



Modern fetal surgery—a historical review of the happenings that shaped modern fetal surgery and its practices

Lauren L. Evans, Michael R. Harrison

Department of Surgery, Division of Pediatric Surgery, University of California, San Francisco, CA, USA

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Correspondence to: Michael R. Harrison, MD. 550 16th Street, 6th Floor UCSF #0570, San Francisco, CA 94158, USA. Email: Michael.Harrison@ucsf.edu.

Abstract: The history of fetal surgery is one of constant evolution. Over the last 50 years, fetal surgery has progressed from a mere idea to an internationally respected innovative field of surgery. This article aims to provide a historical review of how the enterprise of maternal-fetal surgery came to be its modern version. This review is less focused on the history of specific therapies for a relatively small number of conditions, and more on how the whole field of maternal-fetal surgery evolved. The various internal and external influences that steered the field's evolution are discussed in chronologic order. Since the start of modern fetal surgery in the 1980s, large paradigm shifts have characterized the growth of the field as a whole. Innovative interventions are now based on physiologic manipulation as opposed to simple anatomic repair, fetoscopy has become the more frequently preferred surgical approach, and rigorous scientific evaluation with randomized controlled trials is now the standard expected by the community. In a very similar fashion to when the field first began in the early 1980s, recently community's leaders have risen to protect the integrity of maternal-fetal surgery by publishing ethical guidelines for innovation and clinical practice. This incredible history of innovation, rigorous science and ethical contemplation is the foundation on which modern maternal-fetal surgery rests.

Keywords: Fetal surgery; fetal therapy; innovative therapies; fetoscopy; fetal ultrasonography

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Introduction

Since it was founded, the field of modern fetal surgery has been in constant evolution. This article is a historical review of how the field of maternal-fetal surgery has evolved. We highlight the milestones and events, both good and bad, that made fetal surgery into the successful clinical enterprise it is today. The historical events included are not a comprehensive review of the innumerable noteworthy events in the history of fetal therapy, nor is this review unbiased, since one of the authors lived through it. A more comprehensive review of the field's major historical milestones is summarized in *Table 1*.

The history of maternal-fetal surgery is essentially one

of experimentation and innovation inherently loaded with socially charged ethical dilemmas (44). Addressing the field's unique, and provocative, ethical considerations, has made the enterprise of fetal therapy one of the most successful stories of innovation in history. However, the evolution of maternal-fetal surgery has not been without controversy or criticism (60). The application of new innovative therapies to pregnant women has forced the development of new guidelines for ethical innovation and human trials.

Fetal surgery emerged in 1961 when Sir William Liley completed the first percutaneous fetal transfusion (1). By 1964, Asensio and Adamsons reported direct access to fetal circulation via open hysterotomy (2,61). Work in fetal transfusion around the world resulted in the 1966

Table 1 Major milestones in the evolution of modern maternal-fetal surgery

Milestone	Year	Location	Key contributors
Needle-based intrauterine blood transfusion for Rh disease	1961	Auckland, New Zealand	Liley (1)
Hysterotomy for fetal vascular access for complete exchange transfusion for Rh disease	1964	San Juan, Puerto Rico	Asensio, Figueroa-Longo, Pelegrina (2)
International meeting of innovative researchers of fetal transfusions	1966	Aspen, CO	(3)
Diagnostic fetoscopy for obtaining fetal blood samples	1974	New Haven, CT	Hobbins, Mahoney (4)
Diagnostic fetoscopy with 0.7mm endoscope	1980	London, United Kingdom	Rodeck (5)
Sheep model for experimental pathophysiology and intervention feasibility	1980	San Francisco, CA	Harrison, de Lormier (6-8)
Primate model for maternal safety with fetal intervention	1981	San Francisco, CA	Harrison, Nakayama, Adzick (9-11)
Primate model of congenital hydrocephalus	1981	NIH; Bethesda, MD	Hodgen, Michejda (12,13)
Fetal lamb model of congenital hydronephrosis	1981	San Francisco, CA	Harrison, de Lorimier (14)
Shunt-based fetal repair for LUTO [†] ; Open in-utero repair for LUTO [†]	1982	San Francisco, CA	Harrison, Globus, Filly, Jonsen (15)
Placement of fetal ventriculoamniotic shunt for hydrocephalus	1982	Denver, CO	Clewell, Shikes (16)
Ultrasound-guided direct umbilical vessel puncture for transfusion	1982	Copenhagen, Denmark	Bang, Bock, Trolle (17)
Inaugural meeting of the IFMSS [‡] —“Unborn: Management of the fetus with a correctable congenital defect”	1982	Kroc Foundation; Santa Ynez, CA	Harrison (18)
First edition of <i>Unborn Patient: Prenatal Diagnosis and Treatment</i> published	1984	San Francisco, CA	Harrison, Golbus, Filly
Primate model for spina bifida	1984	Washington, D.C.	Michejda (19)
Open in-utero CCAM [§] resection	1984	San Francisco, CA	Harrison, Golbus (20,21)
<i>Fetal Diagnosis and Therapy</i> founded as the academic journal of the IFMSS [‡]	1986		Michejda, Pringle
Open in-utero repair of CDH [¶]	1986	San Francisco, CA	Harrison, Golbus (22)
Fetoscopic laser coagulation of vascular connections between fetoplacental circulations for TTTS ^{††}	1990	Salt Lake City, UT	De Lia, Cruikshank, Keye (23)
Open in-utero aortic valvuloplasty	1991	London, United Kingdom	Maxwell, Allan, Tynan (24)
Fetal lamb model for fetoscopic surgery with CO ₂ ^{‡‡} insufflation	1992	San Francisco, CA	Harrison, Estes (25)
NIH ^{§§} trial—Open in-utero CDH [¶] repair	1993	San Francisco, CA	Harrison, Filly (26)
Fetal lamb model for endoscopic MMC ^{§§§} repair	1993	Nashville, TN	Copeland, Bruner (27)
Fetal lamb model of TO ^{¶¶} for CDH [¶]	1994	San Francisco, CA	Harrison, Hedrick (28)
Fetoscopic umbilical-cord ligation of an acardiac twin	1994	Detroit, MI	Quintero, Romero (29)
EXIT ^{†††} procedure for airway obstruction	1995	San Francisco, CA	Harrison, Goldberg (30)
Percutaneous diagnostic fetal cystoscopy for etiology of lower urinary tract obstruction	1995	Detroit, MI	Quintero, Evans (31)
Fetal lamb model for open MMC ^{§§§} repair	1995	San Francisco, CA	Meuli, Meuli-Simmen, Adzick (32)

