

Fetoscopic laser photocoagulation for twin–twin transfusion syndrome

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Abstract

The aim of this study was to review fetoscopic laser photocoagulation (FLP), which ablates placental vascular anastomoses to treat twin–twin transfusion syndrome (TTTS). A review of studies reporting on the procedures, outcomes, complications and nonconventional applications of FLP for TTTS was conducted. FLP has been established as the primary treatment for monochorionic twin pregnancy associated with TTTS at 16–26 weeks. FLP is the only therapy that directly addresses the underlying pathophysiology. The recent technique modification of FLP, referred to as the ‘Solomon technique’, induces selective coagulation to connect the anastomoses ablation sites and has been introduced to reduce residual anastomoses. The perinatal survival following FLP improved significantly with advances in the technique after its introduction. The recent survival rates of both twins and at least one twin are 70% and more than 90%, respectively. However, there is still an 11–14% risk of long-term neurodevelopment impairment. The premature rupture of membranes that leads to preterm labor is a common complication after FLP. FLP is a valuable treatment option for fetofetal transfusion syndrome in triplets and for TTTS after 26 weeks. FLP for selective intrauterine growth restriction may be potentially beneficial when accompanied by abnormal Doppler findings and oligohydramnios. FLP is the optimal treatment option for TTTS at 16–26 weeks of gestation. FLP appears to be applicable in triplets, TTTS after 26 weeks and cases of selective intrauterine growth restriction with abnormal Doppler findings and oligohydramnios. FLP is the most common and successful fetal intervention. Improvement in the neurodevelopmental outcomes after FLP is a future focus.

Key words: fetal therapies, fetofetal transfusion, fetoscope, laser therapy, twins.

Introduction

Twin–twin transfusion syndrome (TTTS), which affects 10% of monochorionic (MC) twin pregnancies, results in high perinatal morbidity and mortality.^{1,2} MC twins share the same placenta, and vascular anastomoses allow blood to flow between the two fetuses. The etiology of TTTS is thought to be a hemodynamic and probably hormonal discordance secondary to a chronic blood flow imbalance between twins through placental vascular anastomoses.^{3,4} Fetoscopic laser

photocoagulation (FLP), which occludes placental vascular anastomoses, is thought to be useful for treating TTTS by directly coping with the underlying pathophysiology. The original technique of FLP was first described by De Lia *et al.* with laparotomy⁵ and developed by Ville *et al.* as a minimally invasive, percutaneous approach to be performed under ultrasound guidance.^{6,7} Retrospective studies have noted that FLP resulted in high survival rates and low rates of neurological complications.^{7–9} The prospective randomized trial by the Eurofoetus group demonstrated

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that FLP is a superior and more effective first-line treatment than serial amnioreduction.¹⁰ A meta-analysis also showed that FLP is associated with better outcomes than serial amnioreduction.¹¹ FLP is widely accepted and routinely offered for TTTS to improve the survival rate and neurological outcomes in fetal treatment centers across the world.

The purpose of this review was to update the knowledge regarding FLP relating to our clinical practice. We reviewed the procedures, outcomes and complications of FLP for TTTS and outlined the nonconventional applications of FLP and the status of FLP in Japan.

Staging of TTTS

TTTS is diagnosed on cases of MC twin pregnancy complicated by polyhydramnios with a maximum vertical pocket (MVP) ≥ 8.0 cm (with a distended bladder) in the recipient and oligohydramnios with an MVP ≤ 2.0 cm (with a nondistended bladder) in the donor. The Quintero staging system based on ultrasound findings (bladder invisibility, Doppler findings, hydrops and demise of the fetus) is simple and remains the most commonly used classification for TTTS.¹² Murakoshi *et al.* subclassified Quintero stage 3 into classical and atypical cases based on the visibility of the donor bladder.¹³ Stage 3 atypical cases that show abnormal Doppler findings with a visible bladder have a significantly higher incidence of arterioarterial anastomoses and intrauterine fetal demise than classical cases. However, although the Quintero staging system is useful for describing the severity of the disease, it does not reflect the progression of the disease. Chronic blood flow imbalance via vascular anastomoses is understood to cause a fetal cardiovascular loading condition.¹⁴ Fetal echocardiographic changes are used to modify the staging system. The Children's Hospital of Philadelphia cardiovascular score and Cincinnati staging system have been proposed.^{15,16} However, these scores have not proven to be significantly useful in clinical settings.

