Fetal Surgery: Past, Present, and Future Perspectives

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PAST

The pioneers of fetal surgery were mainly pediatric surgeons, with Michael Harrison considered one of the fathers of fetal surgery. He founded the Fetal Treatment Center at the University of California, San Francisco in the early 1980s and performed the first open fetal surgery in 1981, a vesicostomy for congenital hydronephrosis.[1,2] Enthusiasm for fetal surgery quickly grew, and soon many animal and human trials were launched.

Like any other rapidly evolving field, however, fetal surgery was controversial and often misunderstood. To regulate its development and provide collaborative opportunities, specialists in maternal-fetal medicine, pediatrics, surgery, ultrasound, bioethics, and physiology who were interested or involved in fetal surgery met for the first time in Santa Ynez, California, in 1982 and eventually founded the International Fetal Medicine and Surgery Society (IFMSS). They advocated for collaborative research and the development of guidelines and registries to rapidly assess the outcomes of fetal surgery. According to their first statement, published in the *New England Journal of Medicine* in 1982, fetal surgery was to be considered only in cases of a simple fetal structural defect with a predictable clinical course and for which in utero surgery would be beneficial.[3] At that time, only congenital diaphragmatic hernia (CDH), hydronephrosis, and hydrocephalus were candidates. This collaborative effort allowed for productive research and ultimately the development of the IFMSS criteria for fetal surgery, which were the following:

1. The fetal defect or disease could be accurately diagnosed and distinguished from other anomalies.
2. Ultrasound imaging was able to determine which cases were severe enough to warrant in utero intervention.
3. There was a good understanding of the pathophysiology and natural history of the defect or disease.
4. Animal models had shown benefit from in utero surgery.
5. Maternal risk was low.[4]

Unfortunately, open fetal surgery carried significant morbidity for both mother and fetus, with fetal mortality being very high. With the advent of minimally invasive surgical techniques, maternal-fetal medicine specialists progressively took on a more active role in fetal surgery and helped create the two main collaborative research groups: Eurofoetus (Europe) and, subsequently, the North American Fetal Therapy Network (NAFTNet). Through these collective efforts, fetal surgery has expanded its reach to treat multiple conditions and has become standard of care for certain disorders.

PRESENT

Today, the most commonly performed fetal surgery is undoubtedly fetoscopic laser photocoagulation of placental anastomoses in twin-twin transfusion syndrome, a complication of monochorionic pregnancies that is characterized by the unequal sharing of blood between twins through vascular placental anastomoses. Severe cases, if left untreated, often lead to the loss of one or both fetuses. Performed through a single port, laser photocoagulation aims to obliterate these vessels, thereby resolving the underlying disorder. Because of its proven efficacy and relatively low complication rate, it is now considered standard of care.[5] Other monochorionic pregnancy complications such as twin reverse-arterial perfusion or selective intrauterine growth restriction, when severe,

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can lead to the death of a twin and cannot be cured with fetoscopy. The death of a twin in a monochorionic pregnancy immediately puts the surviving twin at risk of death or neurologic sequelae as a result of placental anastomoses and rapid hemodynamic changes. To prevent compromise of the healthy twin, selective fetal reduction by cord occlusion using radiofrequency ablation is offered in such cases.[5]

Minimally invasive techniques are also used in cases of severe CDH. Fetal endoluminal tracheal occlusion performed early in the third trimester aims to improve lung development in utero by simply trapping intrapulmonary fluids and increasing intrapulmonary pressures. In this procedure, a fetoscope is inserted into the uterus and then into the fetal mouth, and a small endoluminal balloon is placed and inflated in the trachea. The balloon is then removed with fetoscopy approximately 4 to 6 weeks later. Although this procedure is still considered experimental, preliminary studies show that it may improve neonatal outcomes in severe cases, and trials are currently under way.[6]

Another area of interest for fetoscopic procedures is fetal lower urinary tract obstruction. Regardless of the underlying disorder, the obstruction is often fatal because it causes progressive oligohydramnios and leads to pulmonary hypoplasia and chronic kidney disease. Intrauterine vesicoamniotic shunting can bypass the obstruction, but the shunt is often dislodged and can malfunction. Recently, fetal cystoscopy and ablation of urethral valves has been evaluated, but long-term outcomes in these infants remain problematic.[7]

Fetal therapy has also evolved to treat non-lethal conditions. Although not clearly stated in the IFMSS consensus, the main focus of fetal surgery historically was fetal defects that would otherwise be life-threatening. This was the case until the advent of fetal surgery for myelomeningocele (MMC), a non-lethal condition for which the main focus of repair became functional improvement. There is a "two-hit" hypothesis in MMC explaining the functional impairment in these children, the first hit being the neural tube defect itself. The second hit happens when neural tissue is exposed to the deleterious effects of amniotic fluid.[8] Perhaps the most notorious trial in the history of fetal surgery is the management of myelomeningocele study (MOMS), a randomized controlled trial comparing intrauterine repair of MMC through open hysterotomy at 19–26 weeks gestation and traditional postnatal repair.[9] The trial was stopped early because of proven efficacy reflected by improved functional status and reduced ventriculoperitoneal shunts at 1 year. Since the MOMS trial, centers all over the world have begun offering this procedure, but it does not come without risks to the mother and fetus. Rates of preterm labor, preterm premature rupture of membranes, placental abruption, and preterm birth are very high. Fetoscopic techniques are being refined to avoid the need for hysterotomy.

Another interesting procedure currently investigated for a non-lethal condition is ultrasound-guided fetal aortic valvuloplasty for hypoplastic left heart syndrome. The objectives of the procedure are to prevent the progression of critical aortic stenosis and to maintain biventricular function. At this time, it is unclear whether fetal aortic valvuloplasty is superior to expectant management.

FUTURE PERSPECTIVES

The future of fetal surgery is exciting and largely unknown. The path it will take depends not only on improvements in operative technologies but also on the evolution of related fields such as neonatology and regenerative medicine. Risks and benefits of fetal surgery must constantly be weighed against improvements in neonatal medicine so that the best outcome for the fetus is achieved. One clear example is CDH. Its neonatal mortality has dramatically dropped since the first fetal surgical procedures in the 1980s; therefore, prenatal intervention is now considered only in severe cases.

Fetal surgery also continuously aims to be as minimally invasive as possible. However, one important problem that remains, even in the case of fetoscopy, is the relatively high risk of preterm rupture of membranes, which often leads to preterm delivery. The reason for this complication is that the amnion simply does not reseal. To most surgeons, this problem is considered the Achilles' heel of fetal surgery. Therefore, a tremendous amount of research is being done to look for ways to either plug or heal the amnion after surgery. So far, the results of studies of collagen plugs, tissue sealants, and even platelet-rich plasma have been mixed.

Yet the real future of fetal surgery lies most likely in stem cell and gene therapy, which would not only improve the outcomes for structural anomalies but also broaden our reach and treat genetic disorders. Transamniotic stem cell therapy allows for transplantation of stem cells before the full development of the fetal immune system so that the fetus would hopefully identify these cells as "self" rather than "foreign." Simple transamniotic injection of mesenchymal stem cells derived from the amniotic fluid has resulted in partial or complete closure of MMC defects in animal studies.[10] Tissue engineering has also had interesting results in CDH and MMC, and intrauterine hematopoietic stem cell transplantation is currently under investigation for various hematologic diseases. These new perspectives may still

be in the embryonic stage of development, but they will undoubtedly provide a bright future for the field of fetal therapy.

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