



Fetal therapies as standard prenatal care in Japan

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With recent advances in fetal medicine, various attempts have been made to save fetuses facing perinatal death or devastating consequences despite optimal management after birth. The concept of the fetus as a patient has been established through the application of *in utero* treatments. This paper reviews fetal therapies in order to highlight the role of perinatal medicine as standard prenatal care. Fetal therapies consist of medical therapy, percutaneous ultrasound-guided surgery, fetoscopic surgery, and open fetal surgery. In the 1980s, with advances in ultrasound imaging, percutaneous ultrasound-guided surgeries such as vesicoamniotic shunting for lower urinary tract obstruction and thoracoamniotic shunting (TAS) for fetal hydrothorax (FHT) were started. In the 1990s, fetoscopic laser surgery (FLS) for twin-twin transfusion syndrome (TTTS) was introduced, and later, a fetoscopic approach for congenital diaphragmatic hernia was also established. The revival of open fetal surgery, introduced in the 1980s by pediatric surgeons, began in the 2010s after a successful clinical study for myelomeningocele. Although many fetal therapies are still considered experimental, some have proven effective, such as FLS for TTTS, TAS for primary FHT, and radiofrequency ablation (RFA) for twin reversed arterial perfusion (TRAP) sequence. These three fetal therapies have been approved for coverage by Japan National Health Insurance as a result of clinical studies performed in Japan. FLS for TTTS, TAS for primary FHT, and RFA for TRAP sequence have become standard prenatal care approaches in Japan. These three minimally invasive fetal therapies will help improve the perinatal outcomes of fetuses with these disorders.

Keywords: Fetoscopy; Fetal therapy; Fetofetal transfusion; Radiofrequency therapy; Ultrasonography

Introduction

With recent advances in fetal medicine, the concept of the fetus as a patient has led to the application of treatments *in utero*. The aim of fetal therapy is to save fetuses who are facing perinatal death or devastating consequences despite optimal management after birth. The first fetal intrauterine blood transfusion, performed in the early 1960s, is thought to mark the beginning of fetal therapy [1]. The milestones of fetal surgical therapy are shown in Table 1. With advances in ultrasound imaging in the 1980s, fetal blood transfusion [2], vesicoamniotic shunting for lower urinary tract obstruction (LUTO) [3], and thoracoamniotic shunting (TAS) for hydrothorax [4] were performed with ultrasound guidance. Pediatric surgeons at the University of California at San Francisco (UCSF) introduced open fetal surgery for performing direct surgical procedures on fetuses with hysterotomy for LUTO [5], congenital pulmonary airway malformations (CPAM) [6], and congenital diaphragmatic hernia (CDH) [7]. In the 1990s, fetoscopic laser surgery (FLS) for twin-twin transfusion syn-

drome (TTTS) was first performed, showing great success [8-11]. Open fetal surgery for CDH was changed to a fetoscopic procedure and established as fetoscopic endoluminal tracheal occlusion (FETO) in the 2000s [12,13]. The revival of open fetal surgery began in the 2010s after a successful clinical study for myelomeningocele (MMC) [14].

After 50 years, a number of fetal therapies are now being

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performed as clinically useful treatments, although others are still considered experimental treatments. Most achievements in fetal therapy have been made in the US and Western Europe [15]. We in Japan have contributed a bit through the promotion of fetal therapy in prenatal care in our country. Indeed, our findings have led three fetal therapies—FLS for TTTS [16], TAS for hydrothorax, and radiofrequency ablation (RFA) for twin reversed arterial perfusion (TRAP) sequence—to be approved for coverage by Japan National Health Insurance (Table 2). This means that these three fetal therapies are recognized as standard prenatal care, and fetuses are recognized as patients by the administration.

We herein review the present state of fetal therapy to highlight its role in perinatal medicine as standard prenatal care.

