

# INVASIVE FETAL THERAPY: GLOBAL STATUS AND LOCAL DEVELOPMENT

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## SUMMARY

There are few congenital anomalies that can be treated *in utero*, despite the rapid development of fetal medicine. The number of available antenatal treatments is growing with the advance of supplementary tools, especially ultrasound and endoscopy. Disorders involving accumulation of excessive fluid in the amniotic cavity (polyhydramnios), chest (hydrothorax), abdomen (ascites) and urinary system (obstructive uropathy) are regularly treated using aspiration or shunt drainage under ultrasound monitoring. Electrolyte solutions or concentrated blood component supplements are used to treat oligohydramnios (amnioinfusion and amniopatch) and fetal anemia (fetal transfusion). Placental tumor (chorioangioma) and fetal tumors (cystic hygroma and sacrococcygeal teratoma) are also successfully treated by antenatal injection of medications. Fetoscopic procedures, especially obstetric endoscopy, are now used regularly in North America, Europe, Australasia and Japan after the validity was established in the treatment of twin-twin transfusion syndrome when compared with traditional amnioreduction. However, most procedures involving surgical fetoscopy or open fetal surgery remain experimental. Their validity and efficacy are not confirmed in a number of fetal diseases for which they were claimed to be effective. A brief review of the global status and history of invasive fetal therapy is given, and its status in Taiwan is also described. Future development in this field relies on greater understanding of the basic physiology and pathology of the diseases involved, as well as on the progress of sophisticated instrumentation. [*Taiwanese J Obstet Gynecol* 2004;43(4):185-192]

**Key Words:** thoracoamniotic shunt, vesicoamniotic shunt, fetal transfusion, amnioinfusion, amnioreduction, fetoscopy, open fetal surgery, hydrops fetalis, cystic hygroma, twin-twin transfusion syndrome

## Introduction

Invasive fetal therapy has thrived since the advent and development of ultrasound after Sir Albert Liley published his now-classic report regarding fetal transfusion in 1963 [1]. The appearance of another milestone, success-

ful shunt treatment of fetal obstructive uropathy in 1987, marked the maturation of invasive techniques assisted by ultrasound [2]. Prompt antenatal treatments thus provide effective alternatives to termination for various fetal structural anomalies. Meanwhile, fetal surgery, whether endoscopic or open, for various fetal malformations including congenital cystadenomatoid malformation (CCAM), open neural tube defects, obstructive uropathy and congenital diaphragmatic hernia (CDH) developed from the 1980s and attracted a lot of attention [3-6]. Professional societies and organizations focusing on fetal therapy were also organized, such as the International Fetal Medicine and Surgery Society (IFMSS) and the International Society of the Fetus as

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a Patient, reflecting the life of this emerging highly specialized profession. The authors give a concise introduction to invasive fetal therapy here because it is impossible to cover the fascinating history and development of this challenging field. The article adopts a mainly disease-, rather than procedure-, oriented layout to enhance readability.

## Accumulation of Excessive Fluid in Obstructive Fetal Diseases

Excessive fluid accumulation often results in irreversible damage to developing fetal organs by compressing the parenchyma of adjacent organs. Prompt decompression is thus mandatory. Aspiration and shunt placement are frequently the treatment modalities of choice.

### Obstructive uropathy

Fetal obstructive uropathies represent a wide variety of entities involving the upper and lower urinary tract. Detailed discussion of the diagnostic criteria for these disorders is omitted here, but interested readers should refer to the review by Johnson and Freeman [7]. Obstruction leading to oligohydramnios (i.e. fetal anuria because of obstructive uropathy) may require antenatal intervention.

Common obstructive fetal uropathies can be classified into upper (UUTO) and lower urinary tract obstructions (LUTO). Ureteropelvic junction stenosis (UPJS) is the most common cause of postnatal hydro-nephrosis, followed by reflux, vesicoureteral junction stenosis (VUJS) and posterior urethral valve. Urinary diversion is necessary for oligohydramnios or when there is evidence of progressive nephropathy diagnosed by fetal urine sampling. Markers used for evaluation of fetal renal function include sodium (< 100 mg/dL), chloride (< 90 mg/dL), osmolality (< 200 mOsm/L), calcium (< 8 mg/dL),  $\beta_2$ -microglobulin (< 6 mg/dL) and total protein (< 20 mg/dL) [7].

