表 1. 患者概要（出生前因子）

Patient characteristics (prenatal data)	median (range), n (%)
Gestational age at diagnosis (wks)	28 (17-40)
Lung to head ratio	1.59 (0.37-4.2)
Liver position	
up	40 (36.7)
down	69 (63.3)
Stomach position	
0	21 (19.3)
1	50 (45.9)
2	15 (13.8)
3	23 (21.1)
Polyhydramnios	
present	22 (20.3)
absent	86 (79.6)

表 2. 患者概要（出生後状況）

Patient characteristics (postnatal data)	median (range), n (%)
Gestational age at birth	268 (199-287)
Birth weight	2.79 (1.04-4.03)
Sex	
male	59 (54.1)
female	50 (45.9)
Mode of delivery	
vaginal	51 (46.8)
caesarean section	58 (53.2)
Apgar score at 1 minute	4 (1-9)
NO inhalation used	87 (79.8)
High frequency oscillation (HFO) used	108 (99.1)
ECMO used	16 (14.7)
Diaphragmatic repair performed	98 (89.9)
Diaphragmatic closure	
direct	52 (53.1)
patch	46 (46.9)

表 3. 治療成績

Survival at 90 days	87 (79.8%)
Survival at discharge	81 (74.3%)
Significant morbidities at discharge	
need for respiratory support	7
need for tube feeding	5
need for vasodilator	2
Intact discharge	71 (65.1%)

表 4. 90 日生存に対する出生前因子の単変量解析

	OR(95% CI)	P value
Gestational age at diagnosis(<30wk / 30wk≦)	0.8 (0.3-2.0)	0.594
liver-up	19.9 (5.4-74.1)	<0.0001
stomach position	8.3 (2.9-23.7)	<0.0001
grade 0	1.0	<0.0001*
grade 1	2.7 (0.3-24.2)	
grade 2	5.0 (0.5-53.7)	
grade 3	21.8 (2.5-190.8)	
polyhydramnios	2.4 (0.8-7.0)	0.100
LHR(<1.0 / 1.0≦)	2.7 (0.7-10.5)	0.218
		* p-value for trend

表 5. 合併症なき退院に対する出生前因子の単変量解析

	OR(95% CI)	P value
Gestational age at diagnosis(<30wk / 30wk≦)	1.2(0.5-2.6)	0.662
liver-up	17.6 (6.6-47.2)	<0.0001
stomach position	16.8 (5.1-55.2)	<0.0001
grade 0	1	<0.0001*
grade 1	6.3 (0.8-52.1)	
grade 2	13.3 (1.4-127.6)	
grade 3	95.0 (9.7-928.3)	
polyhydramnios	1.4 (0.5-3.8)	0.461
LHR(<1.0 / 1.0≦)	6.2 (1.5-25.5)	0.014
		* p-value for trend

表 6. 出生前診断された左横隔膜ヘルニアの細分類

	90 day survival (%)	discharge (%)	intact discharge (%)
Overall (n=109)	79.8 (n=87)	73.4 (n=80)	65.1 (n=71)
Liver down (n=69)	95.7 (n=66)	95.7 (n=66)	87.0 (n=60)
Liver up (n=40)	52.5 (n=21)	37.5 (n=15)	27.5 (n=11)
stomach grade 0-2 (n=19)	63.2 (n=12)	63.2 (n=12)*	47.4 (n=9)*
stomach grade 3 (n=21)	42.9 (n=9)	14.3 (n=3)*	9.5 (n=2)*
Liver up and 1.0ŠLHR (n=25)	52 (n=13)	44 (n=11)	28 (n=7)
Liver up and LHR<1.0 (n=8)	50 (n=4)	12.5 (n=1)	12.5 (n=1)
Liver up and 1.2ŠLHR (n=19)	47.4 (n=9)	42.1 (n=8)	31.6 (n=6)
Liver up and LHR<1.2 (n=14)	57.1 (n=8)	28.6 (n=4)	14.3 (n=2)
			* P<0.05

