior to SLPCV. The visualization of the bladder and hydrops was recorded. Association between the parameters and IUFD was analyzed using multiple logistic regression analysis. The study was approved by the Institutional Review Board and patients gave their informed consent. ***Results:*** The IUFD incidence was 25.5% (14/55) in the donors and 12.7% (7/55) in the recipients. Twelve donors and 4 recipients of them ended in unexplainable IUFD. In the analysis of 53 donors, absent or reversed end-diastolic flow of umbilical artery (UAAREDF) was only associated with IUFD ($p = 0.016$). No parameters could predict IUFD in 52 recipients. ***Conclusions:*** UAAREDF may be useful for predicting IUFD of the donor after SLPCV.

Introduction

Twin–twin transfusion syndrome (TTTS) develops in approximately 10% of monochorionic twin pregnancies and is associated with high mortality rates [1, 2]. The anatomical basis for this syndrome may be the existence of intertwin placental vascular anastomoses [3, 4]. The establishment of unbalanced blood flow from the donor twin to the recipient twin through the communicating vessels can result in profound hemodynamic disturbances in each twin. Consequently, the donor twin becomes hypovolemic, leading to oligohydramnios, whereas the recipient twin becomes hypervolemic and develops polyhydramnios and hydrops.

Recently, several favorable outcomes have been reported in which fetoscopic laser photocoagulation of placental communicating vessels has been used for treating TTTS [5–8]. The fetal survival rates were significantly higher in patients subjected to laser treatment than in those treated by serial amniodrainage. Furthermore, the incidences of abnormal neonatal brain scans were also lower in the group treated by selective laser photocoagulation of communicating vessels (SLPCV). Nonetheless, intrauterine fetal demise (IUFD) after laser surgery did occur in at least 23.2% of the fetuses [7–10]. Preoperative ultrasound

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assessment was performed and these parameters were believed to reflect the condition of each fetus immediately prior to surgery; this condition may occasionally be related to the outcome of surgery. The aim of this study was to evaluate the use of ultrasound assessment prior to SLPCV for TTTS in predicting IUFD after surgery.

Methods

Fifty-five Japanese women were diagnosed with TTTS and underwent SLPCV between July 2002 and February 2005. The four Japanese institutions that participated in the Japan Fetoscopy Group are as follows: Seirei Hamamatsu General Hospital, National Center for Child Health and Development, Yamaguchi University Hospital, and Niigata University Graduate School of Medical and Dental Sciences. TTTS was diagnosed on the basis of standard diagnostic criteria: presence of a polyhydramnios amniotic pocket >8 cm in the recipient twin, oligohydramnios amniotic pocket <2 cm in the donor twin, single placenta, thin dividing membrane, and similar external genitalia. All patients met the following criteria for SLPCV: (1) the gestational age was less than 26 weeks (median: 21; range: 16.25) and (2) on the basis of the Quintero staging system, they were in either stage II, III, or IV; stage II, 6 cases; stage III, 37 cases; and stage IV, 12 cases [11]. The surgical procedure of SLPCV was performed by a previously reported method [12, 13]. Patients gave their written consent after intensive counseling, and the study was approved by the ethical committee of each institution.

Routine preoperative ultrasound assessment was performed including fetal biometry and estimation of the amniotic fluid volume, placental location, and umbilical cord insertion. This was followed by color and pulsed Doppler examination within 24 h prior to the surgery. The presence or absence of the fetal bladder in donors was assessed sonographically and the presence or absence of fetal hydropic signs such as ascites, pleural effusions, and skin edema in recipients was documented. The discordant rate (DR) of the estimated fetal weight was calculated as (A-B/A)·100, where A is the estimated fetal weight of the larger twin and B is that of the smaller twin. Doppler samplings were performed using a 3.5-MHz or 5-MHz curved array transducer with spatial peak temporal average intensities of less than 100 mW/cm^2. The high-pass filter was set at the lowest level. In the Doppler studies, the occurrence of absent or reversed end diastolic blood flow velocity in the umbilical artery (UAAREDF), absent or reversed blood flow during atrial contraction in the ductus venosus (DVARF), and pulsatile umbilical venous flow (PUVF) was regarded as critically abnormal. Flow velocity waveforms were recorded during the absence of fetal breathing and/or movements. Umbilical arterial and venous waveforms were recorded from a free loop of the umbilical cord or at the placental cord insertion site. The sample volume for the ductus venosus (DV) was determined from its inlet portion at the umbilical vein (UV).

The study outcome was IUFD after SLPCV. The interval from the procedure to the occurrence of IUFD was noted. If there was an obvious explanation for IUFD such as miscarriage following preterm PROM and umbilical cord entanglement, it was described and excluded in the statistical analysis.

Multiple logistic regression analysis was used to analyze the following ultrasound factors in relation to IUFD after SLPCV: the absence of bladder filling, UAAREDF, DVARF, PUVF, and DR in the donor twins and the occurrence of hydrops fetalis, UAAREDF, DVARF, PUVF, and DR in the recipient twins. Data management and statistical computations were performed with the SPSS v 12.0 (Chicago, Ill., USA) software. The p value for this analysis was set at <0.05.

Results

Sonographic measurements were obtained and complete surgical procedures were performed in all 55 cases. All the patients had already delivered, and the median gestational age at the time of delivery was 31 (range: 21.38) weeks. Recurrence of polyhydramnios after surgery was not observed, and elective abortion after SLPCV was not selected in these cases. Of the 55 pregnancies, both fetuses survived to live-birth in 39 (70.9%), only one fetus survived in 12 (21.8%), and both fetuses died in utero in 4 (7.3%). In one of these 4 cases, the reason for both IUFD could not be explained. Hence, the rate of at least one fetus surviving to live-birth was 92.7% (52/55).

IUFD of the donor twin occurred in 25.5% (14/55) of the patients; the data are shown in table 1. One donor fetus died due to umbilical cord entanglement following iatrogenic perforation of the dividing membrane between twins by laser coagulation. The miscarriage of another donor fetus occurred due to premature rupture of the membrane immediately after the surgery. With the exception of these 2 cases, there was no explanation for the cause of IUFD in 12 cases. IUFD in 11 of these 12 donors occurred within 3 days of SLPCV. Preoperative sonogram confirmed the absence of bladder filling in 58.3% (7/12) of the donors with IUFD, while it was 85.3% (35/41) in the case of live-birth donors. UAAREDF was noted in 91.7% (11/12) of the donors in the IUFD group and in 29.3% (12/41) of those in the live-birth group. DVARF and PUVF were detected in 25.0% (3/12) and 8.3% (1/12) of the donors in the IUFD group and in 0.0% (0/41) and 4.9% (2/41) of those in the live-birth group, respectively. The median (range) of DR in the IUFD group was 39.9% (14.8–49.7), while it was 34.4% (0.0–60.9) in the live-birth group. Multivariate analysis in terms of the above-mentioned ultrasound factors related to donor twins, using multiple logistic regression analysis, showed a significant correlation between UAAREDF and IUFD in donor twins ($p = 0.016$; odds ratio = 18.9; 95% confidence interval = 1.8–204.9) (table 2).