Vesicoamniotic shunting is currently the standard treatment for LUTO [2]. The most widely used shunting instruments approved by the US Food and Drug Administration for human use include a British-made, Rodeck-style double-pigtailed shunt (Rocket Medical Plc, Watford, Herts, UK) and an American-made Harrison fetal bladder stent set (HFBS; Cook Obgyn<sup>®</sup>, Spencer, IN, USA).

Complications, including migration, dislodgment and displacement of the shunt, have led to the emergence of a new promising technique, fetal cystoscopic ablation of the posterior urethral valve, to alleviate the obstruction, although it is still experimental [8].

### Fetal pleural effusion

Congenital chylothorax occurs in 1 in every 12,000–15,000 pregnancies and is the most common form of pleural effusion encountered in the perinatal period [9, 10]. It is associated with fetal pulmonary hypoplasia, especially if it develops in the second trimester as a result of impaired fetal lung growth due to compression. A lymphocyte count of more than 85% in the pleural fluid is suggestive of the diagnosis. The pleural fluid is straw-colored. Antenatal treatment includes maternal dietary modification [11], repeated thoracentesis [12], thoracoamniotic shunting [13], and pleurodesis with OK-432 (Picibanil<sup>®</sup>, Chugai Pharmaceutical Co, Tokyo, Japan) [14–17], a lyophilized incubation mixture of group A *Streptococcus pyogenes* of human origin, or maternal blood [10]. The perinatal mortality rate varies in different series from 15% to 53% [10,16,18,19] and prognosis is poorer if the disease is associated with hydrops fetalis, bilaterality or preterm delivery.

Non-chylous fetal pleural effusion is extremely rare and treatment should be aimed at correcting the underlying disorder (e.g. fetal transfusion for fetal anemia or intravenous immunoglobulin for viral infections) as well as providing decompression. Several Taiwanese obstetricians have made significant efforts to tackle this condition [12,13,17].

### Fetal ascites

Fetal ascites can be part of the clinical presentation of hydrops fetalis or an isolated finding in the antepartum period. Treating the underlying causes of hydrops fetalis is the best therapy when fetal ascites is part of the clinical spectrum of hydrops fetalis. However, aggressive aspiration of fetal ascites is controversial. The perinatal outcome is good if meconium ascites is not present [20, 21]. Pleural effusion may develop when fluid has effused through the diaphragm from massive ascites, when paracentesis may be indicated. We have encountered massive ascites caused by meconium leakage that needed to be aspirated regularly to keep the fetus free from effusive hydrothorax. The outcome of that baby was excellent [unpublished data].

### Hydrops fetalis

Fetal hydrops can be classified as immune or non-immune. Immune hydrops fetalis often results from maternal alloimmunization to fetal antigens. Progressive fetal anemia results in fetal cardiac failure, hydrops fetalis and death. The prevalence of rhesus isoimmunization in Caucasians promoted the rapid development of fetal transfusion to tackle the disease in the West. Sir Albert Liley was the first to use intraperitoneal transfusion, and since then, intravascular transfusion has

become the treatment of choice with the assistance of sophisticated ultrasound [1,22].

In Scotland, the incidence of non-immune hydrops fetalis is 1 in 830 deliveries; 35% of the cases remained idiopathic despite extensive antenatal and postnatal investigations [23]. Viral infection, cardiovascular abnormalities, twin-twin transfusion syndrome (TTTS), chromosomal abnormalities and fetomaternal hemorrhage accounted for most of the 65% of cases for which etiologies were elucidated. Intravascular transfusion improves the outcome of this previously lethal disorder [23].

It is extremely rare for rhesus isoimmunization to be found in ethnic Chinese populations. Non-immune hydrops fetalis, especially homozygotic  $\alpha$ -thalassemia-1, comprises the majority of hydrops fetalis in Taiwan [24]. However, a substantial number of non-immune hydrops fetalis cases that are categorized as idiopathic may be due to human parvovirus B19 infection, since human parvovirus B19 is not regularly tested for in Taiwan. Fetal transfusion will certainly help these patients [25].