図 1. 胃泡の位置分類

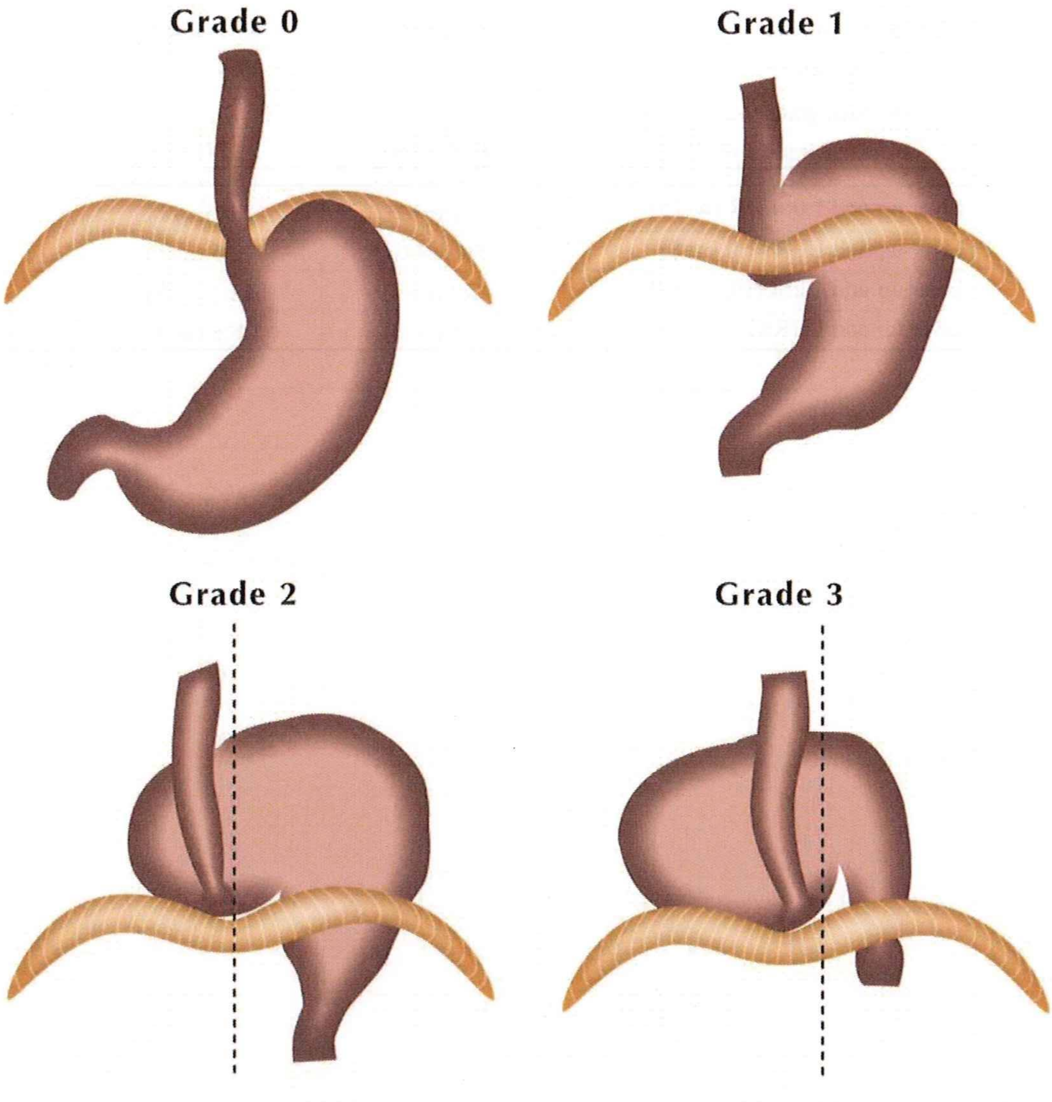


図 2. 胃泡の位置の grade 別頻度

全体の 34.9%に胃泡の右胸腔内脱出を認めた。特に肝脱出例で頻度が高い。

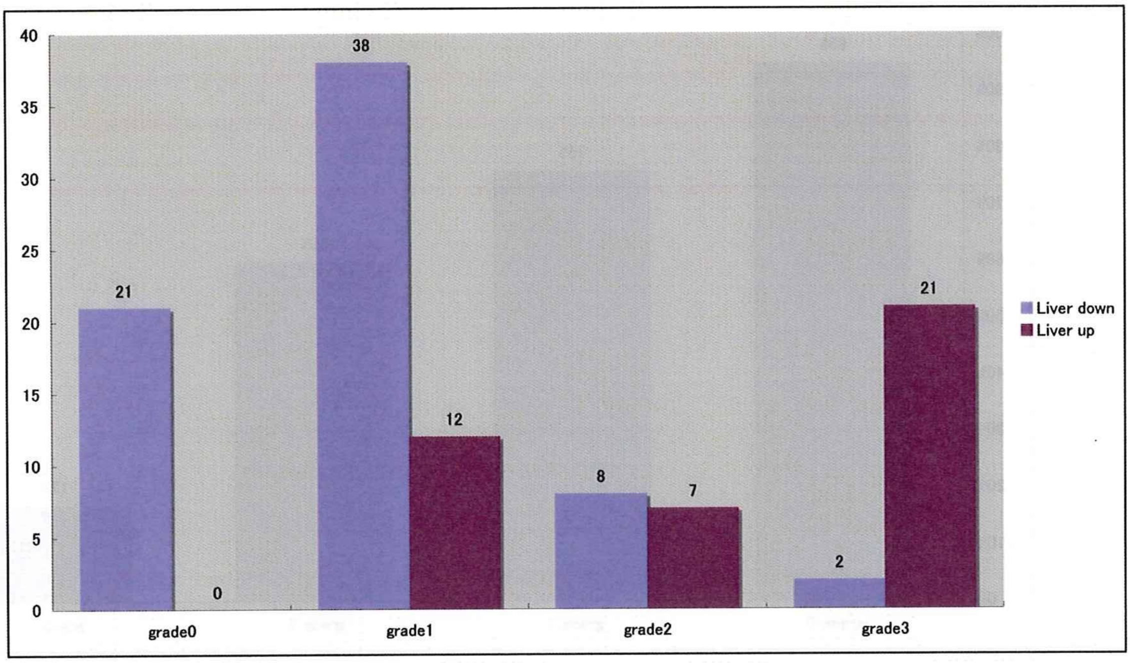