FLP procedure

The procedure is illustrated in Figure 1. FLP uses intrauterine fetoscopy with a laser fiber. Under adequate anesthesia (regional or local), a small skin incision is performed. A 3.8-mm cannula is percutaneously inserted into the recipient sac under ultrasound guidance either directly using reusable trocars with pyramidal tips (Karl Storz) or by the 'Seldinger' technique for vascular access. The site of entry on the maternal abdomen is crucial when performing the procedure. Although optimal positioning is

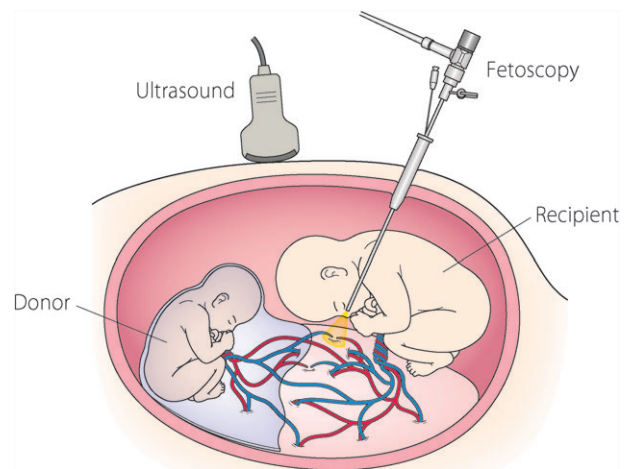


Figure 1 A schematic representation of fetoscopic laser photocoagulation for twin-twin transfusion syndrome. A fetoscope is percutaneously inserted into the recipient sac through a cannula.

sometimes limited by the location of placenta, a site not covered by the placenta that maximizes the chance of visualizing the vascular equator of the placenta should be chosen whenever possible. The virtual vascular equator of the placenta can be envisioned based on the two cord insertion sites and the body axis of the donor.¹⁷

Most operators use a 2-mm fetoscope with a 3-mm sheath (Karl Storz). Some operators use a 3.5-mm diagnostic and a 3-mm operating fetoscope (Richard Wolf). A 1.3-mm fetoscope is also used for cases younger than 20 weeks of gestation. A rigid fetoscope with a straight sheath is used for a posterior placenta, and a semi-rigid fetoscope with a curved sheath is used for an anterior placenta. A 600- μ m laser fiber is passed through the operative channel of the sheath of the fetoscope, and a neodymium: yttrium-aluminum-garnet (Nd:YAG) laser or diode (semi-conductor) laser is used. Although a diode laser is cheaper, an Nd:YAG laser is more commonly used.

All communicating vessels between the twins on the chorionic plate of the placenta (including arteriovenous [AV], arterioarterial [AA] and venovenous [VV] anastomoses) are coagulated using an output of 20–60 watts with a nontouch technique. The goal of surgery is to ablate all intertwin anastomoses.

Coagulation methods

Advances in the coagulation methods have been made. Initially, all vessels crossing the dividing membrane

were coagulated (nonselective coagulation).⁶ While this method interrupts vascular anastomoses between the twins, many vessels that are not involved in anastomoses are also coagulated. Unnecessarily coagulated vessels result in a reduced vascular territory, which leads to a higher risk of fetal death. To overcome this problem, only communicating vessels between the twins are coagulated (selective coagulation), a process that was first described by Quintero *et al.*¹⁸ These authors reported a sequential selective coagulation technique, in which the order of coagulation was determined by the type of anastomoses in order to reduce donor hypotension.¹⁹ A modified sequential selective coagulation technique was proposed by Nakata *et al.*, involving the reversal of the order of coagulation of AA or VV anastomoses in the sequential coagulation.²⁰ Coagulation of AV anastomoses follows that of AA and VV anastomoses. The ideal order of coagulation is still being debated. For selective coagulation, all vascular anastomoses must be identified. However, it is sometimes difficult to observe all of the vascular equator, in which communicating vessels are found, due to its location under the donor body. Thus, most procedures are performed as a combination of selective and nonselective coagulation.¹⁷

