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Title

Minimally Invasive Fetal Surgery.

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<https://escholarship.org/uc/item/38n7s241>

Journal

Clinics in perinatology, 44(4)

ISSN

0095-5108

Authors

Graves, Claire E
Harrison, Michael R
Padilla, Benjamin E

Publication Date

2017-12-01

DOI

10.1016/j.clp.2017.08.001

Peer reviewed

Minimally Invasive Fetal Surgery

Claire E. Graves, MD^a, Michael R. Harrison, MD^b, Benjamin E. Padilla, MD^{c,*}

KEYWORDS

- Fetal surgery • Fetal therapy • Fetal diagnosis • Prenatal diagnosis
- Fetoscopic surgery • Fetoscopy

KEY POINTS

- The goal of minimally invasive fetal treatments is to decrease maternal risk and premature rupture of membranes.
- Real-time ultrasound imaging is crucial to the implementation and success of minimally invasive fetal procedures.
- Multidisciplinary fetal procedural teams, including a fetal surgeon, ultrasonographer, perinatologist, and anesthesiologist, are critical to the delivery of quality care.

INTRODUCTION: NATURE OF THE PROBLEM

History and General Principles

In the past 50 years, fetal therapy has progressed from mere concept to an accepted and viable treatment modality. A better understanding of embryology and fetal development, coupled with the advent of high-resolution noninvasive fetal imaging, led to a fundamental shift in thinking of the fetus itself as a patient.¹ With earlier and more accurate diagnosis of many congenital defects, the window of opportunity for intervention widened. Throughout the second half of the 20th century, physician and surgeon scientists took a rigorous scientific approach in tackling the problem of fetal surgery: identifying the clinical need, studying the natural history of diseases in the human fetus, understanding the pathophysiology and proposed treatments in the laboratory, and safely implementing fetal interventions in humans. Through these efforts, fetal therapy has improved survival and decreased morbidity for many devastating congenital defects, while minimizing risk to the mother. Technical advances, coupled with

Disclosure Statement: The authors have nothing to disclose.

^a Department of Surgery, University of California, San Francisco, 550 16th Street 5th Floor UCSF Mail Stop 0570, San Francisco, CA 94158-2549, USA; ^b University of California, San Francisco, 550 16th Street 5th Floor UCSF Mail Stop 0570, San Francisco, CA 94158-2549, USA; ^c Division of Pediatric Surgery, Department of Surgery, University of California, San Francisco, 550 16th Street 5th Floor UCSF Mail Stop 0570, San Francisco, CA 94158-2549, USA

* Corresponding author.

E-mail address: Benjamin.Padilla@ucsf.edu

Clin Perinatol ■ (2017) ■-■

<http://dx.doi.org/10.1016/j.clp.2017.08.001>

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perinatology.theclinics.com

ongoing efforts to make fetal procedures safer for the mother, have led to ongoing innovation in the field, including the development of minimally invasive therapies and procedures.

Although many minimally invasive fetal operations are simply adaptations of the open operation, others were developed specifically for minimally invasive techniques. Indeed, some can only be performed in this way. The first modern fetal intervention was needle based. In 1963, Liley performed the first fetal transfusion by inserting a 16-G Touhy needle into the fetal peritoneal space.² In this era before modern ultrasound imaging, Liley localized the fetal abdomen by injecting contrast into the amniotic cavity and allowing it to be swallowed by the fetus to opacify the fetal bowel. Given the success of this needle-based technique, enthusiasm for existing open transfusion procedures waned.³ In the 1970s, direct visualization of the fetus with endoscopy was first introduced for diagnostic purposes, such as to obtain fetal blood or biopsy tissue, but therapeutic use was limited because of its invasiveness and the technical skill required.⁴ Fetoscopic diagnosis became essentially obsolete when ultrasound examination became more widespread, shifting instead to percutaneous needle-based techniques under ultrasound guidance. It was not until the early 1990s, when smaller cameras and endoscopes coupled with the increasing popularity of laparoscopic surgery, led to a resurgence of interest in fetoscopic and minimal access procedures.⁴⁻⁷ **Box 1** highlights some milestones in the development of minimally invasive fetal procedures. Some of the early challenges in the development of these techniques have been summarized elsewhere.⁸

Ethical Considerations

Fetal intervention raises unique ethical issues surrounding maternal autonomy and decision making. Although the goal of fetal intervention is to cure or better the health of the fetus, any intervention, whether surgical or pharmacologic, necessarily affects the pregnant mother. The pregnant woman gains nothing in terms of personal health benefits, and the unborn child gets all potential benefit. Protecting the pregnant woman and mitigating risk is the greatest responsibility of fetal therapy teams. Therefore, explicit informed consent is required for all fetal interventions, and must be obtained with a comprehensive discussion of her unique risks. Moreover, women must also be informed of, and provided access to, alternatives to intervention, including post-natal therapy, palliative care, or pregnancy termination in a nondirective manner.^{9,10}

Innovation in fetal therapy, including the development of minimally invasive procedures, is necessary to continue to expand the benefits of fetal treatment and reduce risks to pregnant women. However, formal clinical research in this population is often

Box 1

Milestones in the development of minimally invasive fetal surgery

Milestone	Year
First fetal transfusion	1963
First fetal vesicoamniotic shunt placement	1982
First open fetal surgery	1982
First fetal thoracoamniotic shunt placement	1987
First laser ablation for twin-twin transfusion syndrome	1990
First fetoscopic repair of myelomeningocele	1997
First "Fetendo" tracheal clipping for congenital diaphragmatic hernia	1997
First fetoscopic release of amniotic band	1997
First fetoscopic balloon tracheal occlusion for congenital diaphragmatic hernia	2001

difficult, owing to the lack of appropriate animal models in some diseases, as well as small patient numbers. Therefore, fetal innovation benefits from collaboration between and among disciplines as well as between multiple centers. To guide practitioners in responsible innovation, the North American Fetal Therapy Network has developed guidelines regarding medical innovation in maternal–fetal therapy.¹¹

