Introduction

From the beginning of man's evolution, the human fetus has enjoyed a privileged environment "shielded from the eyes" of the physician. The specialty of radiography allowed for still images of the unborn baby to be obtained but invasive procedures such as intraperitoneal transfusions required injection of radio-opaque dye to localize target areas. It was through the advent of real-time ultrasound in the late 1970s that marked the true beginning of the diagnostic era of fetal medicine. Structural abnormalities could now be diagnosed in-utero.

In the book *King of Hearts*, author Wayne Miller tells the story of Dr. Walt Lillehei – the early pioneer of open heart surgery for congenital heart disease. His first surgical failure to correct a ventricular septal defect was followed by two successes. The first patient's mother wrote to Lillehei: “Though it is hard not to feel bitter that little Greg couldn't have lived to rejoice with the other two, we just have to accept it as the Lord's will and we know that his death wasn't in vain as it has given these other two children another chance to live and no doubt many more … May God bless and guide you in the wonderful work that you are doing.”

Faced with major neonatal morbidity and mortality, it is not surprising that pediatric surgeons would “lead the charge” in attempting to correct congenital problems while the fetus remained in the mother's womb. Later, perinatologists would step into the picture when it was realized that minimally invasive techniques (fetoscopy) would result in significantly lower premature labor rates and corresponding early delivery when compared to open hysterotomy for the repair of fetal anomalies. In the first edition of his text *The Unborn Patient*, Michael Harrison concludes with the following statement: “A fetal abnormality of any type should never be treated simply “because it is there” and never by someone unprepared for the awesome responsibility.” [2]. In 1982, the Kroc Foundation funded an invited multidisciplinary conference in Santa Ynez Valley, California that included experts in fetal intervention from 13 centers from 5 countries. This would later be recognized as the origin of the *International Fetal Medicine and Surgery Society*. The group proposed the following guidelines for fetal intervention:

1. The fetus should be a singleton with no other anomalies as determined by Level II ultrasound and karyotype, alpha-fetoprotein and viral cultures by amniocentesis.
2. The family should be fully counseled regarding the risks and benefits and should agree to the treatment including long-term follow-up to determine efficacy.
3. A multidisciplinary team including a perinatal obstetrician experienced in fetal diagnosis and intrauterine transfusion, an ultrasonographer experienced in the diagnosis of fetal anomalies, and the pediatric surgeon and neonatologist who will manage the infant after birth should concur on the innovative treatment and obtain the approval of an institutional review board.
4. There should be access to a Level III high-risk obstetrical unit and high-risk nursery and to bioethical and psychosocial consultation [3].

Later Luks [4] would propose six parameters that should be met to consider a fetal intervention:

1. The diagnosis of the condition can be made accurately.
2. The condition can be differentiated from other, non-surgical anomalies.
3. The natural evolution of the disease, if left untreated, should be predictable, and the condition should be lethal or severely debilitating.
4. The morbidity of antenatal intervention is acceptable.
5. No adequate postnatal treatment is available.
6. The proposed in-utero operation should be technically feasible.

Initial therapies such as intrauterine transfusion for severe hemolytic disease of the fetus were undertaken based on sound physiological principles and an understanding of the basic pathogenesis but were never subjected to randomized clinical trials. More recent targeted interventions for such conditions as treatment for severe twin-to-twin transfusion,
myelomeningocele and diaphragm hernia have been the subject of well-designed randomized investigations. This chapter will elucidate the history and the basis for the treatment of these four conditions.

### Innovative surgery versus randomized trials

An innovative surgery is described as a new or modified procedure that differs from currently accepted local practice, the outcomes of which have not been described and which may entail risks to the patient [5]. The American Society of University Surgeons has stated that "surgeons are trained to perform continuous situational assessment, decision analysis and improvisation in preparation of the challenges and creativity required by nearly every clinical case." Unlike pharmaceutical development where new therapies undergo rigorous progressive testing before widespread implementation, surgical innovation can spread from the hands of a few individuals to almost universal acceptance in a short period of time. As described in the four diseases that follow in this chapter, fetal intervention represents the pinnacle of surgical innovation. The Balliol Collaboration has recently described five stages of surgical innovation (Table 1.1) [6]. The authors point out that although the ultimate evaluation of a new surgical procedure should be through a randomized clinical trial, it may be difficult to decide when to shift from an early exploratory phase of a new procedure to a formal investigation. Further refinements in technique or instrumentation as well as assessment of a learning curve [7] should be undertaken before a randomized clinical trial is planned. These points were evident in the National Institutes of Health (NIH)-funded US randomized trial of aminoreduction versus fetoscopic laser therapy for the treatment of severe twin-to-twin transfusion. A nine-month hiatus was undertaken to implement new fetoscopic instrumentation and additional training of the interventionists [8, 9]. Other impediments to a randomized surgical trial include risks associated with "sham" procedures, difficulty in masking (leading to physician bias), and patient preferences (high rates of cross-over in trials or decisions to seek therapy at other centers not participating in the trial – the "back-door"). As an example, the US trial for aminoreduction versus laser was stopped prematurely after enrolling only 29% of the planned sample size due to poor recruitment. These limitations probably contribute to the paucity of controlled, randomized surgical trials – 9% in 1993 and only 8% of studies reported in 2006 [6]. Indeed, in a recent editorial, Mike Harrison (considered by many to be the father of fetal intervention) stated "I have come to believe that the tyranny of demanding gold standard evidence (i.e. multicenter, randomized, controlled trials) does not serve our fetal patients with life-threatening diseases such as congenital heart disease." [10].