The recent modification of coagulation referred to as the 'Solomon technique' that coagulates the entire vascular equator has been reported.^{21–23} This technique was developed to reduce residual anastomoses that cause recurrence of TTTS or twin anemia-polycythemia sequence (TAPS).²⁴ It was shown that the 'Solomon technique' was associated with a reduction in TAPS (3% vs 16% for the standard treatment) and recurrence of TTTS (1% vs 7%) by an open-label randomized controlled trial.²⁵ The 'Solomon technique' involves initially completing coagulation of all visible anastomoses and then performing coagulation to connect the anastomoses' ablation sites from one edge of the placenta to the other (Fig. 2). This method enables MC placenta to be dichorionized by coagulating placental vessels and the surface of placenta. Although the occurrence of TAPS following FLP using selective coagulation was found to be low in our study (2.6%),²⁶ we expect it to be further reduced using the 'Solomon technique'.

Survival outcomes

We reported our initial 181 consecutive cases of TTTS subjected to FLP at four centers in Japan between 2002 and 2006.²⁷ The mean gestational ages at FLP and delivery were 21.2 and 32.9 weeks, respectively.

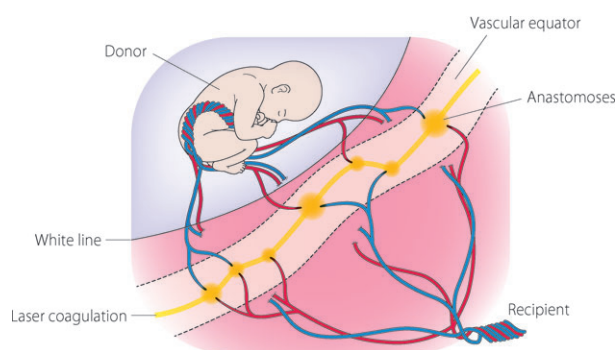


Figure 2 A schematic representation of the 'Solomon technique'. Initially, all visible anastomoses are coagulated, and then coagulation is performed to connect the anastomoses' ablation sites from one edge of the placenta to the other.

The survivals of both twins and at least one twin at 6 months of age were 61.9% and 90.1%, respectively, and those in 148 cases between 2003 and 2009 at our center were 71.6% and 93.2%, respectively.²⁸ A systematic review reported that the perinatal survival following FLP improved significantly with the evolution of the coagulation technique such as selective coagulation and the 'Solomon technique' and with a learning curve effect after the introduction of FLP in 1990.²⁹ The mean survival of both twins increased from 35% to 65% and that for at least one twin from 70% to 88% over the past 25 years in a total of 34 studies including 3868 cases. The mean gestational age at delivery remained stable over the years at 32 weeks of gestation. The largest single-center experience for FLP in TTTS with 1020 cases was reported.³⁰ The survival of both twins increased from 50% in the first 200 cases to 69.5% in the latter 220 cases. The survival of at least one twin increased from 80.5% in the first 200 cases to 91.8% in the latter 220 cases. Thus, with the recent significant improvement of survival rates, survival rates of 70% for both twins and more than 90% for at least one twin can be expected after FLP.