SURGICAL TECHNIQUES AND PROCEDURES

Surgical Team

In fetal surgery, in which there are complex diseases and multiple patients, careful planning and open communication before, during, and after surgery between the members of the multidisciplinary care team are essential. The disciplines that may be involved include pediatric surgery, obstetrics, pediatric anesthesia, obstetric anesthesia, cardiology, radiology, otolaryngology, neonatology, neonatal nursing, and operative room nursing.¹² At our institution, regular, weekly multidisciplinary meetings are held to discuss upcoming patients and come to consensus on treatment plans.

During most minimally invasive procedures, ultrasound imaging is used to provide guidance to the proceduralist (usually a pediatric surgeon and/or obstetrician) and to monitor the fetus during surgery. These practitioners actively communicate with the anesthesia team, as well as nursing and scrub staff, throughout the procedure. Owing to the specialized equipment required, an active and knowledgeable technical support staff is essential.

Surgical Approach

Minimally invasive fetal surgery is broadly divided into 2 categories: (1) needle based and (2) fetoscopic. For both, the mother is usually positioned supine with the right side angled up or elevated with a bump to minimize compression of the inferior vena cava. Intraoperative, real-time ultrasound imaging is critical to both types of procedures. Upon initial access, it is used to identify a safe entry point on the uterus, free of large vessels and placental attachments. To minimize the risk of bleeding, placental abruption, and fetal morbidity, traversing the placenta is avoided if at all possible. Ultrasound imaging is also important for determining the location and position of the fetus and assessing its well-being throughout the operation by monitoring fetal heart function and umbilical artery blood flow.

Minimally invasive fetal operations are performed through a small skin incision on the mother's abdomen. The location of the incision is based on the position of the placenta, as well as the intrauterine target. The needles used to access the fetus are approximately 1 to 2 mm in diameter, as small as possible to minimize maternal morbidity. In cases of anterior placenta, curved instruments may be used to access target structures.¹³ Through needle-based fetal access, fluid associated with ascites, pleural effusions, cystic structures, or the bladder can be aspirated or drained with a shunt into the amniotic space. In addition, needle-based access is used in fetal cardiac valvuloplasty and ablative procedures, such as radiofrequency ablation (RFA) in the management of complications of twin gestation.

Fetoscopic procedures are usually performed via a single 2.3- to 4.0-mm (7- to 12-Fr) port that accommodates 1.2- to 3-mm endoscopes, with or without a working channel ([Fig. 1](#)).⁸ When only a single access port is used, a small skin incision is made on the mother's abdomen to access the uterus. When multiple ports are required, multiple small incisions may be made, or the uterus may be visualized through a larger laparotomy before port insertion. The scope can be inserted directly into the amniotic cavity using a sharp trocar within the sheath of the fetoscope itself, or a cannula

Fig. 1. Fetoscopic procedures are performed using 1.2- to 3.0-mm endoscopes. Pictured is a 3 mm 0° endoscope, adjustable length, with a 1-mm working channel.

can first be inserted to create a working port, either with a trocar or via Seldinger technique.¹⁴ Again, ultrasound imaging is essential for safe uterine access and is an adjunct to the fetoscope for visualizing the fetus. If the amniotic fluid is not clear enough to allow for a good image via a small endoscope, amnio-exchange with warmed crystalloid solution may improve visualization. The fetoscopic technique is currently used when direct visualization is required in addition to ultrasonography, for example, in the treatment of twin-twin transfusion syndrome (TTTS), posterior urethral valves (PUV), constricting amniotic bands, and tracheal balloon occlusion for congenital diaphragmatic hernia (CDH).

Anesthetic Considerations

Anesthesia during fetal procedures is based on an understanding of both maternal and fetal physiology.¹² Minimally invasive fetal procedures require varying degrees of maternal analgesia and anesthesia, as well as fetal analgesia and/or immobility, depending on procedure complexity and the instrumentation required.

Typically, needle-based and single port fetoscopic procedures are well-tolerated by the mother under local anesthesia. For complex procedures requiring multiple ports or when backup Caesarian section could be necessary, regional anesthesia such as epidural or combined spinal epidural anesthesia may be used.^{15,16} The fetus does not receive any anesthesia or analgesia from maternal local or regional techniques. Therefore, additional fetal anesthesia is usually required for endoscopic procedures performed directly on the fetus. Fetal anesthesia is typically administered intramuscularly and consists of opiates and nondepolarizing muscle relaxants.^{12,15} Atropine is often given simultaneously to prevent fetal bradycardia.¹⁷ For procedures on the placenta or cord, which do not have direct contact with the fetus, the risks of fetal anesthesia likely outweigh the benefits.

Complications

The complications of minimally invasive fetal surgery are similar to those of open fetal surgery, including bleeding, amniotic fluid leak, chorioamniotic separation, chorioamnionitis, premature rupture of membranes (PROM)/preterm prelabor rupture of membranes (PPROM), preterm birth, and fetal demise. PROM/PPROM is the most common complication of minimally invasive fetal surgery, with potentially significant morbidity, including oligohydramnios, chorioamnionitis, and preterm delivery. However, accurate analysis of the frequency of PROM and PPRM in these procedures is made difficult by the variations in both the assessment of the complication as well as reporting methods.¹⁸ In TTTS, the rate of PROM is estimated at approximately 26% to 40%.^{14,18,19} Complications of other procedures are discussed further elsewhere in this article.

