て検討した.

II 対象および方法

妊娠110日前後の羊5頭に対して，シングルポート法による胎仔鏡下バルーン気管閉塞術を行った．胎仔鏡としては，カールストルツ社製 Straight Forward Telescope（外径2 mm，0度 K26008AA）と Fetoscopy Sheath（外径4.3 mm，チャンネル径1.7 mm 26161CN）を組み合わせて用いた（図1A）．気管内に留置するバルーンはデリバリーカテーテル（Nycomed 社製 CIFN 130 cm 3 Fr）に装着した離脱型バルーン（Nycomed 社製 Goldvalve GVB16: inflated size 8×21 mm, deflated diameter 1.5 mm, max volume 0.8 ml）を用いた（図1B）．母獣は術前48時間絶食（絶飲水は24時間）とした．酸素とイソフルレン5%の吸入にて麻酔導入して気管内挿管した．静脈ラインを確保後に抗生剤を投与した．麻酔の維持はイソフルレン1～3%で行い，マスキュラックス，ネンブタールを適宜追加した．下腹部縦切開にて開腹し，子宮壁を露出して胎仔の位置を確認後，マスキュラックス0.2 mg/kg を子宮外から胎仔の筋肉内に投与した．子宮壁に小切開をおいて5 mm ポートを挿入し，温生食で子宮内を環流した．このポートより胎仔鏡を挿入し，胎仔の頸部を伸展して舌根部を持ち上げるようにしながら胎仔鏡を喉頭まですすめた．次に，喉頭蓋の裏側にある声門を確認して，胎仔鏡を気管内まで挿入した．胎仔の気管内に入ると，気管軟骨輪が明瞭に観察できるためその確認は容易であった（図2A，B）．次に胎仔鏡の観察下に離脱型バルーンを挿入し，デリバリーカテーテルより水0.8 ml を注入してバルーンを inflate した．バルーンが気管内に固定されていることを確認した後に，デリバリーカテーテルを引き抜きバルーンを気管内に留置した（図2C，D）．ポートを抜去して子宮壁を縫合閉鎖し，母体を閉腹して手術を終了した．麻酔から覚醒後に超音波を用いて胎仔の生存を確認した．術後妊娠継続できた場合は，1週間後に胎仔の生死を確認後に，ネンブタールによる過剰麻酔により母獣を安楽死させた．胎仔を取り出し，気管および肺を観察して気管閉塞の効果を判定した．胎仔の肺・体重比を測定後，胎仔肺の組織学的検索を行った．なお気管閉塞例ではバルーンを除去して肺水を流出させてから肺重量を測定した．肺・体重比の正常参考値としては，他の急性実験に用いた同じ週数（110日前後）の羊胎仔3例の平均値を用いた．

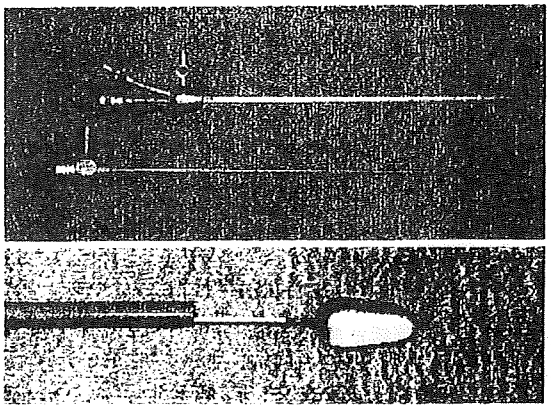

図1 胎仔鏡と離脱型バルーン

2 mm 胎仔鏡と鉗子口付きシース（カールストルツ社製）（A），Goldvalve 離脱型バルーン（Nycomed 社製）（B）．

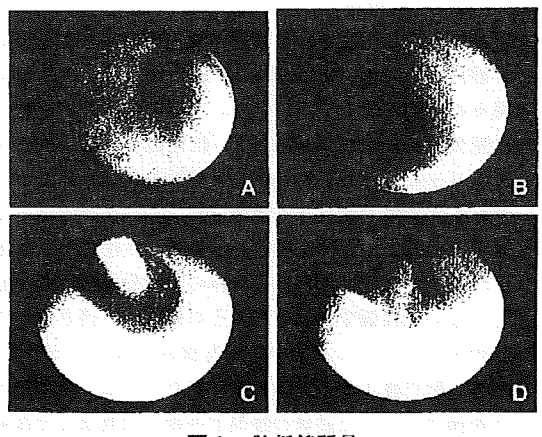

図2 胎仔鏡所見

A：喉頭，B：気管内腔，C：離脱型バルーンの挿入，D：離脱型バルーンの留置．

III 結 果

胎仔鏡の視野は羊水中でも良好であり，5頭すべてで胎仔鏡下に気管内にバルーンを留置することができた．手術時間は約90分で，胎仔鏡操作時間は20分前後であった．術中出血は少量で，合併症はなく，手術終了時には全例で胎仔の生存を確認することができた．5頭中3頭では妊娠継続できず術後2～3日目に流産したが，残りの2頭では1週間妊娠を継続できた．うち1頭では，肺が腫大して腹水が貯留している超音波所見がえられ，剖検でも気管内に留置されたバルーンを確認できた（図3）．他の1頭では胎仔肺の腫大や腹水貯留の所見はみられず，バルーンの逸脱が確認された．肺体重比は正常参考値が平均0.034（0.032～0.036）であったのに対して，

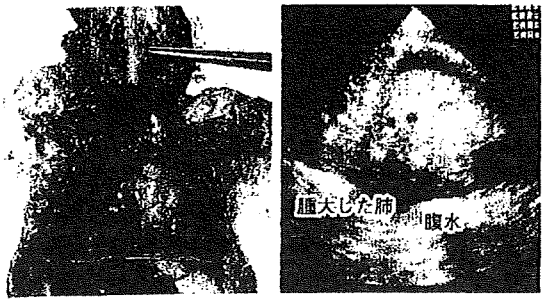

図3 胎仔肺肉眼所見と胎児エコー(気管閉塞1週間後)
腫大した肺(左),胎仔腹水と腫大した肺(右).

気管閉塞の1例では0.060と高値であり,1週間の気管閉塞による胎仔肺の拡張が確認できた.気管閉塞された胎仔肺の組織学的検索では,末梢気道の拡張がみられたものの肺胞は正常構造を保っていた.またバルーンが留置されていた気管壁は肉眼的にも組織学的にも異常を認めなかった.

IV 考 察

今回検討したシングルポート法による手技は,1998年にPapadakisらが羊を対象とした胎仔気管鏡として報告している[12].人への応用はHarrisonら[10]が,妊娠26週の重症CDH 2例に対してバルーン気管閉塞術を施行した.しかしこの時の手技は,母体の開腹下に子宮を露出して行われたため侵襲が大きく,以後の米国での臨床試験でもその有効性は証明されなかった.一方,母体の開腹を伴わない経皮的アプローチは欧州のグループを中心として行われてきた.Deprestらは,24例の重症CDHに対して経皮的シングルポート法によるバルーン気管閉塞術を施行して,12例の長期生存例が得られたと報告している[11].この臨床試験は,検証的な前方視試験ではなかったため,その有用性に関する結論は得られていない.経皮的シングルポート法は従来の開腹法に比べて格段に低侵襲であるが,胎児だけでなく母体にとっても侵襲的であることに変わりはなく,その臨床応用にあたっては,可及的に低侵襲な手術手技が求められる.そういった意味で,本実験系のように,人の胎児を想定して手術手技を習得できるモデルは,極めて重要となる.今回の実験で用いた妊娠110日前後の羊胎仔の体重は0.9~1.3 kgであり,胎児治療適期とされる人胎児の26~28週に相当していた.また,胎仔の喉頭は人胎児のものと類似し,臨床で用いる胎児鏡システムが使用可能であったことより,本実験系は胎児治療の臨床応用に向けたトレーニングシステムとして有用と考えられた.今回の実験では,全例でバルーンの留置が可能で,胎仔の生存も確認できたことより,技術的な確実性は検証できたと考えられる.しかし術後妊娠継続できたのは5頭中2頭のみと,流産の比率が高いという問題が残った.今回の実験では手術手技に重点を置き,術後のモニタリングや子宮収縮抑制の対策を行わなかったことが,高い流産率の一因と考えられた.今後は,手術手技の低侵襲化だけでなく,術後の妊娠継続をより確実なものにする検討が必要と考えられた.