Nevertheless, the Balliol Collaboration has proposed the IDEAL (innovation, exploration, assessment, and long-term study) model for surgical innovations (Table 1.2) [11]. Stage 1 involves a proof of concept. Animal models are first employed whenever possible. When cases are first undertaken in humans, the authors recommend that research ethics approval is unnecessary as long as there is clear informed consent with an ethical obligation to the competent patient. In the Development stage (2A), an initial small group (10–30) of patients undergoes the procedure. Technical advancements and learning curves are established. Although the authors do not recommend formal institutional review board (IRB) approval, they state that the patient risks should be minimized in an agreement between the surgeon, the institution, and the ethics committee. These "case series" should be reported in the literature and should include inclusion criteria and complications. In stage 2B (Exploration stage), a larger patient experience is accumulated usually at multiple centers. Formal IRB approval should be sought. Stage 3 (Assessment stage) should involve a well-designed randomized clinical trial. Finally in stage 4 (Long-term study), a registry and ongoing assessment of outcomes is undertaken to detect rare deleterious complications of the procedure. Application of the IDEAL model will be examined in the description of the four fetal interventions that follow in this chapter.

### Hemolytic disease of the fetus and newborn (HDFN)

Descriptions of the newborn affected by HDFN can be found as far back as the writings of Hippocrates. Yet it was not until 1932 that Diamond and colleagues described a continuum of neonatal disease that included hydrops, icterus, anemia, and erythroblastosis fetalis [12]. Seven years later, Levine and Stetson [13] described an antibody in a woman who gave birth to a stillborn fetus. In 1941, Levine et al. [14] were able to demonstrate a causal relationship between RhD antibodies in RhD negative women and HDFN in their offspring.
Neonatal exchange transfusion was introduced by Wallerstein in 1945 as the first real therapy for this disease [15]. In those early years, routine induction of labor at a premature gestation was the only therapy that could be offered to attempt to curtail the inevitable death due to HDFN that occurred in 30% of cases. However, a clinical trial in England failed to find that this resulted in improved neonatal outcome because prematurity itself was often associated with neonatal death [16]. Sentinel work by Bevis in England and later Liley in New Zealand followed, indicating that spectrophotometric analysis of amniotic fluid for bilirubin could determine when the fetus was in peril for imminent death [17, 18]. Unaware of the previous work of Liley, Freda at Columbia-Presbyterian Hospital in New York began a specialized Rh antepartum clinic to test the idea that serial amniocenteses could be used to predict the severity of HDFN. His elegant description of the management of the 245 pregnancies (presented in a 33 page article in the American Journal of Obstetrics and Gynecology complete with hand annotated spectrophotometric graphs!) demonstrated a reduction in the perinatal mortality from a baseline of 30% to a rate of 9% over the course of five years [19].

The first attempt at fetal intervention for HDFN was undertaken by Bevis [20]. Injecting radio-opaque dye into the mother, he used fluoroscopy to outline the placental vasculature and attempted to inject blood directly into fetal vessels in the placenta. Several fetuses succumbed before one was born with evidence of RhD negative red cells in its circulation. Bevis soon abandoned further attempts and did not publish his results. Sir William Liley is credited with the first successful fetal intervention – the intraperitoneal fetal transfusion (IPT) [21]. He learned from a visiting young geneticist who had returned from Nigeria that missionaries had successfully infused red cells into the peritoneal cavity of neonates with sickle cell disease and noted normal appearing red blood cells on peripheral blood smear. On a previous occasion, Liley had inadvertently entered the peritoneal cavity of a fetus at the time of amniocentesis as evidenced by the marked contrast in the yellow hue of the ascitic fluid as compared to amniotic fluid. He injected air into the cavity and then placed radio-opaque dye into the amniotic fluid as the needle was removed. A radiograph taken a short time later revealed an exquisite image of the fetal peritoneal cavity with the ingested dye outlining the fetal intestines. Liley postulated that purposeful entry into the fetal peritoneal cavity could be accomplished for the infusion of red cells. A review board of three senior obstetricians (including Liley) was convened and a decision made to move forward on the procedure. After three unsuccessful attempts that resulted in fetal demises, the fourth fetus was delivered at 344/7 weeks’ gestation after undergoing two IPTs at 321/7 and 334/7 weeks. Innovations in the technique followed including the use of metal grids to immobilize the fetus.