Table 1 (continued)

Table 1 (continued)

Milestone	Year	Location	Key contributors
Fetal lamb model for fetoscopic surgery with amnioinfusion—‘Fetendo’	1996	San Francisco, CA	Harrison, Skarsgard (33)
Open in-utero resection of fetal SCT ⁺⁺⁺	1996	San Francisco, CA; Philadelphia, PA	Graf, Harrison (34); Adzick, Quinn (34,35)
Fetoscopic laser ablation of fetal SCT ⁺⁺⁺	1996	Hamburg, Germany	Hecher, Hackeloer (36)
Fetal lamb model of fetoscopic in-utero TO ^{¶¶} procedure for CDH [¶]	1996	San Francisco, CA	Harrison, Skarsgard (37,38)
Fetoscopic repairs of MMC ^{§§§} attempted	1996	Nashville, TN	Brunner, Tulipan, Richards (39)
Fetoscopic TO ^{¶¶} with tracheal clip for CDH [¶]	1997	San Francisco, CA	Harrison, VanderWall (40)
Successful open repair of fetal MMC ^{§§§}	1997	Nashville, TN	Brunner, Tulipan (41,42)
“Eurofoetus” Consortium founded by European Commission—forms European consortium of fetal treatment centers, collaboration with Karl Storz	1998	European Commission; Brussels, Belgium; Karl Storz; Tuttlingen, Germany	Deprest (43,44)
Eurofoetus trial—Multi-center RCT ^{¶¶¶} for endoscopic laser coagulation for severe TTTS ^{††} . First European RCT ^{¶¶¶}	1999	Poissy, France	Senat, Ville (45)
NIH ^{§§} Trial—Fetoscopic TO ^{¶¶} for CDH [¶] . First US RCT ^{¶¶¶}	1999	San Francisco, CA	Harrison, Albanese (46)
Initial planning for MOMs ⁺⁺⁺⁺ trial starts during the 19 th annual meeting of the IFMSS [‡]	2000	Nantucket, MA	Adzik, Flake, Farmer (3)
Percutaneous therapeutic fetal cystoscopy—ablation of posterior urethral valves	2000	Tampa, FL	Quintero, Bukkapatnam (47)
Open resection of fetal pericardial teratoma	2000	San Francisco, CA	Sydorak, Albanese (48)
Fetoscopic TO ^{¶¶} with detachable tracheal balloon	2001	San Francisco, CA	Harrison, Filly (49)
Fetal endoscopic TO ^{¶¶} balloon with fetoscopic balloon removal	2001	Leuven, Belgium	Deprest (50)
Open resection of fetal cervical teratoma	2001	San Francisco, CA	Hirose, Farmer (51)
MOMs ⁺⁺⁺⁺ NICHD ⁺⁺⁺⁺ trial—RCT ^{¶¶¶} evaluating open fetal repair of MMC ^{§§§}	2002	San Francisco, CA; Philadelphia, PA; Nashville, TN	Adzick, Farmer, Spong, Brock, Johnson, Sutton, Gupta, Tulipan, D’Alton (52)
NIH ^{§§} Trial—selective fetoscopic laser photocoagulation for TTTS ^{††}	2002	Cincinnati, OH; Philadelphia, PA; San Francisco, CA	Crombleholme, Young (53)
Initial investigations into preemptive membrane sealant technique to prevent amniotic leak after fetoscopy	2005	San Francisco, CA	Harrison, Cortes (54)
North American Fetal Therapy Network is established	2005		(55)
TOTAL trials—multicenter RCTs ^{¶¶¶} evaluating FETO ^{§§§§} in the spectrum of CDH [¶] severities	2009	Leuven, Belgium	Deprest (56)
Maternal-Fetal Medicine Task Force established by the NICHD ⁺⁺⁺⁺	2011	Bethesda, MD	(3)
CECAM trial—phase I trial for fetoscopic repair of MMC (myelomeningocele)	2013	Sao Paulo, Brazil	Pedreira (57)
North American Fetal Therapy Network publishes guidelines for medical innovation in maternal-fetal therapy	2015	Providence, RI	Luks (58)

Table 1 (continued)

Table 1 (continued)

Milestone	Year	Location	Key contributors
Phase 1 trial of In Utero stem cell transplantation for treatment of fetal alpha thalassemia major	2017	San Francisco, CA	MacKenzie (59)