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文 献

1) Okuyama H, Kubota A, Oue T, et al: Inhaled nitric oxide with early surgery improves the outcome of antenatally diagnosed congenital diaphragmatic hernia. J Pediatr Surg, 37: 1188-1190, 2002.
2) Inamura N, Kubota A, Nakajima T, et al: A proposal of new therapeutic strategy for antenatally diagnosed congenital diaphragmatic hernia. J Pediatr Surg, 40: 1315-1319, 2005.
3) 日本小児外科学会学術・先進医療検討委員会:わが国の新生児外科の現況—2003年新生児外科全国集計—.日小外会誌,40: 919-934, 2004.
4) Metkus AP, Filly RA, Stringer MD, et al: Sonographic predictors of survival in fetal diaphragmatic hernia. J Pediatr Surg, 31: 148-152, 1996.
5) Kamata S, Hasegawa T, Ishikawa S, et al: Prenatal diagnosis of congenital diaphragmatic hernia and perinatal care: Assessment of lung hypoplasia. Early Hum Dev, 29: 375-379, 1992.
6) Hedrick MH, Estes JM, Sullivan KM, et al: Plug the lung until it grows (PLUG): A new method to treat congenital diaphragmatic hernia in utero. J Pediatr Surg, 29: 612-617, 1994.
7) DiFiore JW, Fauza DO, Slavin R, et al: Experimental fetal tracheal ligation reverses the structure and physiological effects of pulmonary hypoplasia in congenital diaphragmatic hernia. J Pediatr Surg, 29: 248-257, 1994.
8) Flake AW, Crombleholme TM, Johnson MP, et al: Treatment of severe congenital diaphragmatic hernia by fetal tracheal occlusion: Clinical experience with fifteen cases. Am J Obstet Gynecol, 183:

1059-1066, 2000.
9) Harrison MR, Mychaliska GB, Albanes CT, et al: Correction of congenital diaphragmatic hernia in utero IX: Fetuses with poor prognosis can be saved by fetoscopic temporary tracheal occlusion. J Pediatr Surg, 33: 1017-1023, 1998.
10) Harrison MR, Albanese CT, Hawgood SB, et al: Fetoscopic temporary tracheal occlusion by means of detachable balloon for congenital diaphragmatic hernia. Am J Obstet Gynecol, 185: 730-733, 2001.
11) Deprest J, Jani J, Schoubroeck DV, et al: Current consequence of prenatal diagnosis of congenital diaphragmatic hernia. J Pediatr Surg, 41: 423-430, 2006.
12) Papadakis K, Luks FI, Deprest JA, et al: Single-port tracheoscopic surgery in the fetal lamb. J Pediatr Surg, 33: 918-920, 1998.

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Single-Port Fetoscopic Tracheal Occlusion With a Detachable Balloon: An Experimental Study in the Fetal Lamb

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Purpose: Recently fetoscopic balloon tracheal occlusion has been expected to be an effective treatment for severe congenital diaphragmatic hernia. However, technical refinement is essential to apply the fetoscopic treatment to clinical cases. In this study, we evaluate the safety and technical aspect of this technique in a fetal lamb experiment.

Methods: Using the single-port technique, 5 fetal lambs underwent tracheal occlusion with a detachable balloon at 110 days' gestation. Under general anesthesia, the gravid ewes underwent a laparotomy for uterine exposure. Through a 5-mm port in the uterus wall, a fetoscope was advanced into the fetal trachea. Through the instrument channel of the fetoscopy, a detachable balloon was introduced and left in the fetal trachea. One week after the operation, fetuses were sacrificed, and the effect of tracheal occlusion was evaluated.

Results: Balloon tracheal occlusion was successfully performed in all of the 5 fetuses under excellent visualization. There was no intraoperative complication. Two fetuses were alive at the end of this experiment. At autopsy, the balloon was found in the trachea in one fetus with a dilated lung and ascites.

Conclusion: Fetoscopic balloon tracheal occlusion using the single-port technique is thought to be feasible in the fetal treatment of severe CDH.

Key words: congenital diaphragmatic hernia, fetal treatment, fetal tracheal occlusion, fetoscopy

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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 $\pm$ 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

Table 4 Logistic regression for donor fetal demise

	IUFD ($n = 18$)	Live-birth ($n = 34$)	Univariate analysis		Multivariate analysis	
			Odds ratio (95% CI)	*P*-values	Odds ratio (95% CI)	*P*-values
DVARF	5 (28%)	1 (3%)	12.7 (1.35–119)	0.015		0.050
PUVF	3 (17%)	1 (3%)		0.110		0.18
AA	14 (78%)	4 (9%)	5.00 (1.36–18.4)	0.019		0.08
VV	5 (28%)	5 (15%)		0.287		0.31
Modified SQLPCV	3 (17%)	20 (59%)	0.14 (0.034–0.58)	0.007	0.09 (0.016–0.57)	0.01
Discordant rate >25%	13 (82%)	21 (75%)		0.72		–
EFW < –2SD	8 (50%)	16 (57%)		0.757		–

Abbreviations as in Tables 1 and 2. Data are presented as number (%) or median (range).

IUFD occurred in two modified SQLPCV group cases (18%); this finding was significantly lower than that of the SLPCV group (70.6%; $P = 0.018$). If AA anastomoses were present, ratio of donor IUFD was significantly higher than that in the cases without AA anastomoses in the SLPCV group ($P = 0.025$), but not in the modified SQLPCV group. In regard to the recipients, the modified SQLPCV did not significantly improve fetal survival; however, there was only one IUFD in the group. Consequently, the overall IUFD rate per fetus was significantly lower in the modified SQLPCV group than that of the SLPCV group (9% vs 38%; $P < 0.001$); this finding was independent of the presence or absence of AA anastomoses. Multiple logistic regression analysis showed that the modified SQLPCV significantly reduced donor IUFD; however, no other factors contributed to IUFD in donors with UA-AREDF (Table 4). In regard to the recipients, any covariate was not associated with recipient IUFD (data not shown).

Discussion

This study shows that modified SQLPCV is useful for the prevention of fetal demise in cases of TTTS in which the donor had UA-AREDF. The number of overall IUFD per fetus was significantly decreased in patients who underwent SQLPCV rather than SLPCV (9% vs 38%; $P < 0.001$). This decreased rate of overall IUFD was primarily due to the decreased rate of donor IUFD.

Recently, Quintero *et al.*[10] presented the potential efficacy of sequential coagulations in AV anastomoses (SQLPCV). The difference between SLPCV and SQLPCV involves basing the decision to coagulate placental anastomoses in a phased manner on the types of anastomoses present. The SQLPCV was developed for the purpose of adjusting imbalanced blood flow volume between two fetal circulations even during the laser procedure itself, essentially designed to preserve blood flow volume in donors by coagulating all AVDR prior to AVRD. The umbilical blood flow (UBF) of donors in TTTS was significantly lower before laser surgery than it was following surgery.[23,24] Recently, Becker *et al.*[25] reported that, when compared with uncomplicated monochorionic twins, a significant decrease in donor UBF in donors was seen only at stage III or IV. They also reported a significant increase in UBF in recipients regardless of the stage of severity. These findings indicate that, in our study, the donor was hypovolemic or the recipient was hypervolemic before the laser surgery because a markedly abnormal Doppler (UA-AREDF) was seen in all cases. Although it was impossible to measure the direction and volume of blood transfused through AV anastomoses in the course of laser surgery, the significant improvement of overall fetal survival in modified SQLPCV may reflect not only the potential increase in donor blood flow but also the potential decrease in recipient blood flow. In particular, a significant improvement of fetal survival in cases without AA anastomoses may reflect the potential benefit of the sequential coagulation of all AVDR prior to AVDR because the influence of blood flow through AA anastomoses can be disregarded and the result supports the Quintero's original concept.