Table 1. Data of cases with IUFD of donor twins

No.	Stage	GA	Bladder	UAAREDF	DVARF	UVPF	DR, %	Day of IUFD
1	IIIa	24	visible	yes	no	no	14.8	1
2	IIIa	24	visible	yes	no	no	45.3	1
3	III	19	invisible	yes	no	no	40.9	1
4	IIIa	20	visible	yes	no	yes	33.3	3
5	IV	23	invisible	yes	yes	no	43.9	1
6	IIIa	19	visible	yes	no	no	40.0	1
7	III	19	invisible	yes	no	no	23.9	1
8	III	24	invisible	yes	no	no	33.4	1
9	III	19	invisible	yes	yes	no	49.4	12
10	IV	17	invisible	yes	no	no	49.7	2
11	III	25	invisible	no	no	no	39.8	1
12	IIIa	23	visible	yes	yes	no	33.3	1
13	IV	20	invisible	no	no	no	21.2	26[a]
14	III	21	invisible	no	no	yes	35.8	0[b]

[a] IUFD due to umbilical cord entanglement following perforation of the dividing membrane by laser.
[b] Miscarriage due to premature rupture of the membrane immediately after surgery.
Day of IUFD = Interval from surgery to IUFD; DR = fetal weight discordant rate; DVARF = absent or reversed blood flow during atrial contraction in the ductus venosus; GA = gestational age at procedure; IIIa = stage III atypical; Stage = Quintero classification for twin–twin transfusion syndrome; UAAREDF = absent or reversed end diastolic flow in the umbilical artery; UVPF = umbilical venous pulsatile flow.

Table 2. Multiple logistic regression analysis of IUFD after surgery on preoperative abnormal ultrasound parameters in donor twins

	IUFD (n = 12)	Live-birth (n = 41)	
Absence of bladder	7 (58.5%)	35 (85.3%)	NS
UAAREDF	11 (91.7%)	12 (29.3%)	p = 0.016*
DVARF	3 (25.0%)	0 (0.0%)	NS
UVPF	1 (8.3%)	2 (4.9%)	NS
DR, % median [range]	39.9 [14.8–49.7]	34.4 [0.0–60.9]	NS

* Odds ratio = 18.9; 95% CI = 1.75–204.9.
DR = Fetal weight discordant rate; DVARF = absent or reversed blood flow during atrial contraction in the ductus venosus; NS = not significant; UAAREDF = absent or reversed end diastolic flow in the umbilical artery; UVPF = umbilical venous pulsatile flow.

In recipient twins, 7 of 55 fetuses (12.7%) resulted in IUFD after SLPCV (table 3). Two recipient twins died due to umbilical cord entanglement following iatrogenic perforation of the dividing membrane and 1 ended in miscarriage caused by premature rupture of the membrane immediately after surgery. Unexplained IUFD occurred in another 4 fetuses within 2 days of the surgery. In these 4 recipient twins with IUFD, hydrops fetalis was noted in 3 (75.0%), while it was observed in 9 of the 48 surviving recipient twins (18.8%). UAAREDF was noted in 0.0% (0/14) of the patients in the IUFD group and in 2.1% (1/48) of those in the surviving group. DVARF and PUVF were observed in 50.0% (2/4) and 50.0% (2/4) of the recipients with IUFD and in 33.3% (16/48) and 60.4% (29/48) of the patients in the live-birth group, respectively. The median (range) of DR in the IUFD group was 33.4% (33.3–40.1), while that of the surviving group was 36.6% (0.0–60.9). Multiple logistic regression analysis of

Table 3. Data on cases with IUFD of recipient twins

No.	Stage	GA	Hydrops	UAAREDF	DVARF	UVPF	DR, %	Day of IUFD
1	IV	25	yes	no	yes	yes	40.1	1
2	IV	21	yes	no	yes	yes	39.8	2
3	IIIa	23	no	no	no	no	33.3	1
4	IV	20	yes	no	no	no	21.2	2
5	III	25	no	no	yes	yes	36.0	27[a]
6	III	19	no	no	no	yes	40.9	58[a]
7	III	21	no	no	no	yes	35.8	0[b]

[a] IUFD due to umbilical cord entanglement following perforation of the dividing membrane.
[b] Miscarriage due to premature rupture of the membrane immediately after surgery.
Day of IUFD = Interval from surgery to IUFD; DR = fetal weight discordant rate; DVARF = absent or reversed blood flow during atrial contraction in the ductus venosus; GA = gestational age at procedure; IIIa = stage III atypical; Stage = Quintero classification for twin–twin transfusion syndrome; UAAREDF = absent or reversed end diastolic flow in the umbilical artery; UVPF = umbilical venous pulsatile flow.

Table 4. Multiple logistic regression analysis of IUFD after surgery on preoperative abnormal ultrasound parameters in recipient twins

	IUFD (n = 4)	Live-birth (n = 48)	
Hydrops fetalis	3 (75.0%)	9 (18.8%)	NS
UAAREDF	0 (0.0%)	1 (2.1%)	NS
DVARF	2 (50.0%)	16 (33.3%)	NS
UVPF	2 (50.0%)	29 (60.4%)	NS
DR, % median [range]	33.4 [33.3–40.1]	36.6 [0.0–60.9]	NS

DR = Fetal weight discordant rate; DVARF = absent or reversed blood flow during atrial contraction in the ductus venosus; NS = not significant; UAAREDF = absent or reversed end diastolic flow in the umbilical artery; UVPF = umbilical venous pulsatile flow.

the above factors related to recipient twins revealed no significant association of IUFD in the case of recipient twins (table 4).

Discussion

SLPCV has resulted in a favorable perinatal outcome in patients with TTTS, when all fetuses could not have been rescued. At present, there exists a possibility that affected fetuses undergoing SLPCV may die in utero. In reports on the outcomes of laser surgery for TTTS, the frequency of IUFD in donors was higher in the case of recipient twins [5–10]. Our data, in which 22.6% of the 53 donors and 8.3% of the 52 recipients ended in unexplainable fetal demise, appear to agree with these findings. In particular, the incidence of unexplained IUFD in donors was higher than in recipients (Fisher's exact probability test, p = 0.030); severe placental insufficiency of the donor twins due to unequal placental sharing might be related to fetal death [9, 10, 14]. Unexplained double fetal demise occurred in only one case. Fourteen surviving co-twins after single fetal death resulted in live-birth though their neurological condition had not been analyzed in this study. These results may imply the extent of the ability of laser surgery in IUFD at this stage, while laser surgery has a protective effect to the death of co-twin after one fetal death has occurred. It is noteworthy that unexplained IUFD occurred in 10 of the 11 donor twins (90.9%) and in all 4 recipient twins (100.0%) within a few days of the surgery. This might be due to the effect of surgery, as inferred before [10]. Obliteration of the

placental vascular anastomoses was confirmed by air injection test in these cases except for the cases with fetal demise whose placenta could not be evaluated because of massive placental infarction.