Factors affecting the morbidity of minimally invasive fetal procedures include the number of ports used and the diameter of the instruments. A systematic review of 1376 minimally invasive fetal procedures for TTTS, lower urinary tract obstruction (LUTO), and twin reversed arterial perfusion (TRAP) sequence identified maximum diameter of the instrument and maximum number of ports as predictors of iatrogenic PPROM.¹⁸ Maximum instrument diameter also significantly decreased gestational age at birth. Though there was initially great enthusiasm that multiport fetoscopic surgery, with smaller uterine incisions, would decrease morbidity, multiport fetoscopic surgery has thus far proven disappointing. In the largest experience with multiport fetoscopic surgery, myelomeningocele (MMC) repair, this technique has yet to decrease complications when compared with open surgery.^{20–23}

Although fetal surgery has not been demonstrated to have an adverse effect on future fertility,²⁴ open fetal surgery requires planned Caesarian delivery before labor for the affected fetus and future pregnancies to prevent dehiscence at the fetal surgery hysterotomy scar. This factor does increase the risk of delivery complications and is a critical aspect of maternal counseling.²⁵ Importantly, minimally invasive fetal surgery does not preclude vaginal delivery. Although the long-term follow-up of subsequent pregnancies after these procedures is lacking, avoiding the complications of repeat Caesarian section is considered a significant advantage of minimally invasive procedures.

SPECIFIC CONDITIONS AND MINIMALLY INVASIVE PROCEDURES

Twin Gestations

Twin–twin transfusion syndrome

TTTS is a severe complication of monochorionic pregnancies that arises from an imbalance of flow through intertwin placental vascular anastomoses. Clinical effects, generally not seen until the second trimester, are related to a discrepancy in the intravascular volume. The donor twin develops hypovolemia, leading to oliguria and oligohydramnios from reduced renal perfusion, and the recipient twin suffers the consequences of hypervolemia, including polyuria and polyhydramnios.²⁶ Both twins are at risk for significant morbidity: the donor from hypoxic–ischemic injuries and growth restriction, and the recipient from cardiac decompensation and hydrops. In addition, these babies frequently suffer from long-term neurodevelopmental complications.²⁷ Disease severity is staged using clinical and ultrasonographic criteria developed by Quintero and colleagues²⁸ (Table 1). If left untreated, severe TTTS is lethal, with perinatal mortality rates of up to 80% to 90%.^{26,29,30}

Table 1
Staging of twin–twin transfusion syndrome

Stage	Ultrasound/Doppler Findings
I	Polyhydramnios and oligohydramnios
II	Stage I plus donor bladder not visualized
III	Stage II plus critically abnormal Doppler (umbilical artery absent or reversed end-diastolic velocity, ductus venosus reversed flow, pulsatile umbilical venous flow)
IV	Stage III plus hydrops
V	Fetal demise

Adapted from Quintero RA, Morales WJ, Allen MH, et al. Staging of twin-twin transfusion syndrome. J Perinatol 1999;19:550–5.

Initial interventions for TTTS focused on removing the excess amniotic fluid surrounding the recipient twin, with the goals of preventing preterm delivery secondary to polyhydramnios and improving fetal circulation by decreasing pressure on the chorionic plate.^{30,31} In 1990, an alternative procedure was proposed that used a fetoscopic laser to coagulate the superficial blood vessels that cross the separating membrane of the placenta, separating the 2 fetal circulations and destroying the intertwin vessels that cause discordant twin–twin transfusion.³² Currently, placental laser ablation is the preferred treatment of TTTS between 16 and 26 weeks of gestation. The procedure is performed through a single uterine access site using a fetoscope and thin laser fiber (Fig. 2).

The superiority of laser ablation compared with amnioreduction was first demonstrated in 2004, when a multicenter, randomized, controlled trial by the Eurofoetus Consortium compared selective laser ablation with serial amnioreduction in severe TTTS between 16 and 26 weeks of gestation.²⁹ Patients treated with laser ablation had a significantly higher survival rate of at least 1 twin to 6 months of age (76% vs 51%; $P = .002$). Moreover, twins treated with laser ablation were more likely to be free of neurologic complications at 6 months of age (52% vs 31%; $P = .003$). These data were pooled in a 2014 Cochrane review with a 2007 multicenter, randomized, controlled trial in the United States, sponsored by the National Institute of Child Health and Human Development.³³ This review found no difference in overall death between the laser ablation and amnioreduction groups (relative risk [RR], 0.87; 95% CI, 0.55–1.38), but did report a higher percentage of babies alive at 6 years of age without neurologic abnormality in the laser group (RR, 1.57; 95% CI, 1.05–2.34). The authors of the Cochrane review concluded that endoscopic laser coagulation of anastomotic vessels should continue to be considered in the treatment of all stages of TTTS to

Fig. 2. Diagram of fetoscopic laser ablation for twin–twin transfusion syndrome. Under ultrasound guidance, a fetoscope is placed into the amniotic space. Using both ultrasound guidance and fetoscopic visualization, intertwin vessels are destroyed with laser ablation.

improve neurodevelopmental outcomes.³⁰ Although some debate exists over whether the benefit outweighs the risks of intervention in stage I TTTS, a recent multicenter, retrospective review demonstrated improved outcomes with prenatal intervention (amnioreduction or laser) over observation.³⁴