図 3. 胃泡の位置別の合併症なき退院率

Cochran-Armitage trend test において p<0.0001

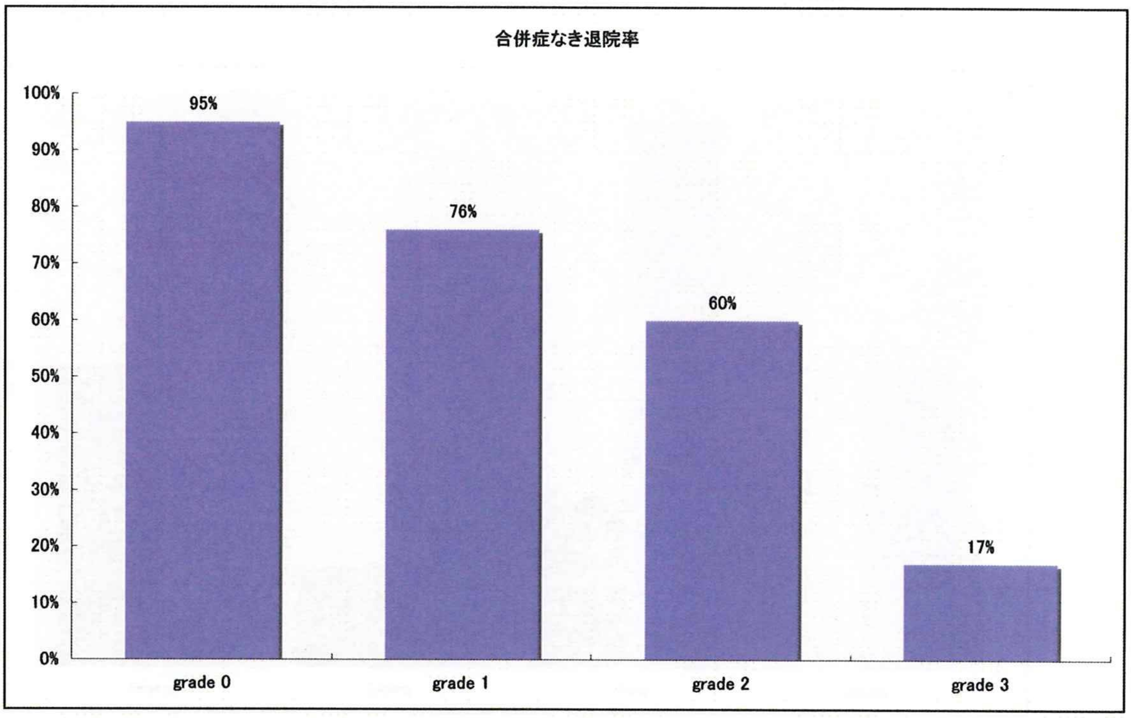
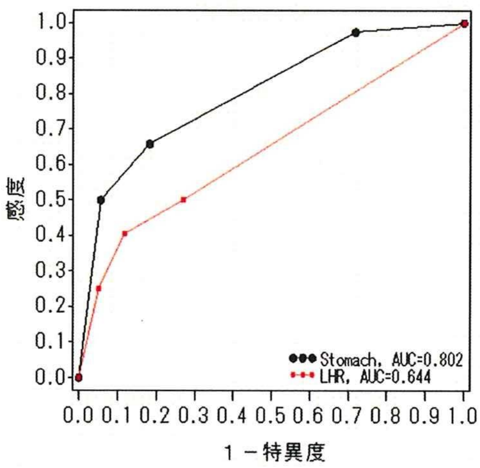