Detailed analyses by ultrasound, including ordinary Doppler examinations for each fetus with TTTS, should be performed prior to laser surgery. Multiple regression analysis on preoperative sonographic parameters for donor twins revealed a significant correlation between UAAREDF and IUFD after SLPCV. UAAREDF was detected in 23 of the 53 donors prior to surgery (43.4%), and 11 of the 23 (47.8%) resulted in IUFD. This abnormal finding may be considered to be the result of maldevelopment of the placenta and/or uneven placental distribution between each twin. UAAREDF in donors has been regarded as an important prognostic factor for IUFD in cases treated with laser surgery. Ville et al. [5] described UAAREDF as a risk factor for perinatal death of donors after laser surgery in 132 cases treated by laser. Zikulnig et al. [9] reported a lower survival rate of donors with UAAREDF in 121 cases treated by laser surgery without significant difference among these cases. While both studies included the neonatal outcome, Martinez et al. [10] reported that UAAREDF prior to surgery could predict IUFD of donor twins.

In contrast, live-birth after SLPCV occurred in 12 of the 23 donors (52.2%) who had UAAREDF preoperatively, although postoperative Doppler data could not be obtained in this analysis. Even if donor twins show absent or reversed flow in the UA prior to surgery, it is possible that half of them could survive after surgery. UAAREDF of the donors appears to reflect not only the placental insufficiency, but also the fetal hypotension secondary to hemodynamic imbalance. Previous studies have shown that some of the donors with AREDF preoperatively showed reappearance of end-diastolic flow and a decrease in the Pulsatility Index values in the UA after the procedure. This phenomenon could be due to a change in the hemodynamic situation and an increase in the blood volume [9, 10]. This explanation is indirectly supported by the increase in the umbilical venous blood flow volume in donors after laser surgery [15, 16]. DVARF and UVPF, as abnormal venous Doppler, have been regarded to be signs of deterioration of fetal oxygenation in intrauterine growth restricted fetuses [17]. Donor twin could have an aspect as intrauterine growth restricted fetuses, but these parameters were not associated with the IUFD of donors in this study. Further, the incidence of these findings in the veins of donors was much less than that of UAAREDV. However, it was notable that all 3 donors with DVARF ended in fetal demise; this suggests that DVARF might be an indicator of IUFD.

With regard to recipient twins, this analysis showed that there was no association between the preoperative ultrasound parameters and IUFD following SLPCV. These results were consistent with those in a previous study [10]. UAAREDF, which was an important factor in donors, was noted in only one recipient and this fetus was born alive. Many of the recipient twins had abnormal venous velocities before SLPCV, where DVARF and UVPF were observed in 34.6 and 59.6% of the 52 fetuses, respectively. However, neither of these was correlated with IUFD. Of the 52 recipients, 12 (23.1%) showed hydropic symptoms prior to surgery. Three of the 4 recipients with IUFD had shown a few hydropic signs, while 9 hydropic recipients resulted in live-birth.

In comparison with other treatment options, laser surgery for TTTS has resulted in a much better perinatal outcome. In this situation, we anticipate a problem that needs to be overcome: how could the rate of IUFD be decreased after SLPCV? As mentioned above, UAAREDF in donors, as the preoperative prognostic factor for IUFD, may reflect both the placental insufficiency and fetal hypotension. If intraoperative transfusion between twins via placental vascular anastomoses could impact the blood volume of each twin, as suggested by Martinez et al. [10], laser coagulation of arteriovenous anastomoses from the donor to the recipient prior to arteriovenous anastomoses from the recipient to the donor should be adopted for cases with UAAREDF in donors. This may prevent not only the postoperative severe fetal anemia but also IUFD in donors. However, further evaluation of the pre and postoperative fetal hemodynamic status is required for understanding the impact of intraoperative blood transfusion between twins on their prognosis.

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RESEARCH LETTER

Prenatal rupture of right ventricular diverticulum: a case report and review of the literature

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KEY WORDS: ventricular diverticulum; fetoscopic laser photocoagulation; pericardial effusion

INTRODUCTION

Congenital cardiac diverticulum is a rare abnormality that may occur as an isolated malformation. Few cases diagnosed in fetal life have been reported. We report a case of right ventricular diverticulum below the tricuspid valve leading to intrauterine fetal death. This is the first report of cardiac diverticulum after fetoscopic laser photocoagulation of the chorioangiopagus for the treatment of twin–twin transfusion syndrome (TTTS).

CASE REPORT

A 25-year-old healthy nulliparous woman had a natural pregnancy of monochorionic diamniotic twins. She was referred owing to remarkable difference in amniotic fluid volume between the fetuses at 19 weeks of gestation. She was diagnosed on the third stage of Quintero's classification for TTTS, because stuck-twin phenomenon and absence of end-diastolic flow in the umbilical artery of the donor were found. There were no abnormal echocardiographic findings in the recipient fetus. She underwent selective fetoscopic laser photocoagulation of the 13 communicating vessels for the treatment of TTTS at 20 weeks of gestation. The donor fetus died one day after operation. In the recipient fetus, a high echogenic focus on the right ventricle and mild pericardial effusion were depicted at 21 weeks of gestation (Figure 1(a)). Further, ultrasound imaging at 24 weeks of gestation demonstrated an area of myocardial discontinuity just below the tricuspid valve, leading to a thin-walled saccular dilatation (7 mm × 10 mm) contained within the pericardial space (Figure 1(b)). Color-flow mapping and pulsed-wave Doppler imaging showed bidirectional flow into and from this structure, compatible with a cardiac ventricular diverticulum (Figure 1(c)). No other structural abnormalities were identified. There was no evidence of maternal or fetal infection. The woman was hospitalized at 25 weeks of gestation. Low-degree pericardial effusion in the fetus was still detected but no further increase was observed. The cardiac function followed a normal course. However, intrauterine fetal death occurred at 29 weeks of gestation. The cause of fetal death was unknown because postmortem examination was declined. However, expansion of the heart and remarkable increase in pericardial effusion were depicted on ultrasonography, suggesting a rupture of the ventricular diverticulum (Figure 1(d)).

A cardiac ventricular diverticulum is a localized protrusion of the wall of the cardiac ventricle with a narrow connection to the ventricle. In contrast, a cardiac aneurysm has a wide connection to the ventricle (Hamaoka *et al.*, 1987). The pathogenesis of ventricular diverticulum remains unknown. It is generally recognized that the wall of a diverticulum contains the three layers of a normal cardiac wall (peri-, myo-, and endocardium) whereas the myocardium of a true aneurysm is intermingled with fibrous tissue (Carles *et al.*, 1995). However, the two terms are often used interchangeably in the literature. In the present case, a diagnosis of diverticulum was made because jet flow was observed indicating a narrow connection to the ventricle.

DISCUSSION

The etiologies of cardiac diverticula and aneurysms in fetal life are poorly understood. They may occur as a result of focal weakening of the ventricular wall due to an interruption during embryogenesis, infection, or localized ischemia of the ventricular wall due to stenosis, hypoplasia or intimal proliferation of the coronary arteries (Carles *et al.*, 1995; Cavalle-Garrido *et al.*, 1997) McAuliffe *et al.* reported two cases in which the diverticula were detected in the first trimester, suggesting that these defects may occur early in pregnancy or even during embryogenesis (McAuliffe *et al.*, 2005).