In cases with AA anastomoses, modified SQLPCV, obliteration of AA anastomoses prior to any other type of anastomosis, is more likely to prevent IUFD of donors with UA-AREDF compared with the SLPCV group. The presence of AA anastomoses has been considered to play a protective role against the development of TTTS in monochorionic pregnancies.[26] It has also been reported that detection of AA anastomoses by ultrasonography in fetuses who developed TTTS could confer a survival advantage[27] and that the detection at treatment could increase the chance of perinatal

survival, independent of stage.[28] However, the management consisted of conservative treatments such as amnioreduction and septostomy in the former report; laser surgery was performed in only three of 95 cases in the latter report. As the prognosis for AA anastomoses treated with laser surgery is currently unclear, it is necessary to clarify the role of AA anastomoses on the prognosis of fetuses following laser surgery. Murakoshi *et al.*[29] indicated that AA anastomoses could behave as functional AV anastomoses, in which a hemodynamic equator, a collision front between opposing blood flows along the AA anastomoses, displaced toward one side or the other depending on the pressure gradient between two fetuses. We speculated that an acute net transfusion via the direct communication of arteries could occur, depending on the pressure gradient between the fetuses, and considered that even a small change in the pressure gradient between the two fetuses following coagulation of AV anastomoses might cause a significant blood flow exchange via AA anastomoses while the anastomoses were still patent, which could result in a deterioration of hemodynamic status in both the hypotensive donor and the hypertensive recipient. The risk of patent AA anastomoses after coagulation of AV anastomoses may be explained in part by the following hypothesis. Removal of hypotension in the donor twin following coagulation of AV anastomoses may displace the hemodynamic equator toward the recipient's side, and the blood flow from the donor twin could enter the drainage vein into the recipient twin if the hemodynamic equator would displace beyond the confluence of the drainage vein; thus, transforming the AA anastomoses into a functional AVDR. Consequently, the donor may rapidly lose a significant amount of blood through the functional AVDR, which could aggravate the hypotensive or hypovolemic status of the donor. Conversely, when the hemodynamic equator displaces toward the donor's side secondary to the donor's progressive hypotension, the condition may worsen unless AA anastomoses work as a functional AVRD. Considering the fact that 86% of fetuses survived *in utero* after initial obliteration of AA anastomoses by modified SQLPCV, our hypothesis seems to be feasible.

This study had several limitations. First, the study population was limited to cases with UA-AEDF in the donors. As the primary purpose of the study was to elucidate the efficacy of modified SQLPCV on postoperative fetal survival, the high mortality rate, which has been noted in the subset of donors with UA-AREDF,[11–14] could become a useful indicator of the procedure's efficacy. It is unclear whether this modified method is effective in cases without donor UA-AREDF; therefore, further investigation is indicated. Second, another potential limitation is the sequence of coagulation in the SLPCV group, in which we included any cases incompatible to the sequence or included cases without a precise description of the sequence. However, considering the overall survival rate above 80% for at least one fetus in SLPCV, we assume these limitations are unlikely to affect the main conclusion. Third, we admit that this technique is a modification of a currently proposed technique by Quintero *et al.*, and the sequence of coagulation in the modified SQLPCV is correspondent to SQLPCV if the superficial anastomoses are absent. In this study, we dared to use the term 'modified SQLPCV' in all categorized cases because the procedure was intended prior to the treatment. Fourth, it is still unclear whether modified SQLPCV might be superior to SQLPCV. As this study was limited to the case with UA-AREDF, this result could not be comparable to the previous study of SQLPCV reported by Quintero *et al.* Thus, we can only say that modified SQLPCV is more efficacious than SLPCV not but SQLPCV. Further studies are needed in order to determine the optimal sequence.

In conclusion, modified SQLPCV, which may both preserve blood flow volume in donor twins and prevent an acute net transfusion via AA anastomoses, can improve fetal survival rate in TTTS with UA-AREDF in the donor. This study is a preliminary report and the rationale behind the procedure is a matter for speculation; however, we believe that utilization of the procedure could improve the outcome for fetuses with TTTS.

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References

1. De Lia JE, Cruikshank DP, Keye WR Jr. Fetoscopic neodymium: YAG laser occlusion of placental vessels in severe twin–twin transfusion syndrome. *Obstet Gynecol* 1990; **75**: 1046–1053.
2. Ville Y, Hyett J, Hecher K, Nicolaides K. Preliminary experience with endoscopic laser surgery for severe twin–twin transfusion syndrome. *N Engl J Med* 1995; **332**: 224–227.

3. Quintero RA, Morales WJ, Mendoza G *et al.* Selective photocoagulation of placental vessels in twin–twin transfusion syndrome: Evolution of a surgical technique. *Obstet Gynecol Surv* 1998; **53**: S97–S103.
4. Senat MV, Deprest J, Boulvain M, Paupe A, Winer N, Ville Y. Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome. *N Engl J Med* 2004; **351**: 136–144.
5. Huber A, Diehl W, Bregenzer T, Hackeloer BJ, Hecher K. Stage-related outcome in twin–twin transfusion syndrome treated by fetoscopic laser coagulation. *Obstet Gynecol* 2006; **108**: 333–337.
6. Rossi AC, D'Addario V. Laser therapy and serial amnioreduction as treatment for twin–twin transfusion syndrome: A metaanalysis and review of literature. *Am J Obstet Gynecol* 2008; **198**: 147–152.
7. Hecher K, Plath H, Bregenzer T, Hansmann M, Hackeloer BJ. Endoscopic laser surgery versus serial amniocenteses in the treatment of severe twin–twin transfusion syndrome. *Am J Obstet Gynecol* 1999; **180**: 717–724.
8. Quintero RA, Dickinson JE, Morales WJ *et al.* Stage-based treatment of twin–twin transfusion syndrome. *Am J Obstet Gynecol* 2003; **188**: 1333–1340.
9. Quintero R, Ishii K, Chmait R, Bornick P, Allen M. Sequential selective laser photocoagulation of communicating vessels in twin–twin transfusion syndrome. *Am J Obstet Gynecol* 2005; **193**: S155–S155.
10. Quintero RA, Ishii K, Chmait RH, Bornick PW, Allen MH, Kontopoulos EV. Sequential selective laser photocoagulation of communicating vessels in twin–twin transfusion syndrome. *J Matern Fetal Neonatal Med* 2007; **20**: 763–768.
11. Ville Y, Hecher K, Gagnon A, Sebire N, Hyett J, Nicolaides K. Endoscopic laser coagulation in the management of severe twin-to-twin transfusion syndrome. *Br J Obstet Gynaecol* 1998; **105**: 446–453.
12. Martinez JM, Bermudez C, Becerra C, Lopez J, Morales WJ, Quintero RA. The role of Doppler studies in predicting individual intrauterine fetal demise after laser therapy for twin–twin transfusion syndrome. *Ultrasound Obstet Gynecol* 2003; **22**: 246–251.
13. Cavicchioni O, Yamamoto M, Robyr R, Takahashi Y, Ville Y. Intrauterine fetal demise following laser treatment in twin-to-twin transfusion syndrome. *BJOG* 2006; **113**: 590–594.
14. Ishii K, Hayashi S, Nakata M, Murakoshi T, Sago H, Tanaka K. Ultrasound assessment prior to laser photocoagulation for twin–twin transfusion syndrome for predicting intrauterine fetal demise after surgery in Japanese patients. *Fetal Diagn Ther* 2006; **22**: 149–154.
15. Karsdorp VH, Dirks BK, van der Linden JC, van Vugt JM, Baak JP, van Geijn HP. Placenta morphology and absent or reversed end diastolic flow velocities in the umbilical artery: A clinical and morphometrical study. *Placenta* 1996; **17**: 393–399.
16. Krebs C, Macara LM, Leiser R, Bowman AW, Greer IA, Kingdom JC. Intrauterine growth restriction with absent end-diastolic flow velocity in the umbilical artery is associated with maldevelopment of the placental terminal villous tree. *Am J Obstet Gynecol* 1996; **175**: 1534–1542.
17. Vanderheyden TM, Fichera A, Pasquini L *et al.* Increased latency of absent end-diastolic flow in the umbilical artery of monochorionic twin fetuses. *Ultrasound Obstet Gynecol* 2005; **26**: 44–49.
18. Chang YL, Chmait RH, Bornick PW, Allen MH, Quintero RA. The role of laser surgery in dissecting the etiology of absent or reverse end-diastolic velocity in the umbilical artery of the donor twin in twin–twin transfusion syndrome. *Am J Obstet Gynecol* 2006; **195**: 478–483.
19. Hecher K, Jauniaux E, Campbell S, Deane C, Nicolaides K. Artery-to-artery anastomosis in monochorionic twins. *Am J Obstet Gynecol* 1994; **171**: 570–572.
20. Bermudez C, Becerra CH, Bornick PW, Allen MH, Arroyo J, Quintero RA. Placental types and twin–twin transfusion syndrome. *Am J Obstet Gynecol* 2002; **187**: 489–494.
21. Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin–twin transfusion syndrome. *J Perinatol* 1999; **19**: 550–555.
22. Shinozuka N, Okai T, Kohzuma S *et al.* Formulas for fetal weight estimation by ultrasound measurements based on neonatal specific gravities and volumes. *Am J Obstet Gynecol* 1987; **157**: 1140–1145.
23. Gratacos E, Van Schoubroeck D, Carreras E *et al.* Impact of laser coagulation in severe twin–twin transfusion syndrome on fetal Doppler indices and venous blood flow volume. *Ultrasound Obstet Gynecol* 2002; **20**: 125–130.
24. Ishii K, Chmait RH, Martinez JM, Nakata M, Quintero RA. Ultrasound assessment of venous blood flow before and after laser therapy: Approach to understanding the pathophysiology of twin–twin transfusion syndrome. *Ultrasound Obstet Gynecol* 2004; **24**: 164–168.
25. Becker J, Hernandez-Andrade E, Munoz-Abellana B, Acosta R, Cabero L, Gratacos E. Stage-dependent fetal umbilical blood flow changes induced by laser therapy and amniodrainage in twin-to-twin transfusion syndrome. *Ultrasound Obstet Gynecol* 2006; **28**: 674–680.
26. Denbow ML, Cox P, Taylor M, Hammal DM, Fisk NM. Placental angioarchitecture in monochorionic twin pregnancies: Relationship to fetal growth, fetofetal transfusion syndrome, and pregnancy outcome. *Am J Obstet Gynecol* 2000; **182**: 417–426.
27. Taylor MJ, Denbow ML, Duncan KR, Overton TG, Fisk NM. Antenatal factors at diagnosis that predict outcome in twin–twin transfusion syndrome. *Am J Obstet Gynecol* 2000; **183**: 1023–1028.
28. Tan TY, Taylor MJ, Wee LY, Vanderheyden T, Wimalasundera R, Fisk NM. Doppler for artery-artery anastomosis and stage-independent survival in twin–twin transfusion. *Obstet Gynecol* 2004; **103**: 1174–1180.
29. Murakoshi T, Quintero RA, Bornick PW, Allen MH. In vivo endoscopic assessment of arterioarterial anastomoses: Insight into their hemodynamic function. *J Matern Fetal Neonatal Med* 2003; **14**: 247–255.

