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Validation of Quintero stage III sub-classification for twin–twin transfusion syndrome based on visibility of donor bladder: characteristic differences in pathophysiology and prognosis

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KEYWORDS: arterioarterial anastomosis; Doppler; fetal therapy; Quintero staging system; TTTS; twin–twin transfusion syndrome

ABSTRACT

Objective To validate the Quintero stage III subclassification for twin–twin transfusion syndrome (TTTS) based on visibility of the bladder of the donor twin.

Methods Between July 2002 and August 2006, there were 131 pregnant Japanese women affected by severe TTTS before 26 weeks' gestation, treated with fetoscopic laser surgery at five centers in Japan, whose pregnancies continued beyond 22 weeks. Outcome data were available in all cases and surviving infants were followed up for at least 6 years. This study focused on the Stage III TTTS patients. These were subclassified into Stage III atypical (abnormal Doppler flow with visible donor bladder) and Stage III classical (abnormal Doppler flow with non-visible donor bladder) groups. Perioperative data and postnatal outcomes were compared between the groups.

Results Seven Stage I, 22 Stage II, 82 Stage III and 20 Stage IV pregnancies continued beyond 22 weeks. There was a significantly higher incidence of absent or reversed end-diastolic velocity in the umbilical artery (UA-AREDV) of the donor in Stage III atypical than in Stage III classical patients (83.8% vs. 53.3%, $P = 0.004$). Stage III atypical cases also had a significantly higher incidence of arterioarterial (AA) anastomoses (72.9% vs. 17.8%, $P < 0.001$) and intrauterine fetal demise (IUFD) of the donor (43.2% vs. 13.3%, $P = 0.002$). However, there were no differences in overall survival or in abnormal brain scans of surviving infants. Donors with both UA-AREDV and AA anastomoses had a significantly higher incidence of IUFD compared with the others (53.3%, $P < 0.001$).

Conclusions Quintero stage III atypical was characterized by a high incidence of AA anastomoses and UA-AREDV of the donor, resulting in IUFD. Subclassification of Stage III based on visibility of the bladder of the donor twin was adequate for and compatible with differentiating prognosis and pathophysiology. Copyright © 2008 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Twin–twin transfusion syndrome (TTTS) affects 10–15% of monochorionic twin pregnancies, and cases left untreated are associated with high perinatal morbidity and mortality[1,2]. The anatomical basis for this syndrome is unequal blood distribution between twins and the recent advent of fetoscopic laser ablation of placental anastomoses has proved very useful in its treatment. With its significantly higher perinatal survival rate compared with amnioreduction and the reduced risk of neurological complications in surviving children[3–6], fetoscopic laser surgery for severe TTTS has evolved as the best therapeutic option.

The concept of staging a disease was developed to help describe and compare prognoses. Quintero's staging system[7] for TTTS is simple and useful for describing the severity of the syndrome; however, while Stages I, II and IV correspond well to perinatal outcome after laser surgery[4–6], there is a considerable range of potential outcomes associated with Stage III. Stages I and II focus on the renal function of the donor, with visibility of the donor bladder reflecting donor morbidity, and Stage IV

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reflects morbidity in hydropic affected fetuses, usually recipients, while Stage III is associated with critically abnormal Doppler findings in either or both twins. Although Quintero *et al.*[7] originally subclassified Stage III into two substages based on visibility of the donor bladder, they did not discuss the prognosis for these substages[7].

The aim of this study, therefore, was to validate the Quintero stage III subclassification based on whether the donor bladder is visible and to investigate the clinical characteristics and perinatal outcomes of the two subgroups.

METHODS

Between July 2002 and August 2006, 138 pregnant Japanese women affected by severe TTTS before 26 weeks' gestation were treated with fetoscopic laser surgery at five centers in Japan. Seven (5.1%) cases resulted in miscarriage (< 22 weeks) and were excluded. Outcome data were available in all cases and surviving infants were followed up for at least 6 months by the Japan Fetoscopy Group, established in 2002 to record follow-up data of TTTS patients treated by laser surgery. TTTS was diagnosed based on standard criteria: monochorionic twin pregnancy with discordant amniotic fluid volume, the deepest vertical pocket measuring at least 8.0 cm in the recipient twin and at most 2.0 cm in the donor twin. All patients met the following criteria for laser surgery[7]: (1) gestational age < 26 weeks and (2) TTTS classified as being Quintero stage I–IV. All participating institutions followed the same clinical protocol for laser surgery of placental communicating vessels, based on a published method[8]. Briefly, after adequate anesthesia (including general, regional and local as appropriate for the patient) was achieved in the mother, a 3.8-mm trocar was inserted into the recipient's amniotic sac. All communicating vessels, including arteriovenous (AV), arterioarterial (AA) and venovenous (VV) anastomoses were ablated by Nd:YAG (neodymium:yttrium-aluminum-garnet) laser under fetoscopic guidance. After intensive counseling, all patients provided written consent to undergo surgery and to participate in the study, which was approved by the ethics committee of each institution.

The current study focused on the 82 Quintero stage III patients whose pregnancies continued beyond 22 weeks. Quintero stage III was classified into two substages on the basis of whether the donor bladder was visible on ultrasound[7,9]: Stage III 'atypical' was defined as abnormal Doppler flow in either twin and visible donor bladder ($n = 37$) and Stage III 'classical' was defined as abnormal Doppler flow in either twin without visible donor bladder ($n = 45$). Perioperative data, including gestational age at laser surgery, operation time, placental location, characteristics of anastomoses and Doppler findings were noted.

Principal outcome measures were intrauterine fetal demise (IUFD), neonatal survival rate (number of fetuses surviving 6 months postnatally/total number of fetuses), survival rate per pregnancy (two survivors, one survivor, no survivors) and abnormal findings on brain scan (e.g. Grade III or IV intraventricular hemorrhage or periventricular leukomalacia). Brain ultrasonography was performed in all infants routinely and magnetic resonance imaging was performed when ultrasound suggested an abnormality or when the delivery was very premature. The perioperative data and outcomes were compared between Stage III atypical and Stage III classical subgroups.

Statistical analysis

The chi-square test or Fisher's exact test was used as appropriate for comparison of categorical variables. Continuous variables were examined for normality, and expressed as mean ± SD or median (range). Student's *t*-test or the Mann–Whitney *U*-test were used as appropriate. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using JMP software (JMP 5.1.2 for Macintosh; SAS Institute, Cary, NC, USA).

RESULTS

Of the 131 TTTS cases treated with laser surgery and delivered (either live or stillborn following IUFD) after 22 weeks' gestation, surviving infants being followed up for at least 6 months, seven were Quintero stage I, 22 were Stage II, 82 were Stage III and 20 were Stage IV. The overall survival rate of infants was 78.2%. Abnormal brain scans were observed in 4.4% of the live infants (3.4% of all fetuses).

Table 1 compares the perioperative clinical characteristics between Quintero stage III atypical and classical cases. The two groups did not differ with respect to gestational age at laser surgery, operation time or placental location. Stage III atypical donors had significantly more amniotic fluid (1.3 cm vs. 0.4 cm), and were more likely to have absent or reversed end-diastolic velocity in the umbilical artery (UA-AREDV) (83.8% vs. 53.3%) and AA anastomoses (72.9% vs. 17.8%) compared with Stage III classical donors.