Classification of fetal therapy

Fetal therapy consists of medical therapy and surgical therapy, including percutaneous ultrasound-guided surgery, fetoscopic surgery, and open fetal surgery [17]. Medical fetal therapy involves the administration of medicine to the mother, where it is then transported to the fetus via the placenta or amniotic fluid. Fetal pharmacotherapy is used to manage arrhythmias, especially tachyarrhythmias, congenital adrenal hyperplasia and thyroid disorders [17]. Percutaneous ultrasound-guided surgery involves the insertion of a needle or catheter via the mother's abdomen into the fetus under ultrasound guidance. Percutaneous surgery includes shunt therapy for LUTO or hydrothorax, RFA for TRAP sequence, and intracardiac catheter procedures for aortic or pulmonary

Table 1. Milestones of surgical fetal therapy

Percutaneous ultrasound-guided surgery	Fetoscopic surgery	Open fetal surgery
1981 Intrauterine blood transfusion		
1982 Vesico-amniotic shunting		1983 Nephrostomy
		1984 Resection of CPAM
1986 Thoraco-amniotic shunting		1989 CDH repair
	1990 FLS (laparotomy)	
1991 Balloon dilation (aortic valve)	1993 Cord ligation for TRAP sequence	
	1995 FLS (percutaneous)	1995 EXIT
	1997 FETENDO (CDH)	1997 MMC repair
	2000 FETO	
2002 RFA for TRAP sequence	2004 Eurofetus trial for FLP	
		2011 MOMS trial for MMC

CPAM, congenital pulmonary airway malformation; CDH, congenital diaphragmatic hernia; EXIT, *ex utero* intrapartum treatment; FETENDO, fetal endoscopic surgery; FETO, fetoscopic endoluminal tracheal occlusion; FLS, fetoscopic laser surgery; MMC, myelomeningocele; MOMS, management of myelomeningocele study; RFA, radiofrequency ablation; TRAP, twin reversed arterial perfusion.

Table 2. Fetal therapies covered by Japan National Health Insurance

Disorder	Treatment	Approval	References of our study
Twin-twin transfusion syndrome	Fetoscopic laser surgery	April 2012	Sago et al. [22]
Primary fetal hydrothorax	Thoraco-amniotic shunting	July 2012	Takahashi et al. [43]
Twin reversed arterial perfusion sequence	Radiofrequency ablation	March 2019	Sugibayashi et al. [56]
			Wagata et al. [57]

valvuloplasty for stenosis. Fetoscopic surgery involves placing an endoscope in the amniotic fluid space for treatments. FLS uses a laser to coagulate the placental vessels, and FETO places a detachable balloon in the trachea of the fetus. Open fetal surgery is surgery performed directly on the fetus by laparotomy and hysterotomy, after which the hysterotomy is closed to keep the fetus in the uterus. Of note, it is associated with extensive morbidities for both the mother and the fetus. Most cases of open fetal surgery are performed for MMC.

Assessment of fetal surgical therapy

To assess the effectiveness of therapy, good-quality evidence is required. However, clear evidence in the field of fetal therapy is limited because of the rarity of the targeted diseases and difficulties enrolling unborn patients. Only three randomized control trials (RCTs) have suggested any benefits of fetal treatments thus far [11,14,18]. Two of these RCTs were for FLS, while the other was for open fetal surgery for MMC. We assessed the effectiveness of select fetal surgical therapies by scoring them AA to C (AA: effective according to RCT, A: effective, B: expected, C: unknown) based on previous reports and our own experience (Table 3). The availability of fetal therapy in Japan is also presented.

Percutaneous intracardiac catheter procedures for critical aortic stenosis, fetoscopic laser for LUTO, or open fetal surgery for MMC have not yet been performed in Japan, although we are preparing to perform them in the near future. The costs of three fetal therapies (FLS for TTTS, TAS for hydrothorax, and RFA for TRAP sequence) are compensated by Japan National Health Insurance. FLS for TTTS is the most common fetal therapy performed, followed by TAS for hydrothorax and RFA for TRAP sequence. These three minimally invasive fetal therapies constitute 85% of all treatments for fetuses performed at our center [16].