It is interesting that this case was discovered after the demise of one twin following fetoscopic laser photocoagulation for the treatment of TTTS. Despite successful laser therapy, there is still a potential for neurological pathology in the twins, particularly if one subsequently demises, likely as a consequence of persistent

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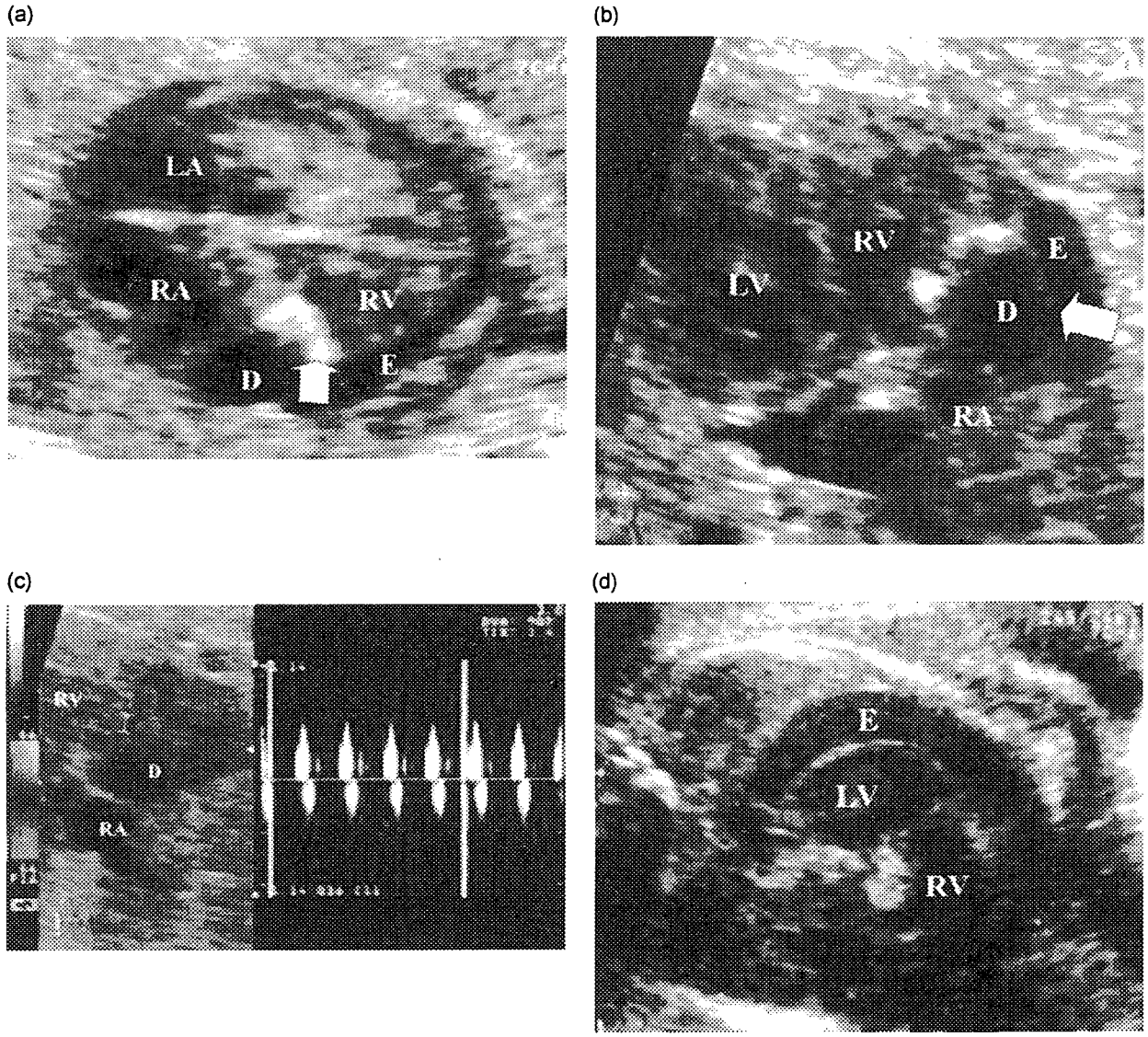

Figure 1—(a) Cardiac ultrasound imaging at 21 weeks of gestation. A high-echogenic focus (arrow) on the right ventricle (RV) and mild pericardial effusion (E) are depicted. LA: left atrium; LV: left ventricle, D: diverticulum, (b) Cardiac ultrasound imaging at 24 weeks of gestation. A thin-walled saccular dilatation (arrow) is identified just below the tricuspid valve. RV: right ventricle; LV: left ventricle; RA: right atrium; E: pericardial effusion; D: diverticulum, (c) Pulsed-wave Doppler imaging at 24 weeks of gestation. Bidirectional flow into and from the cardiac diverticulum is shown. RA: right atrium; RV: right ventricle; D: diverticulum; (d) Cardiac ultrasound imaging just after fetal death. Expansion of the heart and a remarkable increase in pericardial effusion (E) are depicted. RV: right ventricle; LV: left ventricle

vascular connections between the twins (Marton *et al.*, 2002). Marton *et al.* reported a case with left chamber myocardial infarction of the heart in the recipient twin in TTTS (Marton *et al.*, 2002). High-echogenic focus in the myocardium of the recipient twin has been described and is thought to perhaps reflect an area of infarction or at least ischemia. Tennstedt *et al.* reported that the echogenic, intramyocardial focus described at the prenatal sonographic examination appeared histologically as coarse, focal calcifications surrounded by fibrotic tissue (Tennstedt *et al.*, 2000). Abnormal development of the microvasculature, involving terminal branches of the coronary artery leading to early ischemic changes in the papillary muscle, has been suggested as the etiology in some cases (Tennstedt *et al.*, 2000). Therefore, it is suggested that this ventricular diverticulum may be a consequence of myocardial ischemia caused by TTTS or fetoscopic laser photocoagulation. Accumulation of the reported cases would answer the question why this might have happened in the present set of twins and not in others.

Our search of the literature identified 34 reported cases of congenital ventricular diverticulum or aneurysm diagnosed during the prenatal period (Carles *et al.*, 1995; Cavalle-Garrido *et al.*, 1997; Bernasconi *et al.*, 2004; McAuliffe *et al.*, 2005; Prefumo *et al.*, 2005; Gardiner *et al.*, 2005; Del Rio *et al.*, 2005). Table 1 summarizes 35 cases including the present case. The ventricular diverticulum or aneurysm was found at the right ventricle in 14 cases and at the left ventricle in 21 cases.