#### ***Fetal hydrocephalus***

Early shunting in the neonatal period improves both the survival and long-term prognosis in hydrocephalic infants and, therefore, investigators used an *in utero* catheter shunt (one-way-valved ventriculoamniotic shunt) to treat fetal hydrocephalus. However, of the 34 infants (83%) who survived, only 12 (35.3%) developed normally [26]. Meanwhile, the sole manufacturer of the one ventricular shunt available for clinical use discontinued production of the device as a result of decreasing demand. Therefore, invasive fetal shunt therapy is not currently recommended.

### **Disorders of Amniotic Fluid Volume**

#### ***Polyhydramnios***

Polyhydramnios is defined as an amniotic fluid index (AFI) of more than 25 cm or maximal vertical pool depth (MVPD) of more than 8 cm. Cases can be further classified as mild (MVPD, 8–12 cm), moderate (MVPD, 12–15 cm) or severe (MVPD,  $\geq$  15 cm). Severe polyhydramnios may produce maternal abdominal discomfort, respiratory embarrassment, renal failure and uterine irritability (which will result in preterm delivery). There is a 5% chance of aneuploidy, so karyotyping is sometimes indicated.

The criteria for amnioreduction, as adopted by Professor Fisk's group in London, are an AFI of more than 40 cm or an MVPD of more than 12 cm [27]. An

easy formula shows how much amniotic fluid needs to be drained: a 1 cm decrease in AFI corresponds to a need to remove 100 mL of amniotic fluid [28]. Prostaglandin synthetase inhibitors, including indomethacin and sulindac, are used to alleviate polyhydramnios because they can reduce hourly fetal urine production. Sulindac is safer than indomethacin with regard to the side effect of *in utero* premature closure of the ductus arteriosus [27].

#### ***Oligohydramnios***

Oligohydramnios is noted in 3–5% of pregnancies in the third trimester but only in 0.2% in the midtrimester. It is defined as an AFI of less than 5 cm or an MVPD of less than 2 cm [27]. Oligohydramnios may be associated with increased perinatal morbidity and mortality except in isolated oligohydramnios that develops near term [29]. A variety of conditions, including membrane rupture, fetal urinary tract abnormalities such as megacystis caused by posterior urethral valve, and pre-renal abnormalities involving uteroplacental insufficiency, can result in oligohydramnios [30]. Amnioinfusion is used antepartum to prolong the gestation as well as to reduce the sequelae of Potter sequence, including fetal growth restriction, pulmonary hypoplasia, limb deformity and amniotic band syndrome [31]. Meanwhile, intrapartum amnioinfusion can reduce the cesarean rate, meconium aspiration syndrome, umbilical acidosis (pH < 7.1) and low Apgar score at 5 minutes [32]. We have also used serial transabdominal antepartum amnioinfusion with warm lactate Ringer's solution with a hard spinal needle in a number of patients and the results seem favorable [unpublished data].

### **Open Neural Tube Defects**

Spina bifida and meningomyelocele result from failure of the closure of the midline bony defect and failure of caudal neurulation during the fourth week of gestation. Intrauterine closure of the exposed spinal cord tissue prevents secondary neurologic injury in animals with a surgically created spinal defect. The two-hit hypothesis (embryologic error plus secondary injury of nervous tissue by chemicals in the amniotic fluid) was therefore accepted from the growing experimental evidence [33]. Chiari II malformation, including herniation of the cerebellum and hindbrain, is usually present and is associated with hydrocephalus. Many children with meningomyelocele manifest developmental delay and learning disabilities. A ventriculoperitoneal (VP) shunt is usually necessary for patients with hydrocephalus. Bruner et al published their experience of treating fetal

myelomeningocele using fetal surgery and the outcome in their patients [34]. Their data showed a decrease in the incidence of hindbrain herniation and shunt-dependent hydrocephalus in infants with spina bifida. However, the motor and sensory nervous dysfunction in the lower extremities as well as in genitourinary systems showed little improvement.