Several investigators challenged this approach since it did not mimic the neonatal exchange transfusion that was so effective after birth. Direct access to the fetal circulation was needed.

Investigators at Columbia University in New York were the first to attempt the direct transfusion of red cells to the fetus. After practicing access to the fetal superior sagittal sinus in a single rhesus monkey, they decided to proceed to a human case at 32 weeks’ gestation. A hysterotomy was performed and blood was aspirated from the sagittal vein; however, catheter access could not be achieved; a perinatal loss occurred after a premature delivery several days later [20]. Subsequently, several attempts were undertaken to transfuse the anemic fetus by direct access via hysterotomy using the fetal femoral artery, saphenous vein, and internal jugular vein [22–24]. All resulted in premature delivery and perinatal loss. Adamsons et al. attempted to place an indwelling catheter into the fetal peritoneal cavity for the periodic infusion of red cells. Four attempts failed, but a fifth procedure performed in Brazil at 24 weeks’ gestation resulted in a live born infant eight weeks later [25].
Section 1: General principles

These heroic attempts for vascular access were abandoned as Liley came to the US on sabbatical to instruct American physicians on the IPT method. Early attempts at IPT utilized fluoroscopy for needle guidance. A large 14- or 16-gauge Touhy needle was inserted into the peritoneal cavity of the fetus and radio-opaque dye was injected to confirm the location. An epidural catheter was then placed through the needle and the catheter was then withdrawn. Blood could then be infused through the catheter; at the conclusion of the transfusion it too was removed. With the introduction of real-time ultrasound in the late 1970s, radiation exposure to the fetus was eliminated through the use of real-time ultrasound guidance to direct the transfusion needle. A Boston group reported a 53% rate of survival for non-hydropic fetuses and 7% survival with hydrops. After the introduction of ultrasound for needle guidance, a survival rate of 62% was reported; however, survival in the hydropic fetus remained poor with a salvage rate of only 29% [26]. No further refinements in the IPT method occurred until 1985 when intramuscular paralytic agents were introduced to cause cessation of fetal movements [27]. Smaller diameter needles could now be used and indwelling catheters were no longer necessary.

All centers continued to experience poor rates of survival with hydrops fetalis as it appeared that the moribund fetus would not absorb intraperitoneal blood when ascites was present – presumably due to a functional obstruction of the lymphatic system. Once again, direct fetal access was needed. In 1981, Rodeck et al. [28] is credited with the first intravascular fetal transfusion (IVT) using a fetoscope to guide the transfusion needle into a placental plate vessel. One year later, Bang and coworkers [29] performed the first ultrasound-guided IVT using the intrahepatic portion of the umbilical vein. French investigators reported that direct vascular access could be safely obtained through the umbilical cord – the intravascular intrauterine transfusion was born and has now become the standard method of intervention for HDFN [30]. Today a survival rate of 92% in non-hydropic fetuses and 78% in hydropic ones has been reported from a national referral center in the Netherlands [31].

The story of the conquest of HDFN teaches us important lessons in fetal intervention. Several key pioneer innovators working at times in different parts of the world on parallel tracks were fundamental to the new developments. Electronic communication and the internet were not yet invented – the dissemination of new methods and ideas slow. International collaboration and the sharing of data were non-existent. The lack of an animal model for HDFN precluded investigators from studying their innovative approaches in the laboratory before moving to human attempts. Randomized clinical trials were not as yet on the horizon to determine the efficacy of their approaches. Based on the IDEAL model, only stage 1 occurred before widespread acceptance of intravascular transfusion into clinical practice. Such a rapid implementation of innovation would no longer be accepted as new fetal therapies came on the horizon.

Twin-to-twin transfusion syndrome (TTTS)

The realization that a “third circulation” can be found in the placenta of monochorionic twins dates back to studies of the placental vasculature in the late 1800s [32]. In an excellent review, Bernische [33] summarized the available literature and suggested that placental arteriovenous connections contributed to the pathophysiology of twin-to-twin transfusion. Denbow et al. [34] studied the vascular patterns in 82 cases of monochorionic twins of which 26% (21) were complicated by TTTS. The finding of one or more arteriovenous anastomoses in conjunction with a lack of arterioarterial anastomoses was noted in 78% of the cases of TTTS. Since no animal model for TTTS exists, several computer models have been developed. Umur et al. [35] included ten computational equations each for the donor and recipient fetus, and were able to demonstrate that unidirectional flow through arteriovenous connections in the placenta accounted for the TTTS phenotype. Discordance in placental territory (common in TTTS cases) exacerbated the progression of the disease. In a later refinement of their model, this group demonstrated that arterioarterial anastomoses were protective for the development of TTTS [36]. Interestingly, the findings of these models were not published until almost a decade after investigations into laser therapy for TTTS had been initiated.