Perinatal outcomes corresponding to Quintero Stage III subgroup are summarized in Table 2. There were no significant differences between groups in terms of gestational age at delivery and birth weight of donor or recipient. The survival of donors at 6 months was significantly lower in Stage III atypical than in Stage III classical cases (54.1% vs. 77.8%), while there was no such difference in recipients. The rate of IUFD in donors was also significantly greater in Stage III atypical than in Stage III classical cases (43.2% vs. 13.3%), while there was no such difference in recipients or in both twins combined. In particular, the rate of IUFD in donors with UA-AREDV was significantly higher in Stage III atypical compared with Stage III classical cases (51.6% vs. 20.8%). The incidence of abnormal brain scan findings in surviving infants was no different (3.8% vs. 2.8%) between Stage III atypical and Stage III classical cases.

Table 1 Comparison of clinical characteristics, incidence of vascular anastomoses and preoperative Doppler findings in 82 pregnancies with Quintero stage III twin–twin transfusion syndrome, between atypical and classical subgroups[7]

Characteristic	*Stage III atypical (n = 37)*	*Stage III classical (n = 45)*	P
GA at laser surgery (weeks)	21.7 ± 2.5	21.0 ± 2.5	0.21
Operation time (min)	87.1 ± 48.5	73.9 ± 28.9	0.15
Anterior placenta	20 (54.1)	22 (48.9)	0.64
MVP			
Donor (cm)	1.3 (0–2.0)	0.4 (0–2.0)	<0.01
Recipient (cm)	9.8 (8.0–12.4)	10.0 (8.0–16.5)	0.24
EFW			
Donor (g)	313 ± 182	261 ± 168	0.18
Donor (Z-score*)	−2.3 ± 0.9	−2.3 ± 1.1	0.71
Recipient (g)	489 ± 240	403 ± 223	0.10
Recipient (Z-score*)	0.2 ± 0.9	−0.2 ± 0.9	0.09
Weight discordance (%)†	37.3 ± 12.5	35.4 ± 16.0	0.66
Anastomoses			
AA	27 (72.9)	8 (17.8)	<0.01
VV	6 (16.2)	4 (8.9)	0.31
AV	37 (100)	45 (100)	—
Abnormal Doppler flow in donor	31 (83.8)	27 (60.0)	0.02
UA-AREDV	31 (83.8)	24 (53.3)	0.004
UV pulsation	3 (8.1)	7 (15.6)	0.31
DV reversed flow	0 (0)	2 (4.4)	0.19
Abnormal Doppler flow in recipient	14 (37.8)	38 (84.4)	<0.01
UA-AREDV	1 (2.7)	3 (6.7)	0.41
UV pulsation	13 (35.1)	33 (73.3)	<0.01
DV reversed flow	2 (5.4)	22 (48.9)	<0.01
Presence of AA anastomoses			
With UA-AREDV of donor	24 (64.9)	6 (13.3)	<0.01
Without UA-AREDV of donor	3 (8.1)	2 (4.4)	0.49
Absence of AA anastomoses			
With UA-AREDV of donor	7 (18.9)	18 (40.0)	0.04
Without UA-AREDV of donor	3 (8.1)	19 (42.2)	<0.01

Data are shown as mean ± SD, median (range), or *n* (%). Stage III defined as abnormal Doppler flow in either twin, 'atypical' subgroup having visible donor bladder and 'classical' subgroup being without visible donor bladder[7]. *Z-scores were calculated with reference to the Japanese standard singleton growth formula (Japan Society of Ultrasonics in Medicine). †Weight discordance = (estimated fetal weight of recipient − estimated fetal weight of donor)/estimated fetal weight of recipient. AA, arterioarterial; AREDV, absent or reversed end-diastolic velocity; AV, arteriovenous; DV, ductus venosus; EFW, estimated fetal weight; GA, gestational age; MVP, maximum vertical pocket; UA, umbilical artery; UV, umbilical vein; VV, venovenous.

Table 3 focuses on donor IUFD rates, divided into different subgroups with respect to donor UA-AREDV and AA anastomoses. There was a significantly higher incidence of IUFD in donors with UA-AREDV in Stage III atypical than in Stage III classical cases (52% vs. 21%). Donors with both UA-AREDV and AA anastomoses had a significantly higher incidence of IUFD compared with the others (53.3%, $P < 0.001$), although showed no difference between Stage III atypical and classical subgroups (54% vs. 50%). In addition, UA-AREDV of donors and presence of AA anastomoses were associated in all Stage III patients ($P < 0.001$), and 64.9% of Stage III atypical cases were characterized by the presence of both UA-AREDV of the donor and AA anastomoses (Table 1).

DISCUSSION

The Quintero stage III atypical subgroup was characterized by a high incidence of AA anastomoses, UA-AREDV of the donor and IUFD of the donor, whereas the Stage III classical subgroup was characterized by a lower incidence of AA anastomoses, abnormal Doppler flow in the recipient, and a similar incidence of IUFD between the donor and the recipient.

The incidence of AA anastomoses in TTTS is generally considered to be lower (19–31%) than it is in uncomplicated monochorionic diamniotic twins (73–89%)[9–13]. However, similar to another study[9], we found the incidence of AA anastomoses to be 73% in the Stage III atypical subgroup, while in our Stage III classical subgroup it was 18%. Quintero Stage III atypical was defined as abnormal Doppler findings with visible donor bladder. Although the reasons for the donor bladder being visible in Stage III atypical cases are not clear, the fact that AA anastomoses behave functionally like AV anastomoses[9,14] (so-called 'rescue transfusion') suggests a possible explanation. Through this behavior, the donor twin could receive part of the recipient's blood volume[15], which could be sufficient to rescue renal function, resulting in the increased maximum vertical pocket seen in the Stage III atypical cases.

Our data revealed the different Doppler findings characteristic of each substage. The fact that Stage III atypical

Table 2 Comparison of perinatal outcomes in 82 pregnancies with Quintero stage III twin–twin transfusion syndrome, between atypical and classical subgroups[7]

Outcome	*Stage III atypical* (n = 37)	*Stage III classical* (n = 45)	P
GA at delivery (weeks)	32.2 ± 4.0	32.3 ± 4.5	0.46
Time from procedure to delivery (days)	78.1 ± 37.3	78.8 ± 36.5	0.93
Birth weight (g)			
Donor	1270 ± 703	1438 ± 607	0.26
Recipient	1813 ± 696	1679 ± 572	0.39
Survival rate at 6 months			
Donor	20 (54.1)	35 (77.8)	0.02
Recipient	32 (86.5)	36 (80.0)	0.44
IUFD			
Donor	16 (43.2)	6 (13.3)	0.002
Recipient	4 (10.8)	6 (13.3)	0.73
Both	2 (5.4)	1 (2.2)	0.45
Donor with UA-AREDV	16/31 (51.6)	5/24 (20.8)	0.02
Donor with normal UA Doppler	0/6 (0)	1/21 (4.8)	0.59
Abnormal brain scan of live infant*	2/52 (3.8)	2/71 (2.8)	0.75
Donor	1/20 (5)	0/35 (0)	0.18
Recipient	1/32 (3.1)	2/36 (5.6)	0.63
Pregnancy			
2 survivors	18 (48.7)	30 (66.7)	0.10
1 survivor only	16 (43.2)	11 (24.4)	0.07
0 survivors	3 (8.1)	4 (8.9)	0.90
At least 1 survivor	34 (91.9)	41 (91.1)	0.90

Data are shown as mean ± SD or *n* (%). Stage III defined as abnormal Doppler flow in either twin, 'atypical' subgroup having visible donor bladder and 'classical' subgroup being without visible donor bladder[7]. *Abnormal brain scan defined as Grade III or IV intraventricular hemorrhage or periventricular leukomalacia. AREDV, absent or reversed end-diastolic velocity; GA, gestational age; IUFD, intrauterine fetal demise; UA, umbilical artery.