図 4.

LHRのカテゴリ 0～1未満, 1～1.2未満, 1.2～1.4未満、1.4以上



D. 考察

本症と出生前診断された胎児に理想的な生後治療行った際の自然歴は、今後胎児治療を検討するに当たって必要不可欠な情報である。本研究では母体搬送、治療施設での分娩、出生直後からの gentle ventilation を含めた集中治療を理想的な生後治療と考え、本症の予後に関する横断的調査研究を日本ではじめて実施した。プロトコールを作成し、臨床試験に準じた症例調査票を用い、データマネージメント、統計家による統計処理を行った。調査施設は 5 施設に限定し、データの信頼性が高く精度の高い研究を目指した。

第一の目的は、日本の主要施設で実施されている生後治療の成績評価である。低侵襲化が進んでいるとはいえ、胎児治療には母体に対するリスクが存在する。生後治療に改善の余地が残されているなら、まずそちらの改善を試みることが要求される。第二の目的は、出生前評価によって理想的な生後治療を行っても生命的・機能的予後が不良である一群を選別できるかどうかである。

結果として、最近 6 年間の 117 例を集計することができた。全体の治療成績については奥山からの報告で詳細に検討され、本研究の第一の目的が達成された。今後両親に対して提供する貴重なデータとなるだろう。

出生前に容易に測定可能な諸項目の検討の結果、肝脱出の有無と並んで胃の右胸腔内脱出の有無が重要な予後因子であることが判明した。これは世界的にみても新しい知見である。健側肺の大きさを画像で評価するには熟練を要し、測定誤差が大きく、カットオフ値の設定が難しい、などの欠点がある。それに対して胃泡の位置判定は容易でどの施設でも可能であり、今後普及する可能性が高い。

肝脱出例のなかでも胃の高度右胸腔内脱出を伴う症例の予後は、合併症なき退院率が 9.5%で、現在の理想的な治療を持ってしても極めて厳しい。少数ながら、この一群に対しては胎児治療が検討されてもコンセンサスが得られるものと考えられた。

E. 結論

胎児左横隔膜ヘルニアでは胃の右胸腔内脱出がまれでない。胃泡の位置は肝脱出の有無と並んで重要な予後因子である。胃泡の位置によって肝脱出例の予後をさらに細分化することが可能である。

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H．知的所有権の出願登録状況

なし

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

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Ⅳ. 研究成果の刊行物・別刷

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Modified sequential laser photocoagulation of placental communicating vessels for twin–twin transfusion syndrome to prevent fetal demise of the donor twin

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Abstract

Aims: Twin–twin transfusion syndrome (TTTS) complicated with absent or reversed end-diastolic flow in the umbilical artery (UA-AREDF) of the donor has a high perinatal mortality rate. To improve the prenatal outcome, we introduced and modified the technique of sequential selective laser photocoagulation of communicating vessels (SQLPCV), and assessed the clinical efficacy.