Left untreated, the second trimester presentation of TTTS was associated with a perinatal mortality of up to 70% [37]. Early attempts to prolong gestation with amnioreduction of the polyhydramnios in the recipient’s sac met with some improvement in survival; however, neurological morbidity was high and therefore remained problematic [38]. A randomized clinical trial between amnioreduction and intertwin membrane septostomy proved the two therapies equal in therapeutic outcome [39].

In 1983, investigators began to explore whether the neodymium:yttrium-aluminum-garnet (NG-YAG) laser could be introduced into the uterus to enable therapeutic cutting and coagulation maneuvers for fetal interventions [40]. In two fetal lambs, a hysterotomy was performed and YAG laser energy transmitted through a 600 micron quartz fiber was used to sever the tail, limb, and umbilical cord in an avascular fashion. In two additional cases, a fetoscope was introduced at the time of septostomy proved the two therapies equal in therapeutic outcome [39].

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and the laser fiber was introduced into the amniotic cavity through the side port of a pediatric cystoscope. Placental vessels were visualized and lasered. Subsequently, these vessels were retrieved through a hysterotomy and submitted to histological evaluation – they showed complete obliteration of their lumen with minimal damage to surrounding placental tissues. Subsequent work by De Lia in 12 rhesus monkeys targeted the vascular connections in their bilobed placentae [42]. The first case was a failure when the laser fiber was introduced through a separate incision from the fetoscope. Subsequent cases involved attachment of the fiber to the side of the scope with a suture. Interestingly in only one of these cases was the planned coagulation successful. Other cases were complicated by stillbirth, abortion, infection, uterine hypertonicity, and inadvertent coagulation of vessels on the wrong placental disk. De Lia went on to extensively study the shared vasculature of placentae from monochorionic twin gestations (J. E. De Lia, personal communication, 1990). In 1990, he reported his first three cases of laser for TTTS in human pregnancies [43]. The cases presented with severe hydramnios at 18.5, 22, and 22.5 weeks. All fetuses survived the initial surgery. Delivery after preterm premature rupture of the membranes occurred 8.5 and 12 weeks later in the first two cases; the third case was delivered 6.5 weeks after the laser procedure due to severe maternal preclampsia. One donor and one recipient died early in neonatal life from complications of prematurity. Placental injection studies revealed complete obliteration of the anastomoses in the first two cases and two patent arterioarterial anastomoses in the third case.

In the United States, De Lia in Salt Lake City (later in Milwaukee) and Quintero in Detroit (later in Tampa) began to offer laser therapy for TTTS. Considerable doubt remained in the obstetrical community regarding the benefit of laser therapy. How could one possibly visualize all of the possible anastomoses between the twins? And then there were the reported complications including abortion, premature rupture of the membranes, and even a maternal death. Amnioreduction of the polyhydramnios of the recipient's sac was routinely employed at the end of the procedure. Critics pointed out that amnioreduction alone had proved therapeutic in some reported cases of TTTS. In a subsequent series of 26 patients, De Lia reported that 35% of cases had dual survivors (three survivors in one set of triplets), 31% had one survivor, and 35% had no survivors [44]. A second center at the Harris Birthright Centre, King's College in London embraced this new therapy and Nicolaides and Ville described their experience with 45 cases. Much like De Lia, their outcomes were almost equally divided between dual survivors, single survivors, and no survivors [45]. Soon thereafter, these investigators formed a European consortium (EUROFETUS) and worked with the Karl Storz Corporation to develop improved fetoscopic instrumentation specific for laser therapy.

Between 1999 and 2002, a randomized clinical trial was undertaken in Europe to compare laser therapy to the gold standard of amnioreduction [46]. However, a “back-door” was still available to patients as lasers were offered at centers in London, Hamburg, and Barcelona. The study was stopped by the data safety monitoring committee at the 50% enrollment point when 142 patients had been randomized. Patients in the laser group were significantly more likely to have at least one survivor at 28 days of neonatal life (76% vs. 56%, p = 0.009) and to have surviving infants free of “neurological abnormalities” at 6 months of age (52% vs. 31%, p = 0.003). One year after the laser trial was published, the results of a randomized trial between amnioreduction and septostomy (a purposeful needle perforation of the intervening twin membrane) indicated that the two therapies were equivalent in perinatal survival. Thus, fetoscopic laser therapy became accepted as the standard therapy for advanced cases of severe TTTS. Many fetal interventionists from around the world visited centers in Europe and returned home to offer laser therapy. Evidence soon became available regarding a learning curve until expertise was achieved [7]. The most recent data from the combined experience of two centers in the USA indicate that the overall rate of survival at 30 days of age of at least one neonate is 91% and the survival of both neonates of the twin pair is 67% [47].

