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Fetal Survival Immediate after Fetoscopic Laser Ablation in Twin to Twin Transfusion Syndrome

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ABSTRACT

Background: The purpose of this study was to determine prognostic factors that can affect the fetal survival immediate after fetoscopic laser ablation.

Methods: The study population consisted of consecutive twin pregnant women who underwent fetoscopic laser ablation with the diagnosis of twin to twin transfusion syndrome (TTTS) from 2011 to 2018 in Seoul National University Hospital. Fetal survival immediate after procedure was defined as survival to 48 hours after procedure and neonatal survival was defined as survival to 28 days of life. Clinical characteristics and ultrasound findings were compared according to the fetal survival immediate after procedure.

Results: A total of 57 pregnant women with TTTS were included, and the overall fetal survival immediate after procedure was 71.1% (81/114) after fetoscopic laser ablation. Fetuses who survived immediate after procedure had higher gestational age at procedure and lower frequency of abnormal Doppler studies than those did not survive. However, the frequency of hydrops was not different between cases with fetal survival and those with fetal death. The earlier gestational age at procedure and the presence of abnormal Doppler studies were significant risk factors for fetal death even after adjustment.

Conclusion: Based on this data, the fetal survival immediate after procedure (fetoscopic laser treatment) in TTTS can be affected by the gestational age at procedure and the presence of abnormal Doppler studies.

Keywords: Twin to Twin Transfusion Syndrome; Fetoscopic Laser Ablation; Donor Twin; Recipient Twin

INTRODUCTION

Twin to twin transfusion syndrome (TTTS) is a complication in approximately 5%–15% of monochorionic twin pregnancies, with 90% of perinatal mortality if untreated.^{1,2} Because of high mortality, several treatments such as amnioreduction, selective feticide, and fetoscopic laser ablation have been suggested, and among these treatment modalities fetoscopic laser ablation is the only method reversing the pathophysiologic problem in TTTS. Indeed, fetoscopic laser ablation is now considered as the first choice of treatment in TTTS with stage 2–4 before 26 weeks, because fetoscopic laser ablation showed better outcome.³

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Kweon SY, Lee SM, Jun JK. Data curation: Kweon SY, Lee SM, Jun JK. Formal analysis: Kweon SY, Lee SM. Funding acquisition: Lee SM, Jun JK. Investigation: Kweon SY, Lee SM, Cho K, Park CW, Park JS, Jun JK. Methodology: Kweon SY, Lee SM, Jun JK. Project administration: Kweon SY, Lee SM, Jun JK. Resources: Kweon SY, Lee SM, Jun JK. Software: Kweon SY, Lee SM. Supervision: Kweon SY, Lee SM, Jun JK. Validation: Kweon SY, Lee SM, Jun JK. Visualization: Kweon SY, Lee SM, Jun JK. Writing - original draft: Kweon SY, Lee SM. Writing - review & editing: Kweon SY, Lee SM, Cho K, Park CW, Park JS, Jun JK.

The reported neonatal survival after fetoscopic laser ablation is 45%–70%, and several studies have issued the prognostic factors associated with neonatal survival.^{4,5} However, until now there is a paucity of information on the factors which are associated with fetal survival or death immediate after the fetoscopic laser ablation, although fetal death immediate after the procedure is one of the major complications we should consider on the decision of the procedure.

The aim of this study was to determine prognostic factors that can affect the fetal survival immediate after fetoscopic laser ablation in TTTS.

METHODS**Study population**

In this retrospective study, twin pregnant women who underwent fetoscopic laser ablation for TTTS in Seoul National University Hospital from July 2011 to June 2018 were included. Cases in-utero fetal demise before the procedure were excluded. Fetal survival immediate after procedure was defined as survival to 48 hours after procedure. Clinical characteristics and ultrasound findings were compared according to the fetal survival or death immediate after procedure.

Ultrasound findings

In monochorionic twin, TTTS was diagnosed as the presence of polyhydramnios in one twin and oligohydramnios in the other twin, and cases were categorized according to the Quintero staging system.⁶ Abnormal Doppler finding was defined as 1) absence of end-diastolic flow or the presence of reversed flow in umbilical artery Doppler or 2) the presence of pulsatile flow in umbilical venous Doppler or 3) the absence of end-diastolic flow or the presence of reversed flow in ductus venosus. Hydrops was defined as fluid accumulation in at least two of the body compartments (subcutaneous edema, pleural effusion, pericardial effusion, or ascites).