Table 3 Donor intrauterine fetal death rates in 82 pregnancies with Quintero stage III twin–twin transfusion syndrome[7] according to different subgroups

		UA Doppler		*AAA*		
Subgroup	*IUFD* (n (%))	*AREDV* (n = 55)	*Normal* (n = 27)	*Present* (n = 35)	*Absent* (n = 47)	*AREDV with AAA* (n = 30)
Stage III atypical (*n* = 37)	16 (43)	16/31 (52)*†	0/6 (0)*	13/27 (48)	3/10 (30)	13/24 (54)
Stage III classical (*n* = 45)	6 (13)	5/24 (21)†	1/21 (5)	3/8 (38)	3/37 (8)	3/6 (50)
All Stage III (*n* = 82)	22 (27)			16/35 (46)	6/47 (13)	
UA-AREDV (*n* = 55)	21 (38)			16/30 (53)‡§¶	5/25 (20)§¶	
Normal UA Doppler (*n* = 27)	1 (4)			0/5 (0)‡¶	1/22 (5)¶	

Data are shown as *n* (%). Overall donor IUFD rate was 27% (22/82). Symbols indicate which results were compared by chi-square test to produce the following *P*-values: *$P = 0.02$; †$P = 0.02$; ‡$P = 0.03$; §$P = 0.01$; ¶$P < 0.001$. AAA, arterioarterial anastomoses; AREDV, absent or reversed end-diastolic velocity; IUFD, intrauterine fetal demise; UA, umbilical artery.

was characterized by a significantly higher incidence of abnormal Doppler in the donor than in the recipient, while Stage III classical was characterized by a similar incidence of abnormal Doppler findings in donor and recipient, may suggest that Stage III atypical has more uniform characteristics than does Stage III classical TTTS. In singleton and dichorionic twin pregnancies, UA-AREDV usually reflects placental insufficiency and fetal hypoxia[16]; however, the changes in UA Doppler waveforms which manifest as UA-AREDV in monochorionic diamniotic twins cannot be interpreted in the same manner[15,17–19], as they represent a combination of the effects of placental insufficiency and intertwin vascular connections[20]. Despite this, it can be a prognostic factor predicting donor IUFD following laser surgery[21–26], which has a high incidence (41–75%) of donor IUFD. Donors with UA-AREDV recovering to positive diastolic flow after laser surgery had a good chance of survival[20,22,27], implying that elimination of anastomoses can improve donor hypotension and/or hypovolemia by increasing the hemodynamic volume of the donor[27,28].

In our Stage III series, donors with UA-AREDV and AA anastomoses had a significantly higher incidence of IUFD after laser surgery than did those with UA-AREDV without AA anastomoses (53.3% vs. 20.0%). Kontopoulos *et al.*[26] also reported that 31% of donors that died after laser surgery had AA anastomoses compared with 17% of donors that survived. One explanation for the poorer

prognosis associated with the presence of AA anastomoses may be that their elimination by laser therapy can lead to insufficient circulation in the donor, such as severe hypovolemia or hypotension, since rescue transfusion is performed mainly by these anastomoses[15]. On the other hand, paradoxically, while the donor's circulation could have adequate blood volume (visible bladder and amniotic fluid) thanks to rescue transfusion by AA anastomoses, the donor could also have UA-AREDV (signifying insufficient blood flow). It is possible that there is some as yet unknown mechanism involved.

Subclassification of Quintero's stages based on the presence or absence of AA anastomoses was reported by Tan *et al.*[29]. They explained that in Stages I–III, fetal survival was higher at each stage in fetuses with AA anastomoses than in those without; however, the majority of their cases were treated conservatively or by amnioreduction therapy and there was no description of neurological morbidity. Furthermore, their sensitivity of 67% would seem to indicate that the sonographic detection of AA anastomoses is rather difficult and inadequate for the subclassification of Quintero stages in TTTS.

Quintero's subclassification system for Stage III based on visibility of the donor bladder is not ideal because of its limited pathophysiological nature; however, it may be helpful clinically because it is associated with prognosis, particularly in the donor. This could prove important in preoperative counseling regarding Stage III, particularly when there is UA-AREDV of the donor with AA anastomoses, which is associated with the potential risk of donor IUFD after laser surgery. One possibility in these cases is conservative management; however, if AA anastomoses are left intact and one fetus dies, the other fetus will have less chance of survival. Further prospective study is required to improve the poor prognosis of these cases.

In conclusion, the Quintero stage III atypical subgroup is characterized by a high incidence of AA anastomoses and UA-AREDV, resulting in IUFD of the donor after laser therapy. A simple subclassification based on whether the donor bladder is visible (Stage III atypical) or not (Stage III classical) may thus help in clearly differentiating Stage III subgroups with respect to fetal prognosis following laser surgery and help in understanding the pathophysiology of Stage III TTTS.

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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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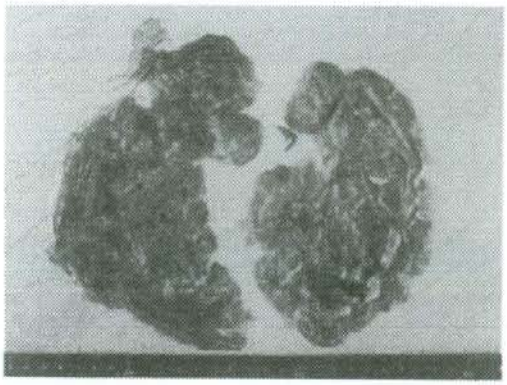

Figure 1—No patent placental vascular anastomosis was detectable according to placental vascular casting. Green, artery of donor twin; red, vein of the donor twin; blue, artery of the recipient twin; yellow, vein of the recipient twin

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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Transitory Increase in Middle Cerebral Artery Peak Systolic Velocity of Recipient Twins after Fetoscopic Laser Photocoagulation for Twin-Twin Transfusion Syndrome

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Key Words
Fetoscopic laser photocoagulation · Middle cerebral artery peak systolic velocity · Twin-twin transfusion syndrome

Abstract
Objective: It was the aim of this study to elucidate the clinical features of recipient twins with increased middle cerebral artery peak systolic velocity (MCA-PSV) after fetoscopic laser photocoagulation (FLP) for twin-twin transfusion syndrome. ***Methods:*** Serial Doppler velocimetry of the MCA was performed in 30 recipient twins before and after FLP. Clinical data and perinatal outcome were compared between cases with and without increased MCA-PSV. ***Results:*** Increased MCA-PSV was observed in 7 recipients (23.3%) within 14 days after FLP. MCA-PSV gradually decreased to <1.5 multiples of median in 6 recipients; however, 1 patient resulted in fetal demise subsequent to the demise of the co-twin. The incidences of fetal and neonatal demise and neurological morbidity were similar. No recipient was diagnosed as anemic at birth. ***Conclusions:*** The increase in MCA-PSV in recipients following FLP appeared to be generally transitory; this differs from twin anemia-polycythemia sequence.

Introduction

Twin-twin transfusion syndrome (TTTS) develops in approximately 15% of monochorionic twin pregnancies [1] and is associated with a high mortality and morbidity [2, 3]. The existence of intertwin placental vascular anastomoses has been recognized as the anatomical prerequisite of this pathological condition [4, 5]. The development of unbalanced blood flow from the donor twin to the recipient twin through the placental communicating vessels can result in hemodynamic disturbances in both twins.