Subsequent modifications in the technique have included the move from non-selective to selective to sequential, selective coagulation of placental anastomoses [48, 49]. The latter technique has resulted in a higher rate of donor survival. There continues to be a need for further refinement in the treatment of TTTS. A randomized trial of amnioreduction versus laser therapy for stage I TTTS is planned. A second trial on the use of preoperative calcium channel blockers for afterload reduction in the recipient fetus with advanced cardiac disease in an effort to enhance survival is also planned. The treatment of twin-to-twin transfusion represents yet another historical story in the conquest of a lethal perinatal disease. Again an animal model for the entity was not available for study. Unlike the innovative treatments for Rhesus disease, preliminary animal work was undertaken to study technical issues. At least one well-designed randomized clinical trial was undertaken before widespread implementation of this therapy occurred. Based on the IDEAL guidelines, an orderly progression of stages occurred before widespread implementation into clinical practice. Laser therapy for TTTS would set the stage for the future study of other fetal interventions.

**Myelomeningocele (MMC)**

Fetal intervention for MMC would push the boundaries of in-utero repair of congenital lesions once again. In this case the fetal disease was not lethal; instead it was associated with significant life-long morbidity.

An experiment in nature would be the first clue that the neurological damage noted at birth in infants with MMC was progressive in utero. In a series of 16 fetuses with congenital hemimyelocele (a duplication of the lower spinal cord in association with a typical appearing MMC), only the lower extremity ipsilateral to the exposed hemicord demonstrated neurological compromise at birth [50]. The covered portion of
Section 1: General principles

the cord was associated with normal lower extremity function as well as normal bladder and anal sphincter control. Further studies in human fetuses with MMC suggested progressive damage with advancing gestation. Osaka et al. [51], studied 92 human embryos and four fetuses with myeloschisis. They found that the Chiari II malformation was notably absent from embryos up to 55 days of age although it was present in fetuses with myeloschisis.

Investigation next turned to an animal model. Michejda [52] is credited with the first attempt at in-utero repair of MMC. Previous attempts to induce MMC in the rhesus monkey model using maternal administration of corticosteroids proved problematic. Instead the investigators moved to the surgical creation of a spinal defect at day 110–125 of gestation (term: 160–164 days). Immediate repair was undertaken with allogeneic bone paste with skin closure in five animals; in three controls the lesion was allowed to remain open. At delivery, repaired animals exhibited normal neurological function and normal spinal cord morphology on histology. Control animals were paraplegic with urinary incontinence and somatosensory loss below the level of the induced lesion. Histology in these animals showed evidence of spinal cord necrosis. Heffez et al. [53] surgically created MMC in rats on day 18 of their 22 day gestation. Closure of the defect was undertaken on day 19. When compared with controls, these pups exhibited normal neurological function and normal spinal cord histology. The authors proposed a “two-hit” hypothesis for the neurological damage of MMC – an initial congenital myelodysplasia followed by progressive intrathecal injury due to either direct trauma or exposure to the toxic effects of amniotic fluid or both. The ovine model was also used to investigate the effect of in-utero repair of MMC on clinical outcome. Meuli et al. [54] surgically created an MMC in 12 fetal sheep on day 75 of gestation (term: 150 days). At 100 days, seven fetuses remained alive and all underwent repair of their MMC. Three fetuses survived to be delivered by C-section at 145 days. Clinical evaluation revealed some reduction in hindlimb strength but no signs of stool or urinary incontinence. All had evidence of normal somatosensory-evoked potentials in all limbs. Histological evaluation revealed minimal loss of neural tissue.

Based on these preliminary data, investigators at Vanderbilt University attempted in-utero repair in four human fetuses using endoscopy [55]. Under general anesthesia, a maternal laparotomy was undertaken and three endoscopic ports were inserted into the amniotic cavity. Amniotic fluid was removed and a small amount of carbon dioxide insufflated into the amniotic cavity. A split thickness skin graft from the maternal thigh was then used to cover the MMC. One case resulted in an intraoperative fetal demise secondary to abruption of the umbilical cord was associated with normal lower extremity function - 100 randomized to in-utero repair of MMC. One year later, Tulipan and Bruner [56] reported their ongoing efforts to undertake fetal MMC repair. Three patients underwent open hysterotomy under general anesthesia with fetal repair being undertaken using standard surgical techniques typically employed in the neonate with MMC. The three infants were delivered at 33, 34, and 36 weeks’ gestation. One pregnancy was complicated by a posterior uterine dehiscence with prolapse of the fetal arm into the maternal peritoneal cavity necessitating delivery. Only one of the three infants required a ventriculoperitoneal (V-P) shunt. The authors concluded that open fetal surgery for MMC repair was feasible.