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Two cases of reversal of twin-twin transfusion syndrome diagnosed by measuring hourly fetal urine production

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Abstract

Reversal of twin-twin transfusion syndrome (TTTS) is a rare complication of monochorionic pregnancy. Diagnostic criteria and satisfactory therapeutic options have not been reported. We make a suggestion of diagnosis and therapy for reversal of TTTS. We report two cases of reversal of TTTS. Measurement of the fetal urine production rate was useful for management and better comprehension of the cases. In case 1, double intrauterine fetal demise occurred before the criteria for TTTS were fulfilled, in which each fetal urine production rate reversed prior to the change of amniotic fluid volume. In case 2, elevated urine production was noted prior to progressive polyhydroamnios and congestive heart failure in the new recipient and the fetoscopic laser photocoagulation of the placental communicating vessels was performed successfully before the criteria for TTTS were fulfilled. Both infants required intensive care, but developed normally and showed no neurologic complications at 2 years after birth. Hourly fetal urine production rate was useful for immediate diagnosis of reversal of TTTS, and laser photocoagulation of the placental communicating vessels is thus a method for the correction of the fetal blood flow imbalance in cases of reversal of the donor-recipient phenotype in TTTS.

Key words: hourly fetal urine production, monochorionic twin, reversal of twin-twin transfusion syndrome, twin-twin transfusion syndrome.

Introduction

Twin-twin transfusion syndrome (TTTS) is defined sonographically as the presence of polyhydramnios in the sac of one twin and oligohydramnios in the sac of the other twin. This typical feature of TTTS is thought to be caused by an imbalance in net blood flow through the placental communicating vessels on the surface of the monochorionic placenta. Several cases of reversal of the donor-recipient phenotype have been reported.[1,2] The pathophysiology, incidence, and optimal treatment options for reversal of TTTS are unclear. However, it is reported that once reversal of TTTS occurs, especially before 26 weeks of gestation, the perinatal prognosis is poor.[1–3] We report two cases of reversal of TTTS; one case had a poor outcome of double intrauterine fetal demise, but the other had a favorable outcome of double fetal survival as a result of early intervention by fetoscopic laser photocoagulation of the placental communicating vessels.

Case Reports

Case 1

A 27-year-old primigravida woman was referred to our hospital at 22 weeks and 1 day of gestation for evaluation of a complicated monochorionic diamniotic twin pregnancy with amniotic fluid discordance. Initial ultrasound examination showed 17.5% discordance in

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estimated fetal weight (EFW), in which the EFW of twin A was 496 g, and the EFW of twin B was 409 g, without structural abnormalities. The maximum vertical pocket (MVP) of the amniotic cavity differed distinctly between the fetuses (the MVP of twin A was 9.2 cm; the MVP of twin B was 2.2 cm). TTTS was suspected, in which twin A was considered the recipient fetus and twin B the donor fetus. But the MVP of twin B was more than 2 cm, the criteria of TTTS was not fulfilled and fetoscopic laser photocoaglation was not indicated. Doppler ultrasonography showed no critically abnormal Doppler waveforms, such as absent end-diastolic flow in the umbilical artery (UA-AEDF), reversed flow during atrial contraction in the ductus venosus (DV-RF) or pulsatile umbilical venous flow (PUVF) in either fetus. Despite polyhydramnios, the bladder of twin A was small, whereas the bladder of twin B was large, despite oligohydramnios. The hourly fetal urine production rate (HFUPR) was estimated by ultrasonography as described by Rabinowitz *et al.*[4] Measurements were made with ultrasonic calipers at 5 min intervals for 1 h. The greatest longitudinal bladder view was identified and measured to estimate bladder volume. The slope of the filling phase, calculated by regression analysis, is used to estimate the hourly fetal urine production rate. Contrary to the presence of polyhydramnios in twin A and oligohydramnios in twin B, the HFUPR for twin A was 1.4 mL/h, and that for twin B was 11 mL/h, suggesting oliguria in twin A and polyuria in twin B. Daily ultrasound examinations documented a gradual decrease of amniotic fluid in twin A and a sudden increase of amniotic fluid in twin B (Fig. 1), which was interpreted as reversal of TTTS. At 22 weeks and 6 days of gestation, typical features of congestive heart failure were observed in twin B, who showed DV-RF and cardiomegaly in addition to progressive polyhydramnios. The MVP of twin A decreased to the lowest limit of the normal range due to persistent oliguria. Although reversal of TTTS was strongly suspected, the MVP in twin A was maintained at greater than 2 cm, which did not fulfill the criteria for fetoscopic laser photocoagulation for TTTS at our institution at that time. At 23 weeks and 2 days of gestation, the status of twin B deteriorated, and included UA-AEDF with DV-RF and ascites. Fetal demise of twin B occurred on the same day. To prevent potential perimortem feto-fetal transfusion, intrauterine rescue transfusion was attempted, but twin A also died. Twin A was 488 g and pale, and twin B was 676 g and plethoric at birth. Pathologic examination of the placenta showed a single artery-to-artery (AA) anastomosis and two artery-to-venous (AV) anastomoses from twin B to twin A on the surface of the chorionic plate.