## Placental and Fetal Tumors

### *Chorioangioma*

Chorioangioma is a benign placental vascular tumor and is regarded as a hamartoma. Most cases are typical capillary hemangiomas arising from just beneath the chorionic plate. The incidence is about 1% of all placentas. Chorioangiomas that are large enough to be visualized by ultrasound are uncommon, accounting for only 1 in 3,500–9,000 births [35]. Complications of chorioangiomas arise only when the tumors are larger than 4–5 cm in diameter. The arteriovenous (AV) shunt produced by the tumor causes progressive fetal cardiac failure. Hydrops fetalis, polyhydramnios, preterm delivery and pre-eclampsia develop thereafter. Nicolini et al were the first to inject 100% alcohol into the large veins of the tumors, producing two healthy infants [36]. Several other authors followed [35]. Alcoholization of placental tumors is now a promising and easy treatment modality. Alcohol spillage is a theoretical fear, although no cases have been observed.

### *Cystic hygroma*

Cystic hygromas are congenital malformations of the lymphatic system and consist of dilated endothelium-lined space. Infections and/or chemical irritants can damage the endothelial lining. OK-432 has been used to treat pediatric and adult cystic hygroma and is widely accepted [37]. OK-432 is well known as a biologic response modifier with anti-tumor effects. Some researchers, mostly from Japan, have used it in treating neonatal and even fetal cystic hygroma with some success [38–43]. The pathway of action of OK-432 within the cystic hygroma is thought to be cellular and cytokine-mediated [41]. The elevated cytokine levels probably increase the permeability of the vascular endothelium within the cystic hygroma. Leukocytes are recruited and the local inflammatory reaction further increases the permeability of the lining endothelium and accelerates drainage of the accumulated lymph. Involution of the tumor then ensues [41]. An 81.5% fetal demise rate has been observed in fetuses with cystic hygroma [44]. The prognosis is poorer if the condition is associated with chromosomal abnormalities, hydrops fetalis or struc-

tural abnormalities, although a case of spontaneous regression of hydrops fetalis and cystic hygroma after birth has been reported [40,45]. Three reported cases have successfully been treated antenatally with OK-432, but only the case from our group was associated with hydrops fetalis [17,42,43]. Three other cases with fetal cystic hygroma and hydrops fetalis receiving antenatal OK-432 injection died *in utero* or within 1 month after birth [39,40]. Thus, our result seems to be satisfactory when compared to others [17].

### *Sacroccygeal teratoma*

Sacroccygeal teratoma may steal fetal circulation with a large AV shunt and causes fetal cardiac failure. Thus, antenatal intervention may be indicated when the tumor is growing very fast, when the absolute size is large or when fetal cardiac failure is obvious. Open fetal surgery was first tried by a team led by Dr. Harrison, the most respected fetal surgeon in the world, in the late 1980s, but considerable fetal death or preterm delivery hampered its development [46]. Radiofrequency ablation, absolute alcohol injection and fetoscopic resection gradually replaced open fetal surgery. Ablation of feeder vessels is the main goal of antenatal treatment. Complete resection of the tumor can be reserved until after birth [47].

### *Congenital cystadenomatoid malformation and other space-occupying lung lesions*

CCAM, bronchogenic cyst and bronchopulmonary sequestration are common space-occupying lesions that may hamper fetal lung development, impair venous return followed by hydrops fetalis and adversely affect perinatal outcome. Thoracoamniotic shunting is sometimes helpful when the lesions are cystic. However, excision of the tumor or even fetal lobectomy is indicated when lesions are not cystic [48,49]. Thorpe-Beeston and Nicolaides reported that the prognosis of antenatally diagnosed CCAM is excellent in the absence of signs of severe fetal distress [50]. The need for surgery should be judged on appropriate postnatal investigations rather than antenatal prognostic markers [51], which downgrade the value of fetal surgery.

## Complications of Monochorionic Multiple Pregnancies

Although Taiwan provides excellent medical care, fetoscopy is largely unavailable. This lack makes the progress of a truly innovative fetal therapy elusive. However, we will describe the current state of fetoscopy as well as its main application: treating complications of monochorionic multiple pregnancies, especially the

TTTS and twin reversed arterial perfusion sequence (TRAP; the so-called acardiac monster). Alternatives to fetoscopy are discussed.

