Intrauterine Fetal Surgery Current Approaches

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ABSTRACT

Though prenatal diagnosis has advanced a lot along with surgical techniques, intrauterine fetal surgery often not the preferred option. This is because the risks involved for both the mother and the fetus during and after the operation are often much more than the benefit to be achieved. Moreover, the infrastructure require ments and the costs of such operations are quite high. Fetal intervention is only possible in circumstances where the operation will correct abnormalities of the fetus which hamper normal growth, thus enabling normal fetal development (Twin-to-twin transfusion syndrome, congenital diaphragmatic hernia, Space-occupying thoracic lesions, Obstruction of lower urinary tract ect). It is mainly indicated in diseases that can result in intrauterine fetal death or whose effects could not be corrected postnatally (congenital aortic valve stenosis, hypoplastic left heart syndrome ect.). The proven pathophysiology and proper identification of the defect or disease is thus necessary before attempting such intervention. Since intrauterine fetal surgery entail high risks for both the fetus and the mother, there are ethical controversies regarding research in fetal surgery. Suitable surgical techniques, appropriate and effective high end methods to monitor fetal and uterine development and prevention of uterine contractions after surgery (tocolysis) are a few of the key bottlenecks that need to be addressed urgently to make intrauterine fetal surgery more useful. This article reviews recent intrauterine fetal interventions and their risk and success rates.

Keywords: Fetal therapies, Surgery, Fetoscopy, Fetal research

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Introduction

Fetal surgery refers to a wide range of surgical techniques that are employed to treat birth defects, for example neural tube defects such as spina bifida, in fetuses in the pregnant uterus.[1] The appeal of fetal surgery is the disruption in utero of the progression of a fetal condition. Fetal surgery is performed for conditions which interfere with the normal fetal growth, which upon correction will allow normal fetal development. There are various types of fetal surgery including open fetal surgey as well as less invasive methods such as fetal endoscopic surgery (FETENDO suregery), fetal image guided surgery (FIGS) and ex-utero intrapartum treatment procedure (EXIT).[2,3]

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What is a fetal intervention?

Fetal intervention entails treatment of a fetus inside the uterus. Truly astonishing developments have been possible due to the rapid progression in skill in detection of fetal problems over the last few decades. Though genetic and imaging techniques enable a precise diagnosis of several diseases before birth, intervention is seldom required prior to birth. Interventions will normally occur in the case of simple anatomic complications that do ongoing damage to the growing fetus. Examples of conditions in which intrauterine surgery is most commonly carried out include repair of myelomeningocele and treatment of twin-to-twin transfusion syndrome (TTTS) or congenital diaphragmatic hernia (CDH).3 While judging the benefits versus risk of in utero fetal surgery, the health and safety of the mother and her future reproductive prospects are the most vital considerations. The intervention is intended to benefit the fetus with a clinical problem. The mother is effectively an innocent bystander, accepting some risks for the unborn child.

Techniques of fetal intervention

Intrauterine fetal intervention includes a few techniques that have gained importance in the recent past, among which open fetal surgery is the most invasive and definitive.[2] Other less invasive techniques include FETENDO, FIGS and EXIT.

Open Fetal Surgery

During open fetal surgery, the mother is placed under general anesthesia along with an epidural to help with pain control. Medication as necessary is also applied to the fetus for pain control and to prevent movement. An incision of about 25.4 cm is made into the abdomen of the mother and an incision of approximately 12 cm into the uterus using equipment to minimise both bleeding and membrane separation during the operation. Continuous infusion of warm fluids into the uterus is carried out to maintain safe amniotic fluid levels for both the baby and mother. The uterus is closed after performing the surgery on the fetus in utero.[2]

Fetal Endoscopic (FETENDO) Surgery

A number of life-threatening malformations can be rectified before birth with intrauterine fetal surgery. Regardless of recent improvements in fetal intervention, preterm labor due to the large incision of the uterus in open surgery needed for proper fetal exposure remains a major setback. Thus, less invasive, endoscopic methods are preferable where possible. The overall risk of fetal surgery may be reduced, for example, by fetal endoscopic surgery (FETENDO surgery), which avoids large incision of uterus, thereby causing less uterine trauma and less preterm labor. The name FETENDO referes to fetal endoscopy, a fetoscopic intervention that was built up in the 1990s to avoid uterus incision and hopefully, to minimize preterm labor.[3] The power of visualizing the fetus with very small endoscopes, which have been accessible for several decades, was advanced to facilitate surgical manipulation of the fetus using very small instruments and assisted by use of a television monitor for direct fetoscopic view. During the development of these techniques, it was discovered that visualization of the fetus can be best carried out in real-time by simultaneous use of sonographic and endoscopic techniques. The combination of both image and sonography-guided manipulation has shown to be quite efficient in solving several fetal problems. FETENDO can be percutaneous or may demand a small incision in the mother's abdomen (mini-laparotomy). The advantage of FETENDO is that it is less invasive than open surgical intervention. It reduces the preterm labour and also the risk of mother with respect to postoperative recovery. Thus, monitoring and drugs are usually still a necessity. Technically FETENDO is complicated approach and required the development of many new techniques and devices for allowing visual access through the amniotic fluid while retaining the fetal position and accomplishing the delicate work within the fetus.