[†], Lower Urinary Tract Obstruction; [‡], International Fetal Medicine and Surgery Society; [§], Congenital Cystic Adenomatoid Malformation; [¶], Congenital Diaphragmatic Hernia; ^{††}, Twin-Twin Transfusion Syndrome; ^{‡‡}, Carbon Dioxide; ^{§§}, National Institute of Health; ^{¶¶}, Tracheal occlusion; ^{†††}, Ex Utero Intrapartum Treatment; ^{‡‡‡}, Sacrococcygeal Teratoma; ^{§§§}, Myelomeningocele; ^{¶¶¶}, randomized, controlled trial; ^{††††}, Management of Myelomeningocele; ^{‡‡‡‡}, National Institute of Child Health and Human Development; ^{§§§§}, Fetoscopic Endoscopic Tracheal Occlusion.

international meeting of innovative researchers in fetal transfusions (3). Around the same time, the high morbidity and mortality with open interventions quickly came to light. Open hysterotomy was abandoned and it would be over a decade before open fetal surgery would be investigated again (3). Early innovators in fetal therapy were ahead of their time. Better supportive measures, including anesthesia and prenatal imaging, were needed before fetal surgery could truly emerge and reach its full potential.

An idea becomes reality—the foundation of modern maternal-fetal surgery

It's generally recognized that modern fetal surgery hatched in the mind of Michael Harrison (3,44). In 1969, as an eager intern at Massachusetts General, Harrison assisted Dr. Hardy Hendren with a congenital diaphragmatic hernia (CDH) repair. Despite Harrison's post-op vigil in the intensive care nursery, the infant passed away the following day (62,63). The frustrating outcome sparked his first "crazy idea" of repairing a defect before birth. This first experience would shape Harrison's career, eventually draw him to the University of California San Francisco (UCSF), and ultimately make CDH central to the development of fetal therapy.

After residency, Harrison spent 6 months in Oslo, Norway investigating the natural history of CDH. Norway's national registry tracked all neonatal and prenatal deaths with autopsy reports, and provided a unique opportunity to determine the true incidence and mortality of CDH (63). Harrison uncovered that 50% of infants with CDH died before they could be accounted for officially. He dubbed the previously unappreciated deaths the "hidden mortality" (64). Harrison's discovery highlighted that the natural history of a disease discovered before birth was not necessarily the same if diagnosed after birth (63). Establishing the pathophysiology and evolution of fetal pathology

before attempting intervention remains a cornerstone of innovation in fetal therapy.

Diagnostic fetoscopy and fetal ultrasound (US) were developed in parallel in the 1970s–1980s. In 1974, Hobbins and Mahoney reported the first successful diagnostic fetoscopy (4), however, further adoption of therapeutic fetoscopy was hindered by difficulty and invasiveness.

At King's College Hospital, Rodeck was a fierce champion of fetoscopic innovation for both diagnostic and therapeutic uses (5). Simultaneously, the development of fetal US gained enormous momentum. In 1977, Garrett and Kossoff reported the accurate prenatal diagnosis of CDH with US (3). By 1982, Bang reported the first US-guided direct umbilical vessel puncture (17). Just as wide availability of reliable ultrasound made fetoscopy essentially obsolete, Rodeck successfully achieved direct access to fetal circulation under fetoscopic guidance (65). The improved accuracy and wide availability of US helped usher in the modern era of fetal surgery (3,63).

As prenatal diagnostics reached new heights with landmark advancements in fetal US, Harrison arrived at UCSF. Al DeLorimier's work in fetal physiology and his fetal lamb model of CDH made Harrison confident UCSF was the best place to start the enterprise of maternal-fetal surgery (63). Almost immediately, Harrison adopted the fetal-lamb model and began work establishing the pathophysiology of CDH and the physiologic effects of repair (6–8). Harrison and deLorimier's stepwise experimental approach in the fetal lamb model established both pathophysiology and feasibility of repair. Their paradigm had 4 central steps: surgically create a lesion, evaluate the resulting pathophysiology, perform the repair, and study the resulting physiologic effects (63). Harrison and deLorimier's experimental methodology for animal model work was rapidly adopted and remains the gold standard for initial investigations in fetal therapy today (66). Harrison went on to establish the pathophysiology and

feasibility of repair in a large variety of neonatal pathologies, including fetal hydronephrosis due to lower urinary tract obstruction (LUTO) (14,67), hydrocephalus, and eventually myelomeningocele (MMC).

Harrison's team established a primate model for hysterotomy at the University of California Davis in 1981. For each intervention, the primate model established the corresponding maternal-fetal safety profile (9-11). The monkey colony also enabled investigators to examine long-term effects on the mother following intervention. The close evaluation of maternal future fertility and reproductive potential led to the elimination of metal staples and the invention of absorbable staples for hysterotomy closure, a key step in ensuring safe maternal-fetal surgery (63). At the National Institutes of Health (NIH), Hodgen and Michejda established a primate model of hydrocephalus (12,13). The early work establishing an animal model and experimental paradigm for repair of fetal pathologies set the stage for the successes the following year.

Fetal hydronephrosis due to LUTO and fetal hydrocephalus were the first disease processes to attract serious attention for fetal interventions (63). Both had established animal models and were highly amenable to ultrasound evaluation. In 1982, Harrison, and the early members of the UCSF Fetal Treatment Program (FTP), brought the concept of fetal therapy to life. In rapid succession, the first two fetal interventions were completed, both for congenital hydronephrosis. First, was the successful in-utero placement of a fetal vesicoamniotic shunt for LUTO (68). Shortly after, and unexpectedly, a desperate case presented with severe LUTO and complete oligohydramnios, not amenable to stent placement (63). In March, just weeks after their first triumph, the first ever open intervention for decompression of the fetal urinary system was a success (15,63). By June, Clewell successfully placed a ventriculoamniotic shunt for fetal hydrocephalus (16). In just a few short months, the young enterprise of maternal-fetal surgery was off to a rapid start.