### **Fetoscopy**

There are two types of fetoscopy: obstetric endoscopy and endoscopic fetal surgery [52]. Obstetric endoscopy deals with the placenta, umbilical cord and fetal membranes. Laser coagulation (using an Nd-YAG laser) of placental vessels in TTTS and cord occlusion in monochorionic pregnancy are the most common applications. Endoscopic fetal surgery deals with *in utero* fetal surgery and remains highly experimental. Fiber optic rather than rod lens fetoscopes with scope diameters between 1.2 and 2 mm and an external sheath of approximately 3 mm are used. Hartmann solution or other isotonic electrolyte solutions can be used for amnioinfusion to distend the uterine cavity and to enhance the working area for fetoscopy. A single-port system is favored over multiple ports because it leads to fewer complications such as preterm delivery and preterm premature rupture of fetal membranes (PPROM). Procedures should be practiced on animal models, especially sheep, before performing them in human fetuses. The Eurofoetus group in Europe, three leading centers in London (led by Rodeck, Fisk and Nicolaides) and some centers in the USA (e.g. Quintero in Florida, Evans at Wayne State, De Lia in Milwaukee, Adzick in Philadelphia, and Harrison in San Francisco) and Japan regularly perform advanced fetoscopic procedures.

### **Twin-twin transfusion syndrome**

TTTS occurs in 15% of monochorionic twin pregnancies. Perinatal loss exceeds 80% if left untreated. However, overall perinatal survival rates (usually only one twin survives) improve to around two-thirds with a variety of treatment modalities including amnioreduction [53], septostomy [54], selective reduction and laser ablation of the communicating vessels. Diagnosis of TTTS includes a polyhydramnios-oligohydramnios sequence as well as other minor ultrasound findings such as stuck twin, discordant twin and the cocoon sign [55,56]. Quintero et al classified TTTS into the widely used five stages based on severity: Stage I, bladder of the donor visible, normal Doppler; Stage II, bladder of the donor invisible, normal Doppler; Stage III, critically abnormal Doppler in either twin; Stage IV, hydrops fetalis; and Stage V, demise of one or both twins [57]. Monochorionic placentae are characterized by a certain degree of sharing of one or more cotyledons by the two fetal circulations. Some authors therefore regard the imbalance of intertwin transfusion (AV communication) as the cause of TTTS; however, artery-artery

(AA) communication usually confers protection against TTTS. In other words, communication between two fetal circulations is almost universal in monochorionic twins, but asymmetric AV communication may result in TTTS [58]. The result of treating TTTS is unsatisfactory, which may be due to a lack of understanding of the placenta. However, since the Eurofoetus group published their data comparing serial amnioreduction with/without septostomy versus fetoscopic laser coagulation of communicating vessels, fetoscopic laser coagulation has gradually become the treatment of choice in TTTS [59,60]. Hecher et al showed comparable fetal survival (61% in laser group vs 51% in amnioreduction group) but a much lower incidence of abnormal ultrasound findings in the neonatal brain (6% in laser group vs 18% in amnioreduction group) with laser coagulation compared with amnioreduction [59]. However, there is a procedure-related fetal loss rate of 15–50% in fetoscopic laser coagulation, so amnioreduction still has a role in Stage I–II TTTS [56].

Selective feticide is indicated when one twin is about to die, because the living twin will exsanguinate into the dead twin, resulting in anemia and ischemic changes in the brain. Quintero et al demonstrated this phenomenon with fetoscopy by visualizing the dead as well as the living twin within 3 hours of the demise of the donor twin [61]. Thus, selective feticide may be helpful in preventing exsanguination. Routes for feticide include the intrafetal and funicular approaches. Injection with potassium chloride, xylocaine, enbucrilate gel and absolute alcohol under ultrasound guidance is an easy but less effective approach [62]. Radiofrequency ablation [63], monopolar coagulation, bipolar coagulation and cord ligation are more effective but also more expensive. The option chosen depends on local conditions. Selective feticide is less effective in TTTS than TRAP because the flow rate in the fetal circulation is much higher in TTTS than in TRAP [60].