Fetoscopic laser ablation

After counseling on the benefit and risk of the fetoscopic laser ablation, written informed consent was obtained from all patients. Under ultrasonographic guidance, a 1.3 mm trocar was inserted into the amniotic sac through the small skin incision. The 8 Fr. curved sheath (11540KB Operating Sheath, curved; Karl Storz SE, Tuttlingen, Germany) or 8 Fr. straight sheath (11540KA Operating Sheath, straight; Karl Storz SE) was introduced according to the location of the placenta. The 11540AA Miniature Straight-Forward Telescope, semirigid, (1.3 mm out diameter, 0° angle of view) was used. After systemic fetoscopic evaluation along the placental vascular equator, selective coagulation of anastomosing vessels was performed. At the end of the procedure, amnioreduction in recipient fetus was done until the recipient amniotic fluid volume became adequate before withdrawing the trocar. After the procedure tocolytics was administered at the discretion of the attending physician.

Statistical analysis

The continuous variables are described as means with standard deviations and were compared with Mann-Whitney U test. Categorical variables were analyzed with Fisher's exact test. Logistic regression was conducted for multivariate analysis. Receiver operating characteristic (ROC) curves for the prediction of fetal death immediate after the procedure were generated for gestational age at procedure, and used to determine the best cutoff values for gestational age at procedure. A *P* value of < 0.05 was considered statistically significant. SPSS version 21.0 software (SPSS Inc, Chicago, IL, USA) was utilized.

Ethics statement

We follow the ethical standards for human experimentation established in the Declaration of Helsinki. This study protocol was reviewed and approved by The Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. 1311-045-533). The informed consent was waived by the board because of its retrospective nature.

RESULTS

A total of 46 twin pregnant women with TTTS were underwent the fetoscopic laser ablation during the study period. **Table 1** shows the outcome of fetoscopic laser ablation. The mean gestational age at procedure was 20.46 weeks, and the overall fetal survival immediate after fetoscopic laser ablation (< 48 hours) was 67.4%: dual fetal survival rate was 47.8% and at least one fetus survival rate is 87.0%. The mean gestation age at delivery was 29.63 weeks, and the overall neonatal survival rate to 28 days of life after delivery was 57.5%. The neonatal survival of least one infant was achieved in 72.5% and dual survival was noted as 42.5%.

Table 2 compares the clinical characteristics and ultrasound findings according to the fetal survival or death immediate after the procedure. Fetuses who survived immediate after procedure had higher gestational age at procedure and lower frequency of abnormal Doppler studies than those did not survive. Cutoff value of gestational age for prediction of fetal death was derived from the ROC curves (area under the ROC curve 0.663; 95% confidence interval [CI], 0.562–0.765), and the gestational age at procedure \leq 21.6 weeks was significantly associated with the risk of fetal death. However, the frequency of hydrops was not different between cases with fetal survival and fetal death. Cases with fetal survival had lower frequency of advanced stage (Quintero stage III or IV) than cases with fetal death, but this difference did not reach statistical significance.

In multivariate analysis, the risk of fetal death immediate after procedure increased with abnormal Doppler findings (odds ratio [OR], 2.838; 95% CI, 1.137–7.085; $P = 0.025$) and lower gestational age at procedure (\leq 21.6 weeks; OR, 8.185; 95% CI, 1.789–37.451; $P = 0.007$) (**Table 3**).

Table 1. Outcomes of 57 cases of TTTS after fetoscopic laser ablation

Outcomes	Value
GA at procedure, wk	20.52 \pm 2.42
GA at delivery, wk	29.29 \pm 6.49
Interval from procedure to delivery, day	46.53 \pm 48.91
Fetal outcome immediate after procedure (within 48 hr)	
Pregnancies with at least one survival	50/57 (87.7)
Pregnancies with two survivals	31/57 (54.4)
Pregnancies with one survival only	19/57 (33.3)
Pregnancies with no survival	7/57 (12.3)
Overall fetal survival immediate after the procedure (114 fetuses)	81/114 (71.1)
Neonatal outcome (28 days after birth) ^a	
Pregnancies with at least one survival	32/47 (68.1)
Pregnancies with two survivals	20/47 (42.6)
Pregnancies with one survival only	12/47 (25.5)
Pregnancies with no survival	15/47 (57.4)
Overall neonatal survival after delivery (96 fetuses) ^b	52/96 (54.2)
Neonatal outcome (excluding FDIU after procedure)	
Overall neonatal survival after delivery (81 fetuses)	52/81 (64.2)

Data are presented as mean \pm standard deviation or number (%).