Still FETENDO has not replaced open fetal surgery for all fetal problems. It has proven especially useful for treating problems related to the placenta, for example in fetoscopic laser coagulation for TTTS.[3-5] Another example would be its use in balloon insertion in the fetal trachea during temporary fetoscopic endoluminal tracheal occlusion (FETO), which can be carried out to correct CDH without maternal laparotomy or incisional hysterotomy.[3-6] It has also been used in treatment of fetal bladder obstruction.[3]

Fetal Image Guided Surgery (FIGS)

FIGS uses ultrasound to direct the region of instrument insertion into the uterus to rectify a defect in the unborn fetus. Possible maternal complications of FIGS may include leakage of amniotic fluid, infection of the uterus, bleeding during fetal surgery, infertility and psychological stress and it may also result in Cesarean delivery. Fetal Image Guided Surgery for therapy or intervention (FIGS-IT) involves manipulating the fetus without making an incision in the uterus or having in utero endoscopic view. Surgery is performed totally under real-time cross-sectional view offered by the sonogram. As in FETENDO, it can be performed either through the mother's skin or, in some instances, with a small incision in the mother's abdomen. It may often require local or regional anesthesia, for example a spinal or epidural may be employed. FIGS minimizes problems associated with the mother in terms of preterm labour, discomfort or hospitalization, as it is the least invasive of the fetal access techniques. Image-guided surgery was first used for fetal blood sampling and amniocentesis. In recent times it can be applied to a variety of fetal manipulations that includes resolving of problems with anomalous twins using radio frequency ablation, proper placement of catheter-shunts in the chest, abdomen or bladder, and for certain cardiac manipulation. However, use in percutaneous ultrasound-guided balloon valvuloplasty to attempt to severe fetal aortic valve obstructions, for example, has met with limited success.[7]

In terms of level of invasiveness, fetal intervention can be categorized as open surgery being most invasive, FIGS-IT least invasive and FETENDO intermediate between the two. Non-invasive access to the fetus can be also achieved through the mother's circulation, wherein nutrients and medicines passed to the fetus by giving them to the mother and letting them cut through the placenta, as in case of treating fetal cardiac arrhythmias.[8]

Ex-Utero Intrapartum Treatment Procedure (EXIT)

Babies with airway compression problems due to, for example, CDH, tracheal occlusion surgery or congenital high airway obstruction syndrome (CHAOS), can be delivered using a specialized surgical delivery method called ex utero intrapartum treatment procedure (EXIT).[9] A number of rare congenital disorders, including congenital cystic adenomatoid malformation, bronchopulmonary sequestration, lung or pleural tumor, such as pleuropulmonary blastoma and lip or neck tumor-like trauma can cause airway compression in newborn infants. Airway compression at birth constitutes a medical emergency. In many instances, however, the airway compression is detected during prenatal ultrasound tests, permitting time to design a secure delivery with the help of the EXIT process or in other ways. During EXIT, airway constriction in

the baby is operated on outside the uterus, while keeping the umbilical cord intact so that the baby does not need a functional airway passage to breath. Upon successful clearance of the obstruction, when the doctor is sure about the functioning of the airway passage, the umbilical cord is detached. A hospital with a team of specialists, including an anaesthesiologist, a pediatric surgeon, obstetrician and neonatologist is a must to consider performing EXIT.