The UCSF FTP was essential to the early success of the enterprise. Frustrations with limited treatment options for many fetal pathologies brought together the disciplines involved in perinatal medicine. Collaboration between obstetrics, radiology, pediatric surgery, pediatrics and neonatology established the high-quality patient care required to deliver effective perinatal fetal care. The newly created UCSF FTP became the means of facilitating close collaboration between medical specialties that otherwise would not have worked together closely (63). This

collaborative, multi-disciplinary delivery of patient care became the paradigm for human fetal surgery that guided the UCSF team and programs that later emerged (62).

Promising but unproved

A massive media frenzy erupted in response to reports of the first successful fetal interventions. The newly born enterprise had already caught the attention of the world. Harrison recognized early on that the enterprise was very fragile, and the relationship between fetal therapy and the world would need to be carefully nurtured. The delicate ethical issues of maternal-fetal surgery had the potential to create a hugely negative reaction from the public and the entire field of medicine (62). The early pioneers of fetal surgery knew that the future of the enterprise depended entirely on how the field would come to be viewed in the eyes of patients, medical colleagues and the general public (62).

The early international leaders of fetal therapy made a concerted effort to band-together and create a unified enterprise. In July of 1982, the UCSF team invited a multidisciplinary group of 24 experts, from 13 centers representing 5 countries, to gather at the Kroc Foundation property in Santa Ynez, CA. That first meeting, "Unborn: Management of the fetus with a correctable congenital defect", had Sir William Liley as an inspirational keynote speaker. In comfortable informality that encouraged openness, the group had frank, productive discussions on the future of the enterprise and strategies for moving forward (63). The group drafted a set of mutually agreed upon ethical guidelines for fetal interventions that were later published in a consensus statement (18). The guidelines first put forward by the group remain the foundation for the ethical practice of maternal-fetal surgery today (Table 2) (18). Spearheaded by Manning, the first two national registries for outcomes reporting were established for fetal hydrocephalus and fetal hydronephrosis. Just 4 years later, Manning published the registries early results showing shunts for congenital hydrocephalus produced discouraging outcomes. His report led to an international voluntary moratorium on shunts for hydrocephalus lasting almost 20 years (63,68). Many of the participants of that initial meeting also contributed to the first textbook in the field: *The Unborn Patient: Prenatal Diagnosis and Treatment* by Michael Harrison, Mickey Golbus, and Roy Filly. Participants Michejda and Pringle collaborated on and later founded *Fetal Diagnosis and Therapy* in 1986, a journal that became the official academic voice of the International

Table 2 Criteria for consideration of maternal-fetal surgery as outlined by the consensus statement from the International Fetal Medicine and Surgery Society after their inaugural meeting (18)

The disorder is the result of a structural defect that interferes with organ development and repair may result in normalization of fetal development

The natural history of the disorder has been defined in the untreated human fetus, including the spectrum of severity and associated prognoses

Prenatal diagnosis is accurate and can determine the severity of disease, evaluate for disease progression over time, and identify any additional congenital anomalies

There are no effective alternative postnatal treatment options otherwise available

The pathophysiology of the disorder and feasibility, efficacy and safety (fetal and maternal) of the proposed intervention have been validated experimentally in a pre-clinical animal model

Interventions are performed by a collaborative multidisciplinary provider team at a specialized fetal treatment center

Access to both high-risk obstetric and neonatal intensive care units as well as to bioethical and psychosocial consultation

All cases, regardless of outcome, are reported to a fetal treatment registry or are published in the medical literature, ideally both

Informed parental consent includes extensive family counseling, including potential risks and benefits of the intervention, all alternative treatment options, and familial agreement to continued long-term follow-up

Fetal Medicine and Surgery Society (IFMSS) (63). The group reconvened a year later and formally became the IFMSS (44). Potentially the most important standard established at the first meeting, and reinforced at every IFMSS meeting since, was participant's commitment to their responsibility for the stewardship of the field of fetal therapy as a whole (63).

Despite those early efforts, Harrison's apprehensions about the delicacy of the young enterprise would soon become a reality. Harrison describes the initial enterprise as "thriving, bawling, vibrant and rapidly growing... with the exploration of many new therapies" (63). Over the next decade, the early unfettered success of the field's inaugural years would give way to tribulations that almost lead to its premature (stillborn) demise. However, the lessons learned from early hurdles would help shape the future of the enterprise on an international scale (63).

By the early 1980s, the natural history and pathophysiology of CDH was established (69) and the feasibility of fetal repair had shown promising results in a fetal lamb model (6-8,70,71). In 1984, Harrison's group performed the first open fetal repair of severe CDH (63). Between 1983 and 1989, the group completed a total of 6 open fetal repairs for the most severe cases of CDH. The experience was frustrating as well as disheartening. Despite the promising results with the initial lamb work, the human mortality rate was 77% (63). Most discouraging, 5 of 6 infants were found to have liver herniation, which

made them unreparable (72,73). For the first time, the experimental results established in an animal model were not indicative of the clinical outcomes (72).

The first experience confirmed that outcome heavily depends on the presence of liver herniation and informed the decision to exclude patient's with liver herniation in future studies. In 1986 the first successful open fetal repair for CDH was completed and by 1990 the group reported 2 successful repairs (22). With a few wins under their belt, Harrison's group embarked on planning a proper NIH-funded phase I trial evaluating open fetal repair for CDH (26). Submitting a novel fetal therapy to a rigorous trial was bold and dangerous but the trial was a coming of age moment. It put modern fetal therapy on the map, while simultaneously almost causing the total ruin of the whole enterprise (63). An unprecedented amount of work was required to get the trial through the approval processes at the NIH and UCSF Committee on Human Research (CHR) (63). But in 1994, after a grueling 2-years of effort, the trial opened (26). Unfortunately, the real challenges had yet to start.