Selective fetal reduction

In addition to TTTS, monochorionic twin pregnancies are susceptible to a variety of other serious complications, including selective intrauterine growth restriction, structural anomalies, twin anemia polycythemia sequence, and TRAP sequence, or acardiac twinning.³⁵ In some complicated monochorionic pregnancies at high risk of hemodynamic compromise or intrauterine fetal death, elective fetal reduction is recommended to prevent neurologic injury or demise of the cotwin.^{36,37} Because of risk of transmission between twins, fetal intracardiac potassium chloride injection is contraindicated in these pregnancies, and selective termination must be performed with interruption of blood flow to the fetus. Methods used to achieve this have included ligation of the umbilical cord, fetoscopic laser coagulation, ultrasound-guided bipolar cord coagulation, and RFA (Fig. 3).³⁸

The most convincing evidence for benefit of selective reduction in complicated twin pregnancies has been demonstrated for TRAP sequence. In TRAP sequence, 1 twin has an absent or rudimentary heart, as well as absence of other vital structures, including the head, making it incompatible with life. This twin has no placental share, and it receives its blood supply through direct vascular connections from the normal or “pump” twin. Left untreated, the normal twin develops high-output cardiac failure, resulting in greater than 50% mortality.³⁹ By stopping flow to the acardiac twin, the normal twin is protected. In the largest series to date, a 2013 review of the North American Fetal Therapy Network registry data from 12 fetal centers identified 98 patients who underwent percutaneous RFA of an acardiac twin.³⁹ In this series, the overall survival of the pump twin to 30 days was 80%.

Lower Urinary Tract Obstruction

Congenital LUTO is most often caused by PUV, urethral atresia, or the prune belly syndrome.⁴⁰ The condition is usually diagnosed on routine prenatal screening ultrasound examination, typically performed at 20 weeks' gestation. Hallmarks of diagnosis include a dilated bladder with thickened bladder wall, as well as dilation of the

Fig. 3. Radiofrequency ablation (RFA) of the cord of an anomalous twin in a monochorionic pregnancy. (A) External view of maternal abdomen with ultrasound and RFA probes. (B) Sonographic view of probe aimed at umbilicus of target fetus.

posterior urethra—the “keyhole sign.”⁴¹ When associated with early oligohydramnios, consequent pulmonary hypoplasia can lead to perinatal mortality of up to 50%,⁴² and children who survive are at high risk for chronic kidney disease or end-stage renal disease.⁴³

The basis of fetal intervention on LUTO is that the relief of urinary obstruction and resultant increase in amniotic fluid promotes lung development and maturity.⁴⁴ Moreover, animal models of LUTO indicate that renal damage caused by outflow obstruction is greater the earlier in gestation it occurs and the longer it is sustained.^{45,46} The first fetal interventions for congenital LUTO were developed in the fetal lamb and primate models, and then translated to human treatment at the University of California San Francisco in the early 1980s.^{44,47–49} These early interventions initially involved open fetal procedures with cutaneous ureterostomies, as well as minimally invasive approaches such as ultrasound-guided aspiration of fetal urine through needles or catheters and internal drainage through indwelling shunts.

Currently, 2 main techniques are used in specialized centers. In the first, vesicoamniotic shunting (VAS), a double pigtail stent is placed percutaneously under ultrasound guidance, usually in conjunction with amnioinfusion (Fig. 4). The second technique is fetal cystoscopy, in which a fetoscope is placed through a trocar within the fetal bladder, to diagnose the source of obstruction and to ablate PUV. Various methods have been used to ablate the valve, including guide wires, hydroablation, and laser ablation.⁵⁰

Table 2 summarizes recent studies on minimally invasive therapy for LUTO. Initial reports of VAS consisted of small case series using a variety of surgical techniques and different criteria for fetal selection. A metaanalysis of these early studies through 2002, which included a total of 342 fetuses, suggested that bladder drainage improved perinatal survival (odds ratio, 2.5; $P = .03$), most markedly in fetuses with poor prognoses.⁵¹ However, complications of shunting included failure of placement, catheter occlusion, dislocation, and fistula. To more rigorously evaluate the effect of in utero VAS, and gather data on long-term outcomes in these infants, a multinational, randomized, controlled trial, “Percutaneous vesicoamniotic shunting versus conservative management for fetal Lower Urinary Tract Obstruction” (PLUTO), was performed in the United Kingdom, Ireland, and the Netherlands from 2006 to 2012.⁵² Although planned enrollment was 150, the study closed early with only 31 participants (16 assigned to VAS, 15 to conservative management) because of recruitment

Fig. 4. (A) Megacystitis in fetus with lower urinary tract obstruction (LUTO) owing to posterior urethral valves (PUV). (B) Decompressed bladder 2 days after fetoscopic valve ablation.

Table 2
Selected reports of minimally invasive fetal intervention for lower urinary tract obstruction

Authors	Year	Design	N	Outcomes
Ruano et al, ⁴¹ 2010	2010	Retrospective single institution: cystoscopy vs expectant management	23	Improved survival (62.5%) vs (11.1%) with prenatal cystoscopy; normal postnatal renal function in 62.5% after cystoscopy vs 11.1% in control
Morris et al, ⁵² 2013	2013	Prospective randomized: VAS vs observation	31	Trend toward improved survival with VAS (RR, 1.88); poor long-term outcomes; 2/31 (6.4%) with normal renal function at 2 y (29% of survivors)
Ruano et al, ⁵³ 2015	2015	Retrospective multicenter: cystoscopy vs VAS vs observation	111	Significantly improved survival with fetal intervention cystoscopy (adjusted RR, 1.86) and VAS (adjusted RR, 1.73) vs observation; trend toward improved renal function with cystoscopy, but not with VAS
Sananes et al, ⁵⁴ 2016	2016	Retrospective multicenter cohort: cystoscopy	50	Overall survival at 1 y (37.5%). In cohort with PUV ablation, 1-y survival (56.7%), normal renal function at 2 y: 25.0% of original cohort, 75.0% of survivors

Abbreviations: PUV, posterior urethral valves; RR, relative risk; VAS, vesicoamniotic shunting.

difficulties. Preterm labor, number of live births, or neonatal requirement of ventilation did not differ significantly between the 2 groups. Survival to 28 days was better in the VAS group (intention-to-treat RR, 1.88 [$P = .27$]; as-treated RR, 3.20 [$P = .03$]), but long-term clinical outcomes were poor in both groups, with only 2 infants having normal renal function at 1 and 2 years (both in the VAS group). The authors suggest that irreversible damage to the renal parenchyma may take place before the time of diagnosis.