TTTS = twin-twin transfusion syndrome, GA = gestational age, FDIU = fetal death in utero.

^aAmong 10 cases, 5 cases are excluded due to follow-up loss, 5 cases are excluded due to on-going pregnancy;

^bData for both fetuses are included in 47 cases, data for only one fetus are included in 2 cases.

Table 2. Clinical characteristics according to the fetal survival immediate after procedure (within 48 hours after operation)

Characteristics	Fetal survival (n = 81)	Fetal death (n = 33)	P value
Maternal age, yr	32.1 ± 3.8	31.1 ± 3.8	0.289
Nulliparity	46 (56.8)	22 (66.7)	0.402
GA at procedure, wk	20.9 ± 2.6	19.5 ± 1.7	0.006
GA at procedure ≤ 21.6 wk	53 (65.4)	31 (93.9)	0.002
Interval from procedure to delivery	49.6 ± 48.2	39.0 ± 50.5	0.723
Stage at procedure			0.466
I	9 (11.1)	3 (9.1)	
II	18 (22.2)	4 (12.1)	
III	39 (48.1)	21 (63.6)	
IV	15 (18.5)	5 (15.2)	
V	0 (0)	0 (0)	
Advanced stage (III or IV)	54 (66.7)	26 (78.8)	0.261
Presence of abnormal Doppler	18 (22.2)	15 (45.5)	0.022
Presence of abnormal UAD	17 (21.0)	14 (42.4)	0.035
Presence of abnormal DV Doppler	3 (3.7)	7 (21.2)	0.006
Hydrops	7 (8.6)	2 (6.1)	1.000
Recipient twin	43 (53.1)	14 (42.4)	0.409
Location of placenta (anterior)	34 (42.0)	16 (48.5)	0.540

Data are presented as mean ± standard deviation or number (%).

GA = gestational age, UAD = umbilical artery Doppler, DV = ductus venosus.

Table 3. Logistic regression for fetal death immediate after procedure

Characteristics	OR	95% CI	P value
GA at operation ≤ 21.6 wk	8.185	1.789–37.451	0.007
Abnormal Doppler	2.838	1.137–7.085	0.025
Hydrops	0.754	0.136–4.193	0.747

OR = odds ratio, CI = confidence interval, GA = gestational age.

Out of 33 fetuses with abnormal Doppler findings, 4 fetuses were recipient twins and 29 fetuses were donor twins. The survival rate of these fetuses was similar (55.2% in donor twin [16/29]; 50% in recipient twin [2/4]; $P = 1.000$).

Table 4 compares clinical characteristics and ultrasound findings between cases with at least one fetal survival and cases with double fetal death (per pregnancy). Cases with double fetal death had earlier gestational age at procedure and higher frequency of abnormal Doppler in

Table 4. Clinical characteristics per pregnancy according to the fetal survival immediate after procedure (within 48 hours after operation)

Characteristics	At least one fetal survival (n = 50)	Double fetal death (n = 7)	P value
Maternal age, yr	32.1 ± 3.8	30.1 ± 3.1	0.265
Nulliparity	29 (58.0)	5 (71.4)	0.689
GA at procedure	20.7 ± 2.5	19.1 ± 1.6	0.069
Interval from procedure to delivery	51.8 ± 49.9	8.6 ± 17.1	0.158
Stage at procedure			0.526
I	5 (10.0)	1 (14.3)	
II	11 (22.0)	0 (0.0)	
III	25 (50.0)	5 (71.4)	
IV	9 (18.0)	1 (14.3)	
V	0 (0)	0 (0)	
Advanced stage (III or IV)	34 (68.0)	6 (85.7)	0.662
Presence of abnormal Doppler in at least one fetus	27 (54.0)	6 (85.7)	0.220
Location of placenta (anterior)	22 (44.0)	3 (42.9)	1.000

Data are presented as mean ± standard deviation or number (%).

GA = gestational age.

Table 5. Complications after the procedure

Complications	No. (%)
Intraoperative bleeding at placental surface	10.5 (6/57)
Cerclage after procedure	8.8 (5/57)
Preterm labor with cervical change	15.8 (9/57)
Preterm uterine contraction	36.8 (21/57)
PPROM	17.5 (10/57)
Immediate PPRM	5.3 (3/57)
Remote PPRM	12.3 (7/57)
Iatrogenic monoamnioticity	3.5 (2/57)

PPROM = preterm premature rupture of membranes.

at least one fetus. However, these differences did not reach statistical significance, probably because of small number of cases.