Table 1—Summary of clinical variables in 35 cases (including the present case) of cardiac diverticulum or aneurysm reported in the literature

Case No.	Diag-nosis	GA at diagnosis	Location	Reason for referral	Outcome	Reference.
1	A	32	Apex/LV	Arrhythmia	Asymptomatic up to 2Y	Gembruch 1990
2	D	33	Apex/LV	CM	Alive	Kitchiner1990
3	A	33	Lateral wall/LV	ND	Surgical resection	Jacobson1991
4	D	31	Below TV	Abnormal 4CV	Asymptomatic up to 1Y	Hornberger1994
5	A	28	Apex/LV	Arrhythmia	Asymptomatic up to 4M	Hornberger1994
6	A	25	Apex/LV	Arrhythmia	Asymptomatic up to 10M	Hornberger1994
7	D	13	Apex/LV	PE, arrhythmia	TOP at 14W	Carles1995
8	A	19	Apex/LV	Hydrops	Hydrops, TOP at 19W	Sepulveda1996
9	A	24	Apex/LV	PE	Hydrops, IUFD at 31W	Sherman1996
10	D	19	Apex/RV	PE	Asymptomatic up to 16M	Johnson1996
11	D	17	Apex/LV	PE	TOP at 22W	Cesko1998
12	D	36	Below TV	CM	Asymptomatic up to 18M	Cavalle-Garrido1997
13	A	21	Apex/LV	Abnormal 4CV	Asymptomatic up to 24M	Cavalle-Garrido1997
14	A	18	Apex/LV	Abnormal 4CV	Mild LVH, alive	Cavalle-Garrido1997
15	D	19	Apex/RV	PE	Asymptomatic up to 12M	Cavalle-Garrido1997
16	A	19	Below MV	Abnormal 4CV	IUFD (MR, hydrops) at 31W	Cavalle-Garrido1997
17	D	20	Apex/RV	PE	Asymptomatic up to 22M	Cavalle-Garrido1997
18	D	20	Below MV	PE	IUFD at 26W	Cavalle-Garrido1997
19	A	26	Apex/LV	PE, CM (MR+)	IUFD at 33W	Matias1999
20	A	21	Apex/LV	CM (MR+)	Neonatal death	Matias1999
21	A	22	Lateral wall/LV	CM	TOP at 23W	Matias1999
22	A	25	Apex/LV	Abnormal 4CV	Asymptomatic up to 12M	Pipitone2002
23	A	21	Below TV	Abnormal 4CV	Asymptomatic up to 6M	Pipitone2002
24	D	32	Apex/LV	ND	Asymptomatic up to 6M	Brachlow2002
25	A	24	Apex/RV	PE	Well going at 30W	McCaffrey 2002
26	A	29	Apex/LV	PE	ND	Sharma2002
27	D	24	Below MV	PE	IUFD (rupture) at 24W	Bernasconi2004
28	D	13	Apex/RV	PE	Term delivery	McAuliffe2005
29	D	16	Apex/RV	PE	Term delivery	McAuliffe2005
30	D	14	Apex/RV	PE	Asymptomatic up to 22M	Prefumo2005
31	D	12	Apex/LV	PE	Asymptomatic up to 17M	Prefumo2005
32	D	14	Apex/RV	PE, CM	TOP	Gardiner2005
33	D	14	Apex/RV	PE, CM	Term delivery	Gardiner2005
34	D	13	Apex/RV	PE	Term delivery, surgical correction	Del Rio2005
35	D	24	Below TV	HEF, PE	IUFD (rupture) at 29W	This report

GA: gestational age; A: aneurysm; D: diverticulum; RV: right ventricle; LV: left ventricle; TV: tricuspid valve; MV: mitral valve; CM: cardiomegaly; ND: not documented; 4CV: 4 chamber view; PE: pericardial effusion; MR: mitral regurgitation; HEF: high-echogenic focus; TOP: termination of pregnancy; IUFD: intrauterine fetal death; Y: years after birth; M: months after birth; W: gestational age in weeks.

In another aspect, the ventricular diverticulum/aneurysm was located at the apex in 26 cases, below the atrioventricular valve in 7 cases, and on the lateral free wall in 2 cases. The outcomes of 30 cases were documented well in these reports. Among them, 5 cases ended in termination of pregnancy. Intrauterine fetal death or early neonatal death occurred in 7 of the remaining 25 cases. When examined by location of the diverticulum or aneurysm, 4 of 7 subvalvular cases and 3 of 18 apical cases resulted in fetal or neonatal death. Ventricular diverticula located below the atrioventricular valves had significantly poorer prognosis compared with those at the apex (^{2} test, $p < 0.05$). This poor prognosis could be explained by the observation that they were often accompanied with a thin fibrous wall and/or regurgitation of valves.

Most cases of ventricular diverticulum have been diagnosed prenatally by ultrasound examination for other cardiac complications such as pericardial effusion, arrhythmia, cardiomegaly, or abnormal 4 chamber view (Table 1). Since the concept of the disease is not well known, many asymptomatic cases of ventricular diverticulum are probably not diagnosed and hence not reported. Further case reports are necessary to predict prenatal and postnatal outcome, which will allow efficient parental counseling.

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RESEARCH LETTER

Anemia in a recipient twin unrelated to twin anemia–polycythemia sequence subsequent to sequential selective laser photocoagulation of communicating vessels for twin–twin transfusion syndrome

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KEY WORDS: twin–twin transfusion syndrome; laser therapy; fetal anemia

A 34-year-old woman, gravida 2, para 2, was admitted to our hospital following the diagnosis of twin–twin transfusion syndrome (TTTS) at 22 weeks of gestation. Ultrasonography was performed, revealing normal gross anatomy in the recipient twin. Estimated fetal weight (EFW) was 528 g, and maximum vertical pocket (MVP) of the amniotic fluid measured 9.3 cm. Doppler studies for the umbilical artery, umbilical vein, and *ductus venosus* yielded normal results. The donor twin also displayed normal gross anatomy, with a visible small bladder and an EFW of 400 g. No measurable pocket of amniotic fluid was noted. Doppler ultrasonography yielded normal results in the donor twin. The patient was diagnosed with Quintero stage I TTTS (Quintero *et al.*, 1999) with posterior placenta. Peak systolic velocity in the middle cerebral artery peak systolic doppler velocimetry (MCA-PSV) was 0.90 multiples of median (MoM) in the recipient twin and 0.88 MoM in the donor twin, respectively (Mari *et al.*, 2000). Fetoscopic laser photocoagulation (FLP) was performed at 22 + 5 weeks of gestation under epidural anesthesia. The patient provided written informed consent and the Institutional Review Board at the institute approved all study protocols. Eleven placental vascular anastomoses including an arterioarterial (AA) anastomosis and a venovenous (VV) anastomosis were identified and coagulated in the same way described as sequential selective laser photocoagulation of communicating vessels (SQLPCV) (Quintero *et al.*, 2007). While MVP of each twin normalized within 3 days, MCA-PSV of the recipient twin increased to 1.84 MoM by 3 days after FLP and continued to remain at high levels from at least 1.80 MoM up to 2.37 MoM. Conversely, MCA-PSV of the donor generally continued to be flat at 0.94–1.16 MoM.

Percutaneous umbilical blood sampling for the recipient twin 42 days after FLP indicated that hemoglobin (Hb) level was 7.2 g/dL and hematocrit (Ht) was 22.4%. MCA-PSV of the recipient twin decreased to <1.5 MoM just after subsequent intrauterine red blood-cell transfusion. The twins were delivered by emergent cesarean section because of fetal bradycardia due to abruptio placenta at 33 weeks of gestation. The recipient twin weighed 1440 g and Apgar scores were 9/9. No hypovolemic shock developed, although she was managed in the NICU for the prematurity. Meanwhile, the donor twin weighed 1380 g and died due to severe asphyxia. Hb values of the recipient and donor were 10.2 and 14.9 g/dL and Ht were 31.4 and 47.2% in umbilical venous blood at birth, respectively. Reticulocyte counts were 6.8% in the recipient and 3.8% in the donor. Placental vascular casting by allowing dissolution of placental tissue with retention of the vasculature (Wee *et al.*, 2005) as well as macroscopic investigation of the placental surface revealed complete obliteration of placental vascular anastomoses (Figure 1). No neurological complications in the recipient twin had been recognized as of 1 year after birth.