Fetoscopic laser surgery

TTTS, which occurs in one-tenth of monochorionic (MC) twin pregnancies, has high perinatal morbidity and mortality [19]. TTTS is diagnosed in cases of MC twin pregnancy complicated by polyhydramnios with a maximum vertical pocket

(MVP) ≥ 8.0 cm (with an enlarged bladder) in the recipient and oligohydramnios with an MVP ≤ 2.0 cm (with a small bladder) in the donor [20]. TTTS is considered to be a hemodynamic and likely hormonal disorder derived from a chronic blood flow imbalance between twins by vascular anastomoses on the placenta [21].

FLS, which ablates placental vascular anastomoses, is an effective treatment option for TTTS. The original technique of FLP was first reported by De Lia et al. with laparotomy [8] and advanced by Ville et al. as a percutaneous procedure under ultrasound guidance [9,10]. The RCT by the Eurofoetus group showed that FLS is more useful than serial amnioreduction [11]. FLS is widely accepted and performed as a standard treatment for TTTS around the world [16].

We started the FLS program in Japan in 2002. We reported our initial 181 cases of TTTS treated by FLS at 4 centers [22].

Table 3. Assessments of select fetal surgical therapies and their availability in Japan

Therapy	Assessment	Availability
Percutaneous ultrasound guided surgery		
Intrauterine blood transfusion	A	Y
Shunt		
Lower urinary tract obstruction	B	Y
Hydrothorax	A	Y
Radiofrequency ablation		
Twin reversed arterial perfusion sequence	A	Y
Intracardiac catheter		
Critical aortic stenosis, critical pulmonary stenosis	C	Y
Fetoscopic surgery		
Fetoscopic laser surgery	AA	Y
Fetoscopic endoluminal tracheal occlusion	B	Y
Cystoscopic laser for lower urinary tract obstruction	C	N
Myelomeningocele repair	C	N
Open fetal surgery		
Myelomeningocele repair	AA	N
Congenital pulmonary airway malformation	C	N*

AA, effective by randomized control trial; A, effective; B, expected; C, unknown; N, no; Y, yes.

*Only one case underwent [58].

The mean gestational ages at FLS and delivery were around 21 and 33 weeks, respectively. The survival rates of both twins and at least 1 twin at 6 months of age were 62% and 90%, respectively. Our findings led to recognition of FLS as the first-line treatment option for TTTS, and the costs of this procedure have been compensated by Japan National Health Insurance since April 2012 [16]. FLS was the first fetal

therapy to be compensated by Japan National Health Insurance and is now established as a standard prenatal care procedure.

The procedure is illustrated in Fig. 1, and the details are described in our review [16]. A recent modified version of FLS, referred to as the ‘Solomon technique,’ adds ablation of the placenta to connect the anastomoses’ coagulation sites in order to diminish residual anastomoses [18]. The perinatal outcomes after FLS improved significantly with advances in the technique and learning [23]. The recent survivals of both twins and at least one twin have been reported to be 70% and >90%, respectively [16]. However, despite this ameliorated survival rate, TTTS treated by FLS is still associated with neurodevelopmental impairments, including severe cerebral palsy and neurodevelopment delay. There is still about a 10% risk of long-term neurodevelopment impairment after FLS [16]. Improvement in the neurodevelopmental outcomes of twins treated with FLP is a future point of focus.

FLS is offered as the standard treatment option for TTTS at 16-26 weeks’ gestation, which is considered to be the conventional indication [11,16]. Fetofetal transfusion syndrome (FFTS), which induces perinatal death and neurodevelopmental impairment, occurs in dichorionic triamniotic (DT) or monochorionic triamniotic (MT) triplets [24]. FFTS in triplets accords with TTTS in twins, so FLS is supposed to be a viable treatment option for FFTS in triplets. We and others