Neurological outcomes

Despite an improved survival rate, TTTS treated with FLP is still associated with neurological abnormalities, including severe cerebral injury and neurodevelopmental impairments. Severe cerebral injury such as intraventricular hemorrhaging, cystic periventricular leukomalacia, porencephaly and ventriculomegaly can be detected by ultrasound and/or magnetic resonance imaging in the short-term follow-up. However, neurodevelopmental impairments, such as cerebral

palsy, severe development delay, blindness and deafness, require a long-term follow-up to be assessed. The incidence of severe cerebral injury in the recent cohort ranged from 2.9% to 6%.^{27,31,32} Two systematic reviews with pooled studies revealed the incidence of neurodevelopment impairment to be 11.1% (140/1255) and 13.3% (83/624).^{33,34} Gray *et al.* reported that the incidence of neurodevelopment impairment as assessed by the Griffiths scale at 2 years of age corrected for prematurity was 12.4% (14/113).³⁵ Klink *et al.* reported that the incidence of neurodevelopment impairment assessed by the Bayley scale at 2 years of age corrected for prematurity was 12.4% (38/307).³¹ A recent single-center study using the Ages and Stages Questionnaires showed that the incidence of neurodevelopment impairment between 2 and 5 years of age was 13.5% (17/126).³² Therefore, the risks of neurodevelopment impairment following FLP are assumed to range from 11% to 14%. The incidence of neurodevelopment impairment assessed by the Bayley scale at 2 years of age corrected for prematurity decreased from 18% (28/152; 2000–2005) to 6% (10/155; 2008–2010) over time.³¹ It is very important to confirm the improvements in the long-term neurodevelopment outcomes with advances in the technique for FLP.

Complications

Preterm premature rupture of membranes (pPROM), which leads to preterm labor, is a common complication after FLP.¹⁷ The incidence of pPROM within 7 and 28 days after FLP was 3.9–6% and 7.7–9%, respectively.^{10,27} Chorioamniotic membrane separation, an iatrogenic complication, occurs in approximately 20% of patients following FLP and is associated with pPROM before 28 weeks of gestation.^{28,36} No effective therapies to treat and prevent iatrogenic pPROM have yet been developed.

Maternal complications have also been reported in 10.7% of 150 FLP cases, with 6.0% classified as major and 4.7% as mild.³⁷ Major maternal complications included placental abruption, accounting for the majority, as well as amniotic fluid embolism and Mirror syndrome.³⁷ We experienced one case of placental abruption and two cases of Mirror syndrome in 181 FLP cases.²⁷ Mild maternal complications able to be managed conservatively included intraperitoneal amniotic fluid leakage and bleeding from the uterine wall. Attention for maternal complications should be paid in the management of pregnancy and labor of MC twins following FLP.

Conventional criteria

FLP is offered as the first-line treatment option for TTTS at 16–26 weeks of gestation, which is thought to be the conventional criterion (Table 1).^{10,11,27} There has been some debate recently about the use of FLP to manage TTTS stage 1. A number of TTTS stage 1 cases do not progress or even regress. It was suggested that conservative management of TTTS stage 1 was a reasonable option,³⁸ based on the overall survival rates of 86% in cases of conservative management, 77% after amnioreduction and 85% after FLP in a literature review. The outcome of FLP is key to its application for TTTS stage 1. A recent systematic review of the outcomes of stage 1 TTTS revealed that the survival rates of both twins and at least one twin with expectant management were 70% and 87%, respectively, while those after amnioreduction were 67% and 86%, respectively, and those after FLP 54% and 81%, respectively.³⁹ However, considering recent significant improvements in the survival rates of FLP, a 70% survival rate for both twins and more than 90% survival rate for at least one twin can be expected for all stages of TTTS treated by FLP. These favorable rates therefore make the conservative management of stage 1 TTTS less attractive as a therapeutic option.

The North American Fetal Therapy Network has shown interesting and important results.⁴⁰ Stage 1 TTTS was associated with considerable fetal mortality. Although spontaneous recovery from TTTS was observed in some cases, TTTS progressed in the majority of expectantly managed cases, leading to a worse prognosis. Both amnioreduction and FLP decreased the risk of no survivors, and FLP was able to substantially prevent a poor outcome. FLP is the only therapy that directly halts the pathologic process. Therefore, it is reasonable to use FLP for stage 1 TTTS unless a randomized clinical trial reveals marked disadvantages associated with FLP.