Methods: The modified SQLPCV was designed with the following order of coagulation: (i) artery-to-artery (AA) anastomoses; (ii) venous-to-venous anastomoses; (iii) artery-to-venous anastomoses from donor to recipient; and (iv) artery-to-venous anastomoses from recipient to donor. TTTS patients with UA-AREDF of donors were recruited, and the perinatal outcome and its association with the types of anastomoses were compared in patients who underwent the standard selective laser method (SLPCV).

Results: Twenty-three patients underwent modified SQLPCV and 29 underwent SLPCV. Total intrauterine fetal death (IUFD) was significantly lower in modified SQLPCV than in SLPCV (9% vs 38%; $P < 0.001$). Donor IUFD was significantly lower in modified SQLPCV than in SLPCV (13% vs 52%; $P = 0.007$); however, no significant effect was noted in the recipient IUFD cases. When AA anastomoses were present, donor IUFD was significantly lower in modified SQLPCV than it was in SLPCV (18% vs 71%; $P = 0.018$); however, the difference was not significant when AA anastomoses were not present (8% vs 25%; $P = 0.59$). Logistic regression analysis revealed that modified SQLPCV served as the protective factor against the donor's IUFD (odds ratio = 0.015; 95% confidence interval [0.0001–0.775]; $P = 0.037$).

Conclusion: The modified SQLPCV was useful for the prevention of the donor's IUFD in cases of TTTS with UA-AREDF.

Key words: fetal demise, fetal therapy, laser therapy, twin–twin transfusion syndrome.

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Introduction

Since De Lia *et al.*[1] reported the first clinical application of laser surgery for twin–twin transfusion syndrome (TTTS), the technical evolution of laser surgery has continuously progressed. Ville *et al.*[2] suggested that, using the dividing membrane as a landmark, the communicating vessels should be identified and all intersecting vessels should be photocoagulated. Subsequently, Quintero *et al.*[3] developed a new technique (termed 'selective laser photocoagulation of communicating vessels [SLPCV]') that selectively identifies only those vessels participating in the syndrome so that all individually perfused areas of the placenta could be respected, and this technique has become the standard technique in most centers offering laser therapy for TTTS.[4,5]

Although the laser therapy is currently the procedure of choice for improving fetal outcome in TTTS,[6] the procedure has a definite risk of intrauterine fetal demise (IUFD), which is more likely to be in the donor fetus than in the recipient fetus.[4,7,8] IUFD after laser surgery in the donor fetus could be explained in part for placental insufficiency, but one question could arise whether the sequence in which the anastomoses are lasered could result in further hypotension of the donor twin and an increased incidence of IUFD of the fetus. Recently, Quintero *et al.*[9,10] advocated and published a new technique termed 'sequential laser photocoagulation of communicating vessels (SQLPCV)' in which the artery-to-venous (AV) anastomoses from donor to recipient (AVDR) are lasered first, followed by the AV anastomoses from recipient to donor (AVRD) and the superficial anastomoses such as artery-to-artery (AA) anastomoses and venous-to-venous (VV) anastomoses. The concept of this novel technique is based on the hypothesis that laser obliteration of AVDR first could avoid worsening donor hypotension and decrease the likelihood of IUFD. The result previously reported showed that SQLPCV was associated with a decreased likelihood of IUFD of the donor twin and an increased rate of dual survivors compared to standard SLPCV. This result indicates two points: one is that lasering placental vascular anastomoses in a specific sequence have a potential benefit to improve the perinatal outcome and the other is that hemodynamic alteration even during the course of coagulation of communicating vessels may occur.

Preoperative absent or reversed end-diastolic flow in the umbilical artery (UA-AREDF) in the donor fetus has been considered to be a significant risk factor for IUFD in this fetus after laser surgery; mortality rates of from 38% up to 75% have been reported.[11–14] In singleton pregnancies, the etiology of UA-AREDF has commonly been held to be caused by placental insufficiency.[15,16] On the contrary, placental insufficiency has not been considered to be the sole factor promoting UA-AREDF in monochorionic pregnancies,[17] and the presence of AA anastomoses is considered to be attributed to UA-AREDF.[18] As AA anastomosis is the direct communication of arteries between the two fetal circulations, an acute hemodynamic alteration via AA anastomoses during laser photocoagulation might happen even during the course of laser coagulation. Previous studies by Doppler ultrasonography[19] or fetoscopic assessment[20] have documented an acute hemodynamic change via AA anastomoses. Thus, we hypothesized that laser photocoagulation of AA anastomoses first, followed by any other types of anastomoses, could avoid the potential hemodynamic deterioration in the donor fetus and could improve the survival rate after laser surgery. In this study, in order to assess whether this hypothesis is proper or not, we modified the sequential technique, SQLPCV, and introduced it in cases with TTTS patients with UA-AREDF in donors and compared the perinatal outcome in a specific sequence to the standard laser method.