Recently, large clinical studies including a randomized multicenter study reported the efficacy and advantage of fetoscopic laser photocoagulation (FLP) of the placental communicating vessels for treating TTTS, compared with serial amniodrainage [6–9]. Meanwhile, the prevalence of late complications of laser treatment has been recognized in recent years [10]. Twin anemia-polycythemia sequence (TAPS) is characterized by an isolated marked discordance in hemoglobin levels with both severe anemia and polycythemia without marked amniotic fluid discordance [11]. This situation was also described as a complication subsequent to laser surgery and was caused by patent vascular anastomoses due to failure of surgery [10]. In our clinical experience, several recipients exhibit increased middle cerebral artery peak systolic velocity (MCA-PSV)

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Table 1. Preoperative and perioperative data in cases with and without increased MCA-PSV of recipient twins

	With increase in MCA-PSV (n = 7)	Without increase in MCA-PSV (n = 23)	
GA at surgery, weeks	21 [18–24]	19 [18–25]	NS
Quintero stage, n			NS
I	0	2	
II	5	5	
III	1	1	
IV	0	2	
DR, %	31.0 [13.1–47.7]	40.5 [4.1–63.9]	NS
Deepest AMP, cm	11 [9–13]	10 [8–16]	NS
Anterior placenta, n	3 (42.9)	10 (43.5)	NS
MCA-PSV, MoM	1.1 [0.8–1.5]	0.9 [0.2–1.2]	NS
Operation time, min	54 [37–79]	65 [29–154]	NS

Data are medians, with ranges in brackets. Figures in parentheses are percentages. GA = Gestational age; NS = not significant; DR = estimated fetal weight discordant rate; AMP = amniotic fluid pocket.

after FLP for TTTS; however, they are not anemic at birth. The objective of this study was to document the clinical features and perinatal outcome of recipient twins with increased MCA-PSV after FLP.

Methods

From July 2002 to March 2007, 68 patients were diagnosed with TTTS and underwent FLP at our center. Patients whose sonographic data could not be completely obtained and cases of single or double intrauterine fetal demise or miscarriage within 24 h of the procedure were excluded. Of those, 30 patients who were treated by laser from February 2004 and were followed up at our division for at least 14 days were eligible for this study. TTTS was diagnosed on the basis of sonographic diagnostic criteria in monochorionic twin pregnancies: presence of polyhydramnios and an amniotic pocket ≥8 cm in the recipient's sac and oligohydramnios and an amniotic pocket ≤2 cm in the donor's sac. All patients met the following criteria for FLP: (1) gestational age <26 weeks, and (2) Quintero stage I, II, III or IV [12]. Laser surgery was performed using a previously reported method [9, 13].

Preoperative ultrasound assessment, including fetal biometry and estimation of the amniotic fluid volume and placental location were performed. The examinations were carried out using Voluson 730 Expert (GE Healthcare, Kretztechnik, Zipf, Austria). The presence or absence of the fetal bladder in donor twins was assessed, and that of fetal hydropic signs documented. The discordant rate 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. This was followed by MCA-PSV of the recipient twins just before surgery and at 3, 7 and 14 days after FLP. Measurements of MCA-PSV were performed as described by Mari et al. [14]. Increased MCA-PSV was defined as at least 1 measurement value >1.5 multiples of median (MoM) within 14 days of surgery. Once increased MCA-PSV was recorded, additional measurements of MCA-PSV were performed weekly until the value decreased to <1.5 MoM.

Perinatal outcome included intrauterine fetal demise, neonatal death, transient hydropic signs in donor twins, gestational age at delivery, anemia in recipient twins at birth, and neurological morbidity in recipient twins at the age of 6 months. Dye injection tests were performed in cases with both fetal survival to confirm whether vascular anastomoses were interrupted. Statistical computations were performed using the Statistical Package for the Social Sciences version 12.0 (Chicago, Ill., USA) software. The Mann-Whitney test was used for nonparametric variables. Qualitative variables were compared by means of the χ^2 or Fisher's exact test as appropriate. The p value for the analysis was set at <0.05. The study was approved by the institutional review board, and the patients provided informed written consent.

Results

There were no statistical differences between these groups regarding perioperative data (table 1). Recurrence of TTTS after surgery was not observed in these cases.

MCA-PSV >1.5 MoM was recorded in 7 recipients (23.3%) within 14 days of FLP on days 3 (n = 3), 7 (n = 1) and 14 (n = 3), while it was <1.5 MoM in all recipients before surgery. MCA-PSV in 6 recipients gradually decreased to <1.5 MoM within 28 days of FLP, except in 1 case of fetal demise subsequent to the demise of the donor twin. MCA-PSV in these 6 recipients continued to remain <1.5 MoM since then, without reversed flow for ductus venosus, cardiomegaly or hydropic sign. Conversely, MCA-PSV in 3 co-twins continued to be flat (at least 0.9 up to 1.3 MoM) though MCA-PSV in the other 3 donor twins could not be measured continually due to technical problems.

The perinatal outcome of each group is shown in table 2, and the outline of cases with increased MCA-PSV in the recipients is shown in table 3. There were no statistical differences in both groups. Transient hydropic signs after FLP were noted in 2 of the 6 surviving donors (33.3%) in cases with increased MCA-PSV of recipients and in 4 of 16 donors (25.0%) in cases without increased MCA-PSV of recipients. No recipient was diagnosed with anemia at birth in both groups.

The obliteration of the vascular anastomoses was a confirmed dye injection test for all cases not complicated with fetal demise after surgery.

Table 2. Perinatal outcome in cases with and without increased MCA-PSV of recipient twins

	With increase in MCA-PSV (n = 7)	Without increase in MCA-PSV (n = 23)	
IUFD or NND in recipient twin	1 (14.3)	2 (8.7)	NS
IUFD or NND in donor twin	1 (14.3)	9 (39.1)	NS
Transient hydropic sign in donor twin	2/7 (28.6)	4/16 (25.0)	NS
Median GA at delivery	32 [21–37]	33 [23–40]	NS
Anemia in recipient twin at birth	0/6 (0.0)	0/15 (0.0)	NS
Neurological morbidity in recipient twin	0/6 (0.0)	0/14 (0.0)	NS

Figures in parentheses are percentages; data in brackets indicate ranges.
IUFD = Intrauterine fetal demise; NND = neonatal demise; NS = not significant; GA = gestational age.

Table 3. Data on cases with increased MCA-PSV of recipient twins

No.	Quintero stage	GA at surgery weeks	AMP cm	DR %	Placenta	Operative time min	Day MCA-PSV increased	Day MCA-PSV normalized	Maximum MCA-PSV MoM	IUFD of recipient	IUFD of donor	Hydrops of donor	GA at delivery weeks	Anemia of recipient	Neurological morbidity of recipient
1	3	24	11	29.8	anterior	67	14	28	1.67	no	no	no	33	no	no
2	2	24	12	47.7	posterior	43	3	21	1.66	no	no	no	37	no	no
3[1]	2	18	9	13.1	posterior	37	10	NA	2.69	yes	yes	yes	21	NA	NA
4	2	17	9	39.1	posterior	49	7	28	1.64	no	no	no	33	no	no
5	3	22	16	39.2	anterior	59	3	7	1.87	no	no	no	35	no	no
6	2	19	10	31.0	anterior	65	14	28	1.57	no	no	no	36	no	no
7	2	23	13	18.1	posterior	79	3	21	1.58	no	no	yes	29	no	no

GA = Gestational age; AMP = amniotic fluid pocket; DR = estimated fetal weight discordant rate; IUFD = intrauterine fetal demise; NA = not applicable. Anemia of recipient indicates the presence of neonatal anemia at birth in surviving recipient twin, and neurological morbidity of recipient indicates the presence of neurological morbidity at 6 months of age in surviving recipient twin.
[1] Acute feto-fetal hemorrhage subsequent to fetal demise of co-twin was suspected as a cause of fetal demise of recipient twin in case 3.