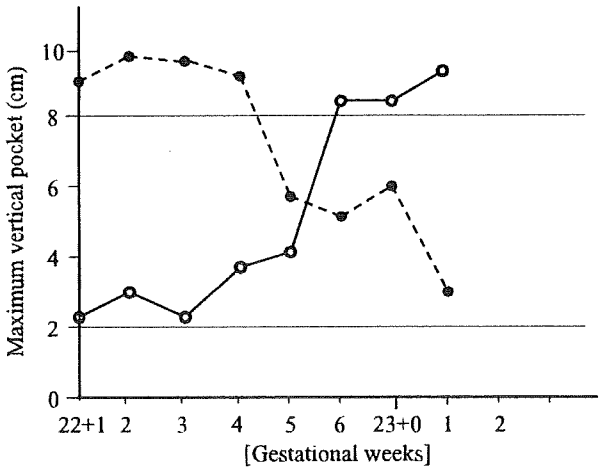

Figure 1 Changes in the maximum vertical pocket (MVP) of twin A (●) and twin B (○) in case 1. Daily ultrasound examinations documented a gradual decrease of amniotic fluid in twin A and a sudden increase of amniotic fluid in twin B.

Case 2

A 25-year-old primigravida woman was referred to our hospital at 19 weeks and 5 days of gestation for evaluation of amniotic fluid discordance in a monochorionic diamniotic twin pregnancy. Initial ultrasound examination showed polyhydramnios in one twin and most likely oligohydramnios in other twin (MVP of twin A was 8.6 cm, and MVP of twin B was 2.5 cm). No structural abnormalities or abnormal Doppler waveforms were observed at that time. Serial ultrasound examinations, including Doppler study and estimation of HFUPR were conducted. Polyhydramnios in twin A gradually improved as the urine production rate decreased, whereas polyhydramnios in twin B progressed as the urine production rate increased dramatically (Figs 2,3). At 22 weeks of gestation, typical features of congestive heart failure, including DV-RF, PUVF, and cardiomegaly, were observed in twin B, who was considered the initial donor and present recipient. Upon diagnosis of reversal of FFTS, laser surgery was considered and approved by the Institutional Review Board in our hospital. After extensive counseling regarding the diagnosis, possible outcomes, and alternative therapeutic options, including expectant management, amnioreduction, and laser

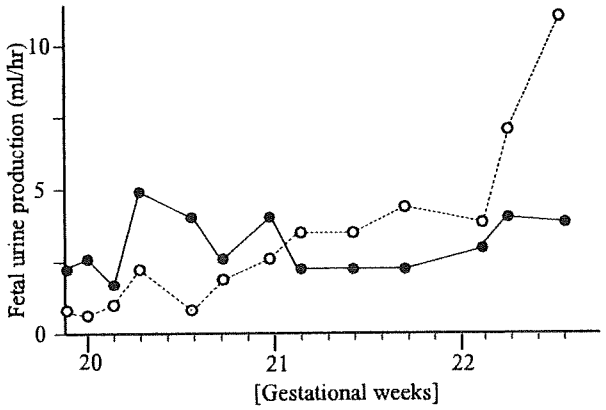

Figure 2 The solid line shows changes in fetal urine production of twin A (●) and the dashed line shows that of twin B (○) in case 2. The urine production rate in twin A gradually decreased, whereas that in twin B dramatically increased.

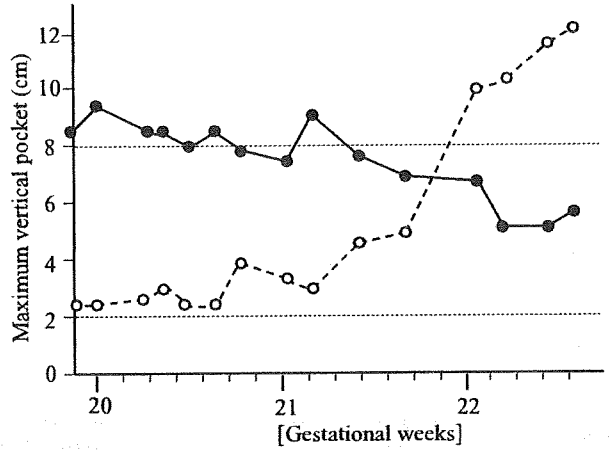

Figure 3 The solid line shows changes in the maximum vertical pocket (MVP) of twin A (●) and the dashed line shows MVP of twin B (○) in case 2. Polyhydramnios in twin A was gradually improved as the urine production rate decreased, whereas polyhydramnios in twin B progressed as the urine production rate increased dramatically.

surgery, the patient and her family provided written informed consent for laser surgery. At 22 weeks and 4 days of gestation, fetoscopic laser photocoagulation of the placental communicating vessels was performed as described previously.[5] In brief, a small skin incision was made under both local and intravenous anesthesia. Under ultrasound guidance, a 3.8-mm trocar (Richard Wolf Medical Instruments, Vernon Hills, IL, USA) was introduced into the sac of twin B. Fetoscopic observation with a 3.3-mm diagnostic endoscope (Richard Wolf Medical Instruments) showed only two anastomoses in the placental surface between the two fetuses, one AV anastomosis from twin A to twin B and another AV anastomosis in the opposite direction. The two vascular anastomoses were of a similar size. A 550-μm neodymium: YAG laser fiber (SlimLine; Lumenis Japan, Tokyo, Japan) was inserted through the operating channel of a 3.3-mm operating endoscope (Richard Wolf Medical Instruments), and all anastomoses were photocoagulated. Two days after surgery, signs of congestive heart failure (DV-RF and PUVF) in twin B diminished, and polyhydramnios had not progressed. The patient delivered two female infants (twin A weighed 999 g and twin B weighed 995 g), by emergency cesarean section because of placental abruption at 27 weeks and 4 days of gestation. The pathological examination of the delivered placenta was consistent with fetoscopic findings and both anastomoses had no patency. Both infants required mechanical ventilation in the neonatal intensive care unit for 1 week due to respiratory disorders, but no neurologic complications, such as intracranial hemorrhage or periventricular leukomalacia, were detected by serial cranial ultrasound studies. The neonatal courses of these infants were uneventful. Both children developed normally and showed no neurologic complications at 2 years after birth.

Discussion

Recently, Wee *et al.*[3] reported five cases of reversal of TTTS diagnosed by reversal of the donor-recipient phenotype; that is, a donor acquiring the features of a recipient and vice versa, and with 30% of perinatal mortality, while double fetal demises occurred in other reports.[1,2] Results of case 2 show the usefulness of fetoscopic laser photocoagulation of the placental communicating vessels for the treatment of reversal of TTTS. Although the pathophysiology of reversal of TTTS is unclear, anastomoses on the monochorionic placenta between the two fetal circulations are the cause of the acute hemodynamic changes seen in the new recipient and new donor. We began to use laser surgery to ameliorate the reversed blood flow imbalance between fetuses, even in cases in which the amniotic fluid in the new donor did not decrease enough to fulfill the diagnostic criteria for typical TTTS. Laser surgery has recently been indicated not only for TTTS, but also for other complications of monochorionic twin pregnancies, such as selective growth restriction[6] and twin

reversed arterial perfusion sequence,[7] in which the placental communicating vessels are involved. Reversal of TTTS may not meet the diagnostic criteria for typical TTTS, but ablation of the communicating vessels is reasonable, considering the potential adverse outcome of this complication.