Twin anemia–polycythemia sequence (TAPS), characterized by an isolated marked discordance in Hb levels without marked amniotic fluid discordance, has been described as a late complication subsequent to laser surgery and was thought to be associated with patent small arteriovenous anastomoses (Robyr *et al.*, 2006; Lopriore *et al.*, 2007). The frequency of TAPS as a complication after laser surgery was 13% according to a previous study. The pathophysiology in this case appears to differ from a type of TAPS, as the donor twin was not polycythemic and patent placental vascular anastomosis was undetected by vascular casting. Laser therapy is defined as SQLPCV, if all arteriovenous

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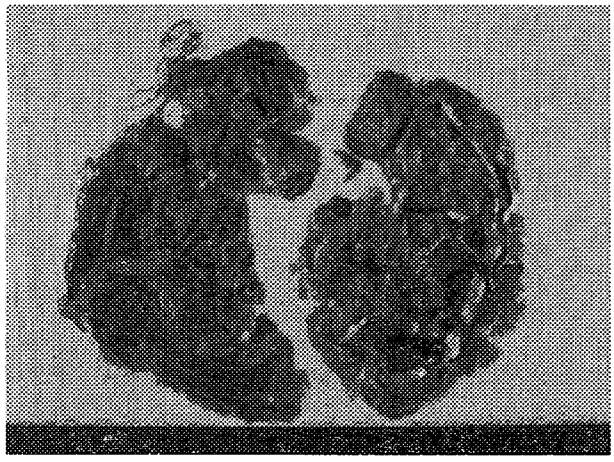

Figure 1—No patent placental vascular anastomosis was detectable according to placental vascular casting. Green, artery of donor twin; red, vein of the donor twin; blue, artery of the recipient twin; yellow, vein of the recipient twin

anastomoses from donor to recipient (AVDR) are coagulated in sequence prior to arteriovenous anastomoses from recipient to donor (AVRD), followed by obliteration of AA or VV (Quintero *et al.*, 2007). The aim of SQLPCV is principally to prevent the donor from hypotension and decrease the likelihood of IUFD of the donor. However, SQLPCV could be associated with an intraoperative transfusion from recipient to donor in theory. It remains possible that the recipient twin might conceivably lose blood volume during laser therapy and thus develop recipient anemia in this case.

In conclusion, this pathological condition with isolated fetal anemia in one twin, in addition to TAPS, should be considered as a clinical entity of fetal anemia when MCA-PSV is increased especially after SQLPCV. Further research is required to determine the incidence and discuss the etiology.

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ワークショップ3「一絨毛膜性双胎の周産期管理」

胎児鏡下胎盤吻合血管レーザー凝固術

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Key words
twin-twin transfusion syndrome
monochorionic diamnionic twin
fetoscopic laser photocoagulation
laser surgery
fetal therapy

はじめに

一絨毛膜双胎（MD双胎）は胎盤を双胎で共有しており，胎盤において双胎間に血管吻合が存在する．この血管吻合による両児間の血流不均衡がMD双胎特有の病態を引き起こし，周産期予後を悪くしていると考えられている．その典型例が双胎間輸血症候群（TTTS）であり，羊水過少と羊水過多を同時に認めることにより診断される．TTTSはMD双胎の約10～15％に発症するといわれており，妊娠中期に発症した場合予後はきわめて不良である．治療法としては羊水過多に対する羊水吸引術（AR）が施行されてきたが満足する成績が得られなかった．そこで新しい治療法として，原因となる胎盤吻合血管を遮断する胎児鏡下胎盤吻合血管レーザー凝固術（FLP）が導入された．本邦でFLPを本格的に施行し始めて5年が経過した．本邦におけるFLPの現状，治療成績，問題点について検討し，MD双胎の管理法としての役割について考察する．

胎児鏡下胎盤血管レーザー凝固術（FLP）

FLPの手術適応と要約を表1に示す．TTTSとは，MD双胎において双胎間の血流不均衡による羊水過少と羊水過多を同時に認める場合であり，超音波検査で，供血児は羊水過少（最大羊水深度2cm以下）で膀胱が小さく，受血児は羊水過多（最大羊水深度8cm以上）で膀胱が大きいという所見により診断される．妊娠26週以降は早期娩出による予後が望まれるので，妊娠26週未満を適応としている．術後は胎児鏡の子宮壁穿通による流早産が問題となるので，頸管長の著明な短縮など明らかな切迫流早産徴候がある場合は適応外としている．

手術方法の概略を図1に示す[1]．まず超音波ガイド下で経皮的にトロッカー（約4mm弱）を羊水過多の羊膜腔（受血児側）に挿入する．レーザーファイバー用の操作チャネルを有した外筒に胎児鏡（ドイツ・カールストルツ製，米国・リチャードウルフ製）を装着し，トロッカーを通して挿入して胎盤表面の血管を観察する．胎盤の端から端まで双胎間羊膜に沿い胎盤血管を観察し，双胎間の吻合血管を見出しYAGレーザーで凝固する．動脈—静脈吻合のみならず，動脈—動脈吻合，静脈—静脈吻合も凝固する．両児間の血管吻合を遮断することにより，両児間の血流不均衡が是正される．また一児死亡した場合の健児から死児への急性血液移行を防ぐことができる．

FLPの歴史

1990年にDe Liaらは，TTTSの3例に対してFLP（小開腹による）を初めて行い報告した[2]．Villeらは1992年に経皮的にFLPを行った1例を報告した．1995年には45例を報告し[3]，以後FLPは原則経皮的に行われるよう

表1　胎児鏡下胎盤吻合血管レーザー凝固術（FLP）の適応と要約

適応
1. TTTS
MD双胎，羊水過多（MVP＞8cm）・羊水過少（MVP＜2cm）
2. 妊娠16週以上，26週未満
要約
1. 未破水
2. 羊膜穿破・羊膜剥離がない
3. 明らかな切迫流早産徴候がない
（頸管長20mm以上原則，10mm以下禁忌）
4. 重篤な胎児奇形がない
5. 母体に大きなリスクがない
6. 母体感染症がない（HBV，HCV原則，HIV禁忌）