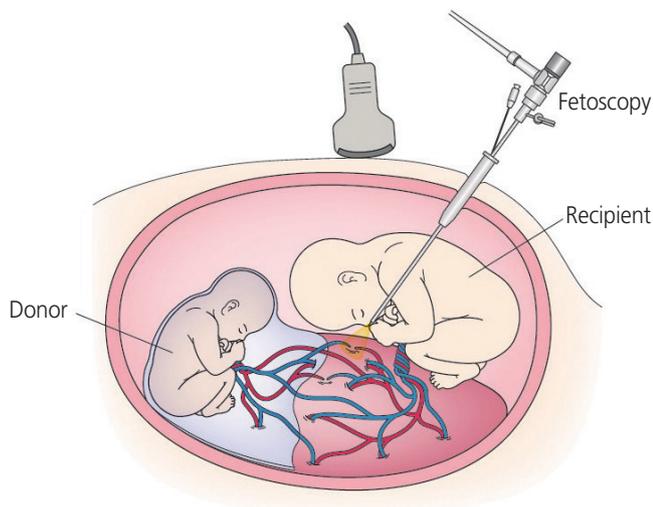


Fig. 1. A schematic representation of fetoscopic laser surgery for twin-twin transfusion syndrome. A fetoscope is percutaneously inserted into the recipient sac through a cannula. Placental vascular anastomoses between twins are ablated by a laser.

Table 4. Our criteria for performing fetoscopic laser surgery

Criteria	Description
Conventional criteria	0. Twin-twin transfusion syndrome at 16–26 weeks <ul style="list-style-type: none"> • Oligohydramnios with an MVP ≤ 2.0 cm in the donor • Polyhydramnios with an MVP ≥ 8.0 cm in the recipient • Gestational age between 16.0 and 25.6 weeks
Non-conventional criteria	1. Triplets <ul style="list-style-type: none"> • Dichorionic triamniotic triplets or monochorionic triamniotic triplets • Feto-fetal transfusion syndrome (MVP ≤ 2.0 cm in the donor and ≥ 8.0 cm in the recipient) • Gestational age between 16.0 and 25.6 weeks 2. Twin-twin transfusion syndrome after 26 weeks <ul style="list-style-type: none"> • Oligohydramnios with an MVP ≤ 2.0 cm in the donor • Polyhydramnios with an MVP ≥ 10.0 cm in the recipient • Gestational age between 26.0 and 27.6 weeks 3. Selective intrauterine growth restriction with oligohydramnios <ul style="list-style-type: none"> • Estimated fetal weight ≤ -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 ≤ 2.0 cm in the smaller twin • Gestational age between 16.0 and 25.6 weeks

MVP, maximum vertical pocket; SD, standard deviation.

have shown that FLS is a useful therapy for FFTS in both DT and MT triplets [25,26]. The optimum gestational age for the therapy of TTTS was set at 16–26 weeks in the Eurofoetus multicenter randomized trial for FLS [11]; however, cases of TTTS after 26 weeks tend to demonstrate a high rate of morbidities despite receiving optimal management after birth. The accumulated results suggest that FLS could be a safe treatment option for TTTS after 26 weeks, especially at 26–28 weeks of gestation [27-29].

With the enhanced awareness of TTTS, more attention is now being paid to selective intrauterine growth restriction (sIUGR), a complicated MC twin pregnancy. sIUGR is diagnosed according to the difference in the fetal body weight of twins. Several studies have shown the application of FLS for sIUGR with absent or reverse end-diastolic velocity (AREDV) in the umbilical artery (UA) [30-32]. FLS may be a promising treatment option for sIUGR when accompanied by both AREDV in UA and severe oligohydramnios of IUGR twins [33,34]. Oligohydramnios in the IUGR twin may be an essential indication for FLP for sIUGR. The FLS criteria for non-conventional applications, including the treatment of triplets, TTTS after 26 weeks, and sIUGR, are shown in Table 4 [16]. FLS is the most successful and commonly performed fetal therapy at present and is recognized as a standard prenatal care approach, despite FLS only being available at select fetal treatment centers.