Methods

The patients who underwent fetoscopic laser coagulation of placental communicating vessels for TTTS were between 16 and 26 weeks' gestation with a preoperative diagnosis of UA-AREDF in the donor twin. A Japan Fetoscopy Group registry for patients with TTTS treated with laser surgery was established in 2002. Five centers were invited to contribute data to the registry, and the data of all cases from July 2002 to May 2006 were gathered. A standardized data sheet was distributed to all recruiting centers to collect information on the diagnostic criteria for each reported case, preoperative Doppler studies, the number and types of anastomoses, intraoperative and postoperative complications, and perinatal outcomes. All patients fulfilled the study inclusion criteria for TTTS based on Quintero *et al.*[21] TTTS was diagnosed on the basis of standard criteria: monochorionic twin pregnancy and the presence of polyhydramnios in the recipient's gestational sac (maximum vertical pocket >8 cm) and oligohydramnios in the donor's gestational sac (<2 cm).

Exclusion criteria were fetal death, ruptured membranes, and/or active labor.

Preoperative assessment consisted of a comprehensive ultrasound examination including fetal anatomy, biometry, amniotic fluid volume, placental location and umbilical cord insertion. Color and pulsed Doppler studies were performed within 24 h of 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 of the estimated fetal weight (EFW) was calculated as $(A - B/A) \times 100$, where A is the estimated fetal weight of the larger twin and B is that of the smaller twin; a discordant twin was defined as a fetus at least 25% larger than the other. Fetal growth restriction was defined as an EFW less than two standard deviations (SD) below the mean for gestational age, using a local reference value modified by a Japanese population study.[22] 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 UA-AREDF, absent or reversed blood flow during atrial contraction in the ductus venosus (DVARF), and pulsatile umbilical venous flow (PUVF) were regarded as critical abnormalities. Flow velocity waveforms were recorded during the absence of fetal breathing movements. Umbilical arterial and venous waveforms were recorded from a free loop of cord or at the placental cord insertion site. The sample volume for the ductus venosus was determined from its inlet portion at the umbilical vein.

Laser surgery was performed by the selective method previously described.[3] In brief, all anastomoses were identified prior to ablation under fetoscopic observation. The annotation of the number and type of anastomoses was carefully made during the procedure. If there was branching of an artery or vein (even a very thin vessel) arising from one twin's umbilical cord, all the branches of this vessel communicating with a vein or artery from the other twin's umbilical cord were selectively coagulated; therefore, each vessel was counted as a separate AV anastomosis. Under our nomenclature, the modified SQLPCV was defined as: (1) Coagulation of all superficial anastomoses; (2) Coagulation of all AV anastomoses from donor to the recipient (AVDR); and (3) Coagulation of all AV anastomoses from recipient to donor (AVRD). If both AA and VV anastomoses were present, AA anastomoses were coagulated before VV anastomoses. As the role of superficial anastomoses in the TTTS currently remains unclear and blood flow direction through superficial anastomoses can not be currently assessed, we coagulated these vessels prior to any AV anastomoses so that the subsequent sequential coagulation of AV anastomoses could preserve the blood flow volume in donors without any interference through a potential compensation via superficial anastomoses. Patients who underwent laser surgery by the aforementioned modified SQLPCV were placed in the modified SQLPCV group. If the sequence of coagulation was not consistent with the above-defined order, the procedure was categorized as the standard laser method or SLPCV group. If the sequence of coagulation was not recorded completely because of difficulty of identification of blood flow direction or lack of recording, the procedure was also categorized as the SLPCV group. Patients gave their written consent after thorough counseling, and the study was approved by the ethics committee of each institution.