Although more invasive than VAS, fetal cystoscopy has the advantage of confirming the diagnosis of PUV, and thus more accurately selecting patients who will benefit from valve ablation. In a recent multicenter retrospective cohort study of 50 fetal cystoscopies for LUTO, 30 fetuses were found to have PUV and were treated with pulsed Nd:YAG laser ablation; the 20 remaining fetuses were diagnosed with urethral atresia ($n = 13$), urethral stenosis ($n = 5$), or trisomy 18 ($n = 2$) and were not treated.⁵⁴ Of the 48 patients with normal karyotype, mean gestational age at delivery was 32.4 weeks, and overall survival to 2 years was 34.8%. For patients with PUV treated with laser ablation, survival to 2 years was 53.6%, although 6 of the 30 (20%) had recurrence of LUTO, and an additional fetal procedure was performed in 3 patients (10%). Ten of the 17 survivors underwent additional postnatal ablation of PUV. At 2 years of age, 12 of the 16 infants (75%) with PUV had normal renal function, which is far more promising than the 29% reported in the PLUTO trial with VAS.

Evidence to date suggests that, in selected cases of LUTO, minimally invasive fetal therapy may improve survival compared with expectant management. However, reports of long-term renal function have been disappointing. The improved renal function with cystoscopy and valve ablation in the cohorts of patients with confirmed PUV^{53,54} have led some practitioners to propose cystoscopy as a first-line intervention

for diagnosis as well as valve ablation when PUV is confirmed. Patients with urethral stenosis, who are not candidates for ablation, could be considered for VAS.

Minimally Invasive Repair of Myelomeningocele

MMC, or spina bifida, is characterized by incomplete closure of the neural tube and exposure of the spinal canal elements. MMC can occur anywhere along the spine, but most commonly affects the lumbar or cervical vertebral levels. Complications include neurologic deficits with motor and somatosensory abnormalities. In addition, injury to the autonomic nervous system can impede bowel and bladder function. Finally, nearly all patients with MMC develop the Arnold-Chiari II malformation of the hindbrain, which results in noncommunicating hydrocephalus and requires ventriculoperitoneal shunting. Although MMC has low mortality in the perinatal period, the long-term morbidity from neurologic abnormalities is severe, and up to 30% of patients die before reaching adulthood.⁵⁵

Fetal intervention in MMC is based on the “2-hit” hypothesis of the neurologic injury, where the first hit is the neural tube defect itself, and the second hit is trauma to the exposed neural elements while the fetus is in utero.^{56,57} Fetal surgery aims to intervene before secondary damage can occur to the exposed structures. Animal models of fetal MMC, primarily in sheep, proved this hypothesis and showed that in utero repair of the MMC improved distal neurologic function and reversed the Arnold-Chiari II malformation.^{58–60}

MMC was the first nonlethal anomaly to be treated with fetal surgery.^{55,61} The first minimally invasive in utero coverage of MMC was performed in 1997, with endoscopic placement of a maternal split-thickness skin graft over the fetal neural placode.⁶² These early fetoscopic repairs were complicated by a high rate of fetal death (50%),⁶³ and efforts shifted to refining an open technique via hysterotomy. These open fetal procedures were promising, demonstrating decreased hindbrain herniation and improved neurologic function.^{64,65} To rigorously assess the benefit of fetal surgery on MMC, the National Institutes of Health sponsored a multicenter randomized trial, Management of Myelomeningocele Study (MOMS), comparing fetal MMC repair at 19 to 26 weeks gestation with conventional postnatal repair.⁶⁶ The study closed early because of the superiority of fetal surgery. Fetal MMC repair reduced the need for ventriculoperitoneal shunting for hydrocephalus at 1 year (fetal group, 40% vs postnatal group, 82%; $P<.001$) and improved motor function, including the ability to walk at 30 months of age (fetal group, 42% vs postnatal group, 21%; $P<.01$). Fetuses treated prenatally were born at an average gestational age of 34.1 weeks of gestation and 13% were born before 30 weeks of gestation.

Although the MOMS trial decisively demonstrated the value of in utero repair of MMC, the morbidity of the disease was still substantial, with 40% of patients in the prenatal group requiring shunts. Moreover, maternal complications in the prenatal surgery group included spontaneous membrane rupture (46%), chorioamniotic membrane separation (26%), and placental abruption (6%). Therefore, techniques to improve prenatal repair, including fetoscopic techniques, continue to be investigated.

Two fetoscopic techniques have been recently reported. The first uses three or four 5-mm trocars, placed in the amniotic cavity via Seldinger technique under ultrasound guidance.²⁰ Partial amniotic carbon dioxide insufflation is performed after removal of a portion of the amniotic fluid to provide visibility throughout the procedure. The malformation is dissected with a needle electrode, and the placode is manually dissected free from surrounding tissues with microscissors and micrograsper. Depending on the anatomy of the lesion, the neural tissue is covered with 1 or more Teflon and collagen patches. The results of a review of 51 cases with this

technique (some outcomes reported in expanded series of 71 cases) are summarized in [Table 3](#) and compared with results from the open fetal surgery cohort in the MOMS trial. In the case series, 2 early infant deaths were reported from severe brain-stem dysfunction owing to Chiari II malformation, which is not seen after open fetal surgery.⁶⁷ Additionally, 28% of patients required postnatal recoverage procedures. The rate of amniotic fluid leakage (PROM) after the procedure was 84%, at a mean gestational age of 29.7 weeks, indicating that smaller access sites fail to lessen this complication.

