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Editorial

The Evolution of Fetal Procedures

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In 1961, Sir William Liley performed the first successful needle-based intrauterine blood transfusion for a fetus with Rh isoimmunization,[1] paving the way for the concept of fetal interventions, which has been in constant evolution since then. Later in 1964, an open hysterotomy was performed to gain access to the fetal circulation to perform an intrauterine exchange transfusion.[1] Unfortunately, the reported complications of this intervention led to an abundance of open hysterotomies for a decade before it was investigated again.

Fetal anemia resulting from Rh isoimmunization was previously diagnosed by an invasive approach using serial amniocentesis to estimate the bilirubin level in the amniotic fluid. Currently, fetal anemia can be diagnosed by Doppler ultrasound using peak systolic velocity of the middle cerebral artery, and fetal anemia is treated by percutaneous intrauterine transfusion with excellent outcomes. Diagnosis and treatment of fetal anemia is an excellent example of profound advances in prenatal diagnosis and fetal interventions over the years.

Similar to intrauterine transfusion, several aspects of fetal interventions have evolved remarkably, with many previously fatal conditions now being treatable with good fetal outcomes. This breakthrough in prenatal diagnosis and intervention was achieved by a better understanding of fetal physiology through extensive research, along with innovations in diagnostic and therapeutic modalities in this field.

In 1982, specialists from several fields in fetal surgery gathered, including the fields of maternal fetal medicine, pediatric surgery, physiology, and ethics, and the International Fetal Medicine and Surgery Society (IFMSS) was founded.[2] The main goal of this organization was to promote and encourage the development and advancement of the field of fetal diagnosis and therapy. Clear criteria to perform fetal surgery were set as follows[3]:

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

Given the high incidence of complications associated with open fetal surgery, minimally invasive fetal surgery was introduced. Two main collaborative research groups in Europe (Eurofoetus) and North America (North American Fetal Therapy Network, or NAFTNet) were created to extend the research on fetal surgery.

After extensive animal-based research and large clinical trials, several fetal procedures became the standard of care for antenatally diagnosed abnormalities that used to be untreatable.

Currently, fetal therapy is a well-established field, with many centers around the world having fetal surgery units that involve many specialties that work as one team to provide the best maternal and fetal outcomes.

One of the most frequently used interventions today is fetoscopy for laser photocoagulation as a treatment of twin-to-twin transfusion syndrome (TTTS). TTTS is a rare complication that occurs in 10–15% of monochorionic diamniotic twin gestation, with a mortality rate reaching 90%.[4] TTTS happens because of abnormal arteriovenous anastomosis in the placenta between the fetuses, leading to hypovolemia of one twin (donor) and hypervolemia of the other (recipient). Five stages of this condition were described by Quintero,[4] beginning with stage I, polyhydramnios of the recipient and oligohydramnios of the donor, and ending with stage V, the intrauterine fetal death of one twin.

This condition was previously managed by serial amnioreduction or septostomy (intentional puncturing of the intertwin septum); however, neither treatment modalities addressed the pathophysiology of the condition, and the main aims were to relieve maternal symptoms resulting from polyhydramnios and normalizing the fluid of both fetuses. In 1990, fetoscopic laser coagulation of vascular connections between fetoplacental circulations for TTTS was introduced as the first treatment modality to address the pathophysiology.[1]

The procedure can be done under local anesthesia in an outpatient sitting with intravenous sedation, al-

though regional or general anesthesia can be used as well. A 2-mm fetoscope is introduced percutaneously, then ablation of the superficial blood vessels on the surface of the placenta that cross the intertwin membrane is performed, leading to cessation of unbalanced twin-to-twin transfusion. This procedure became the standard of care for stage II, III, and IV TTTS. A systematic review of the Eurofoetus randomized controlled trials (RCTs) and two other observational studies that compared laser photocoagulation with amnioreduction confirmed that laser coagulation appears to be more effective in the treatment of TTTS, with less perinatal neurologic morbidity and mortality.[5]

Fetoscopic endotracheal occlusion (FETO) is another fetal intervention that has evolved. It was introduced in 2001[1] to improve the survival of fetuses with isolated congenital diaphragmatic hernia (CDH) diagnosed antenatally. The main concern in fetuses with CDH is pulmonary hypoplasia, resulting from the presence of abdominal organs in the chest, leading to increased perinatal morbidity and mortality. The concept behind this intervention is occlusion of the fetal trachea to allow fluid to accumulate in the lung to promote pulmonary tissue proliferation.