Discussion

Increased MCA-PSV has been regarded as a consequence of increased cardiac output and decreased blood viscosity due to fetal anemia [14, 15]. Mari et al. [14] suggested that fetal MCA-PSV >1.5 MoM indicated moderate or severe anemia, which corresponded to a hemoglobin concentration <0.65 MoM. MCA-PSV >1.5 MoM was noted in several recipients with TTTS within 14 days of FLP. Increased MCA-PSV in 6 cases regressed to <1.5 MoM; the longest duration required for this regression was 28 days after FLP. This phenomenon, namely, the transitory increase in MCA-PSV in recipients, must reflect fetal anemia. The clinical outcomes of these 6 cases were more favorable than those of TAPS without abnormal amniotic fluid discrepancy as a late complication of laser surgery as described by Robyr et al. [10]. The pathophysiology of this phenomenon might be different from a type of TAPS. This is simply because the increase in MCA-PSV in these twins was transient; no fetus suffered from fetal anemia or fetal polycythemia at birth, and patent placental vascular anastomoses were not detected. We should consider both this transitory benign condition and TAPS when the MCA-PSV increases in the recipient twin after laser surgery. This may conceivably forestall unnecessary invasive intervention in some cases, although fetal blood sampling in cases with increased MCA-PSV after surgery is recommended [10].

Although the etiology of the transient increase in MCA-PSV in recipient twins is obscure, this phenomenon is likely to be associated with not only fetal anemia but also hypovolemia. Transient hydropic signs in 25% of the donor twins after laser surgery were considered to be benign conditions as described by Gratacos et al. [16]. This transient phenomenon is speculated to be a consequence of fetal hypervolemia after the interruption of intertwin transfusion via vascular anastomoses. Immediate increase in the venous blood flow in the umbilical vein of

the donor twins after laser surgery, as has been previously described [17, 18], may have caused the hypervolemia. Meanwhile, the decrease in the venous flow of the recipient twins after surgery has also been reported [18]. This change in blood flow can decrease the total blood volume in recipient twins, and perhaps, the MCA-PSV increases as fetal hypovolemia and subsequent anemia worsen. The association between the transient hydrops in the donors and the transitory increase in the MCA-PSV in the recipients could not be defined because in this study, the incidences of transient hydrops were similar between the cases with and without increased MCA-PSV in the recipients. Unlike TAPS, this increase in MCA-PSV might be transitory and specific for recipient twins. Once intertwin vascular anastomoses were completely obliterated, recipient twins could gradually recover their blood volume, including the blood lost after laser surgery.

This study has some limitations as MCA-PSV in the donor twins after FLP could not always be measured accurately because of the sampling difficulties posed due to the small fetal size or fetal position. The possibility of a false positive of an increased MCA-PSV for fetal anemia should also be considered because of a false-positive rate of 12% and a positive predictive value of 65% on the prediction of fetal anemia due to maternal red-cell alloimmunization [14]. However, a pathological condition different from TAPS, which does not appear to be associated with a poor prognosis in recipient twins, may exist. Further research such as a prospective cohort study which includes the variation in the MCA-PSV of donor twins is required to accurately determine the incidence and discuss the etiology of this condition.

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Fetoscopic laser photocoagulation of placental communicating vessels for twin-reversed arterial perfusion sequence

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Abstract

Twin-reversed arterial perfusion (TRAP) sequence is a rare and compromised complication in monochorionic pregnancies. The retrograde blood flow through placental communicating vessels is mainly involved to develop the syndrome. Increased cardiac output in the pump twin can lead to severe clinical manifestations. Various surgical techniques to occlude vascular communications between the pump twin and acardiac twin have been reported. A woman with TRAP sequence, at 22 weeks of gestation, complicated with progressive polyhydramnios underwent fetoscopic laser photocoagualtion of vascular communications on the placental surface. Fetoscopic observation demonstrated one artery-to-artery anastomosis and one venous-to-venous anastomosis from the pump twin to the acardiac twin, and these communications were successfully photocoagulated. The patient delivered a 2308-g female infant at 34 weeks and 1 day of gestation, following premature rupture of membrane. The infant is now 1 year old without any neurological problem. Fetoscopic laser photocoagulation of placental communicating vessels can be the procedure of choice for TRAP sequence.

Key words: fetal therapy, fetoscopic laser photocoagulation, monochorionic twin, twin-reversed arterial perfusion sequence.

Introduction

Twin-reversed arterial perfusion (TRAP) sequence is a rare and compromised complication in monochorionic pregnancies, which affects approximately one in 35 000 births.[1] Although the pathophysiology of TRAP sequence is not clearly understood, it has been considered that retrograde blood flow through an artery-to-artery (AA) anastomosis from a pump twin to an acardiac twin, returning through a venous-to-venous (VV) anastomosis into the pump twin, is mainly involved to develop the syndrome.[2] Increased cardiac output in the pump twin caused by extra perfusion into the acardiac twin can lead to severe clinical manifestations such as hydrops fetalis or progressive polyhydramnios, resulting in poor perinatal outcomes.

Various surgical techniques to occlude vascular communications between the pump twin and acardiac twin have been reported.[3–5] However, the optimal surgical management tailored to patients' situations has not been established yet.

We report a case of TRAP sequence complicated with progressive polyhydramnios at 22 weeks of gestation who underwent fetoscopic laser photocoagualtion of vascular communications on the placental surface, which resulted in a favorable perinatal outcome.

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Case Report

A 39-year-old primigravida woman was referred to our hospital for evaluation of an acardiac twin pregnancy. Initial fetal ultrasound examination at 20 weeks of gestation demonstrated TRAP sequence with color flow Doppler imaging, by which retrograde pulsatile flow toward the acardiac twin was documented. The pump twin was of normal appearance without any sign of cardiac failure and amniotic fluid volume was normal for gestation (5.6 cm maximal vertical pocket [MVP]). The amniotic septum was displayed between two fetal sacs, indicating diamniotic twinning. After detailed counseling about the potential cardiac failure in the pump twin or the progressive growth of the acardiac twin, the patient visited to our hospital 2 weeks later, at 22 weeks and 0 days of gestation, with symptomatic signs of polyhydramnios. The ultrasound examination showed progressive polyhydramnios in the sac of pump twin (12 cm MVP) and apparent hydropic changes in the acardiac twin as well as increasing overall mass (ratio of abdominal circumference of the acardiac twin to that of the pump twin was 1.5), but the acardiac to pump twin weight ratio was 24%. The acardiac twin was stuck to the surface of anterior placenta owing to oligohydramnios. Color flow Doppler imaging showed apparent pulsatile flow into the acardiac twin (ratio of the pulsatility index of the acardiac twin to that of pump twin was 0.62). Insertion sites of both umbilical cords could be identified, which were approximately 5 cm apart. The blood flow toward the acardiac twin through the feeding artery running on the placental surface was clearly documented by color flow Doppler study (Fig. 1).

After extensive discussion of the risk and benefits of alternative management options, the patient and her family decided to undergo fetoscopic laser photocoagulation of vascular communications and gave their written consent. The procedure was approved by the ethical committee in our hospital.

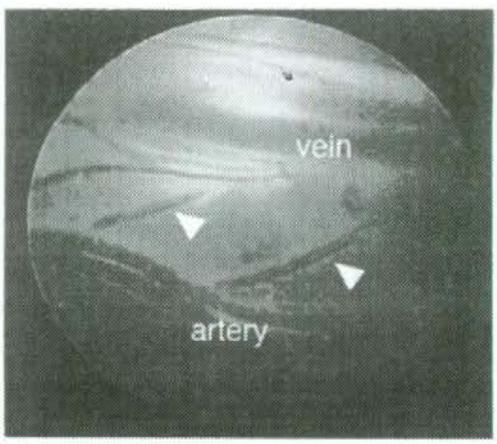

Figure 2 Fetoscopic observation of placental surface. One large artery-to-artery anastomosis and one large venous-to-venous anastomosis between the pump twin and the acardiac twin are shown. Small artery-to-venous communications between the two anastomoses are also noted (arrowhead).