A second technique uses smaller access sites, with two 11-Fr vascular introducers and a third 14-Fr or 16-Fr vascular introducer (or a 5-mm laparoscopic trocar).²³ After partial CO₂ insufflation, the neural placode is released and surrounding skin undermined using 3-mm laparoscopic instruments and a 2.7- to 4.0-mm endoscope. The placode is covered with a biocellulose patch (not sutured in place), and the skin is closed with a 2-0 nonabsorbable monofilament suture. A skin substitute is used for 2-layer closure in larger defects. In a phase I human trial of 10 fetal repairs with this technique, 2 procedures were aborted owing to trocar displacement, with one of these cases resulting in intrauterine death 3 days after surgery owing to severe maternal pre-eclampsia. Mean gestational age at delivery in the remaining cases was 32.4 weeks, with PROM occurring in all cases at a mean gestational age of 30.2 weeks. One neonatal death occurred from sepsis owing to necrotizing enterocolitis. Two cases underwent early postnatal neurosurgical repair, and 3 cases met the criteria for ventriculoperitoneal shunting within 1 year.

Open fetal MMC repair has been rigorously studied and the benefits to the fetus have been proven. Minimally invasive fetoscopic repair is technically difficult, carries high rates of membrane separation and PROM, and the benefits of this technique to

Table 3**Comparison of outcomes of minimally invasive MMC repair and open fetal surgery**

Outcome	MOMS Trial, Prenatal Surgery cohort⁶⁶ (n = 78), n (%)	Case Series Review by Kohl et al²⁰⁻²² (n = 51),^a n (%)
Aborted procedure	0	1 (2)
Chorioamniotic membrane separation	20 (26)	1 (2)
Maternal chorioamnionitis	2 (3)	4 (8)
Spontaneous membrane rupture/amniotic fluid leakage	26 (46)	43 (84)
Placental abruption	5 (6)	0
Mean gestational age at delivery (wk ± SD)	34.1 ± 3.1	33.0 ± 2.8
Gestational age at birth of <30 wk	10 (13)	9 (13) ^a
Gestational age at birth of >35 wk	42 (54)	17 (23) ^a
Perinatal deaths	2 (3)	4 (8)
Death within first year of life	2 (3)	5 (7) ^a
Postnatal re-coverage required	N/A	20 (28) ^a
Shunt required within first year of life	Criteria met: 51 (65) Shunt placed: 31 (40)	32 (45) ^a
Chiari decompression surgery	1 (1)	3 (4) ^a

Abbreviations: MMC, myelomeningocele; MOMS, Management of Myelomeningocele Study; N/A, not applicable.

^a Outcomes reported in expanded series; n = 71.

the unborn child have not been rigorously substantiated. In light of these facts, minimally invasive MMC repair should be considered experimental until further validated.

Congenital Diaphragmatic Hernia

CDH occurs in approximately 1 in 2500 live births and consists of a defect in the fetal diaphragm, leading to herniation of abdominal viscera into the thoracic cavity.⁶⁸ Abnormal development of the lungs and pulmonary vasculature results in pulmonary hypoplasia and pulmonary hypertension, which in turn can result in persistent fetal circulation and respiratory failure. Despite advances in neonatal care, the mortality of infants with isolated CDH remains 20% to 30%.^{69,70} Sonographic indicators of poor prognosis include a low lung-to-head ratio and the presence of liver herniation into the thoracic cavity, and fetal MRI has been used to determine total lung volume in these fetuses.⁷⁰

The goal of fetal intervention in CDH is to counteract the pulmonary effects of the anomaly and promote lung growth in utero. Open fetal repair of CDH was technically feasible, but surgery in fetuses with poor prognosis liver herniation was fraught with high mortality despite treatment, and fetuses with better prognosis (no liver herniation) were just as effectively managed with postnatal repair.^{71,72} These disappointing results prompted new approaches to reverse lung hypoplasia. Based on the observation that fetuses with congenital high airway obstruction or laryngeal atresia are born with hyperplastic lungs,⁷³ it was hypothesized that tracheal occlusion in utero would promote lung growth in fetuses with CDH (**Fig. 5**). This hypothesis was tested extensively in the fetal lamb model of CDH using various methods of tracheal occlusion, including suture ligation,^{74,75} foam-cuffed endotracheal tubes, and expandable foam inserts.⁷⁶ Tracheal occlusion in the fetal lamb model of CDH increased lung volume, decreased herniation of abdominal viscera, and improved postnatal lung function.^{74,75} The effect of in utero tracheal occlusion on lung growth was later corroborated in a rat model of CDH.^{77,78}

In utero tracheal occlusion was first performed in humans in 1996 via maternal laparotomy and open hysterotomy.⁷⁹ However, the large hysterotomy required for adequate fetal exposure led to a high rate of preterm labor. Therefore, fetal

Fig. 5. The effects of tracheal occlusion in fetuses with congenital diaphragmatic hernia (CDH). Occluding the trachea of fetuses with CDH increases lung volume, decreases herniation of abdominal viscera, and improves postnatal lung function.