Triples

Triplet gestations, including dichorionic triamniotic (DT) triplets and monochorionic triamniotic (MT) triplets, are associated with high risks for fetofetal transfusion syndrome (FFTS), which leads to perinatal death and neurological impairments.⁴¹ FFTS in triplets corresponds to TTTS in twins. FLP is thought to be useful for treating FFTS in triplets. Several case series on triplet gestations treated by FLP have been described.^{42,43} Sepulveda *et al.* reported 10 cases (seven of DT and three of MT) in which the overall perinatal

Table 1 Our criteria for performing fetoscopic laser photocoagulation

Conventional criteria	
Twin–twin transfusion syndrome at 16–26 weeks	
	<ul style="list-style-type: none"> • Monochorionic twin pregnancy • Oligohydramnios with an MVP \leq 2.0 cm in the donor • Polyhydramnios with an MVP \geq 8.0 cm in the recipient • Gestational age between 16 + 0 and 25 + 6 weeks of gestation
Nonconventional criteria	
Triplets	
	<ul style="list-style-type: none"> • Dichorionic triamniotic triplets or monochorionic triamniotic triplets • Feto-fetal transfusion syndrome (MVP \leq 2.0 cm in the donor and \geq 8.0 cm in the recipient) • Gestational age between 16 + 0 and 25 + 6 weeks of gestation
Twin–twin transfusion syndrome after 26 weeks	
	<ul style="list-style-type: none"> • Monochorionic twin pregnancy • Oligohydramnios with an MVP \leq 2.0 cm in the donor • Polyhydramnios with an MVP \geq 10.0 cm in the recipient • Gestational age between 26 + 0 and 27 + 6 weeks of gestation
Selective intrauterine growth restriction with oligohydramnios	
	<ul style="list-style-type: none"> • Monochorionic twin pregnancy • Estimated fetal weight \leq -1.5 SD or intertwin estimated fetal weight discordance \geq 25% • Absent or reverse end-diastolic velocity in the umbilical artery in the smaller twin • Oligohydramnios with an MVP \leq 2.0 cm in the smaller twin • Gestational age between 16 + 0 and 25 + 6 weeks of gestation

MVP, maximum vertical pocket; SD, standard deviation.

survival in DT was 66.7% while that in MT was 22.2%.⁴² We reported 16 cases (nine of DT and seven of MT).⁴³ The median gestational ages at surgery and at delivery were 21 and 31 weeks, respectively. The overall perinatal survival in DT was 74% while that of MT was 95%. All 16 cases resulted in at least one survival. FLP is a valuable treatment option for TTTS in both DT and MT triplets.

After 26 weeks of gestation

The gestational age for the treatment of TTTS was limited to 16–26 weeks in the first randomized trial for FLP.¹⁰ This gestational age limit for FLP has widely been adopted; however, cases of TTTS after 26 weeks can prove difficult to treat. The expected burdens associated with performing FLP after

26 weeks include the amniotic fluid potentially becoming more turbid, thereby hampering visualization of the placental anastomoses, and larger placental vessels potentially becoming more difficult to ablate. Valsky *et al.* compared the outcomes of 28 TTTS cases treated with FLP after 26 weeks with 324 cases treated between 16 and 26 weeks of gestation.⁴⁴ Baud *et al.* investigated the outcomes of 18 TTTS cases treated with FLP after 26 weeks with 283 cases treated between 17 and 26 weeks of gestation.⁴⁵ Both studies showed that FLP for TTTS after 26 weeks of gestation was associated with similar outcomes to cases treated before 26 weeks.^{44,45} We performed a small prospective study investigating all cases of TTTS with an MVP \geq 10.0 cm in the recipient at 26–28 weeks of gestation during 2012 and 2013.⁴⁶ Six cases were enrolled and underwent FLP. FLP was completely achieved in all six cases and resulted in the survival of both twins. FLP may still be a safe therapeutic option for TTTS after 26 weeks, especially at 26–28 weeks of gestation.