As the trial got started, initial data from a primate model yielded results supporting the use of nitroglycerin for prevention of preterm labor after hysterotomy (63). Optimistic about its potential clinical impact, maternal nitroglycerin was administered intra-operatively in patients enrolled in the trial. While nitroglycerin resulted in excellent tocolysis, it also caused several patients to develop severe pulmonary edema, resulting in a disaster that endangered

the enterprise and temporarily shut down the FTP. Fortunately, the team's crash investigation revealed that the soluble propylene glycol was the culprit (74,75). However, for the first time, a fetal intervention had resulted in serious, and thankfully reversible, maternal sequelae. Nitroglycerin use was rapidly abandoned but damage had been done, and with serious ramifications, the effects of which would be felt for years.

Trial protocols were immediately suspended and both the CHR and NIH initiated investigations. Overnight, the trial transformed into a focus of anxiety and hostility from the CHR. While the majority of individuals remained supportive, a small group of obstetricians completely lost confidence in the enterprise. They viewed the FTP as a significant maternal threat created by desperate attempts to fix already doomed fetuses. Just after the NIH announced their investigation, Harrison was asked to appear at an urgent Obstetrics and Gynecology department meeting to discuss the future of the FTP. Knowing well that the enterprise of fetal therapy could end that day, Harrison stood alone at that meeting and defended the fledgling field of maternal-fetal surgery for 7-hours (63).

The events of that day would forever leave a mark on fetal therapy at UCSF and arguably influence the course of the international enterprise. The UCSF FTP was dissolved on the spot and relationships with collaborators, as well as the CHR, were shredded. Eventually the trial re-opened but the impact of events lasted. While difficult, the experience proved to be a necessary step to strengthen fetal therapy at UCSF. Immediately after leaving the meeting, Harrison started restructuring fetal treatment at UCSF. The sudden collapse of the FTP almost immediately led to the founding of the UCSF Fetal Treatment Center that exists today (63).

The CDH trial was completed in 1996 after a total of 4 repairs. Results were disappointing. They had previously shown that fetuses with the most severe defects (i.e., herniation of the liver into the chest) could not be fixed and now this trial showed that milder cases did not need in utero repair because, they did just as well with repair after birth (26). Harrison immediately called a moratorium on open fetal repair of CDH. The trial's greatest value was in forcing change and growth of the enterprise of fetal surgery. The lessons learned while navigating the challenges created by the trial would inform the gold-standard research practices that are a cornerstone of the enterprise today. Harrison's early concerns proved correct. The field of fetal therapy was fragile. It could be derailed at any moment and had proven to be quickly demonized by previous supporters.

Despite the ongoing turmoil surrounding the CDH trial, landmark events in maternal-fetal surgery continued. Innovation in fetoscopy and the availability of smaller, less invasive equipment contributed to the revival of fetoscopic and minimally invasive interventions in the late 1980s (76). The further development of fetoscopic capabilities expedited advancements in both animal models and clinical practice. In the 1990s, Rodeck at King's College, Nicolaides at Harris Birthright Centre, and Deprest in Leuven, championed the European resurgence of fetoscopy. Early adoption at major European training centers expedited the dissemination of fetoscopic interventions throughout Western Europe (44).

Early advances in fetoscopy resulted in the rapid adoption of fetoscopic approach for treatment of twin-twin transfusion syndrome (TTTS). De Lia reported the first use of fetoscopic directed laser coagulation for TTTS in 1990 (23). The availability of a minimally invasive option inherently well suited to laser-based interventions, led to the rapid uptake of fetoscopic interventions for TTTS. In just a few years, the adoption of laser coagulation under fetoscopic guidance was steadily increasing in the US and across Europe (77,78).

The application of fetoscopy was being explored across the field of fetal intervention. Quintero, and pediatric urology group at Wayne State, developed percutaneous fetal cystoscopy, reporting the diagnostic use (31) and later its therapeutic use (47). The simultaneous innovation in fetoscopy at several major centers all over the world led to the rapid advancement of fetoscopic techniques. The advances in fetoscopy during the early 1990s were the steppingstones to establishing the field of modern fetoscopic surgery.

Spearheaded by Harrison's group at UCSF, in 1992 therapeutic fetoscopy was developed in a fetal lamb model. The technique was dubbed "Fetendo". The unified international enthusiasm for fetoscopic interventions reflected the community's high hopes that fetoscopy would finally be the answer to decreasing the risk of premature preterm rupture of membranes (PPROM) and preterm labor, allow for earlier fetal intervention and decrease fetal risk overall (25). Work in animal models led to the development of amnioinfusion (79), established fetal safety with intra-uterine pressures of 20 mmHg or less (33), and demonstrated preservation of uteroplacental oxygen delivery with fetoscopy (80). The stage was set for modern fetoscopic surgery.

As the groundwork for modern fetoscopic surgery was

being established, another major shift in the philosophy of fetal interventions was occurring. In the early 1990s, fetal interventions moved away from purely anatomic repairs. Instead, innovative new interventions aimed to strategically manipulate physiology to induce a desired outcome. In the early 1990s, Harrison's group encountered a rare fetal condition in which fetal tracheal obstruction, usually laryngeal atresia, led to overgrowth of the fetal lungs, or "superlungs". Dubbed CHAOS (Congenital High Airway Obstruction Syndrome) by Martinez-Ferro, a research fellow, this discovery led the team down a new path for growing the fetal lung in CDH (81). In 1993, Wilson's group from Boston Children's Hospital reported that fetal tracheal occlusion (TO) results in tremendous lung growth (82) and parallel growth of the vasculature (83). These landmark findings helped usher in a new way of approaching fetal intervention and contributed to the rise of a novel approach to fetal CDH.