Unlike a Cesarean section, to ensure that the uterus is entirely relaxed, the mother is put under general anesthesia. Using a bronchoscope, the pediatric surgeon closely examines the airway through the baby's oral cavity when the head of the baby is delivered. Depending on the type of blockage, the surgeon may choose to try to introduce an endotracheal tube to deliver oxygen to the baby. If this is successful, the infant is delivered followed by cutting the umbilical cord. When this method fails, a tracheostomy tube is placed directly into the trachea through the neck by the pediatric surgeon to bypass the blockage. A tube below the level of the airway obstruction is then placed by the surgeon making an incision in the neck of the baby. The infant is delivered when the surgeon is confident in the functioning of the tube that has been positioned, i.e. it can be used to bring oxygen to the baby. EXIT has also been used in tandem with FETENDO in reversal of pulmonary hypoplasia in CDH.[6] In this case, to avoid premature labor that can be caused by hysterotomy, a video-fetoscopic intrauterine technique of tracheal occlusion termed FETENDO-PLUG (Plug the Lung Until it Grows) was developed in which a foam plug or titanium clip was used to plug the trachea and was then unplugged using EXIT at birth.[6] In fact, use of EXIT has expanded from use purely for management of airway obstruction after fetal surgery, to include various fetal anomalies. This is illustrated in one single centre review on a series of 52 patients who underwent EXIT; 51 were born alive and 27 survived in the longer term.[10] Most of these 52 infants (45) underwent EXIT in order to reverse tracheal occlusion for CDH, either tracheal clip removal or bronchoscopy and tracheal balloon removal and all those who died had CDH.[10] Five of the patients underwent EXIT for neck masses and two underwent the EXIT procedure and tracheostomy for congenital high-airway obstruction syndrome.[10]

Indications for fetoscopic surgery

Fetoscopic surgery uses minimally invasive techniques and instruments to correct the malformation through small incisions. The primary conditions that have been researched are congenital cystic adenomatoid malformation, sacrococcygeal teratoma, extralobar pulmonary sequestration, urinary tract obstruction, twin reversed arterial perfusion syndrome, TTTS, myelomeningocele repair, CDH and congenital heart disease. These and other remaining indications for fetal surgery are shown in Table 1.[11,12]

Table 1: Indications for fetal surgery[11,12]

Fetal intervention	Rationale for intrauterine therapy
a. Surgery on fetus	
Congenital diaphragmatic hernia (CDH)	Prevention of pulmonary hypertension and pulmonary hypoplasia reversion
Sacrococcygeal teratoma (SCT)	Prevention of polyhydramnios
Space-occupying thoracic lesions	Pulmonary hypoplasia prevention
Obstruction of lower urinary tract	Prevention of pulmonary hypoplasia and renal failure
Cardiac anomalies	Prevention of progressing damage to developing heart
Myelomeningocoele	Exposed spinal cord coverage, cerebro-spinal fluid leakage cessation to prevent hind brain herniation
b. Surgery on the placenta, membranes or cord	
Monochorionic pregnancies:	Cessation of of feto-fetal transfusion and its consequences
Twin-Twin transfusion syndrome (TTTS)	Preterm delivery prevention
Twin-reversed-arterial-perfusion sequence (TRAP)	Prevention of damage to co-twin
Twin-anaemia polycythaemia sequence	Cardiac failure and polyhydramnios reversal
Amniotic syndrome	Control of deformities and functional loss
Chorioangioma	Prevention of cardiac failure, polyhydramnios and fetoplacentalis

Risks

The major risk associated with prenatal surgery is nicking of the placenta causing uterine contractions, blood hemorrhage and premature birth of the infant, who may not survive. Babies who have undergone fetal surgery are usually delivered by cesarean section due to scarring of the uterus.[13] Major risks to the mother include potentially fatal side effects from medications required to control premature labor, profuse blood loss, rupture of the uterine incision, infection of the uterus, mental stress, inability to conceive further and death. Premature birth is commonly associated with intrauterine fetal surgery. Infants born prematurely (fetuses delivered 6 weeks before the actual delivery date), are usually at higher risk for delayed walking and talking and for learning problems and

those born more at about 30 weeks of gestation are at risk for cerebral palsy, brain hemorrhages and blindness. Amniotic fluid is present within the uterus, which protects the fetus from infection and is also essential for lung development. During uterine incision some amniotic fluid is often lost due to leakage. This happens to nearly 25% of women undergoing prenatal surgery. With the loss of amniotic fluid the fetal lungs may not develop properly.[14] Other risks to the fetus include membrane separation between the uterus and surrounding tissues of the amniotic sac, causing premature delivery or interrupted flow of blood to some fetal body part such as a leg or arms; birth at the time of surgery; prenatal surgery for spina bifida may cause further damage to the nerves and spinal cord; intrauterine infection leading to immediate delivery; brain damage; deformation of body parts; and death. Given the risks, it is of paramount importance that recognized criteria be followed when deciding whether intrauterine fetal surgery is indicated.

Practice guidelines

A consensus, authorized by the International Fetal Medicine and Surgery Society, recommended the following criteria for intrauterine fetal surgery:[15]

Accurate diagnosis and staging with exclusion of associated anomalies.