### **Twin reversed arterial perfusion sequence**

TRAP is a unique complication of monochorionic twinning and is extremely rare. The incidence of TRAP is only 1 in 35,000 deliveries, 1 in 100 monozygotic twins and 1 in 30 monozygotic triplets [64]. Selective reduction of the acardiac twin is indicated in the presence of poor prognostic factors, including an acardiac-to-pump twin weight ratio of  $\geq 70\%$ , congestive heart failure or hydrops in the pump twin, polyhydramnios, anencephalic acardia or presence of arms in the acardiac twin. The overall perinatal mortality of the pump twin is around 35%. Treatment modalities include embolization, cord ligation by fetoscopy, laser coagulation, bipolar diathermy and monopolar diathermy. A group at Chang Gung Me-

morial Hospital, Taiwan, successfully treated an acardiac acephalus twin using monopolar thermocoagulation [65].

## Congenital Diaphragmatic Hernia

CDH is a disorder caused by an anatomical defect of the fetal diaphragm. The abdominal viscera herniate into the chest and cause fetal pulmonary hypoplasia. The clinical spectrum of CDH ranges from minimally affected infants who do well to severely affected infants who die despite all aggressive interventions. Open fetal surgery is hampered by technical problems. Tracheal occlusion evolved as the mainstream antenatal therapy for this disorder. The accumulated fluid within the fetal lungs due to the tracheal occlusion restores lung volume and improves the perinatal outcome in animal studies [66]. Fetoscopic tracheal occlusion is regarded as better than the open method for tracheal occlusion in many animal studies and, thus, much effort was put into improving the devices and instrumentation of fetoscopy. The endoluminal approach replaced the earlier externally placed titanium clips in achieving tracheal occlusion as fetoscopy progressed. For example, a percutaneous single-port fetoscopic access system has excellent performance in a sheep model, reducing the preterm delivery frequently encountered with the multiple-port fetoscopic system [67].

However, despite considerable research into antenatal treatment of CDH, Harrison et al reported that tracheal occlusion does not improve human fetal survival nor reduce morbidity in fetuses with CDH [68]. Attempts to treat this distressing disorder seemingly ended in failure.

## Fetal Anemia

Useful signs of fetal anemia include a sinusoidal pattern in fetal heart rate (FHR) tracing as well as many ultrasound markers including lengthened fetal liver, increased fetal splenic perimeter, placentomegaly, hydrops fetalis, abnormal waveforms of cerebral arteries (elevated peak systolic velocity), umbilical arteries (absent or reversed end-diastolic velocity), splenic artery, thoracic aorta and ductus venosus (reversed A wave) [69]. However, a low fetal hematocrit (< 30% is indicated for fetal transfusion) in blood obtained from cordocentesis is definitive proof of fetal anemia. Fetal transfusion is the standard treatment for fetal anemia resulting from alloimmunization or human parvovirus B19 infection [70]. However, the efficacy of fetal transfusion

for fetal anemia is reduced in already hydropic fetuses [71]. The incidence of anti-D Rhesus antibody is around 1 in 1,000 live births in the West but almost nil in East Asians. Thus, fetal transfusion may only benefit a subgroup of patients with fetal anemia in Taiwan, with an etiology of human parvovirus B19 infection. Homozygous  $\alpha$ -thalassemia-1 is the main cause of non-immune hydrops fetalis in Taiwan [24]. Intrauterine transfusion can be used as a supportive treatment in this condition but a more definitive treatment awaits postnatal bone marrow transplantation [72]. *In utero* stem cell transplantation has been proposed to treat some lymphohematopoietic disorders, and the European Network for Fetal Transplantation (ENFET) was established to study this highly experimental treatment modality [73].

## Conclusions

Fetal therapy should be aimed at promoting the health of the fetus. Any heroic breakthrough in surgical skills cannot be validated unless it is beneficial to the fetus. Future developments rely on a better understanding of the pathophysiology of fetal diseases. Minimally invasive and endoscopic approaches to correctable anatomic lesions as well as *in utero* cellular transplantation are the most promising territories awaiting further exploration [74]. Complications of monochorionic pregnancy remain the major challenge to fetal therapists in the future.

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