From 1992 to 1996, after halting open repair of CDH, Harrison's group focused on the experimental animal work that laid the groundwork for fetoscopic TO for CDH. The "plug the lung until it grows" (PLUG) approach to reversibly occlude the fetal trachea showed promising results in a fetal lamb model (28). Further development and subsequent refinement of the PLUG approach (84) enabled the development of the Fetendo-plug, an internal foam plug (37), and Fetendo-clip, an external tracheal clip (40). Both techniques were initially developed with an open approach but quickly adapted to fetoscopic approaches. The group's early work culminated in 1997 with success of the first in-human fetal Fetendo-clip procedure (40). Simultaneously, the group developed the Ex Utero Intrapartum Treatment (EXIT) procedure for neonatal upper airway occlusion. The timely clinical readiness of the EXIT procedure ensured the safe reversal of iatrogenic TO in neonates that had undergone prior fetal intervention for CDH (30). Since the time it was first described, the EXIT procedure has been widely adapted to accommodate a range of indications and interventions that benefit from use of continued placental support for fetal oxygenation (51,85-87).

The 1990s would see one more evolutionary milestone for the fetal therapy enterprise that would lead to the first fetal intervention for a non-lethal lesion. The rising interest in fetal intervention for MMC began in the early 1990s. The shift in focus to the repair of a non-lethal lesion is further evidence of the evolving viewpoint of the community. The general acceptance, and later adoption, of fetal intervention for MMC indicates that, for the first

time ever, the field of maternal-fetal surgery was ready to accept the risks of fetal surgery in an effort to reduce post-natal morbidity (3). The openness to fetal intervention to improve morbidity alone despite perioperative risks, is likely also a reflection of advancing surgical techniques and, as a result, reduced perioperative risk.

Several animal models were developed over the course of the 1980s and early 1990s. Since the earliest data from Michejda's work in primates at the NIH, animal work has produced promising results. The fetal lamb model of repair was carried out at UCSF by Meuli, Meuli-Simmen and Adzick. Overall, reported outcomes after repair have indicated improved neurological function, better distal neurologic function, and reversal of the associated Arnold-Chiari II malformation (19,32,88-90).

After demonstrating feasibility in an animal model (27), Bruner and the group at Vanderbilt in 1996 reported the first 2 fetal repairs of MMC, both endoscopic. The group quickly abandoned the endoscopic technique due to a high rate of fetal mortality (39), and went on to complete the first open repair (39,41,91,92). Almost simultaneously, Adzick reported what they believed to be the first open repair for fetal MMC (93). The mortality seen with the initial endoscopic experience in fetal MMC caused the US enterprise to discard endoscopic techniques for MMC for almost 20 years. While development of endoscopic techniques would be re-adopted in Europe (94-97), the US community was more tentative. Today, Farmer's group at UC Davis continues to spearhead evaluation of endoscopic techniques with unprecedented animal model work (98-104). The conversation comparing open and endoscopic approaches is ongoing (105-107).

A standard is established—the rise of randomized, controlled trials and ethics of a rapidly expanding enterprise

The early challenges around the first NIH trial for CDH raised a wide array of troublesome problems. However, addressing those issues are directly responsible for the more resilient version of the enterprise that exists today. Three momentous trends, each a pillar of modern fetal therapy, were set in motion. (I) The innovation and adoption of fetoscopic techniques, (II) the rise of novel interventions developed based on physiologic rationale, as opposed to anatomy, and (III) the community's recognition of the need for randomized, controlled trials (RCT) and rigorous scientific evaluation of fetal interventions to inform clinical

practice (63).

RCTs are widely recognized as the key to advancing medical interventions and therapies. However, RCTs are challenging—randomization can be ethically difficult, studies are often incredibly expensive and difficult to fund, protocols can be problematic to organize, and trials are often difficult to execute well. One of the earliest calls for RCTs was Mannings' report on the early findings of the national outcomes registries in 1986 (68). The NIH CDH trial highlighted the need for more rigorous practices. The lessons learned from navigating the CDH trial heavily contributed to the success of the first few RCTs.

In Europe, support from the European Commission transformed European maternal-fetal surgery into a powerhouse of innovation. The establishment of the Eurofetus Consortium (EFC) in 1998 marked the beginning of a new era. Funded by the European Commission, the EFC made the resources needed for rapid clinical innovation and sound scientific evaluation readily available across Europe. The European Commission supported the fetal enterprise in three essential ways: (I) it established a consortium of major fetal treatment centers, (II) it solidified a collaborative relationship with Karl Storz to stimulate innovation in fetoscopic technology, and (III) it increased the amount and long-term availability of funding dedicated to the field (43,44). In doing so, the EFC effectively dropped the barriers to executing RCTs, made specialized fetoscopic instruments more accessible, and removed the roadblocks to international collaboration across Europe.

The first 2 RCTs of modern maternal-fetal surgery both began in 1999. In Europe, with support from the newly minted EFC, a multi-center RCT comparing fetoscopic laser ablation and amnioreduction for the treatment of severe TTTS started in January. Two years later, after 142 women were randomized, the study was closed early after the interim analysis showed clear superiority of laser ablation. The study was the first step to establishing endoscopic laser coagulation as the preferred intervention for severe TTTS before 26 weeks (45). Follow-up studies reported superior neurological outcomes at 2–4 years of age which further supported the use of laser ablation (108,109). The impact the EFC would have in Europe was evident from the start. In just a few years, the EFC supported the work that would make fetoscopic laser ablation for severe TTTS the first intervention with clearly established benefit and acceptable risks.