Pregnancy outcomes were obtained from all referring physicians. Placentas were sent fresh via express delivery and were assessed for patency of vascular anastomoses using air-injection or dye-injection. To eliminate confounding effects relative to gestational age at delivery or neonatal complications, we chose intrauterine demise as the outcome variable. The interval from the procedure to the occurrence of IUFD was also noted. If there was an obvious explanation for IUFD, such as spontaneous abortion following preterm premature rupture of membrane (PROM), or umbilical cord entanglement following an inadvertent septostomy, placental bleeding during the procedure, or pregnancy termination due to maternal complications, the case was excluded from the study. Cases in which any patency of placental anastomoses was noted were also excluded from the study. Some of the patients in this study were included in a previous study.[14]

Statistical analysis was conducted with SPSS software (SPSS version13.0 for Windows, Chicago, IL, USA). Qualitative data was compared by means of either the χ^2-test or Fisher's exact test, whichever was deemed more appropriate. Continuous variables were tested for normality, and expressed as mean ± SD, or median and range. The two-sample Student's *t*-test or the Mann–Whitney *U*-test was used, whichever was more appropriate. To determine the covariates associated with donor or recipient IUFD, multiple logistic regression analysis was used to investigate the effect of stage on the procedure (stage III or IV), preoperative

Doppler findings (DVARF, PUVF for donor; UA-AREDF, DVARF, PUVF for recipient), superficial anastomoses (AA anastomoses, VV anastomoses) and laser procedure (modified SQLPCV or SLPCV). Because of the small data source, a discordant rate greater than 25% and/or restricted fetal growth (EFW < -2 SD) were only used for univariate analysis. A probability value of less than 0.05 was considered statistically significant.

Results

Perinatal outcomes

A total of 52 patients who underwent laser surgery were eligible for the study. The mean gestational age at the time of the procedure was 21.5 ± 2.2 weeks. The mean gestational age at the time of delivery was 32.0 ± 4.1 weeks. The overall perinatal survival rate was 69% (72/104). Both fetuses survived in 25 of 52 cases (48%), one fetus survived in 22 of 52 cases (42%), and neither fetus survived in five of 52 cases (10%). Therefore, at least one fetus survived in 47 of 52 cases (90%). Donor IUFD occurred in 18 of 52 cases (34.6%). Of the 18 donors, 17 cases (94%) expired less than seven days following laser surgery (14 cases within 24 h). Recipient IUFD occurred in eight of 52 cases (15%); thus, recipient IUFD was significantly lower than donor IUFD ($P = 0.02$, Odds ratio = 0.34 [95% CI; 0.13–0.88]).

Modified SQLPCV

The modified SQLPCV was performed in 23 of 52 cases (44%). As the choice of the laser method was dependent on physicians in each participating center, allocation of the method was not randomized. Preoperative perinatal characteristics, preoperative Doppler assessment, and the number and types of anastomoses in both groups are presented in Table 1. Preoperative

Table 1 Comparison of clinical characteristics, preoperative Doppler findings, number or incidence of vascular anastomoses between SLPCV and modified SQLPCV

Parameter	SLPCV ($n = 29$)	Modified SQLPCV ($n = 23$)	P-value
Gestational age at laser (wks)	21.9 ± 1.9	21.1 ± 2.5	0.19
Discordant rate (%)	40.9 (12.1–63.9)	42.6 (10.3–59.1)	0.59
EFW of donor <–2 SD	16 (55%)	12 (52%)	>0.99
Anterior placenta (n)	15 (52%)	12 (52%)	>0.99
Operation time (min)	90.1 ± 35.7	75.2 ± 21.9	0.06
Donor			
DVARF (n)	4 (14%)	2 (9%)	0.68
PUVF (n)	2 (7%)	2 (9%)	>0.99
Recipient			
UA-AREDF (n)	0 (0%)	0 (0%)	>0.99
DVARF (n)	6 (21%)	5 (22%)	>0.99
PUVF (v)	14 (49%)	8 (35%)	0.40
Number of AVDR (n)	4 (1–14)	5 (0–11)	0.49
Number of AVRD (n)	4 (0–10)	4 (0–13)	0.41
Number of AA (n)	1 (0–2)	0 (0–1)	0.38
Incidence of AA (%)	59% (17/29)	39% (11/23)	0.58
Number of VV (n)	0 (0–3)	0 (0–1)	0.73
Incidence of VV (%)	26% (6/23)	17% (4/23)	>0.99
Total number of anastomoses (n)	8 (2–17)	10 (4–37)	0.19