Only a few reports have been published,[1,2,8] but the incidence and cause of reversal of TTTS are still unknown. Wee *et al.* reported reversal of the donor-recipient phenotype in five of 96 cases of TTTS.[3] At a similar incidence, we encountered the present two cases in the last 3-year period, during which 62 cases of TTTS had been evaluated at our hospital (unpubl. data). Serial ultrasound follow-up is necessary to detect the reversal of TTTS. It is still unclear which placental angio-architecture can cause reversal of TTTS, but paucity of placental anastomoses could attribute to the pathophysiology.[3] Only three communicating vessels in case 1 and two in case 2 were shown. We also conclude that hypotension of the donor and the existence of a large AA anastomosis may explain the reversal of phenotype. However, AA anastomosis seems not to be requisite to the hemodynamic alteration because of no AA anastomosis in case 2.

Measurement of fetal urine production rate was useful in the precise evaluation of urine production in both the hypervolemic and hypovolemic fetuses. Preceding the fluctuations in amniotic fluid volume, the urine production rate had already changed in both fetuses. The new recipient twin developed progressive polyhydramnios as the urine production rate increased. However, the MVP of the new donor sac did not fulfill the diagnostic criteria for oligohydramnios because of the preexisting polyhydramnios. The assessment of the urine production rate may reflect fetal hypervolemia and hypovolemia more precisely than assessment of amniotic fluid volume.

In conclusion, laser photocoagulation of the placental communicating vessels can be used to correct the blood flow imbalance between fetuses with reversal of the donor-recipient phenotype in TTTS.

References

1. Bromley B, Benacerraf BR. Acute reversal of oligohydramnios-polyhydroamnios sequence in monochorionic twins. *Int J Gynecol Obstet* 1996; **55**: 281–283.
2. Mielke G, Mayer R, Frauz H *et al.* Prenatal detected reversal of donor-recipient roles in twin-twin transfusion syndrome following in utero treatment. *Br J Obstet Gynaecol* 1997; **104**: 503–505.
3. Wee LY, Taylor MJO, Vanderheyden T *et al.* Reversal of twin-twin transfusion syndrome: Frequency, vascular anatomy, associated anomalies and outcome. *Prenat Diagn* 2004; **24**: 104–110.
4. Rabinowitz R, Peters MT, Vyas S *et al.* Measurement of fetal urine production in normal pregnancy by real-time ultrasonography. *Am J Obstet Gynecol* 1989; **161**: 1264–1266.
5. Ishii K, Hayashi S, Nakata M *et al.* Ultrasound assessment prior to laser photocoaglation for Twin-Twin Transfusion Syndrome for predicting intrauterine fetal demise after surgery in Japanese patients. *Fetal Diagn Ther* 2006; **22**: 149–154.
6. Quintero RA, Bornick PW, Morales WJ *et al.* Selective photocoagulation of communicating vessels in the treatment of monochorionic twins with selective growth retardation. *Am J Obstet Gynecol* 2001; **185**: 689–696.
7. Hecher K, Lewi L, Gratacos E *et al.* Twin reversed arterial perfusion: Fetoscopic laser coagulation of placental anastomoses or the umbilical cord. *Ultrasound Obstet Gynecol* 2006; **28**: 688–691.
8. Meyberg-Solomayer GC, Fehm T, Mackensen-Haen S *et al.* Hemodynamic changes with phenotype reversal during pregnancy in twin-twin transfusion syndrome. *Perinat Diagn* 2004; **24**: 816–821.

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Prenatal spontaneous disruption of the dividing membrane in monochorionic diamniotic twins detected at the time of fetoscopic laser photocoagulation

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Abstract

Spontaneous antepartum rupture of the dividing membrane occurring in monochorionic diamniotic twins (MD twin) is an extremely rare complication and difficult to diagnose prenatally. We present a case of pseudo-monoamniotic twins derived from an MD twin gestation, which was suspected by ultrasound and was confirmed by antepartum fetoscopy. A 28-year-old woman, gravida 1, para 1 at 24 weeks of gestation was referred because of suspected polyhydroamnios in an MD twin. Ultrasound suggested twin–twin transfusion syndrome stage III, spontaneous rupture of the dividing membranes and cord entanglement. Fetoscopic laser photocoagulation (FLP) was performed using the Nd:YAG laser on 12 placental vascular connections. Fetoscopy revealed the spontaneous rupture of the dividing membrane and cord entanglement. The remainder of the pregnancy was managed as a monoamniotic twin gestation. Elective cesarean section was performed at 32 weeks of gestation following antenatal steroids and concordantly grown healthy male infants were delivered.

Key words: fetoscopic laser photocoagulation, monoamniotic twin, twin–twin transfusion syndrome.

Introduction

Monoamniotic twin gestations, which represent approximately 1% of all twins,[1] have a high perinatal mortality rate (30–70%), with the most common cause of fetal death being cord entanglement.[2] Chorionicity is usually determined by ultrasonography in the first trimester of pregnancy. In rare cases, MD twin gestation diagnosed in the first trimester converts spontaneously to monoamniotic twins as a result of *in utero* disruption of the dividing membrane. Pseudo-monoamniotic twins have been reported previously and their perinatal mortality rate would be equivalent to that of original monoamniotic twins. Although pseudo-monoamniotic twins were reported previously, they were all suspected prenatally by ultrasound and were detected by the macroscopic and pathological findings after birth.[3–12] Meanwhile, fetoscopic laser photocoagulation for placental communicating vessels (FLP) has recently emerged as a treatment option for twin–twin transfusion syndrome (TTTS), which is usually performed before 26 weeks of gestation. We report the first case of constructive monoamniotic twins resulting from an original MD twin gestation antenatally, of which disruption of the dividing membrane was detected prenatally at the time of FLP for the treatment of TTTS.

Case Report

A 28-year-old woman, gravida 1, para 1, was initially diagnosed with monochorionic diamniotic twin (MD twin) pregnancy by ultrasonography in the

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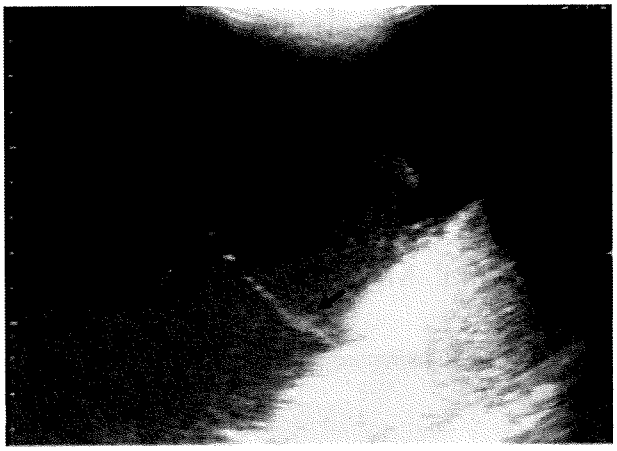

Figure 1 Transabdominal ultrasonography at 24 weeks of gestation shows the 'thin' dividing membrane from the chorionic surface of the posterior placenta (arrows).