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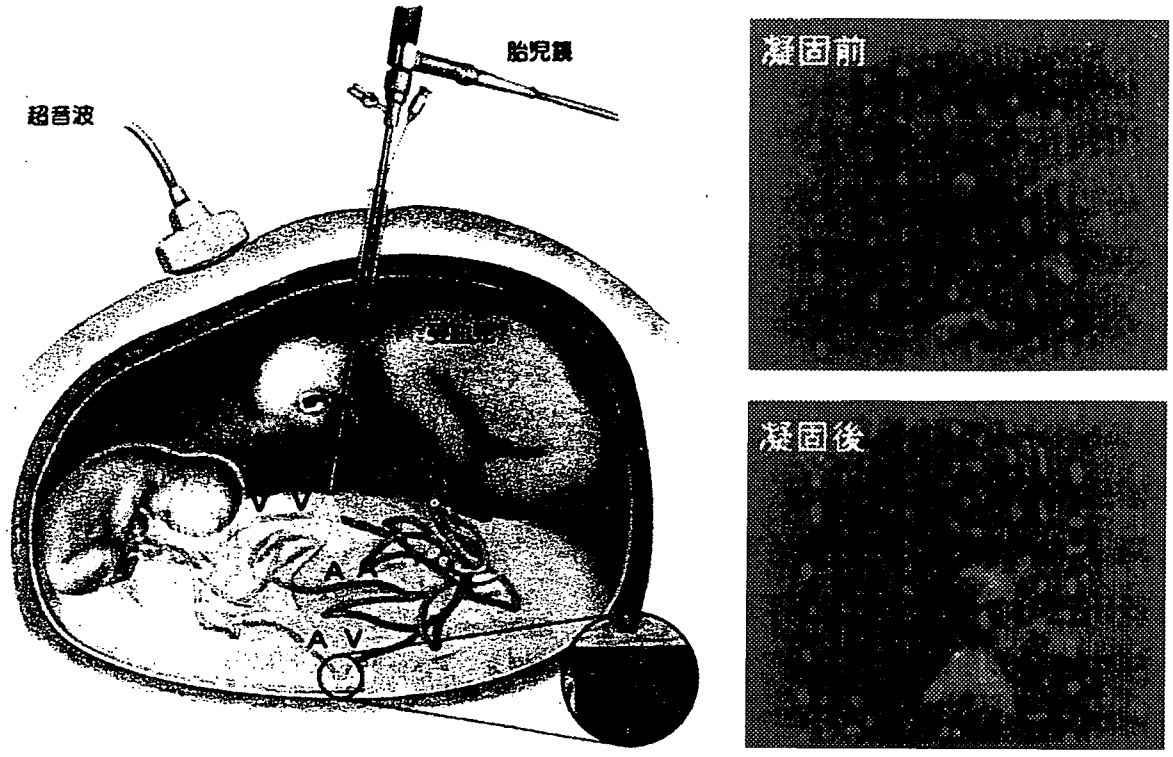
図1 双胎間輸血症候群における胎児鏡下胎盤吻合血管レーザー凝固術(FLP)の模式図と胎児鏡所見(文献1)より一部改変)
羊水過多の受血児側の羊水腔に胎児鏡を挿入し，胎盤表面の血管を観察し，吻合血管をレーザー凝固する．右は胎盤吻合血管レーザー凝固像：右上方の供血児側の動脈と左下方の受血児側の静脈との動脈—静脈吻合をレーザー凝固にて遮断．



になった．1990年代後半から2000年代はじめにかけて，Ville，Hecher[4]，Quintero[5]がそれぞれ100例以上の治療成績を報告し，良好な治療成績によってTTTSの治療法としてFLPは認知された．FLPのほうが羊水吸引術より治療成績が優っているということは，後ろ向きの観察研究で示唆されていた[4,5]が，2004年にEurofoetusの無作為振り分けによる介入試験で証明された[6]．FLP 72例とAR 70例の比較試験が行われ，児生存率（FLP：57％，AR：41％），少なくとも1児が生存する率（FLP：76％，AR：51％），脳障害率（FLP：7％，AR：20％）のすべてにおいてFLPが優っていた．26週未満の重症なTTTSに対してはARに比べFLPがより有効な治療法であることが明らかになった．

本邦におけるFLPの治療成績

本邦においては1992年に名取らによりFLPの第1例が報告された[7]が，その後10年間は報告がまったくなかった．2002年に聖隷浜松病院がFLPを開始し[8]，2003年には国立成育医療センター[9]，2004年には山口大学[10]，新潟大学（現在施行せず）[10]，2005年には国立長良医療センター，2007年には東北大学において開始された．FLP件数の年度別推移を図2に示す．FLPの件数は年々増加し，2006年は80件を超し，2007年は100件を超す見込みである．この6施設（Japan Fetoscopy Group）において施行したFLP症例数は，2007年6月末で計245例であった．そのうち2006年12月末までに妊娠帰結に至り，生後6カ月時の児の予後を把握できた168例について治療成績を検討した．その内訳はstage Ⅰ：12例（7％），stage Ⅱ：28例（17％），stage Ⅲ：103例（61％），stage Ⅳ：25例（15％）で，治療時妊娠週数の平均は21週2日であった．また前壁胎盤は87例（52％）であった．周産期予後についてEurofoetusの成績[6]と比較して表2に示す．流産率は3％で，分娩時妊娠週数の平均値は33週で，治療から妊娠帰結までの術後在胎期間は12週であった．1児生存率は29％，2児生存率も59％で，少なくとも1児生存する率は88％であった．PVL，頭蓋内出血，脳性麻痺などの神経後遺症は4％に認めた．これらの成績はEurofoetusの成績に優るとも劣らない成績であった．

FLP施行に際して重症母体合併症を6例（4％）認めた．詳細を表3に示す．術後出血2例，Mirror症候群2例，常位胎盤早期剥離1例，肺塞栓1例であった．術後出血は手術操作と直接関連があるが，Mirror症候群，常位胎盤早期剥離，肺塞栓は通常の妊娠母体でも起こりうる合併症である．しかし頻度は高く，TTTSの病態はこれらの産科異常を合併しやすいと考えられる．ま

図2　日本におけるFLP手術件数の年度別推移

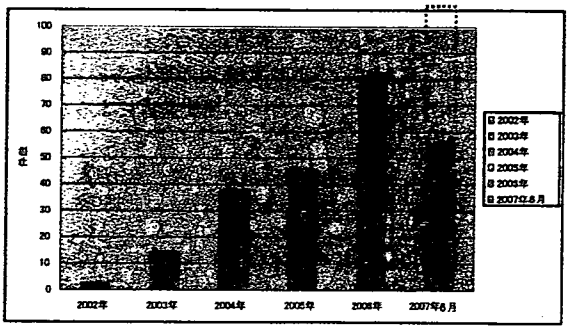


表3　FLPの重症母体合併症

年	合併症	stage	GW	転帰
2002	術後出血(子宮壁)	II	24w2d	開腹止血，両児生存
2003	Mirror症候群	IV	25w1d	IUFD/早産(2児死亡)
2005	術後出血(子宮壁)	II	20w3d	妊娠中断(2児死亡)
2005	常位胎盤早期剥離	III	23w2d	早産(2児死亡)
2006	Mirror症候群	IV	21w3d	軽快，妊娠継続
2006	肺塞栓	I	24w0d	軽快，妊娠継続

表5　FLP術後の胎児生存数と治療成績

	1胎児生存例	2胎児生存例
例数／胎児数	43/43	113/226
分娩週数（平均）	33w4d	32w3d
新生児・乳児死亡	2（5%）	19（8%）
神経後遺症	1（2%）	8（4%）
Intact Survival	40（93%）	199（88%）