In an initial series of patients reported from Vanderbilt with follow-up to 6 months of age, 29 neonates that have undergone in-utero repair were matched to 23 historic controls [57]. V-P shunt placement occurred in 59% of fetal repair cases as compared to 91% of controls. Hindbrain herniation as judged by postnatal MRI was present in 38% of fetal repair cases as compared to 91% of controls. Children’s Hospital of Philadelphia (CHOP) reported a series of 50 cases that had undergone in-utero repair [58]. Perinatal survival was 94%. All surviving fetuses demonstrated reversal of their Chiari II malformation; V-P shunts were required in 67% of thoracic, 44% of lumbar, and 20% of sacral lesions as compared to 100%, 88%, and 68% of historic controls. Over half of the surviving infants exhibited leg function superior to what would have been predicted by their level of lesion. This early promise of a beneficial effect of in-utero repair led to four centers offering procedures – 12 cases were completed at the University of California at San Francisco (UCSF); 54 cases at CHOP, 170 cases at Vanderbilt, and 10 cases at the University of North Carolina.

In January of 1999, investigators at UCSF applied to the NIH for a single-center study of in-utero MMC repair under the Research Project Grant Program (R01) mechanism (S. Adzick, personal communication, 2011). The second application of the grant received a favorable score and was scheduled for funding in December of 2000. In July of 2000, a fetal surgical conference was hosted by the National Institute of Child Health and Human Development (NICHD) in Washington, DC. The final recommendation of the conference was that a multicentered randomized trial was necessary to answer the question as to whether fetal MMC repair was superior to postnatal repair. This recommendation was ground-breaking in that it represented the first effort in the United States to conduct a randomized clinical trial at several centers. The original R01 application by UCSF was tabled and a new U10 RFA was issued. Three centers (UCSF, Vanderbilt, and CHOP with George Washington (GW) University as the independent data monitoring center) ultimately qualified. The official award notice was announced by the NICHD in March of 2002 and the first patient was enrolled in February of 2003.

The Management of Myelomeningocele (MOMS) trial commenced in the spring of 2002 with a predicted period of enrollment period of three years [59]. Two hundred and fifty one infants were to be enrolled – 100 randomized to in-utero repair of

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MMC and 100 randomized to standard neonatal repair by the same neurosurgeons. Over 1000 patients were screened for the trial at GW University and then allocated to one of the three surgery centers based on geographic distribution for further evaluation and randomization. Ultimately enrollment required almost nine years to randomize 183 patients. The primary reason for poor enrollment was conjectured to be the need for patients randomized to in-utero repair to remain in the city where they underwent surgery with an accompanying person for the remainder of their pregnancy. The trial was halted at the fourth interim analysis by the data safety monitoring committee when both the primary (one year) and secondary outcomes (at 30 months) were found to be improved in the in-utero repair group. At one year, half as many infants in the fetal repair group required V-P shunting; at 30 months twice as many children in the fetal repair group walked independently as compared to the group that underwent standard neonatal repair.

The publication of the MOMS trial led to interest by other fetal centers with experience in other open fetal surgical procedures in beginning to offer open MMC repair. The three centers that enrolled patients in the MOMS trial began to offer the procedure within weeks of the *New England Journal of Medicine* report. One center was criticized for offering a three day "course" in the procedure in return for a considerable expense. The other two MOMS centers elected to collaborate with reputable fetal centers by either allowing them to directly observe ongoing patients or to have them come to the experienced center with their own patient to observe the procedure.

The MOMS trial has led to controversy as to how to establish qualified fetal centers. In addition, the quantity and geographic distribution of such centers requires further thought and guidance [60]. At the recent 30th annual meeting of the International Fetal Medicine and Surgery Society, the president called for the organization to formulate guidelines for four strata of fetal centers.

Clearly, in-utero repair of MMC has been the one fetal intervention to date that has most closely adhered to the *IDEAL* guidelines. Due to the foresight of the NIH, stage 3 assessment occurred through the MOMS trial. Stage 4 (establishment of a registry of cases performed subsequent to MOMS) will be the next logical step in the assessment of this new fetal intervention.