surgeons turned to minimally invasive techniques to adequately visualize and access the fetal trachea without a large hysterotomy. Fetal endoscopic (Fetendo) tracheal clipping, first performed in a human fetus in 1997, involved a maternal laparotomy, followed by 4 trocars through the maternal uterus to access and clip the fetal trachea.⁸⁰ Owing to complications of tracheal damage and vocal cord paralysis related to clipping, this technique evolved to the use of fetoscopic balloon tracheal occlusion, which avoids fetal neck dissection and requires only 1 uterine port (Fig. 6).⁸¹

Fetal endoscopic tracheal occlusion (FETO) is generally performed between 26 and 30 weeks of gestation. Under ultrasound guidance, a trocar is placed through the maternal abdomen into the amniotic cavity, and a fetoscope is inserted through the fetal mouth, and advanced into the fetal trachea. Once the carina has been visualized, the balloon is deployed by inflating it with physiologic solution just proximal to the carina. The correct placement is confirmed on ultrasound imaging and the instruments are removed.⁶⁸ In initial studies, the tracheal balloon was removed at the time of delivery via ex utero intrapartum therapy. However, balloon removal before birth not only allows for the possibility of vaginal birth, but also, in a fetal lamb model, was shown to increase type II pneumocyte differentiation, thereby increasing surfactant production.⁸² Currently, tracheal occlusion is reversed in utero, by a second fetoscopic procedure typically at 34 weeks of gestation.⁶⁸

A multicenter European series of 210 cases of FETO in singleton pregnancies with severe CDH (liver up and lung-to-head ratio ≤ 1) found a 48.0% rate of survival to discharge, with a 47.1% incidence of PPROM. When CDH registry data were used to compare outcomes with expectantly managed fetuses, FETO increased survival from 24.1% to 49.1% in fetuses with left CDH, and from 0% to 35.3% in right CDH.⁸³ A recent metaanalysis of all studies comparing survival outcome between FETO and a contemporary control group found that FETO improves survival compared with standard perinatal care in patients with isolated CDH and severe isolated pulmonary hypoplasia (lung-to-head ratio ≤ 1). Fifty-one of 110 fetuses (46.3%) who had undergone FETO survived to discharge, compared with 6 of 101 (5.9%) in the control group, giving the FETO group a significant survival advantage (odds ratio, 13.32; 95% CI, 5.40–32.87).⁸⁴ The true benefits of FETO are

Fig. 6. Fetal endoscopic balloon tracheal occlusion involves a single intrauterine trocar, through which a fetoscope is introduced into the fetal trachea. A balloon is inflated just proximal to the carina.

difficult to gauge from these studies, because the severity of CDH was not measured uniformly and there was great variability in the postnatal care of these infants. An international, randomized trial to further evaluate the role of fetal therapy in patients with moderate and severe pulmonary hypoplasia (TOTAL trial, www.totaltrial.eu) is ongoing.⁸⁵

Amniotic Band Syndrome

Amniotic band syndrome is a congenital malformation with a broad spectrum of clinical features. The presentation, severity, and outcome depend on location of the bands and timing of fetal damage.^{86–88} Constriction bands at the extremities can lead to pseudosyndactyly or limb amputation (**Fig. 7**), whereas more midline bands can result in craniofacial, thoracic, or abdominal defects, and may be fatal. The etiology of this syndrome is unknown, and theories range from a genetic basis⁸⁹ or early disruption of the germinal disc^{87,90} to traumatic disruption of the membranes later in fetal development.⁹¹

In cases of amniotic band syndrome with extremity involvement, fetoscopic band release may salvage normal development and allow the fetus to maintain limb function.^{92–95} Diagnosis is made on obstetric ultrasound imaging, with findings including distal limb edema and abnormal Doppler flow, with or without visualization of the causative band. Although only small case series have been reported, the limited data suggest that fetuses must have abnormal but present arterial Doppler flow to the distal limb to benefit from intervention.⁹⁴ Moreover, data from our institution demonstrate that patients with single limb involvement tend to fare better than those with multiple involved limbs.⁹⁵ Interestingly, rates of PROM with this procedure seem to be higher than for other fetoscopic procedures, with reported rates up to 78%.⁹³ Although this finding may be related to the small number of cases and the learning curve required with any new procedure, it could also be a byproduct of the inherent membrane problems in these fetuses.⁹³

Fig. 7. Amniotic bands may constrict fetal limbs, leading to pseudosyndactyly or limb amputation. More midline bands can result in craniofacial, thoracic, or abdominal defects, and may be fatal.

Sacrococcygeal Teratoma

Fetuses with prenatally diagnosed sacrococcygeal teratoma (SCT) are at risk for perinatal complications and death, often owing to high-output cardiac failure. Fetal surgery has been proposed for SCT when hydrops and/or cardiac insufficiency are present in utero, particularly at previable gestational ages.⁹⁶ Open fetal surgery has been described, but is associated with a high risk of PPROM and preterm delivery.^{97,98} Minimally invasive procedures for SCT focus on interrupting blood flow to the lesion using a variety of techniques, including coiling, embolization, sclerotherapy, monopolar cautery, laser ablation, and RFA.

In a recent systematic review of 34 cases of minimally invasive fetal intervention for SCT from 1980 to 2013,⁹⁹ overall survival was 44% (14/32) and mean gestational age at delivery was 29.7 ± 4.0 weeks. Cardiac failure conferred a worse prognosis, with only 30% survival (6/20) in this cohort. A subsequent review sought to distinguish between methods of minimally invasive interventions, discriminating between “interstitial” interventions, in which the goal is direct tumor ablation, and “vascular” interventions, in which the target is the feeding vessel to the tumor.¹⁰⁰ Of the 33 cases reviewed, 11 were vascular and 22 were interstitial ablations. Survival was 63.6% (7/11) in the vascular ablation group and 40.9% (9/22) in the interstitial ablation group. The authors hypothesized that reducing the tumor blood supply slowly may be safer than causing tumor necrosis that could lead to hemorrhage into the tumor.