Thoracoamniotic shunting

Fetal hydrothorax (FHT) is a form of pleural effusion seen in fetuses. Primary FHT, called isolated FHT, is chylothorax due to lymphatic leakage. Secondary FHT is pleural fluid accumulation associated with fetal diseases, including fetal anemia, viral infection, and structural and chromosomal abnormalities [35-37]. The prognosis of secondary FHT relies on the primary etiology. The incidence of primary FHT is approximately 1/15,000 [38]. Its natural history varies from spontaneous disappearance to the progressive aggregation of fluid and the occurrence of hydrops. Fetuses with primary FHT carry poor prognoses when they develop hydrops, which is thought to be a consequence of decreasing venous return to the heart affected by massive pleural effusion. TAS, which drains the pleural effusion, is a treatment option to improve the perinatal prognoses and has been reported to be associ-

ated with a better outcome in severe primary FHT than no fetal intervention [39-41].

A “double-basket catheter” (Hakko Co., Nagano, Japan) was invented in Japan in the 1990s [42] and has since been frequently used for TAS in Japan. The procedure is illustrated in Fig. 2. We performed a prospective one-arm trial of TAS for isolated FHT using this very thin double-basket catheter [43]. The median gestational age at the procedure and delivery was about 27 and 35 weeks, respectively. The overall survival rate was 79%, and the survival rate in the hydropic fetuses was 71%. Drainage of fetal pleural effusions with a double-basket catheter was shown to be safe and effective. Our results led to the approval of the “double-basket catheter” as a medical device, and the costs of TAS have been compensated by Japan National Health Insurance since July 2012. TAS was the second fetal therapy to be compensated by Japan National Health Insurance and is now established as a standard prenatal care approach.

We conducted a nationwide survey on fetuses with primary FHT delivered after 22 weeks’ gestation at January 2007 to December 2011 [44]. The survivals for primary FHT with and without hydrops were 58% and 98%, respectively. A lower gestational age at the diagnosis, severe hydrops and severe pleural effusion were predicting factors of poor prognoses. TAS was associated with a significant reduction in the risk

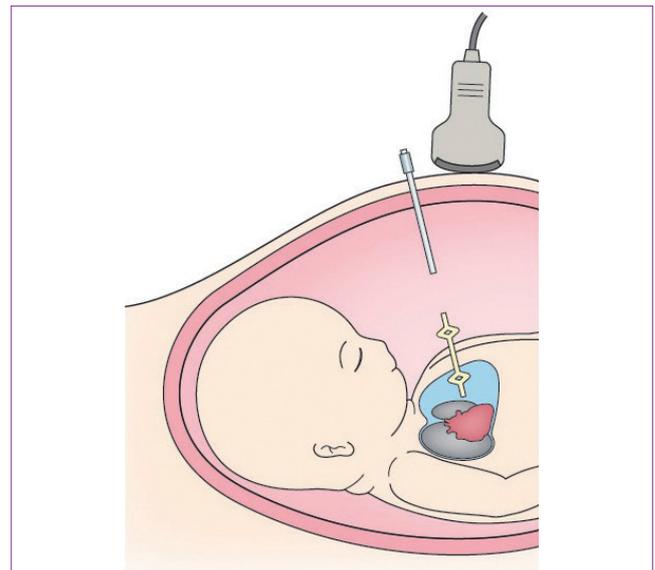


Fig. 2. A schematic representation of thoracoamniotic shunting for fetal hydrothorax. A double-basket catheter is placed in the chest to drain the pleural effusion into the amniotic fluid.

of death in hydropic cases. Down syndrome, or trisomy 21, is frequently associated with FHT. The prognosis of FHT with trisomy 21 is not very bad but is still poorer than that of primary FHT [45]. Fetal therapy is thought to provide no benefits for FHT with trisomy 21 [45].

Radiofrequency ablation

An acardiac twin is an uncommon complicated monozygotic twin pregnancy occurring in 1% of MC twins [46]. The acardiac twin's blood is circulated by the pump twin through arterioarterial and venovenous anastomoses on the placenta. The perinatal outcome is particularly poor in cases with continuing reversed arterial flow, called TRAP sequence, as the pump twin develops high-output cardiac failure, leading to fetal hydrops and/or intrauterine fetal death (IUFD) or preterm birth due to polyhydramnios [47]. Various fetal therapies for interrupting the perfusion of the acardiac twin have been undertaken. These procedures include extrafetal treatment, such as monopolar or bipolar cord coagulation [48,49], and intrafetal treatment, such as laser ablation [50] and RFA [51], which are minimally invasive techniques.

