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Fetal Surgery: A Brief Review

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ABSTRACT

Fetal surgery is the act of opening the gravid uterus, surgically correcting a fetal abnormality, and returning the fetus to the uterus for postoperative recovery and continued gestational development. By this definition, human fetal surgery has now been performed for more than a decade, primarily at a single center. Tremendous progress has been made in our understanding of the natural history and pathophysiology of fetal diseases, in solving the technical challenges of fetal surgery, and in intra- and postoperative care and monitoring of the maternal-fetal unit. However, success and general application of fetal surgery continue to be limited by a number of unsolved and formidable problems. Fetal therapy is a logical extension of fetal diagnosis. A group of disorders amenable to potential improvement by fetal treatment has been identified, including fetal urinary tract obstruction, fetal diaphragmatic hernia, fetal congenital cystic adenomatoid malformation and fetal sacrococcygeal teratoma. The discovery of effective tocolysis would be analogous to the development of effective immunosuppression and would allow fetal surgery to achieve its full potential. The fetal surgical experience with each of these lesions is reviewed and the maternal risk of fetal surgery is discussed in the article. The aim of the review is to identify the effectiveness of maternal-fetal surgery for several congenital abnormalities & surgeries of greatest interest including open fetal surgery and fetoscopic surgery and their comparison to post natal surgeries.

INTRODUCTION

Congenital abnormalities that can be repaired prenatally occur in a small percentage of full-term births, and because of advances in imaging techniques such as ultrasound, many more congenital abnormalities are being diagnosed in utero. As these abnormalities are frequently recognized prior to delivery, maternal-fetal surgical procedures have emerged as a potential option for treating some of these defects[1]. Although postnatal intervention is best for most fetal abnormalities (particularly in light of risks associated with in utero surgeries), for a few conditions, the fetus' condition can deteriorate so rapidly in the womb as to make early intervention necessary either to avoid death or substantially higher morbidity after birth. Substantial questions remain about both the safety and efficacy of fetal surgical corrections. In some cases, the natural history of the conditions is poorly understood, making comparisons to no treatment or difficult postnatal intervention [2].

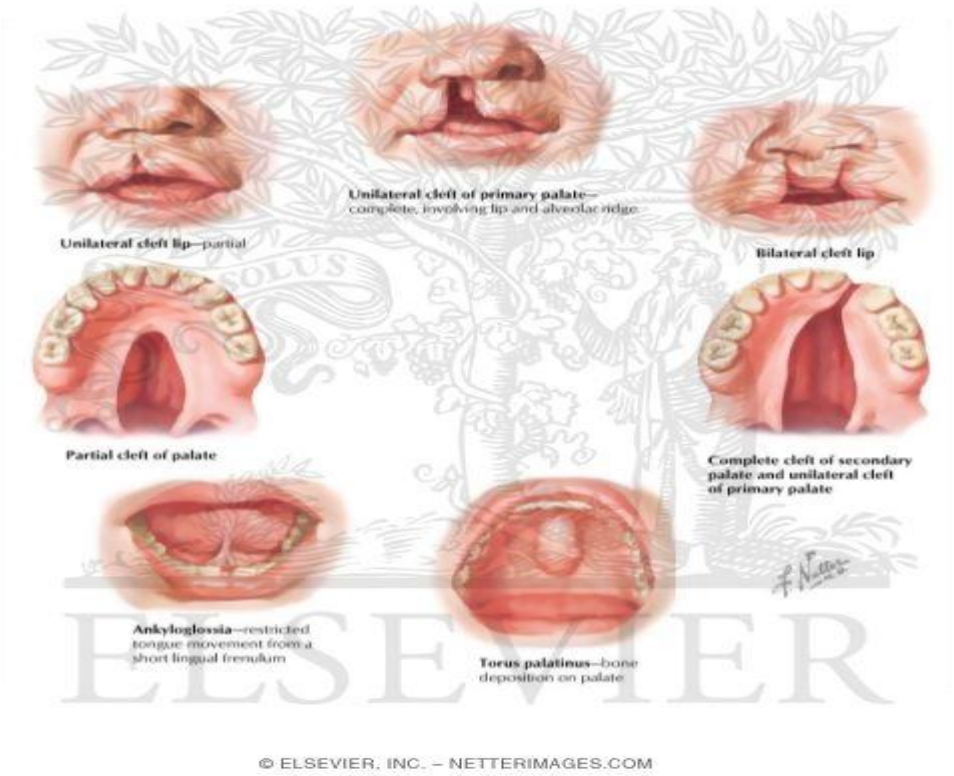

Figure 1. Congenital abnormalities (Birth Defects; Deformities; Congenital Defects) [2]

In addition, comparison of fetal versus postnatal surgery must consider the safety of the mother, yet limited comparative data exist. The issue is particularly complicated because congenital defects are relatively common in aggregate, individual congenital abnormalities occur infrequently, making effective study very difficult. Ongoing trials are evaluating some of the most common fetal surgeries[2].