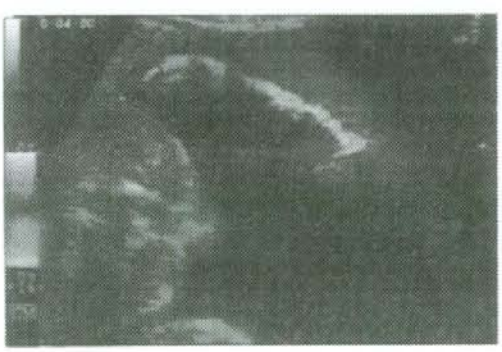

Figure 1 Color Doppler ultrasonography demonstrates the feeding artery from the pump twin to the acardiac twin running on the placental surface.

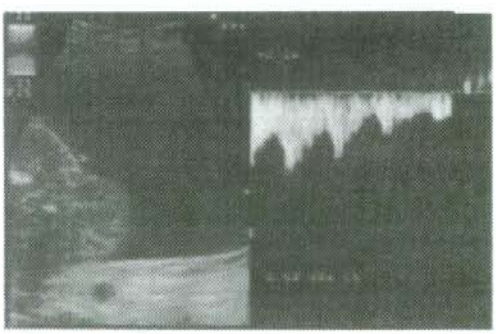

Figure 3 Continuous Doppler examination in the umbilical artery of the acardiac twin shows complete cessation of blood flow after fetoscopic laser photocoagulation of placental communicating vessels.

Under the local and i.v. anesthesia, a 3.8-mm trocar (Richard Wolf, Vernon Hills, IL, USA) was introduced into the amniotic cavity under ultrasound guidance. Fetoscopic observation by a 3.3-mm diagnostic endoscope (Richard Wolf) demonstrated one AA anastomosis and one VV anastomosis on the placental surface. In addition, there were several artery-to-venous (AV) communications between these AA and VV anastomoses (Fig. 2). A 550-um neodymium : yttrium–aluminum–garnet laser fiber (Slimline; Lumenis Japan, Tokyo, Japan) was inserted through the operating channel of a 3.3-mm operating endoscope (Richard Wolf) and all anastomoses were photocoagulated, in which an AA anastomosis was coagulated first followed by a VV anastomosis. As a consequence, all AV communications between AA and VV anastomoses on the placental surface were coagulated. Cessation of blood flow into the acardiac twin was confirmed by color flow Doppler imaging (Fig. 3). Before removal of the trocar sleeve, 1350 mL of amniotic fluid was drained.

After the surgery, ultrasound examination revealed normal growth of the pump twin without progressive polyhydramnios. The patient delivered a 2308-g female infant with Apgar scores of 9 and 9 at 1 and 5 min, respectively, at 34 weeks and 1 day of gestation, following premature rupture of membrane. The neonate had no sign of cardiac failure. The infant is now 1 year old without any neurological problems.

Discussion

Minimally invasive intrauterine treatments, in which the therapeutic strategy is to interrupt the blood supply to the acardiac twin, have currently become the main strategy to prevent perinatal death of the pump twin. Although various techniques for cord occlusion and intrafetal ablation have been reported, there seem to be two main procedures to occlude the blood communication between the acardiac and pump twin in current status: (i) intrafetal radiofrequency ablation (RFA),[5–8] and (ii) fetoscopic laser coagulation of placental anastomoses or the umbilical cord.[9,10] Tan and Sepulveda compared the cases treated by heterogeneous cord occlusion techniques such as embolization, cord ligation, laser coagulation, bipolar and monopolar diathermy with the cases treated by various intrafetal ablation techniques such as alcohol, monopolar diathermy, interstitial laser and radiofrequency, and concluded that intrafetal ablation is associated with a higher clinical success rate than the cord occlusion technique, with an overall pump twin survival rate of 76%.[11] On the other hand, fetoscopic laser photocoagulation of placental anastomoses or the umbilical cord also showed favorable outcome of 77–80% in recent studies.[9,10] The results of a recent two reports[6,7] of RFA were also as successful as those of fetoscopic laser photocoagulation. Recently, ultrasound-guided bipolar cord coagulation was also reported useful for TRAP with a 65% survival rate.[12] Thus, we can conclude that these technical approaches to occlude blood flow communication bring benefits to cases with TRAP. In the present case, we performed fetoscopic laser photocoagulation because we had already equipped modalities for laser surgery and had experienced laser surgery for twin–twin transfusion syndrome.[13]

The main complication associated with these techniques is premature rupture of membrane (PROM). Hecher *et al.* reported that PROM occurred in only 18% of cases at a median interval of 9 weeks after the laser surgery, and PROM rate before 34 weeks was reported as 24% if the bipolar coagulation was indicated.[10] At the time, it seems that which therapeutic modalities should be used depends on which technique physicians are familiar with. Further studies are needed regarding which is the best modality to interrupt the blood supply to the acardiac twin in TRAP sequence.

In conclusion, we experienced a case of TRAP sequence and achieved favorable outcome by fetoscopic laser photocoagulation of placental communicating vessels.

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RESEARCH LETTER

Resolution of mirror syndrome after successful fetoscopic laser photocoagulation of communicating placental vessels in severe twin–twin transfusion syndrome

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KEY WORDS: mirror syndrome; Ballantyne syndrome; twin–twin transfusion syndrome; hydrops fetalis; laser surgery; human chorionic gonadotrophin

Mirror syndrome, also known as Ballantyne syndrome or triple edema, characterizes maternal edema related to severe fetal hydrops and placental edema. In singleton pregnancies, various etiologies associated with this syndrome have been reported: parvovirus B19 infection (Brochot *et al.*, 2006), fetal arrhythmia (Midgley and Harding, 2000), Rh isoimmunization (Kaiser, 1971), sacrococcygeal teratoma (Livingston *et al.*, 2007), and placental chorioangioma (Dorman and Cardwell, 1995). In multiple pregnancies, hydrops related to twin–twin transfusion syndrome (TTTS) (Hayashi *et al.*, 2006; Chang *et al.*, 2007) can cause mirror syndrome; in some cases, however, the etiology is unknown (Heyborne and Chism, 2000).

Several reports have shown that mirror syndrome can be cured provided the hydrops is treated by fetal therapy (Heyborne and Chism, 2000; Midgley and Harding, 2000; Livingston *et al.*, 2007). We report the first case of spontaneous resolution of mirror syndrome after successful fetoscopic laser photocoagulation (FLP) of the communicating placental vessels in TTTS complicated with hydrops fetalis of the recipient twin.