表2　本邦のFLP治療成績と欧米との比較

	Eurofoetus	Japan FG
症例数	72例	168例
stage III・IV	66%	76%
0児生存	24%	12%
1児生存	40%	29%
2児生存	36%	59%
少なくとも1児生存	76%	88%
児生存率	57%	73%
流産率	12%	3%
分娩週数	33w	33w
術後在胎期間	12w	12w
神経後遺症	7%	4%

表4　TTTSのstage分類とFLPの治療成績

	stage I	stage II	stage III	stage IV
症例数	12例	28例	103例	25例
0児生存	0%	14%	13%	16%
1児生存	33%	7%	33%	32%
2児生存	67%	79%	54%	52%
少なくとも1児生存	100%	86%	87%	84%
児生存率	83%	82%	71%	64%
流産率	0%	7%	2%	4%
神経後遺症	0%	2%	5%	3%

た6例とも20週以降の施行例で，4例が23週以降であった．妊娠週数のすすんだ例での合併症の発生が多く，注意が必要である．

TTTSのstage分類（Quintero）とFLPの治療成績を表4に示す．stageが進むにつれて児の生存率は低下し，予後が悪くなっていた．特にStage III以上では2児生存率が低下（1児以上が死亡）していた．stageに沿ってTTTSが進行するとは必ずしもいえないが（stage IIIからはじまる例もある），早期stageに治療することにより予後の改善が期待できる．

FLP術後の胎児生存数と治療成績を表5に示す．1胎児生存例（1児死亡）の予後は，2胎児生存例の予後に優るとも劣らない．FLP後1児死亡となっても吻合血管が遮断されているので，健児から死児への急性血液移行は起こらず影響しないと考えられる．2胎児生存例で神経後遺症がやや高く，多くは32週未満に分娩となった例であった．32週未満で分娩となった例の中には，TTTSの再発（太い吻合血管遺残）やanemia/polycythemia sequence（細い吻合血管遺残）などの例があった．

FLPの今後の課題

Eurofoetus[6]の報告により26週未満の重症なTTTSに対してはFLPが有効な治療法であることが示され，本邦における現在までの治療成績もこれに匹敵もしくは凌駕するものである．前述したFLPの適応と要約を満たすTTTSに対する治療法は，本邦においてもFLPが第一選択となっていくことに疑問の余地はない．今後の課題としてはまずFLPの標準化がある．TTTSを早期に診断し，FLPを安全に受けることができる体制づくりである．TTTSの早期診断のためには，MD双胎では常にTTTS発症に留意して妊娠管理することが重要である．一児（供血児）は羊水過少（最大羊水深度2cm以下）で膀胱が小さく，もう一児（受血児）は羊水過多（最大羊水深度8cm以上）で膀胱が大きいという超音波所見に基づくTTTSの診断基準が一般産科医に周知されることも重要である．現在，上記5施設でJapan Fetoscopy Groupをつくり，適応，治療技術，フォローアップなどの精度が低下しないように情報交換，症例登録・検討，研究を共同して行っている．TTTSでは神経学的合併症の頻度が高いので，FLP治療成績の

評価については，生存率やPVL・脳内出血などの短期的予後のみならず，長期的な精神運動発達予後が重要であり，今後は長期予後成績を解析していきたいと考えている．

次の課題はFLPの適応拡大である．TTTSの診断基準は満たさないがTTTSに近い所見を有し，予後不良なMD双胎が存在する．現在，FLPの適応をTTTSに限定しているが，FLPの治療成績が良好であると認知されるに伴い，これらの予後不良なTTTS関連疾患への適応拡大への期待が大きい．MD双胎の異常は，胎盤血管吻合，固有胎盤領域，臍帯付着部異常など種々の因子が関与していると考えられている．FLPはあくまで胎盤吻合血管を凝固遮断するのみであり，胎盤血管吻合が主因となる病態しか治療できない．またTTTS関連疾患の中には予後不良といえない例もあり，自然歴の詳細は不明である．したがって適応拡大には慎重に望まなければならない．平成19年度厚生労働科学研究費補助金・臨床試験推進研究「科学的根拠に基づく胎児治療法の臨床応用に関する研究」（主任研究者：左合）において適応拡大を慎重に吟味して治療プロトコールを作成し，臨床試験として行うことを計画している．

おわりに

FLP治療後の児生存率は高く，また神経後遺症も少なく，妊娠26週未満の重症TTTSに対してFLPは有効な治療法である．FLPによってTTTSの周産期予後が改善され，ひいてはMD双胎の予後の向上が期待される．しかし，重症母体合併症など母体に対するリスクがあり，FLP施行にあたっては慎重な対応が必要である．今後もFLP件数は増加し，MD双胎管理におけるTTTSの重要な治療法としての役割を担っていくと考えられる．FLP術後の長期予後の解析やTTTS関連疾患への適応の拡大が今後の課題である．

[謝辞]

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特集

Ⅲ．循環管理

双胎間輸血症候群（TTTS）に対するレーザー治療

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Key Words
双胎間輸血症候群
TTTS
FLP
胎児治療
胎児鏡下胎盤吻合血管レーザー凝固術

双胎間輸血症候群（TTTS）は，保存療法では半数に周産期死亡や神経学的後遺症を合併する予後不良の疾患である．胎児鏡下胎盤吻合血管レーザー凝固術は，比較的新しい治療法であるが，胎盤における両胎児間の吻合血管を凝固遮断することで，TTTSの根本的な治療が可能である．生児を得る可能性は9割程度まで向上し，出生後の後遺症の合併は数%と低く，第一選択の治療法として期待されている．

はじめに

双胎間輸血症候群（Twin-Twin Transfusion Syndrome，以下TTTSと略す）は，一絨毛膜性双胎の10～15%に合併する予後不良の疾患である[1]．一卵性双胎の頻度は250分娩に1人であり，一卵性双胎の6～7割が一絨毛膜性双胎となることから，わが国では1年間に250～400人程度のTTTSが発症していると推定される．

TTTSの根本的な原因は，一絨毛膜性胎盤の血管吻合を通じた血流の不均衡であり，臨床症状は，供血児が循環血液量の減少・乏尿・腎不全をひきおこし，受血児は循環血液量の増加・多尿・羊水過多・うっ血性心不全・胎児水腫をひきおこしている．その際，供血児のレニン・アンギオテンシン系の亢進がひきおこされ，血管吻合を通じた物質の移動により，循環血液量負荷に陥った受血児の内分泌環境に影響することがこの疾患の病態を複雑にしている（図1）．

TTTSの胎内診断は，受血児の循環血液量の負荷の臨床症状である羊水過多（最大羊水深度が8 cm以上）と，供血児の循環血液量不足を示す羊水過少（最大羊水深度2 cm以下）の両者を満たす一絨毛膜性双胎であることが条件であり，従来用いられていた，体重差や出生後のヘモグロビン差は用いない．児の体重差は，それぞれの児の固有の胎盤領域によって左右されることが多く，必ずしも血流の不均衡を反映しないこと，ヘモグロビン差は一児死亡に伴うfeto-fetal hemorrhageのような両児の血圧差により，急激にひきおこされる血液移動に伴うことが多く，TTTSとは異なる病態で認めることから，混同をさけるために除外されている．

TTTSに対する治療法として，長年にわたり，羊水過多を是正する目的で羊水除去が行われて

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