Documentation of the natural history of the disease and prognosis is established.

No effective postnatal therapy currently.

Proven intrauterine surgery in animal models, reversing the harmful effects of the condition.

Surgery to be performed in specialized multidisciplinary fetal care centers within strict regimes and approval by the local Ethics Committee with the consent of the mother or parents.

The American Academy of Pediatrics Committee on Bioethics and the American College of Obstetricians and Gynecologists (ACOG) Committee on Ethics issued a committee opinion on maternal-fetal surgery and fetal care centers in 2011.[16] This proposed that:

Intrauterine fetal surgery cannot be performed without the explicit consent of the expecting mother.

Proper information should be provided to the prospective parents about the distinctions between the standard or evidence-based therapies and experimental or innovative interventions.

The information should include a thorough discussion of the benefits and also the risks for both the fetus and the mother.

The organization providing fetal interventions should provide a diverse group of professionals.

Different fetal care centers should be encouraged to cooperate so as to establish collaborative research networks to build up more vigorous short and long term maternal - fetal outcome data on all categories of intrauterine fetal intervention.

Success with intrauterine fetal surgery

For years, experts have been seeking ways of optimizing in utero fetal interventions, reckoning that medical abnormalities might be more easily cured while a fetus is still developing. There have been various successes in terms of treatment of myelomeningocele. The recent Management of Myelomeningocele Study (MOMS), that initially considered 200 pregnant women carrying a child with myelomeningocele, was stopped early after recruitment of 183 patients due to the efficacy of the intrauterine surgery.[17] When compared to postnatal surgery, prenatal surgery performed prior to 26 weeks gestation resulted in decreased risk of death or need for shunting by the age of 12 months in the infants. Prenatal surgery also resulted in improved mental and motor function and likelihood of being able to walk independently by 30 months of age. This was the first time a randomized clinical trial clearly confirmed that prenatal surgery can improve the outcome for patients. In a comparative urodynamic study of 5 patients who underwent prenatal closure of myelomeningocele and 88 patients with similar level lesions who underwent postnatal surgery, Koh et al.[18] showed that all 5 prenatally treated patients had lower lumbosacral lesions on neurological examination whereas 34 out of the 88 patients (39%) in the postnatal cohort lacked sphincter activity. In another study, 48 out of 51 patients underwent successful intrauterine surgery for myelomeningocele.[18]

Intrauterine surgery has also been successfully used in cases of fetal tumors. Successful operative fetoscopy was carried out on a large, potentially fatal fetal oral teratoma in 2010.[19] This operation was perhaps the first case that reported a successful intrauterine treatment of fetal oral tumor.[19] Another study evaluated the efficacy of prenatal surgery of sacrococcygeal teratoma (SCT) via hysterotomy.[20] Three out of five fetuses with SCT (75%) survived and were alive and healthy when monitored between 20 months to 6 years of age.[20]

TTTS is another condition in which intrauterine surgery has bee successfully applied. As part of the randomized, controlled Eurofoetus trial, long-term neurodevelopment of 120 infants with TTTS was followed up to age 6 years.[21] The study results indicated that fetoscopic selective laser coagulation (FSLC) was associated with reduction in the risk of death or long-term neurologic impairment as compared to amnioreduction.[21] A 2014 update demonstrated that endoscopic laser coagulation of anastomotic vessels should be considered in the treating all stages of TTTS so as to improve neuro-developmental outcomes.[22] It utility has been demonstrated by various studies, including one in which long-term neurodevelopment was evaluated following intrauterine laser coagulation for TTTS in 167 children.[23] 86.8% of the children demonstrated normal development, 7.2% showed minor neurological abnor-

malities, and 6% demonstrated major neurological abnormalities. Therefore, intrauterine laser coagulation is considered to be the best method for treatment of severe TTTS.[22] The main complication was neurological impairment in children with TTTS on undergoing amnioreduction, which lessened when they underwent laser therapy.[22]

In terms of CDH, promising results have been obtained. Ruano et al.[24] reported 53% survival rate among seventeen fetuses with severe CDH who were treated with fetal endoscopic tracheal occlusion (FETO) as compared to only one of the eighteen infants who received no prenatal intervention.