Amniotic fluid discordance and selective intrauterine growth restriction

With the increased awareness of TTTS, greater attention is now being paid to MC twin pregnancies complicated with amniotic fluid discordance (AFD) and/or selective intrauterine growth restriction (sIUGR). AFD is diagnosed based on the difference in the amniotic fluid volume of twins, which is thought to be due to discordance in the placental blood flow between the twins. sIUGR is diagnosed based on the difference in the fetal body weight of twins, which is thought to be due to discordance in the shared placental area. Although the concept of AFD differs from that of sIUGR, AFD can overlap with sIUGR. AFD with sIUGR and absent or reverse end-diastolic velocity (AREDV) in the umbilical artery (UA) in one fetus is associated with an extremely high risk for adverse pregnancy outcomes.⁴⁷ However, the clinical management of AFD or sIUGR without signs of TTTS is still controversial, and the application of FLP for AFD or sIUGR is challenging. We performed FLP on 11 cases of AFD bordering on TTTS with AREDV in the UA in one fetus, which represents a high-risk condition for adverse pregnancy outcomes.⁴⁸ The overall and both-twin survival rates were 63.6% and 27.7%, respectively. In our previous study, under expectant management, the overall and both-twin survival rates were 57.9% and 42.1%, respectively.⁴⁹ Our preliminary study shows that FLP does not seem to be a

Table 2 Milestones of fetoscopic laser photocoagulation worldwide and in Japan

Year	World	Japan
1990	De Lia; three cases via laparotomy ⁵	
1992		Natori; one case via laparotomy ⁵⁶
1995	Ville; 45 cases via the percutaneous approach ⁶	
1998	Ville; 132 cases ⁷	
	Quintero; selective coagulation ¹⁸	
1999	Quintero; TTTS staging ¹²	
2002		Start FLP program
2004	Senat; a randomized trial for FLP versus amnioreduction ¹⁰	
2010		Sago; 181 cases ²⁷
2012		Coverage by National Health Insurance
2014	Slaghekke; a randomized trial for Solomon technique ²⁵	

FLP, fetoscopic laser photocoagulation; TTTS, twin–twin transfusion syndrome.

promising treatment option for AFD bordering on TTTS.

Several reports have described the application of FLP for sIUGR with AREDV in the UA. The survival rates of IUGR twins following FLP were 45.5% (5/11), 25% (4/16) and 30.4% (7/23) in the relevant reports, while those of larger twins was 63.6% (7/11), 93.7% (15/16) and 73.9% (17/23), respectively.^{50–52} We showed the natural history and prognostic factors of sIUGR. Of 101 sIUGR twins, 70 (69.3%) IUGR twins and 82 (81.2%) larger twins survived.⁵³ Considering our survival rates of sIUGR twins treated with expectant management, the outcomes of FLP for sIUGR do not appear to be promising. We also showed that both AREDV in UA and severe oligohydramnios were important indicators for the mortality of sIUGR. In 101 sIUGR twins, 11 cases had both AREDV in UA and severe oligohydramnios, and only one IUGR twin (9%) with neurological abnormalities and four larger twins (36%) survived.⁵⁴ We performed FLP in 10 cases

of sIUGR with both AREDV in UA and severe oligohydramnios.⁵⁵ Three IUGR twins (30%) and 10 larger twins (100%) were alive without neurological abnormalities. Recently, we achieved similar results with more than 50 sIUGR cases (Ishii K *et al.*, 2017, unpublished data). FLP for sIUGR may be beneficial when accompanied by both AREDV in UA and severe oligohydramnios of IUGR twins. Oligohydramnios in the IUGR twin may be a key indicator to perform FLP for sIUGR. The FLP criteria for nonconventional applications, including triplets, TTTS after 26 weeks and sIUGR, are shown in Table 1.