The first human studies of tracheal occlusion for treatment of CDH were performed by occluding the trachea surgically with a clip after exposing the fetal head and neck through a hysterotomy, but there were significant risks of preterm labor and uterine rupture, in addition to a high need for aggressive long-term ventilatory support after delivery.[6] These complications were significantly reduced by the fetoscopic approach.

FETO is not widely available, as it requires a highly specialized center with teams capable of performing the procedure and dealing with variable outcomes, including possible maternal and fetal complications. Its use is currently limited to fetuses with poor prognosis based on lung volume as estimated by ultrasound, and there are careful selection criteria for performing the intervention.

The TOTAL trial[7] was conducted as a multicenter RCT to evaluate FETO in the spectrum of CDH severities. The investigators randomly assigned patients with single fetuses with isolated severe left CDH to receive FETO or expectant care at 27 to 29 weeks of gestation, followed by standardized postnatal care. The trial was stopped early due to its efficacy.[1] In an intention-to-treat analysis that included 80 pregnancies, FETO resulted in 40% higher survival both to discharge and to 6 months of age.[6] The most commonly reported complications were preterm delivery and preterm premature rupture of membrane. Other rare complications included failure of balloon removal and neonatal death. The second phase of the TOTAL trial evaluated the FETO for moderate CDH compared to postnatal repair. Results showed that the incidence of pulmonary hypertension among infants who survived to discharge was similar in both groups, with a higher rate of complications in the FETO group.[7]

Fetoscopy has several other applications that are still investigational and need further research to prove their efficacy. Some examples are fetal cystoscopy in cases of lower urinary tract obstruction and fetoscopic repair of myelomeningocele to replace the open repair by hysterotomy.

Other investigational fetal interventions are fetal brain shunt for cases of hydrocephalus and ultrasound-guided fetal aortic valvuloplasty for hypoplastic left heart syndrome. These procedures are still experimental, with further research needed for application in clinical settings.

The most recently described prenatal approach is transamniotic stem cell therapy.[8] This is a novel fetal therapeutic alternative for the treatment of congenital anomalies. This therapeutic modality works by injecting targeted stem cells to promote the repair and significantly ameliorate the effects associated with major congenital anomalies, such as neural tube and abdominal wall defects.

In conclusion, fetal interventions have evolved remarkably from ideas to well-studied interventions that significantly improve the chances of survival in many previously described lethal conditions. Furthermore, many promising interventions are being investigated and extensive research is required in this field.

References

1. Evans LL, Harrison MR. Modern fetal surgery–a historical review of the happenings that shaped modern fetal surgery and its practices. *Transl Pediatr.* 2021;10:1401–1417.
2. Harrison MR. The University of California at San Francisco Fetal Treatment Center: a personal perspective. *Fetal Diagn Ther.* 2004;19:513–524.
3. Harrison MR, Adzick NS. The fetus as a patient. Surgical considerations. *Ann Surg.* 1991;213:279–291; discussion 277–278.
4. Quintero RA. Twin-twin transfusion syndrome. *Clin Perinatol.* 2003;30:591–600.
5. Fox C, Kilby MD, Khan KS. Contemporary treatments for twin-twin transfusion syndrome. *Obstet Gynecol.* 2005;105:1469–1477.
6. Benachi A, Chailley-Heu B, Delezoide AL, et al. Lung growth and maturation after tracheal occlusion in diaphragmatic hernia. *Am J Respir Crit Care Med.* 1998;157:921–927.
7. Deprest JA, Nicolaides KH, Benachi A, et al. Randomized trial of fetal surgery for severe left diaphragmatic hernia. *N Engl J Med.* 2021;385:107–118.
8. Lazow SP, Fauza DO. Transamniotic stem cell therapy. *Adv Exp Med Biol.* 2020;1237:61–74.