Gestational age at laser and Operation time: expressed as mean ± SD. Discordant rate, Number of AVDR, Number of AVRD, Total number of anastomoses: expressed as median (range). AA, artery-to-artery anastomoses; AVDR, artery-to-vein anastomoses from donor to recipient; AVRD, artery-to-vein anastomoses from recipient to donor; DVARF, absent or reversed flow during atrial contraction in the ductus venosus; EFW, estimated fetal weight; PUVF, pulsatile umbilical venous flow; SD, standard deviation; SLPCV, standard selective laser method; SQLPCV, sequential selective laser photocoagulation of communicating vessels; UA-AREDF, absent or reversed end-diastolic flow in the umbilical artery; VV, Venous-to-venous anastomoses.

Table 2 Comparison of perinatal outcome between SLPCV and modified SQLPCV

Parameter	SLPCV (n = 29)	Modified SQLPCV (n = 23)	P-value
Gestational age at delivery (wks)	31.8 ± 4.2	32.2 ± 4.1	0.94
Interval between laser and delivery (days)	69.4 ± 35.8	74.6 ± 32.8	0.54
pPROM after laser <7 days (n)	1 (3%)	0 (0%)	>0.99
IUFD of donor (n)	15 (52%)	3 (13%)	0.007
IUFD of recipient (n)	7 (24%)	1 (4%)	0.06
Survival rate			
Survivor of donor (n)	12 (41%)	17 (74%)	0.03
Survivor of recipient (n)	22 (76%)	21 (91%)	0.27
Overall	34 (59%)	38 (83%)	0.26
Pregnancy outcome			
no survivor (n)	5 (17%)	0 (0%)	
one survivor (n)	14 (48%)	8 (35%)	0.03
two survivors (n)	10 (35%)	15 (65%)	
At least one survivor (n)	24 (83%)	23 (100%)	0.06

Gestational age at delivery and Interval between laser and delivery: Expressed as mean ± SD. IUFD, intrauterine fetal demise; PROM, preterm premature rupture of the membrane; SD, standard deviation; SLPCV, standard selective laser method; SQLPCV, sequential selective laser photocoagulation of communicating vessels.

Table 3 Influence of the presence or absence of artery-to-artery anastomoses on fetal demise rate between SLPCV and modified SQLPCV

	SLPCV	Modified SQLPCV	Odds Ratio (95% CI)	P-value
IUFD of Donor				
AA Absent	3/12 (25%)	1/12 (8%)		0.59
AA Present	12/17 (71%)	2/11 (18%)	0.093 (0.015–0.59)	0.018
IUFD of Recipient				
AA Absent	4/12 (33%)	0/12 (0%)		0.09
AA Present	3/17 (18%)	1/11 (9%)		>0.99
Overall IUFD per fetus				
AA Absent	7/24 (29%)	1/24 (4%)	0.11 (0.012–0.94)	0.047
AA Present	15/34 (44%)	3/22 (14%)	0.2 (0.05–0.81)	0.021

AA, artery-to-artery; CI, confidence interval; IUFD, intrauterine fetal death; SLPCV, standard selective laser method; SQLPCV, sequential selective laser photocoagulation of communicating vessels.

status, such as gestational age at the time of the procedure, and stage at the procedure, did not differ between the groups. Fetoscopic assessment of placental vascular anastomoses demonstrated no significant difference in either the number of AVRD, AVDR and total anastomoses or in the types of superficial anastomoses between the two groups. Furthermore, there was no significant difference in preoperative Doppler findings between the groups. This result indicated that allocation of the laser methods was not dependent on technical limitations.

Perinatal outcomes for both groups are presented in Table 2. Although donor IUFD occurred in 52% of the cases in the SLPCV group, the modified SQLPCV significantly decreased the rate to 13% ($P = 0.007$). Consequently, the donor survival rate was significantly higher in the sequential group ($P = 0.03$). The percentage of recipient IUFD was lower in the sequential group; however, the difference was not statistically significant ($P = 0.06$).

Fetal demise

Table 3 presents the rate of IUFD in regard to absence or presence of AA anastomoses in the two groups. In donors, when AA anastomoses were absent, donor IUFD was only seen in one case in the modified SQLPCV group (not statistically significant). Conversely, when AA anastomoses were present, donor