A 33-year-old gravida 1, para 0 woman was referred to our hospital at 21 weeks and 3 days of gestation for management of TTTS. She conceived and gestated monochorionic twins after *in vitro* fertilization-embryo transfer. The monochorionic twin pregnancy was diagnosed by ultrasonography in the referral hospital at an earlier gestational age. Initial ultrasound examination demonstrated polyhydramnios in the recipient's sac (maximum vertical pocket (MVP), 8.4 cm) and oligohydramnios in the donor's sac (MVP, 0 cm). Moreover, the recipient twin manifested hydrops fetalis with skin edema, ascites, and pleural effusion complicated with hypertrophic cardiomegaly. A Doppler study revealed pulsatile umbilical venous flow and reverse flow of the ductus venosus in the recipient twin, suggesting congestive heart failure, as well as tricuspid regurgitation and hypertrophy of bilateral ventricular wall and intraventricular septum. No other abnormal finding was noted in the donor fetus. In the initial examination, the patient did not complain of any cardiopulmonary symptoms such as dyspnea and palpitation; however, systemic edema was noted, particularly in the lower limbs. Further, she gained 4 kg in the last 1 week. Her laboratory data revealed anemia (hemoglobin, 8.6 g/dL; hematocrit, 27.3%), low albuminemia (albumin, 2.3 g/dL), and extremely elevated serum levels of human chorionic gonadotrophin (hCG) (330,000 mIU/mL), but platelet count (152×10^9/L) and liver trasaminase (ALT = 31 U/L[5–43], AST = 51 U/L[12–34]). No abnormal findings were noted on chest X-ray or electrocardiography, and percutaneous oxygen saturation was maintained at 98% in room air. With a diagnosis of stage IV TTTS based on Quintero's classification, we counseled the patient and her family regarding the possible efficacy of laser surgery, and they provided their written consent for the surgery. The laser surgery was performed under intravenous fetanyl administration (Morimoto *et al.*, 2008) with 300 mL of intravenous fluid transfusion. A 2.7–3.3-mm diagnostic or operative fetoscope (Richard Wolf Inc., Vernon Hills, IL, USA) was inserted percutaneously into the amniotic cavity of the recipient twin. Eight communicating placental vessels were coagulated by using 15–30 W YAG laser energy with a 550-μm fiber successfully, followed by an amnioreduction. Total operating time was 30 min. After the surgery, magnesium sulfate was administered intravenously for tocolysis.

On post-surgery day 1, the patient developed marked systemic edema with oligourea, but her blood pressure remained normotensive. At 4 days after the surgery, under the diagnosis of pulmonary edema, oxygen and diuretics were required. Echocardiography showed that any evidence of volume overload and ventricular functions were normal in both ventricles (left ventricular [LV] ejection fraction was 75%; LV internal diameter

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in diastole was 47 mm). Since the findings revealed hydrops of the recipient twin and placental edema, the patient was diagnosed with mirror syndrome. On the following day, maternal diuresis improved, and the pulmonary and systemic edema then began to resolve, once the signs of hydrops began to disappear in the recipient. At 10 days post-surgery, the patient recovered from mirror syndrome completely, with complete resolution of hydrops. However, 2 days after recovery, she suddenly complained of severe dyspnea due to bacterial pneumonia that later complicated with subsequent sepsis caused by *Acinetobacter Lwoffii*, known to cause nosocomial infections, identified by blood culture. She required intensive care such as continuous positive pressure support and administration of antibiotics, but she soon recovered and was discharged from our hospital without any complications. Blood examination revealed a dramatic decrease in the hCG level to 130 000 mIU/mL and 59 000 mIU/mL on the 11th and 17th days after FLP, respectively. At the referral hospital, the patient delivered healthy twin female infants weighing 1936 g and 2126 g by cesarean section at 37 weeks of gestation. The infants are now of age 1 year and have no neurological complications.

TTTS is one of the serious complications of monochorionic pregnancy and can develop into fetal hydrops. Only two cases of mirror syndrome associated with TTTS have been reported so far (Hayashi *et al.*, 2006; Chang *et al.*, 2007), and the prognosis has been poor. To our knowledge, this is the first case report showing that successful laser surgery for severe TTTS resolved mirror syndrome with favorable outcomes in both twins.

In this case, fetal hydrops and placental edema due to severe TTTS may have accounted for the clinical manifestations of mirror syndrome in the patient, and operative intervention via laser surgery might have mitigated the condition. The clinical onset of mirror syndrome shortly after fetal therapy was reported in the case of laser surgery for TTTS (Hayashi *et al.*, 2006) or fetal peritoneal-amniotic shunt for sacrococcygeal teratoma (Livingston *et al.*, 2007).

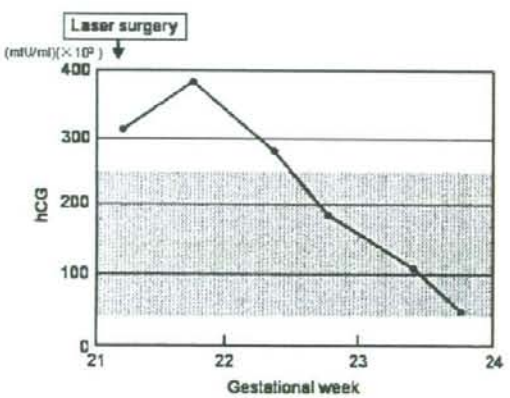

Figure 1—Changes in maternal serum human chorionic gonadotrophin (hCG) level after fetoscopic laser photocoagulation (FLP) of communicating placental vessels. The shading represents the median value of the maternal serum hCG levels (11 000 mIU/mL) (95% confidence interval [CI]: 43 000–250 000 mIU/mL) in 11 cases of twin–twin transfusion syndrome (TTTS) without mirror syndrome; the values were assessed at 20–23 weeks of gestation

Currently, the exact pathophysiology of mirror syndrome remains unclear. However, the temporal changes in the hCG level that accompanied the resolution of mirror syndrome suggest that hCG may be related to the pathophysiology of this syndrome. Two reports suggest that elevated levels of hCG are associated with mirror syndrome (Gherman *et al.*, 1998; Chang *et al.*, 2007). During the study period, we investigated maternal serum hCG levels in 11 cases of TTTS (stage I to III, without hydrops fetalis) without mirror syndrome, with the approval of the Institutional Review Board and informed consent from the patients. The result showed that the median hCG value in TTTS patients without hydrops during 20–23 weeks of gestation was 110 000 mIU/mL (95% confidence interval [CI]: 43 000–250 000 mIU/mL), and this explains the elevation in the hCG level in this case (Figure 1). The temporal changes in the hCG level accompanying the resolution of mirror syndrome in this case indicate that hCG and related substances may be related to the pathophysiology of this syndrome. However, further studies are required to assess this proposed involvement of hCG.

In conclusion, we experienced a case of mirror syndrome in which successful laser surgery for TTTS resolved the syndrome, and a good prognosis was obtained for both twins. Recovery from mirror syndrome can improve, following the resolution of fetal hydrops in severe TTTS treated by laser surgery.

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RESEARCH LETTER

Ileal atresia after fetoscopic laser photocoagulation for twin-to-twin transfusion syndrome—a case report

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KEY WORDS: complication; congenital malformations; fetoscopic laser photocoagulation; ileal atresia; twin-to-twin transfusion syndrome

Fetoscopic laser photocoagulation (FLP) of the communicating vessels has shown promise with respect to the prognosis of twins affected by the twin-to-twin transfusion syndrome (TTTS), and is, therefore, becoming the first line treatment for the management of TTTS (Senat *et al.*, 2004). However, several cases of congenital intestinal atresia or ileal perforation after FLP have been reported (Arul *et al.*, 2001; Schnater *et al.*, 2005). We present a case of congenital ileal atresia which became apparent 9 weeks after FLP and discuss the etiological role of FLP in the pathogenesis of this ileal atresia.