In the US, Harrison's group had continued to develop fetoscopic techniques for reversible fetal TO. After

developing the Fetendo-plug and Fetendo-clip, they next adapted a detachable balloon used in interventional radiology for occlusion of the fetal trachea. The balloon could be placed by fetoscopic bronchoscopy (49). These early techniques were applied clinically in 2 successful in-human cases, both with encouraging results suggesting improved survival (46). In April 1999, patient recruitment began for the first US RCT evaluating the Fetendo-balloon for treatment of severe CDH, excluding patients with liver herniation. After 24 patients were randomized, the trial ended early in July 2001 after interim analysis showed equivocal results. Additionally, all of the mothers in the intervention cohort developed PPRM and preterm labor causing significant maternal morbidity as well as lower average infant birthweight and gestational age at birth (110). Despite far greater prematurity in the intervention group, survival was equivalent to the control group born near term. This suggested that TO had some benefit which helped motivate continued work developing balloon TO in Europe.

As the field's inaugural RCTs were taking place, planning for the Management of Myelomeningocele (MOM) trial was underway. In the late 1990s, the groups at Vanderbilt and CHOP continued growing their experience with open repair of fetal MMC with promising neurological outcomes (42,111). By the end of the year, the calls for more rigorous evaluation of intervention for fetal MMC increased (112). In Sep 2000, at the 19th annual meeting of the IFMSS, early trial collaborators started planning for an RCT (3). Several key decisions were made early: (I) involvement would be limited to only 3 centers (CHOP, Vanderbilt, UCSF), (II) no other centers in North America would offer repair during the trial, (III) surgical techniques would be standardized, and (IV) initial patient assessment would be done by an independent center (George Washington University) (3). Two years of careful planning with close collaboration between all involved centers went into creating the MOMs trial, a multi-center RCT evaluating open fetal repair for MMC. Patients would be screened by the team at George Washington University and, if selected, referred randomly to one of the three MOMs surgical centers. The trial would be expensive but created a way to rigorously evaluate an intervention for an otherwise prohibitively rare pathology. After obtaining funding from the National Institute of Child Health and Human Development (NICHD), the trial opened in 2002, though it would be a year before the first patient was enrolled (3). The international enterprise of maternal-fetal surgery would be changed forever.

From 2002–2010, a total of 299 mothers were referred to a MOMs surgical site, of which 183 were randomized. On December 7th 2010, the data safety and monitoring board recommended the trial terminate due to the clear efficacy of prenatal repair (52). Fetal repair resulted in decreased need for ventriculoperitoneal shunt placement for hydrocephalus, reversal of hindbrain herniation, and improved ability to walk at 30 months (52). However, the rate of maternal complications were not insignificant and the investigators emphasized the maternal morbidity associated with open repair (52).

The success of the MOMs trial was a landmark accomplishment. The creative trial design proved that a multi-center RCT was possible for even rare fetal pathologies. The trial highlighted collaboration among investigators and cooperation between centers as cardinal to the thorough evaluation of fetal therapies, a concept first made evident by the early successes of the EFC. The MOMs trial was a testament to what the cooperative efforts of the fetal therapy community were capable of accomplishing. MOMs set a new standard for the international field of maternal-fetal surgery. High-quality evidence demonstrating the efficacy and safety of fetal therapies was becoming the community's expectation and solidified the need for more rigorous evaluation of interventions (113).

As the MOMs trial was ongoing, investigation of balloon TO for CDH continued in Europe and would eventually become a landmark international multi-center RCT. From the late 1990s into the 2000s, the percutaneous fetoscopic Endoluminal Tracheal Occlusion (FETO) procedure was developed by a European consortium, the FETO task force, established to facilitate the investigation and development of balloon tracheal occlusion for CDH (44). The FETO task force made advances in the timing and techniques for the FETO procedure, that included refining percutaneous uterine access for balloon placement (50). Discoveries made by Flageole and O'Toole improved the understanding of the pathophysiology of tracheal occlusion (114,115) and led to the development of a second procedure to facilitate timed in-utero removal of the balloon (50,116). Not only did timed in-utero balloon removal improve outcomes, but, for the first time ever, also made vaginal delivery possible after fetal intervention. A landmark in improving maternal morbidity by eliminating risks related to C-section delivery.

In 2001, with support from the EFC, a multi-center prospective observational trial (FETO trial) evaluating the FETO procedure for severe CDH was launched. From 2001 to 2008, 210 FETO procedures were performed and

resulted in significant survival benefit in CDH (117,118). Their initial experiences led to further refinement of the balloon, to ensure complete tracheal occlusion, and techniques for balloon removal (50,118). PPROM continued to be a challenge and was found to increase risk of early delivery and infant mortality 5-fold (118).

With the ongoing success of the MOMs trial, the FETO consortium acknowledged that an RCT was required to substantiate the survival benefit shown in the FETO trial (56). Following the blueprint established by the MOMs trial, two multi-center RCTs, named the TOTAL trials, were designed to evaluate the FETO procedure performed either early or late in pregnancy in cohorts of CDH with both severe and moderate pulmonary hypoplasia. The trial design employed standardized surgical techniques, postnatal management and guidelines for patient selection based on rigorous criteria to ensure a homogenous study population (56). The first TOTAL trial for moderate pulmonary hypoplasia launched in 2009 and a second trial for severe pulmonary hypoplasia was launched in quick succession. The TOTAL trials rapidly gained attention from the community and in just a few years expanded to become multi-center, multi-national efforts. By 2014, the trials were reported to be in the process of extending to the US, Canada, Australia and Japan (119). The moderate TOTAL trial was underway in multiple centers in the US by 2017 and had strong support from the international community (120). The moderate TOTAL trial ended recruitment in May 2019 and the results remain highly anticipated. A few months after the moderate arm closed, the same centers began recruiting for the TOTAL trial for severe pulmonary hypoplasia (121).