Use of intrauterine fetal surgery has also been examined in cases of fetal heart defects, but results have been mixed. One study reported that percutaneous balloon valvuloplasty was successfully achieved in seven out of twelve fetuses with severe aortic obstruction, of which only one survived to age 4 years.[7] Another study reported that while in about 74% of fetuses with congenital aortic valve stenosis, ultrasound guided percutaneous balloon valvuloplasty was achieved successfully in utero, ultimately only five of the twenty second-trimester fetuses treated survived with biventricular circulation.[25,26] By 1 month of age, three had two-ventricle circulation and two infants maintained two-ventricle circulation and needed surgical repair.[26] Aortic vulvoplasty was technically successful in 26 out of 30 fetuses with aortic stenosis, with improvement of left heart Doppler characteristic and left ventricular systolic function.[27] Meanwhile, Marshall et al.[28] reported that 19 out of 21 fetuses undergoing intrauterine surgery for atrial septal defect for hypoplastic left heart syndrome attempted between 24 and 34 weeks gestation were technically successful,[28] while Artz and collegues[29] reported that up to 43% of fetal aortic stenosis cases treated with successful prenatal intervention led to biventricular circulation after birth, with 67% of live-born technical successes being biventricular. The increase in left atrial pressure resulting in pulmonary vascular changes may not be reversible after birth, resulting in severe pulmonary edema and cyanosis and demonstrated as pulmonary venous flow abnormalities. Fetal intervention for restrictive atrial septum was proposed to decompress the left atrium as a means to alleviate the development of these pulmonary vascular complications.[30]

Conclusion

It is still debated whether it is ethically right to perform intrauterine fetal surgery as it is associated with high risks to both the mother and fetus. The process has further problems related to complications of premature delivery and the extreme high cost associated. Thus the decision of performing intrauterine fetal surgery is a critical one and has to be taken after careful thought and considerations. The most important factor is accurate prenatal diagnosis. Focus in the future should therefore be on improvement upon the techniques associated with precise prenatal diagnosis. Today's fetal surgery pattern suffers from an eternal conflict between what is the best possible quality and how it can be guaranteed, versus pervasive access and adequate number of patients. But successful operation on a fetus while still in the uterus can be a miraculous achievement. In some cases of fetal illnesses, for example in severe TTTS, intrauterine fetal surgey is now considered to be the optimal treatment. On the other hand in other cases, for example in fetal heart defects, the evidence for efficacy of this type of surgery is less compelling and suggests the necessity of further improvement and refinement of techniques. Intrauterine fetal surgery when applied in carefully considered circumsances is nonetheless now capable of achieving reduced mortality related to complications at birth, and treating physical malformations early on, thereby improving future quality of life.

İntrauterin Fetal Cerrahi: Güncel Yaklaşımlar

ÖZET

Cerrahi tekniklerinde meydana gelen ilerlemelerle prenatal tanının çok ilerlemesine rağmen intrauterin fetal cerrahi hala çok tercih edilen bir seçenek değildir. Bunun nedeni operasyon sırasında ve sonrasında anne ve fetüsün karşılaşabileceği risklerin çoğu zaman ameliyatla elde edilebilecek faydalardan çok daha fazla olmasıdır. Ayrıca alt yapı gereksinimleri ve ameliyat masrafı oldukça yüksektir. Fetüse müdahale ancak fetüsün normal büyümesi önünde bir kısım engellerin olduğu (ikizden ikize transfüzyon sendromu, konjenital diyafragmatik herniler, yer kaplayan torasik lezyonlar, alt üriner sistem obstrüksiyonu vb.) anormal durumların düzeltebileceği ve fetüsün büyümesinin normal hale getirilebileceği durumlarda mümkündür. İntrauterin fetal ölümle sonuçlanabilecek veya etkileri postnatal olarak düzeltilemeyecek olan hastalıklarda da (konjenital aort stenozu, hipoplastik sol kalp sendromu vb.) endikedir. Bu tarz müdahalelerden önce kanıtlanmış patofizyoloji ve defekt veya hastalığın uygun bir çalışmadan geçmiş olması gerekmektedir. İntrauterin fetal cerrahi hem fetüs hem de anne için büyük riskler ihtiva ettiğinden fetal cerrahi araştırmaları etik tartışmalara sebebiyet vermektedir. Fetal cerrahinin daha kullanışlı hale gelmesi için acil olarak uygun ameliyat teknikleri, fetüs ve uterus seyrini monitörize edecek ve cerrahi sonrası uterin kontraksiyonların (tokoliz) önlenmesine yardımcı olacak ileri metodların geliştirilmesine ihtiyaç vardır. Bu makale günümüzde yapılabilen intrauterine fetal müdahaleleri, risk ve başarı oranlarını incelemektedir.

Anahtar Kelimeler: Fetal tedaviler, Cerrahi, Fetoskopi, Fetal araştırma

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