### Congenital diaphragmatic hernia (CDH)

The advent of prenatal ultrasound led to the detection of one of the most lethal of congenital anomalies – congenital diaphragmatic hernia (CDH). Tertiary centers using extra corporeal membrane oxygenation (ECMO) reported neonatal survival rates of >70%; however, cases diagnosed in utero were associated with a "hidden mortality" with reduced survival rates of <60% [61]. Initial experimental work was undertaken in fetal lambs using an inflatable balloon to mimic the space-occupying lesion of the abdominal viscera in CDH. Newborn lambs with inflated intrathoracic balloons rapidly succumbed to pulmonary hypoplasia while those that had undergone deflation of their balloons by day 120 of their 140 days' gestation showed normal pulmonary development [62]. Investigators then went on to create a diaphragm defect in fetal lambs at 100 days of gestation and noted pulmonary hypoplasia similar to that created by the intrathoracic balloon. An attempt to repair the defect in utero on day 120 of gestation resulted in fetal demise in six of six fetuses. They soon realized that the return of herniated viscera to the abdomen increased the intraperitoneal pressure and compromised venous return. A new technique of creating an abdominoplasty with a silastic patch solved this problem and resulted in survival of the lambs with normal pulmonary function [63].

Extensive primate work followed with the development of a specialized device for performing the hysterotomy and new methods for intraoperative monitoring of the fetus. In 1990, after six consecutive failures, Harrison's group reported the first successful in-utero repair of CDH in a human pregnancy [64]. Further experience with fetal repair indicated that with "liver-up" cases, kinking of the umbilical vein during attempts to reduce the incarcerated liver resulted in fetal death during the procedure. The NIH and March of Dimes subsequently funded a non-randomized trial of open CDH repair in "liver-down" cases as compared to standard neonatal repair [65]. Over a 21 month period, 55 cases of CDH were referred to the Fetal Center in San Francisco for evaluation. Four fetuses underwent in-utero repair and outcomes were compared to seven cases that were treated as neonates. Survival in the fetal repair group was 75% compared to 86% in the comparison group; mean gestational age at birth was 32 weeks compared to 38 weeks' gestation. Based on their results, the authors declared a moratorium on further in-utero repair of CDH by open hysterotomy techniques.

A new approach to CDH would be needed. Initially, fetal lung fluid was thought to be the result of amniotic fluid entering the lungs. It was not until the elegant studies in 1948 of Jost and Policard [66] in the rabbit that investigators realized that pulmonary fluid was produced by the fetal lungs and exited the trachea to enter the amniotic cavity. Five fetuses underwent tracheal ligation and exhibited increased alveolar size with histological features of the lungs similar to controls. Later, Alcorn et al. [67] would demonstrate in a sheep model that tracheal occlusion resulted in very large lungs with thinner alveolar walls and a deficit of type II pneumocytes. These studies were unknown to fetal interventionists, until another experiment in nature would lead to a novel suggestion for in-utero therapy for CDH. Jay Wilson would be in the library at Boston Children's Hospital to copy an article about CDH (J. Wilson, personal communication, 2011). On the back page, he would read the abstract of another article that described a case of Fraser syndrome – a genetic syndrome that can be associated with bilateral renal agenesis in conjunction with tracheal atresia [68]. He knew from previous animal investigations that anhydramnios (due to the total absence of urine production in Fraser syndrome) should result in pulmonary hypoplasia. Yet the obstruction to the egress of lung fluid had been associated
with large lungs. Investigators at Boston Children’s Hospital, studied three animals with bilateral nephrectomy (Np), three with tracheal occlusion alone (TO), and three who underwent nephrectomy and tracheal occlusion (Np/TO) [69]. Fetal lung volumes in the TO group and the Np/TO group were four times larger than controls and five times larger than the lungs of the animals in the Np alone group. More importantly the lungs appeared to be histologically mature with the increase in size due to cell multiplication. In a single fetal lamb with a surgically created diaphragm hernia who also underwent TO, the lungs also appeared enlarged and were of sufficient size to displace the previously herniated abdominal viscera from the chest. This led the authors to propose TO as a possible fetal treatment for CDH at the Section on Surgery at the 1992 annual meeting of the American Academy of Pediatrics.

What followed was an extensive series of experiments in ovine, rabbit, and rat models that confirmed the therapeutic effects of TO in cases of fetal CDH [70]. The Fetal Center at UCSF coined the acronym “PLUG” for plug the lung until it grows. Several issues remained before this innovative therapy could be implemented: who was a candidate for therapy, what was the most effective method for occlusion, and how long should the trachea have to be occluded? Metkus et al. [71] were the first to propose the use of ultrasound to measure the size of the contralateral fetal lung and correlate this with neonatal survival. Two measurements of the fetal lung at the level of the four-chamber cardiac view were used to calculate a cross-sectional area which was compared to the ultrasound measurement of the head circumference. Survival was 0% for a right lung area to head circumference ratio (LHR) <0.6, 61% for LHR between 0.6 and 1.35, and 100% for an LHR >1.35. Since the normal fetal lung area increases disproportionally to head circumference with advancing gestational age, Jani and coworkers [72] later introduced an observed-to-expected ratio to correct for gestational age. As technology advanced, fast spin MRI became part of the routine evaluation of the fetus with CDH [73]. Although calculated lung volumes have added little to the prediction of neonatal survival, MRI has proven beneficial in determining whether the liver is intrathoracic in location (“liver-up”). The herniation of the liver into the fetal chest appears to predict a poor prognosis for the fetus as well.