RFA induces coagulation of tissue by delivering high temperatures through a high-frequency alternating current. The first case of TRAP sequence treatment using RFA was shown by the University of California at San Francisco [52]. RFA uses a 17-gauge needle electrode guided by ultrasound. The procedure is illustrated in Fig. 3. RFA has a lower risk of premature preterm rupture of membranes than extrafetal methods [53,54]. Lee et al. [55] reported the North American Fetal Therapy Network registry data of RFA treatment for TRAP sequence and showed the 80% survival rate. Two studies of RFA for TRAP sequence were performed in Japan [56,57]. We reported the outcomes of 40 cases of TRAP sequence treated with RFA, which is the largest single-center study [56]. The overall survival rate was 85%, and the mean gestational age at delivery was 37 weeks for the pump twins. The other study also reported good outcomes of RFA treatment for TRAP sequence, with a survival rate of 88% [57]. Although reports of RFA treatment for TRAP sequence are limited, RFA is thought to be a useful treatment option for TRAP sequence after 15 weeks' gestation. Our results led to the approval of a medical device application for RFA, and the costs of RFA are now compensated by Japan National Health

Insurance as of March 2019. RFA for TRAP sequence is the third fetal therapy to be compensated by Japan National Health Insurance and is considered a standard prenatal care approach for TRAP sequence.

Conclusion

More than 50 years have passed since the first attempt to treat a fetus *in utero*. However, while various efforts have been made, many fetal therapies are still considered experimental. Nevertheless, some fetal therapies are now accepted as effective treatments options, including FLS for TTTS, TAS for primary FHT, and RFA for TRAP sequence. These 3 fetal therapies have been approved for coverage by Japan National Health Insurance based on the results of clinical studies performed in Japan. FLS for TTTS, TAS for primary FHT, and RFA for TRAP sequence are all minimally invasive fetal therapies that have become standard prenatal care approaches in Japan. These 3 fetal therapies will help improve the perinatal

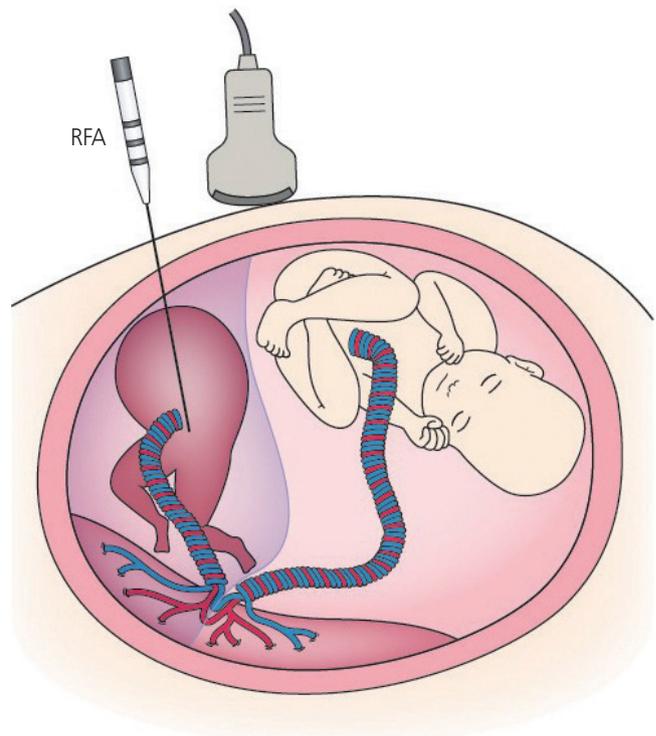


Fig. 3. A schematic representation of radiofrequency ablation (RFA) for twin reversed arterial perfusion sequence. A needle electrode is inserted into the acardiac twin to coagulate the body part, and then the blood flow is discontinued.

outcomes of fetuses with these diseases. The goal of fetal therapy is to ensure the survival of fetuses without complications. Well-designed studies and cautious preparations are essential for effectively promoting fetal therapy.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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