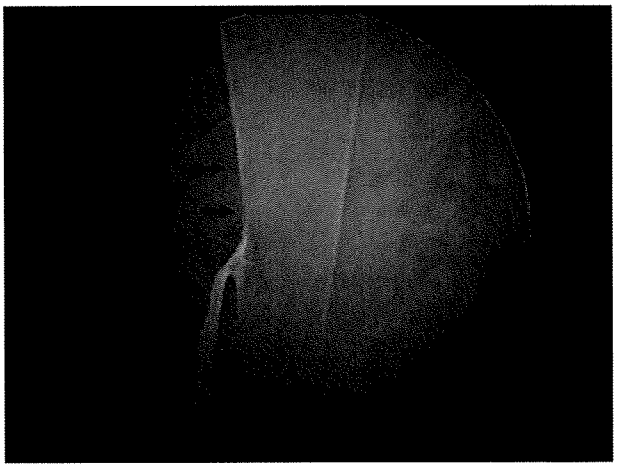

Figure 2 Fetoscopic finding at 24 weeks of gestation of a short falciform remnant of dividing membranes with an irregular margin (arrows).

first trimester of gestation. A dividing membrane and equal amniotic fluid volume in each sac were noted. At 24 weeks of gestation, the twins were found to have polyhydramnios and threatened premature labor with abdominal distention and pain, therefore the patient was transferred to our hospital. Ultrasonography showed a relatively thin dividing membrane with a free-floating edge, mainly close to the chorionic surface of the posterior placenta (Fig. 1). Although the twins obviously had polyhydramnios with 8.4 cm of maximum amniotic fluid pocket, each amniotic fluid pocket was difficult to measure due to the unclear membrane. Estimated fetal weights were 560 g and 720 g. The bladder could not be identified in the smaller fetus and was distended in the larger fetus. A diagnosis of TTTS stage III was made because of an absent end-diastolic flow in the umbilical artery of the larger fetus. On the same day, the patient was referred to the perinatal care center of Yamaguchi University for FLP. Fetoscopy disclosed spontaneous rupture of the dividing membrane (Fig. 2) and cord entanglement. The insertion sites of the two umbilical cords were contiguous, and a short falciform remnant of the disrupted intervening membrane was seen on the placenta between the umbilical cords. Twelve placental vascular communications were coagulated by Nd:YAG laser, and about 3300 mL of amniotic fluid were aspirated. Both fetuses developed transient hydrops, which disappeared at 11 days after FLP. The fetal weight discordancy of the twins resolved gradually. At 26 weeks of gestation the patient was admitted to our hospital for surveillance. Elective cesarean

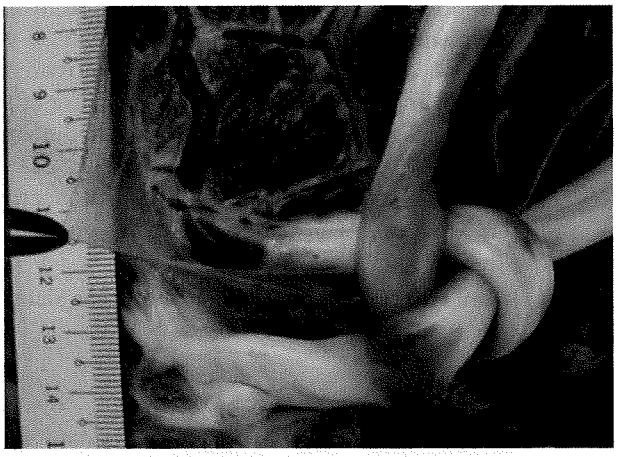

Figure 3 Photograph of the placenta showing contiguous cord insertion sites and a thin short dividing membrane with loose cord entanglement.

section was performed at 32 weeks of gestation following administration of maternal antenatal steroids, and concordant male infants with loosely entangled umbilical cords weighing 1762 g and 1744 g were delivered from a single gestational sac, with an Apgar score of 8 and 9 at 1 and 5 min in each twin. Gross pathological examination showed that the placenta had a dividing membrane between the cord insertions (Fig. 3). The patient's postoperative course was uneventful and the mother and her infants were discharged on postoperative days 8 and 36, respectively.

Discussion

We were able to find 10 articles reporting 17 cases of pseudo-monoamniotic twins derived from MD twins and their perinatal mortality rate is thought to be equivalent to original monoamniotic twins.[3–12] Trauma or physical rupture by the fetuses have been entertained as possible etiological factors.[3] Other possible causes include amniocentesis,[3,6,7] cordcentesis,[5] and other invasive intrauterine procedures.[3] Infection, developmental disturbances,[3] and intrauterine sling formation are other possible causes. Among these proposed causes, intrauterine invasive procedures are the most frequently reported.

We report the first case of pseudo-monoamniotic twins resulting from an original MD twin gestation antenatally detected at the time of FLP for the treatment of TTTS. Fetoscopic findings included a short falciform remnant of the dividing membrane with an irregular margin, indicating that the cause of spontaneous septostomy would be a developmental disturbance or pressure exerted by disproportionate enlargement of one of the two sacs. In addition, although we cannot precisely know the timing of spontaneous septostomy and resulting entanglement, it appears that this occurred midtrimester according to the fetoscopic findings.

The most important concern following antepartum septostomy is cord entanglement, which occurred in 11 out of the 17 reported cases (64%), approximating the reported risk in true monoamniotic twins (70%).[13] Monoamniotic twinning is associated with a per case mortality rate of 54%[14] secondary to prematurity, growth restriction, congenital anomalies, vascular anastomosis and most commonly, umbilical cord entanglement. The perinatal management of this case after FLP was controversial. Pasquini *et al.* reported that sulindac therapy after 20 weeks of gestation, close ultrasound surveillance and elective cesarean section at 32 weeks of gestation following antenatal steroids improved perinatal survival of monoamniotic twins.[15] We managed this case according to this regimen with a successful result.

Most placentas are incompletely examined after birth, and the true incidence of disruption of the dividing-membrane with amniotic plica may be underreported. It is possible that the incidence of true monoamniotic placentation may be even less than 1% of all twins, with many suspected monoamniotic placentas representing disrupted diamniotic-monochorionic placentas. When a 'thin' dividing membrane is visualized at any time during a twin gestation, it is important to remember that rupture of this membrane may subsequently occur. For this reason, a careful inspection of the dividing membrane should be performed at follow-up ultrasound examination. In addition, if a monoamniotic gestation is suspected, the presence of a dividing membrane on previous ultrasound examination cannot rule out the possibility of a dividing membrane rupture with formation of monoamniotic gestation later in pregnancy.

References

1. D'Alton ME, Simpson LL. Syndromes in twins. *Semin Perinatol* 1995; **19**: 375–386.
2. Benirschke K, Kim CK. Multiple pregnancy. 1. *N Engl J Med* 1973; **288**: 1276–1284.
3. Gilbert WM, Davis SE, Kaplan C *et al.* Morbidity associated with prenatal disruption of the dividing membrane in twin gestations. *Obstet Gynecol* 1991; **78**: 623–630.
4. Krause HG, Goh JT. Cord entanglement in monochorionic diamniotic twins. *Aust N Z J Obstet Gynaecol* 1998; **38**: 341–342.
5. Megory E, Weiner E, Shalev E *et al.* Pseudomonoamniotic twins with cord entanglement following genetic funipuncture. *Obstet Gynecol* 1991; **78**: 915–917.
6. Suzuki S, Ishikawa G, Sawa R *et al.* Iatrogenic monoamniotic twin gestation with progressive twin–twin transfusion syndrome. *Fetal Diagn Ther* 1999; **14**: 98–101.
7. Feldman DM, Odibo A, Campbell WA *et al.* Iatrogenic monoamniotic twins as a complication of therapeutic amniocentesis. *Obstet Gynecol* 1998; **91**: 815–816.
8. De Lia JE, Worthington D. Intrauterine sling with umbilical cord entanglement in diamniotic twins. *Ultrasound Obstet Gynecol* 2000; **15**: 447.
9. Cook TL, O'Shaughnessy R. Iatrogenic creation of a monoamniotic twin gestation in severe twin–twin transfusion syndrome. *J Ultrasound Med* 1997; **16**: 853–855.
10. Aisenbrey GA, Catanzarite VA, Hurley TJ *et al.* Monoamniotic and pseudomonoamniotic twins: Sonographic diagnosis, detection of cord entanglement, and obstetric management. *Obstet Gynecol* 1995; **86**: 218–222.
11. Sherer DM, Bitton C, Stimphil R *et al.* Cord entanglement of monochorionic diamniotic twins following spontaneous antepartum septostomy sonographically simulating a true knot of the umbilical cord. *Ultrasound Obstet Gynecol* 2005; **26**: 676–678.
12. Nasrallah FK, Faden YA. Antepartum rupture of the intertwin-dividing membrane in monochorionic diamniotic twins: A case report and review of the literature. *Prenat Diagn* 2005; **25**: 856–860.
13. Pasquini L, Wimalasundera RC, Fisk NM. Management of other complications specific to monochorionic twin pregnancies. *Best Pract Res Clin Obstet Gynaecol* 2004; **18**: 577–599.
14. Carr SR, Aronson MP, Coustan DR. Survival rates of monoamniotic twins do not decrease after 30 weeks' gestation. *Am J Obstet Gynecol* 1990; **163**: 719–722.
15. Pasquini L, Wimalasundera RC, Fichera A *et al.* High perinatal survival in monoamniotic twins managed by prophylactic sulindac, intensive ultrasound surveillance, and Cesarean delivery at 32 weeks' gestation. *Ultrasound Obstet Gynecol* 2006; **28**: 681–687.