Given the extremely poor outcomes of fetuses with large SCTs and fetal hydrops before viability,^{99,101} available data suggest that fetal intervention does confer a survival advantage. However, because SCT is rare, data are limited to small case series, and randomized trials are likely impossible. Long-term outcomes data are also lacking. Because these procedures are associated with significant risks, they should be reserved only for selected severe cases presenting with both high-output heart failure and fetal hydrops before it is safe to deliver, and should be performed only in specialized centers.⁹⁹

Congenital Cystic Adenomatoid Malformations and Pleural Effusions

Congenital cystic adenomatoid malformations are benign intrapulmonary masses that are classified as either microcystic or macrocystic (≥ 1 cysts >5 mm). The prognosis is generally good, with many lesions regressing or becoming undetectable late in gestation, and most infants are asymptomatic at birth.^{102,103} However, some fetuses present with a lesion large enough to cause a mass effect, which leads to heart and lung compression and pulmonary hypoplasia. The presence of hydrops predicts very poor prognosis, with mortality of up to 100% without prenatal intervention.^{101,104} The cystic adenomatoid malformation volume ratio is a useful sonographic marker for risk of hydrops, and a high cystic adenomatoid malformation volume ratio (≥ 1.6 – 2.0) is often used as an indication for fetal intervention.^{105–107} In recent years, maternal betamethasone has become the first-line treatment of choice for large microcystic congenital cystic adenomatoid malformations, with reduction of cystic adenomatoid malformation volume ratio and resolution of hydrops in more than 80%.^{108,109} However, steroid therapy has not been effective in predominately macrocystic lesions. In lesions with a dominant macrocyst or pleural effusion, in utero drainage can relieve the mass effect of excess fluid to allow for pulmonary development.^{110–112}

Indications and known complications of thoracoamniotic shunt placement are summarized in **Table 4**. In the largest series of thoracoamniotic shunt placement for congenital lung mass or pleural effusion to date, which consisted of 75 fetuses at Children’s Hospital of Philadelphia, shunting resulted in a 55% decrease in congenital

Table 4
Indications for and complications of thoracoamniotic shunt placement

Indications	Complications
<32 weeks of gestation with macrocystic lung lesion or pleural effusion	Preterm delivery PPROM
Presence of hydrops or high risk for pulmonary hypoplasia (ie, mediastinal shift, significant heart or lung compression)	Obstruction Dislodgement Bleeding
Reaccumulation after thoracocentesis	Chest wall deformation (↑ risk with younger gestational age) ¹¹³
Nonlethal karyotype	
Lack of significant anatomic abnormalities	
Infectious etiology excluded (in isolated pleural effusion)	

Abbreviation: PPRM, preterm prelabor rupture of membranes.

cystic adenomatoid malformation volume and complete drainage of pleural effusion in 27% of cases (partial drainage in the remaining 73% of effusions).¹¹² Hydrops resolved in 83% of fetuses (43/53) after shunting, and hydrops resolution was strongly correlated with survival. Survival to birth was 93% (70/75), median gestational age was 36 weeks, and overall long-term survival was 68% (51/75). Fifty-six percent of fetuses were delivered preterm (<37 weeks of gestation), at an average of 10 weeks after shunt placement. Survivors had a median duration of stay in the neonatal intensive care unit of 21 days, with 71% requiring intubation for greater than 24 hours. This series affirms the survival benefit of shunting in these high-risk patients, but underscores the risks inherent to in utero intervention, as well as the intensive neonatal therapy required.

FUTURE DIRECTIONS

The future of fetal therapy is undoubtedly moving toward minimally invasive treatment. As always, the goal of fetal therapy is to provide the best possible outcome for the fetus, while minimizing the risk to the mother. To this end, significant efforts are being made toward decreasing the morbidity associated with fetal intervention, particularly PPRM. A multiinstitution collaboration between University of California San Francisco, the University of California Berkeley, and Caltech is currently focusing on the development of a biocompatible adhesive to preseal amniotic membranes before fetal therapy to prevent PPRM (Fig. 8). Current formulations involve

Fig. 8. A biocompatible adhesive, “Amnioseal” is currently under development, which can be delivered just below the uterus to preseal the fetal membrane before amniotic access.

methyldihydroxyphenylalanine-based polymers inspired by the adhesive properties of mussels' attachment to wet rocks.¹¹⁴

Although fetal surgical intervention is limited to the correction of structural anomalies, prenatal stem cell transplantation and gene therapy have the potential to treat a wide range of genetic conditions. The rationale for in utero stem cell transplantation is to take advantage of the process of normal immune development and introduce "foreign" cells before the fetus distinguishes self from non-self.¹¹⁵ Currently, the most promising applications of fetal stem cell therapy for potential clinical use are in utero hematopoietic stem cell transplantation and in utero mesenchymal stem cell transplantation.¹¹⁶ Clinical trials of in utero hematopoietic stem cell transplantation have had limited success in recipients without underlying immunodeficiency,¹¹⁷ but recent experimental data in a large animal model of intrauterine hematopoietic stem cell transplantation have demonstrated clinically relevant levels of chimerism, supporting the path to clinical trials for inherited hematologic disorders.^{118,119} In utero human fetal mesenchymal stem cell transplantation has been described for osteogenesis imperfecta with promising, but transient results.¹²⁰ Finally, fetal gene therapy also has exciting potential for the treatment of genetic disorders, and recent gene-editing technology such as CRISPR is significantly advancing the field. However, the safety and long-term effect of these therapies must be thoroughly investigated in animal models.^{116,121}

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