Table 5 showed complications associated with fetoscopy laser ablation. Most significant complications were intraoperative bleeding which prevents further treatment and endanger the fetuses and immediate preterm premature rupture of membranes (PPROM) which is an important cause of preterm delivery and affects fetal survival.

DISCUSSION

The principal findings of the current study are: 1) after fetoscopic laser ablation, the overall fetal survival immediate after procedure was 67.4% (62/92) and overall neonatal survival rate to 28 days of life after delivery was 57.5%; 2) fetuses who survived immediate after procedure had higher gestational age at procedure and lower frequency of abnormal Doppler studies than those did not survive; 3) the frequency of hydrops was not different between cases with fetal survival and those with fetal death.

In the literature, this study is the first study from Korea regarding TTTS cases treated with fetoscopic laser ablation. The fetal survival rate immediate after the procedure (at least 1 survival rate of 87%) and neonatal survival rate (at least one survival rate of 73%) are comparable to other studies in several other countries (75%–88% of at least one fetal survival and 58%–86% of at least one neonatal survival) (**Table 6**).^{5,7-19}

According to previous reports, neonatal survival after fetoscopic laser ablation can be affected by several factors including the presence of abnormal Doppler finding or hydrops, presence of associated abnormalities, the technical skill of operator, and location of placenta,^{5,17,18,20-22} and these prognostic factors might be used when counseling the result of fetoscopic laser ablation. However, there are several factors considered in the interpretation of these results. First, the neonatal death may not be attributed to fetoscopic laser ablation alone, because many factors such as fetal growth restriction, preterm labor or PPRM, and even postoperative complications such as recurrent TTTS or twin anemia polycythemia sequence. Second, identification of high risk patients for fetal death immediate after fetoscopic laser ablation is another clinically important issue, because these patients may be candidates for other treatment modalities for TTTS. However, to our knowledge, there is a paucity of information on the prognostic factors which are associated with intra-uterine fetal death immediate after the fetoscopic laser ablation, although this is another essential point in clinical practice. Although the result of this study does not provide new guidelines for determining the procedure, the prognostic factors affecting the

Table 6. Comparison of fetal survival outcomes after fetoscopic laser ablation in a single center

Variables	Total No.	Immediate post-procedure (within 48 hr after procedure)			Survival after birth (within 28 days after birth)		
		Total survival	Dual survival	At least 1 survivor	Total survival	Dual survival	At least 1 survivor
Cincotta et al. ⁷	100	-	-	-	-	66	85
Morris et al. ⁸	164	-	-	-	-	38	85
Yang et al. ⁹	30	-	-	-	-	60	83
Rustico et al. ¹⁰	150	-	-	-	-	41	74
Chang et al. ⁵	44	-	-	-	-	50	80
Ek et al. ¹¹	66	-	-	-	-	48 ^a	76 ^a
Halvorsen et al. ¹²	142	80	-	-	47 ^b	-	-
Stirnemann et al. ¹³	507	-	-	-	-	46	78
Teoh et al. ¹⁴	49	-	-	-	-	51	86
Baschat et al. ¹⁵	147	-	60	88	-	-	-
Peeters et al. ¹⁶	340	-	-	-	77	59	86
Has et al. ¹⁷	85	-	-	-	-	26	58
Müllers et al. ¹⁸	105	-	47	75	-	-	-
Diehl et al. ¹⁹	1,019	-	-	-	-	63	87
This research, 2017	57	69	53	87	57	48	70

Data are presented as number (%).

^aLiveborn; ^bAlive at 1 month.

survival rate immediately after procedure can be used in patient counseling regarding the prognosis after procedure.

Among clinical factors related to neonatal survival rate (such as gestational age, Quintero stage, Doppler abnormalities, associated fetal anomalies, ultrasonographic abnormalities, experience of the practitioner, and placental location), only gestational age and abnormal Doppler finding were related to fetal survival immediate after procedure. Why are these determining factors for fetal death immediate after the procedure? Early gestational age at operation usually means early onset TTTS, which might be associated with larger volume of inter-twin communication, and the abrupt interruption of that communication may result in adjustment failure after the procedure. The presence of abnormal Doppler studies means cardiovascular burden to fetuses, which can result in the poor prognosis of fetal outcomes. However, the presence of hydrops was not associated with the risk of fetal death after the procedure. Hydrops was usually present in recipient twin, but recipient itself was associated with better survival than donor twin.^{17,23}

In conclusion, the fetal survival immediate after procedure in TTTS can be affected by the gestational age at procedure and the presence of abnormal Doppler studies.

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