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Perinatal Outcome of Monochorionic Twins with Selective Intrauterine Growth Restriction and Different Types of Umbilical Artery Doppler under Expectant Management

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Key Words
Monochorionic twins · Selective intrauterine fetal growth restriction · Umbilical artery · Perinatal prognosis

Abstract
Objectives: To evaluate the prognosis of monochorionic twins with selective intrauterine growth restriction (sIUGR), classified according to the type of umbilical artery Doppler, under expectant management. ***Methods:*** The outcome of 81 cases with isolated sIUGR was evaluated according to a classification based on umbilical artery (UA) Doppler diastolic flow in the IUGR twin (I: present, II: constantly absent/reverse, III: intermittently absent/reverse). Selective feticide was not considered due to legal constraints. Perinatal outcomes included perinatal death and neurological outcome at 6 months of age. ***Results:*** From 81 cases with the diagnosis of sIUGR, twin-twin transfusion was diagnosed in 18 cases. This left 63 cases, of which 23 were classified as type I (36.5%), 27 as type II (42.9%) and 13 as type III (20.6%). Intrauterine death occurred in 4.3% (1), 29.6% (8) and 15.4% (2) among IUGR twins, and 4.3% (1), 22.2% (6) and 0.0% (0) among larger twins. Neonatal death occurred in 0.0% (0), 18.5% (5) and 0.0% (0) among IUGR twins, and 0.0% (0), 11.1% (3) and 23.0% (3) among larger twins. Neurological abnormalities at 6 months were found in 4.3% (1), 14.8% (4) and 23.1% (3) in smaller twins and 0.0% (0), 11.1% (3) and 38.5% (5) in larger twins, respectively. Intact survival at 6 months was recorded in 91% (21), 37% (10) and 61% (8) in smaller twins and 95% (22), 55% (15) and 38% (5) in larger twins, respectively. ***Conclusion:*** The outcome in monochorionic twins with sIUGR and abnormal umbilical artery Doppler is poor under expectant management. Normal Doppler seems to be associated with a good prognosis.

Introduction

The incidence of selective intrauterine growth restriction (sIUGR) is approximately 11–14% among monochorionic (MC) twins [1–3], and this condition has been shown to be associated with substantial perinatal risks for both fetuses [1, 3–7]. Uneven placental sharing is thought to be the principal cause of this condition, while the clinical process can depend to some degree on the combination of placental vascular anastomoses [3, 6–8]. Recently, a classification system according to the characteristics of

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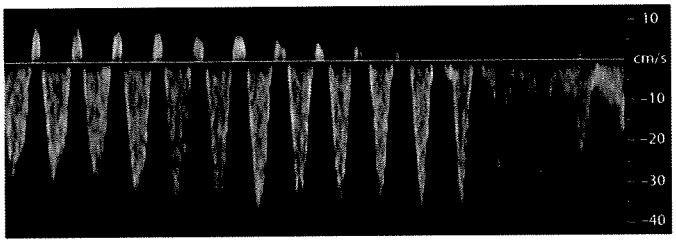

Fig. 1. Typical image of intermittent AREDF in the umbilical artery Doppler waveforms, with cycles intermittently showing AREDF.

diastolic Doppler flow in the umbilical artery (UA) of the smaller twin was advocated by Gratacos et al. [6] to differentiate cases into 3 different clinical forms: type I, normal UA Doppler; type II, persistent absent or reversed end-diastolic velocity flow (AREDF), or type III, intermittent AREDF (iAREDF). While outcomes for type I pregnancies are commonly favorable, IUGR twins in type II cases show in most cases fetal deterioration with a high associated risk of intrauterine fetal death (IUFD) [6]. MC twins with type III sIUGR are characterized by an atypical clinical evolution. About 15% of IUGR twins die unexpectedly and 20% of the larger fetuses show complications of neurological damage due to acute feto-fetal transfusion accidents via arterio-arterial anastomoses [6].

One limitation of previous studies on MC twins with sIUGR is that cord occlusion was performed, either electively [4] or because of fetal deterioration [6]. Therefore, it is unknown whether intervention may have biased the outcome of these clinical series.

In this study, we report the natural history of MC pregnancies complicated with sIUGR in a consecutive series of 81 cases managed expectantly. Perinatal outcome was compared among three study groups established according to the classification system based on the type of UA Doppler in the smaller twin.

Methods

A total of 81 MC twin pregnancies were diagnosed with sIUGR before gestational week 26 in three institutions in Japan from 2001 to 2008. Patients provided informed consent to have their data recorded for clinical studies, which were approved by the Institutional Review Boards at the respective institutions. The definition of sIUGR was an estimated fetal body weight below the 10th percentile in the smaller twin. Twin-twin transfusion syndrome (TTTS) was defined as the presence of ultrasound findings of polyhydramnios in one twin and oligohydramnios in the other, together with markedly discordant bladders, as previously defined [9]. Cases with TTTS or the diagnosis of a fetal malformation at the time of initial diagnosis were not included in this study. Cases with sIUGR were classified into 3 groups based on UA Doppler flow: type I, positive end-diastolic velocity in UA; type II, AREDF constantly observed, or type III, iAREDF defined as the clear observation of abnormal diastolic flow waveforms following an intermittent pattern within a short interval (fig. 1) [6]. Doppler waveforms were recorded using a minimum of three measurements at a free loop in each UA in the absence of fetal or maternal movement. Doppler sampling was performed using a 3.5- or 5-MHz curved array transducer with spatial peak temporal average intensities of <100 mW/cm^2. The angle of insonation was 0° or as close to 0° as possible. The pictures of Doppler exams were available and of good quality from all cases. The diagnosis was established by the characteristics of Doppler at enrolment, but a minimum of two consecutive examinations confirming the initial findings were required at each participating institution.

Fetal condition was monitored by ultrasonography, including fetal growth curves, amniotic pocket and UA Doppler, in combination with fetal heart rate (FHR) monitoring on non-stress test or fetal biophysical profile at these three centers or the referring hospitals. If a case was diagnosed with TTTS before gestational week 26 after the initial diagnosis of sIUGR, laser therapy was contemplated. Selective feticide by cord occlusion was not an option in our clinical setting, and therefore all cases not diagnosed as having TTTS during the observation period were managed expectantly. Indications and route of delivery were decided at the discretion of the attending physicians. Principally, delivery was considered by fetal indications, including fetal deterioration defined by abnormal FHR and/or abnormal biophysical profiling (BPP) score, and by estimated fetal growth arrest at least for 2 weeks after 32 weeks of gestation. Abnormal Doppler waveforms including reversed flow in ductus venosus and reversed flow in umbilical artery were used in some cases, but since the study period was long they were not used consistently for clinical decisions throughout the whole study period.

The occurrence of TTTS was recorded. Perinatal outcome, including the rate of intrauterine and neonatal death, and the rate of neurological morbidity at 6 months of age was recorded in all twins. All neonates were assessed by neonatologists and ultrasonographic brain scan was performed normally and investigation by MRI was indicated when ultrasonography revealed abnormal brain scans within the 6 months' observational period. Any significant abnormal findings on brain ultrasonography or MRI, including intraventricular hemorrhage (grade III or IV), cystic periventricular leukomalacia, blindness, deafness were regarded as neurological morbidity as defined before [9]. The absence of the above mentioned neurological morbidity at 6 months of age was defined as intact survival. Infants were not assessed by any developmental tests in this study.

Results

A total of 81 cases were recorded during the study period, comprising 26 cases of type I, 40 cases of type II and 15 cases of type III. The incidence of TTTS before gestational week 26 after an initial diagnosis of sIUGR was