Status in Japan

The milestones of FLP worldwide and in Japan are shown in Table 2. In Japan, 10 years after the first case was performed via laparotomy,⁵⁶ an FLP program was started in 2002 in Hamamatsu and several months later in our center. Several centers followed in the next several years. These centers formed the Japan Fetoscopy Group, which succeeded the Japan Fetal Therapy Group, a research group for the treatment of unborn patients in Japan.⁵⁷ Our findings resulted in FLP being recognized as the first-line treatment option for TTTS in Japan, with the cost of the FLP procedure being covered by Japan National Health Insurance from 2012. FLP is the first fetal treatment to be covered by Japan National Health Insurance, implying that fetuses are now recognized as patients by the government. The annual number of FLP procedures performed in Japan is shown in Figure 3. The numbers of procedures were collected from all institutions that performed FLP as members of the Japan Fetal Therapy Group.⁵⁷ Only five institutions performed FLP in 2005, with the number increasing to 10 in 2016. The number of FLP procedures has been increasing annually and exceeded 200 cases per year,

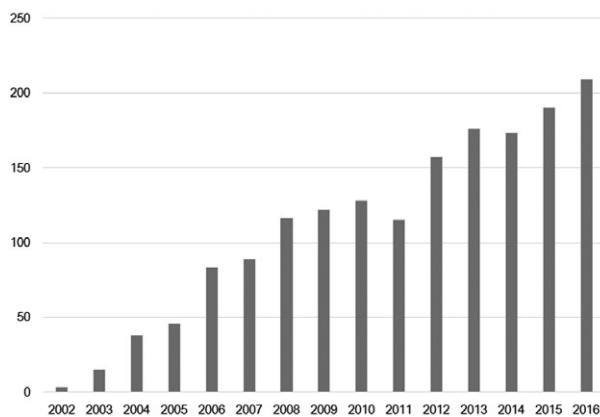


Figure 3 The number of fetoscopic laser photocoagulation procedures performed annually in Japan.

with the total reaching 1660 in 2016. The birth number in Japan in 2016 was about one million. Two cases of FLP per 10 000 births were performed in 2016.

Our center, the National Center for Child Health and Development, is the most active center for fetal diagnoses and fetal therapy in Japan. A total of 794 women received fetal treatment at our center in 2002–2016. FLP was used to treat 561 TTTS patients (70.1% of all fetal therapy cases). Thoracoamniotic shunting (TAS) was performed in 70 cases of severe fetal hydrothorax (8.8% of all fetal therapy cases). Radiofrequency ablation (RFA) was performed to discontinue the blood flow to an acardiac twin and to save the normal-pump twin in 51 cases of twin-reversed arterial perfusion sequence (6.4% of all fetal therapy cases). We conducted a safety and feasibility study of fetoscopic endoluminal tracheal occlusion in the treatment of severe congenital diaphragmatic hernia in 11 cases (1.4% of all fetal therapy cases). The survival rate of TAS in fetal hydrothorax with hydrops was around 63%.⁵⁸ The overall survival of the normal-pump twin following RFA was 85%.⁵⁹ FLP is the most commonly performed and successful fetal intervention at present.

Conclusion

More than 25 years have passed since the first attempt at FLP, and 15 years have passed since the introduction of the FLP program in Japan. Great progress has been made over time, with a number of advances made in techniques for FLP for the treatment of TTTS. FLP is the optimal treatment option for TTTS at 16–26 weeks of gestation. The outcomes following FLP have been dramatically improved, with survival rates of more than 90% for at least one twin and 70% for both twins. However, there is still an 11–14% risk of long-term neurodevelopment impairment. FLP may be a therapeutic option for FETS in triplets and TTTS after 26 weeks as well as for sIUGR associated with AREDV in UA and oligohydramnios. FLP is the most commonly performed and successful fetal intervention to date. Focus in the near future should be placed on improving the neurodevelopmental outcomes.

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Disclosure

None declared.

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