The MOMs trial laid the foundation for the TOTAL trial and many RCTs to come. But the wild success of MOMs, and the clear benefit with fetal repair that was demonstrated, also led to the expansion of the enterprise at an unprecedented rate. After the publication of the MOMs results, new fetal treatment centers were established across the country. Open repair of fetal MMC quickly became the most common fetal surgery performed in the US (122). According to a survey conducted in 2014, 76% of fetal centers in the US had been opened within the last 10 years. Additionally, the survey demonstrated significant variability in practice patterns and resource availability between centers (123).

The accelerated growth of the enterprise as a result of the MOMs trial created major challenges around how to maintain the highest quality of clinical care and ensure

that new innovation and research would be conducted responsibly and ethically. The years after the MOMs trial have been characterized by the actions the community of fetal therapy have taken in an effort to protect the field as a whole. Just as Harrison emphasized when the enterprise was first founded, maintaining credibility with the public is paramount and will always be a delicate matter (60,63). The IFMSS member's commitment to the stewardship of the enterprise were as crucial as ever.

The North American Fetal Therapy Network (NAFTNet) is prime evidence of how the leaders of the fetal therapy community responded to the evolving challenges of the growing enterprise. In January 2004, at a Society of Maternal Fetal Medicine meeting, clinical investigators from the MOMs centers, with the success of the MOMs trial fresh on their minds, came to mutually agree that a new age of cooperation and collaborative research was essential to the advancement of the field of fetal therapy (55). Based on that initial conversation, those 4 centers (UCSF, CHOP, Vanderbilt, University of North Carolina – Chapel Hill) formed the 'Fetal Therapy Working Group' research collaborative (55). In August of that year, in recognition of the emerging field, the NIH organized a workshop on fetal therapy with the intention of developing a national plan for patient diagnosis and dissemination of innovation to improve patient outcomes. At the conclusion of the workshop, the NIH formally recommended the formation of a cooperative group of clinicians and investigators that would define the national agenda for both research and clinical practice in the field of fetal therapy (55). The 'Fetal Therapy Working Group' rose to the occasion.

Just a few months later, the concept and organizational structure of NAFTNet had been established and by the following year the first 12 centers accepted invitations to join as the founding members. Conscientiously structured to be multidisciplinary, NAFTNet was the first official cooperative clinical research network in the US with standardized research practices designed to facilitate the practice of evidence based fetal medicine. NAFTNet was established to meet 4 primary goals: (I) study the natural history of fetal disease, (II) develop prenatal interventions to improve outcomes, (III) provide educational resources for patients and healthcare providers, and (IV) train future leaders in both clinical practice and research in fetal intervention. The success of NAFTNet was immediately apparent. In just a few years, NAFTNet was supporting numerous research efforts and had sponsored an International Consensus Conference on the Management

of Quintero Stage I TTTS. By 2010, the collaborative was involved in 8 active research studies. Today, NAFTNet includes 36 multi-disciplinary advanced fetal treatment centers in the US and Canada and currently supports over 6 active research studies and 4 clinical trials, including the TOTAL trial and the NIH funded Renal Anhydramnios (RAFT) Trial (124). As the field of maternal-fetal surgery has evolved ever more rapidly, NAFTNet has played a crucial role in guiding the national conversation and setting a standard of excellence (125).

Following the example set by the first consensus statement from the IFMSS, publications in recent years have created an ongoing discussion in the literature on the ethical and responsible practice of maternal-fetal surgery. In response to the surge in new fetal treatment centers over the last 10 years, recommendations for standard guidelines and clinical requirements for all fetal treatment centers started to take shape. The same year the MOMs results were published, the NICHD established the Maternal-Fetal Medicine (MFM) Task Force (3) and a joint statement on new fetal treatment centers was published by the ethics committees from the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics (126). In 2014, the MFM task force established operational guidelines for fetal treatment centers that included strongly worded recommendations that all centers offering fetal MMC repair follow the MOMs protocols to ensure centers produce minimal comparable outcomes (127).

The community put forward universal requirements for all centers offering maternal-fetal surgery and worked to establish minimum standards for the multi-disciplinary team necessary for effective delivery of fetal therapy (128). There has been a strong consensus in the literature that transparency should be required of all fetal treatment centers in regards to their clinical capabilities, available resources, case volume and prior experience (60,129). Minimum practice standards and reporting requirements would allow for fetal treatment centers to be ranked on a clinical grading scale, similar to the level of verification assigned for NICUs and trauma centers.

In parallel to clinical standards of care, guidelines for responsible innovation and research in maternal-fetal surgery have also been put forward by the community. The paradox inherent to maternal-fetal surgery is that the surgeon is often the innovator, researcher and clinical-care provider all at once, but must maintain a clear division between the motivations of those roles (60). The ethical

pursuit of innovation demands the complex balance between the risk of morbidity for the pregnant women against the potential benefit for her child (130,131). Recent guidelines have attempted to clarify the previously blurry progression from innovation to clinical practice (60). Three defined stages have been outlined: innovation (pre-research), research and transition to clinical practice (131).

Like the thoughtful recommendations put forward by the IFMSS in 1982, current guidelines have established a clear continuum between innovation, research and clinical practice in an effort to ensure the continued success of the enterprise (131). The IFMSS emphasis on every member's commitment to be a steward of the field is more vital today than ever.

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