Early lamb experiments to determine the optimal method for TO utilized a hysterotomy for placement of an intraluminal foam insert as well as an endotracheal tube with a foam cuff with and without a magnetically activated valve [74]. Later, UCSF investigators successfully implemented an extra-tracheal clip using a three-puncture “Fetendo” (fetal endoscopic surgery) technique in fetal lambs [75]. Human innovative surgery followed. Eight fetuses with CDH complicated by liver herniation into the chest underwent open hysterotomy with TO using a polymeric foam (n = 2), a spring-loaded aneurysm clip (n = 1), and hemoclips (n = 5) [76]. Unfortunately only one neonate survived intact. Once again, fetal interventionists realized that open hysterotomy was not well tolerated by the pregnant human uterus; inevitable premature delivery cancelled any possible benefit from the therapeutic intervention. A novel approach was proposed by Deprest and coworkers in Leuven, Belgium [77]. A specially designed small diameter fetoscope (1.2 mm) was introduced into the trachea of fetal lambs and a detachable endovascular balloon placed. The UCSF group moved quickly to implement this method using a large diameter (4.5 mm) hysteroscope in two fetuses with right-sided CDH [78]. Both infants were delivered by an ex-utero intrapartum therapy (EXIT) procedure with good outcomes. Between April 1999 and July 2001, an NIH-funded randomized clinical trial of TO was undertaken at UCSF [79]. Inclusion criteria included left-sided CDH, liver-up, and LHR <1.4. Thirteen patients were randomized to routine neonatal management and 11 underwent TO. Interestingly, the first two patients in the TO group underwent fetoscopic placement of tracheal clips; subsequently the data safety monitoring committee allowed a change in TO methodology to an intraluminal balloon. Neonatal survival in the TO group was 77% as compared to 73% in the standard treatment group. TO patients delivered six weeks earlier than the standard treatment group. A subanalysis of their data indicated that an LHR of <0.9 was a better predictor of neonatal death than the inclusion criteria of an LHR of <1.4 that the authors had chosen at the start of their trial.

European fetal interventionists watched closely. Additional studies in the fetal lamb of CDH indicated that a period of 15 days was sufficient to stimulate lung growth. Release of the TO prior to delivery allowed for recovery of type II pneumocytes [80]. Extrapolation from the lamb model of pulmonary development to the human fetus led to a proposal to maintain TO for 6–8 weeks in the human fetus with attempted release at 34 weeks’ gestation. The FETO (fetal tracheal occlusion) task force consisted of fetal centers in London, Barcelona, and Leuven. In April of 2002, the investigators decided to move forward with a feasibility trial of FETO using a percutaneous approach and a specially designed 1.2 mm fetoscope [81]. Both left- and right-sided CDH fetuses with “liver-up” and an LHR of <1.0 were candidates. Two hundred and ten cases subsequently were enrolled in the study. Survival for right-sided CDH improved from 0% in a control population to 35% in the FETO group; left-sided hernia survival improved from 24% in controls to 49% in the FETO group. Unlike the UCSF trial, 70% of balloons were removed prenatally through repeat fetoscopy (50%) or ultrasound-directed balloon puncture (19%). Subsequently in a small case–control study in Brazil, 16 fetuses underwent FETO using a 1 mm fetoscope [82]. Outcomes were compared to 18 controls. Survival in the FETO group was 53% versus 6% in the control group. Pulmonary hypertension occurred in 47% of the FETO group and 89% of controls. Pediatric surgeons in the USA have been critical of these results. In many locations in Europe and in Brazil, ECMO is not available for the treatment of the neonate with severe CDH. American surgeons point to an enhanced rate of survival with this technology although their arguments rarely discuss long-term morbidity.

FETO has now entered stage 3 of the IDEAL model. A randomized trial for CDH with “liver-up” and an observed-
to-expected LHR of 0.25–0.35 (moderate CDH) is currently underway in Europe. A second trial for "liver-up" and an LHR of <0.25 (severe CDH) is currently planned for both Europe and North America. The inclusion of centers that offer ECMO in these severe cases will allow for a robust evaluation of FETO as the ultimate in-utero intervention for CDH.

Conclusion
The world of fetal intervention has undergone dynamic changes since the first successful intraperitoneal transfusion was performed almost 50 years ago. Innovative procedures on human fetuses have been replaced by preliminary animal studies, feasibility trials, and randomized clinical trials. The designation of fetal centers of excellence is on the horizon. The human fetus has indeed become a patient and development of treatments are a work in progress.

References
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Section 1: General principles