The patient was a 32-year-old Japanese woman with a previous history of one cesarean section who presented with TTTS, Quintero stage II, at 18 weeks of gestation. No congenital malformations were found in either twin by ultrasonography. FLP of the communicating placental vessels was performed uneventfully at 19 weeks of gestation. The fetal karyotype proved to be 46,XX. Conditions of both the fetuses, including middle cerebral artery peak systolic velocities(MCA-PSV) (Robyr *et al.*, 2006), were monitored once or twice a week by ultrasonography and postFLP course was uneventful until 28 weeks of gestation at which ultrasonography and magnetic resonance imaging (MRI) revealed ascites and dilatation of the stomach and duodenum in the recipient twin (Figure 1). A Doppler study which revealed MCA-PSV of 37–39 cm/s suggested the absence of anemia/polycythemia in either twin. Ileal perforation and meconium peritonitis caused by ileal atresia were strongly suspected. Cesarean section was necessitated because of the generalized edema in the mother (weight gain of 3.9 kg in 10 days) at 30 weeks of gestation, and a female recipient twin with a hemoglobin concentration of 10.3 g/dL and weight of 1802 g and a female donor twin with hemoglobin concentration of 13.1 g/dL and weight of 1542 g were delivered. Injection study of the placental vessels did not reveal any patent anastomoses between the two circulations. Abdomen of the recipient twin was markedly distended and 80 mL of ascites with a color of yellow-green was aspirated. Because the drainage placed in the abdominal cavity of the 1-day-old recipient twin did not improve the condition, resection of the responsible portion that was 26 cm apart from the ileocecal junction and ileostomy were performed at 23 days of age. However, the recipient twin died from septic shock and multiple organ failure at 63 days of age. Ileal atresia with perforation was diagnosed pathologically.

The present case suffered from meconium peritonitis caused by perforation of the ileum and ileal atresia after FLP. Congenital jejunoileal atresia is reported to occur at an incidence of approximately 1 in 3000 (1/400 to 1/5000) infants, and is generally considered to be secondary to vascular compromise of the mesenteric vessels during the fetal period.

To the best of our knowledge, four cases of congenital ileal atresia, including our case, have been reported after FLP for TTTS (Table 1). Some authors (Arul *et al.*, 2001; Schnater *et al.*, 2005) suspect that the FLP procedure itself may be the etiological factor for the intestinal atresia. However, it is reported that the rate of small intestinal atresia is two to three times higher among twins than in singletons according to the data from 2.8 million live-born infants from 1982 to 1988 (Cragan *et al.*, 1994). The increase is more notable among same-sex twins than opposite-sex twins, suggesting an increase among monozygotic twins (Cragan *et al.*, 1994). Further, a significant increase is seen only in jejunoileal atresia, not in duodenal atresia, suggesting a vascular cause (Cragan *et al.*, 1994). FLP was not available in the era of 1982 to 1988. In addition, lesions caused by ischemia have been reported in twins affected by TTTS in the absence of FLP treatment. Our literature search identified 20 twins who had congenital lesions other than that of the brain, which were supposed to be caused by ischemic mechanisms (Table 1). As shown in the table, ischemic damage of several organs, including the liver, limb, and intestine

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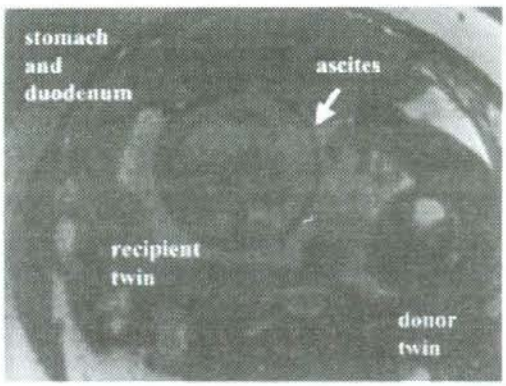

Figure 1—MRI findings in the recipient twin. Marked dilatation of the stomach and duodenum (black arrow), and ascites (white arrow) were found at 28 weeks of gestation

have been reported in twins with TTTS, irrespective of the kind of treatment employed (five cases with no intervention, five cases after amniodrainage and ten cases after FLP). As brain damage is well known in the surviving twin after co-twin death in monochorionic twin pregnancies (Weiner and Ludomirski, 1994; Ville *et al.*, 1998), cases with brain damage alone in TTTS are not included in this table. Among the six cases of intestinal atresia and/or intestinal perforation (Table 1, cases 5, 8, 14, 15, 17, 20), one received no treatment, one underwent amniodrainage, and four received FLP.

Although a shower of emboli caused by laser ablation of the placental vessels cannot be excluded with certainty as the etiological mechanism of the ischemic lesions in the intestine, it would seem highly unlikely that thrombi generated in a placental vein would occlude a mesenteric artery, after venous return through the umbilical cord, ductus venosus, vena cava and right atrium, right ventricle, pulmonary artery, ductus arteriosus, and aorta, as stated by Luks *et al.* (2001). As blood returning from the placenta preferentially flows into the left atrium through the foramen ovale, then is ejected by left ventricle toward the head and upper extremities, if emboli were generated at the site of laser ablation, one would expect a higher incidence of cerebral or upper limb embolization. However, ischemic lesions after FLP are exclusively found in organs that are nourished by branches of the descending aorta (cases 11–20). Further, ischemic lesions were present before the FLP in at least two of the ten cases (cases 11, 16). Hecher *et. al.* found a gangrenous left toe in the recipient twin at the time of the FLP (Hecher *et al.*, 1994). Carr *et. al.* concluded that the ischemic injury occurred 4 weeks prior to the FLP through anatomic assessment of the affected limb (Carr *et al.*, 2004). Thus, FLP or other intervention is not a necessary prerequisite for ischemic injury in twins suffering from TTTS.

It is of interest that ischemic lesions are more likely to occur in the recipient than in the donor twin (17 cases vs three cases). One of the three donor twins with ischemic lesions became polycythemic after FLP and was found to have skin necrosis and hemoglobin concentration of 28.0. g/dL at birth (case 19) (Robyr *et al.*, 2006). In general, intestinal ischemia can be the result of polycythemia, hypovolemia, hypotension, or a vascular accident by a thrombo-embolic process, and the recipient twin may have a high hemoglobin concentration. Some authors have pointed out polycythemia or a high hemoglobin concentration as an etiological

Table 1—Congenital ischemic lesions in twins with TTTS

Authors (published year)	Treatment	Affected twin	Co-twin[a] death	Affected site
1. Margono *et al.* (1992)	None	Recipient	Yes	Right foot
2. van Allen *et al.* (1992)	None	Recipient	Yes	Left hand, Both feet
3. de Laveaucoupet *et al.* (1995)	None	Recipient	Yes	Liver, Brain
4. O'Sullivan *et al.* (2002)	None	Recipient	No	Liver
5. Philip *et al.* (2002)	None	Donor	No	Intestine, Brain
6. Dawkins *et al.* (1995)	AD	Recipient	No	Left leg
7. Scott and Evans (1995)	AD	Recipient	No	Left leg
8. Philip *et al.* (2002)	AD	Recipient	No	Perforated ileum
9. Fox *et al.* (2006)	AD	Recipient	No	Right leg
10. Fox *et al.* (2006)	AD	Recipient	No	Left leg
11. Hecher *et al.* (1994)	FLP	Recipient	Yes	Left foot[b]
12. Stone *et al.* (1998)	FLP	Recipient	Yes	Left leg
13. Lundvall *et al.* (1999)	FLP	Recipient	Yes	Right leg
14. Arul *et al.* (2001)	FLP	Recipient	Yes	Ileal atresia
15. Arul *et al.* (2001)	FLP	Recipient	Yes	Ileal atresia
16. Carr *et al.* (2004)	FLP	Recipient	No	Left leg[b]
17. Schnater *et al.* (2005)	FLP	Recipient	Yes	Ileal atresia
18. Schnater *et al.* (2005)	FLP	Donor	No	Liver
19. Robyr *et al.* (2006)	FLP	Donor[c]	No	Left leg
20. Present case	FLP	Recipient	No	Ileal atresia

AD, Amniodrainage; FLP, fetoscopic laser photocoagulation.
[a] Intrauterine co-twin death (after FLP for cases 11 to 15, and 17).
[b] Lesion was recognized at the FLP for case 11; lesion of case 16 was concluded to be generated 4 weeks prior to the FLP.
[c] Originally donor twin, but became polycythemic after FLP.