What is Fetal Surgery?

Fetal surgery is any of a broad range of surgical techniques that are used to treat birth defects in fetuses who are still in the pregnant uterus[3].

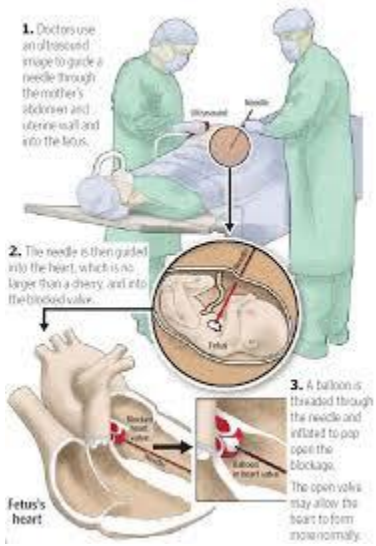

Figure 2. Experimental Fetal Surgery[3]

The goal of the brief review is to describe the current state of literature and practice of maternal-fetal surgical procedures for seven congenital abnormalities ranked of high importance by stakeholders:

- Sacrococcygeal teratoma
- Congenital diaphragmatic hernia
- Thoracic lesions: congenital cystic adenomatoid malformation and bronchopulmonary sequestration
- Obstructive uropathy
- Myelomeningocele
- Twin-twin transfusion syndrome

- Cardiac malformations[3]

Conditions that may require fetal surgery

- Problems which cause hydrops (fetal heart failure) by compressing the heart:
- Massive lung lesions (congenital cystic adenomatoid malformation (CCAM) and bronchopulmonary sequestration)[4]
- Cardiac tumor (teratoma)
- Problems which cause hydrops by stealing blood flow:
- Sacrococcygeal teratoma
- A cardiac twins
- Twin-twin transfusion syndrome
- Twin reversed arterial perfusion syndrome
- Problems with the airway or lungs at birth:
- Congenital high airway obstruction syndrome
- Cervical teratoma
- Massive cystic hygroma
- Problems with small lungs (pulmonary hypoplasia)
- Pleural effusions[4]
- Massive lung lesions
- Severe oligohydramnios
- Problems which can cause irreversible organ or limb damage:
- Bladder Outlet Obstruction (anhydramnios and pulmonary hypoplasia)
- Amniotic Band Syndrome
- Myelomeningocele (Spina Bifida)

Plastic surgery on the human fetus seems implausible, but with recent advances in fetal surgery and the phenomenon of scarless fetal wound healing, it may one day become a possibility.[5] Correcting craniofacial anomalies and other congenital deformities in utero, thereby preventing abnormal tissue growth and disfigurement while leaving no evidence of the operation.

History

The past decade has witnessed the introduction and development of human fetal surgery[6]. At the Fetal Treatment Center of the University of California, San Francisco, life-threatening malformations such as congenital diaphragmatic hernia, obstructive uropathy, and cystic adenomatoid malformation of the lung have been prenatally diagnosed by ultrasound. Using specialized instruments and monitoring techniques, surgeons have been able to correct these malformations in highly selected patients in utero. The success of these extremely intricate procedures remains limited by the problems of peri- and postoperative premature labor and adequate postoperative intensive care management of both mother and fetus[7]. Fetal surgeons have already made great advances from their early experience.

Scarless Fetal Skin Wound Healing

One of the most exciting developments from the human fetal surgery enterprise has been the study of scarless fetal skin wound healing. Unlike adult tissue, fetal dermal repair seems to occur in a fundamentally different way, resulting in scarless wound healing[8]. Fetal skin heals without macroscopic evidence of prior injury, and the dermis reveals a highly organized collagen architecture. This phenomenon of scarless fetal skin repair has been observed in mice, rats, rabbits, monkeys (Figur 3-5), opossum, and humans[8].

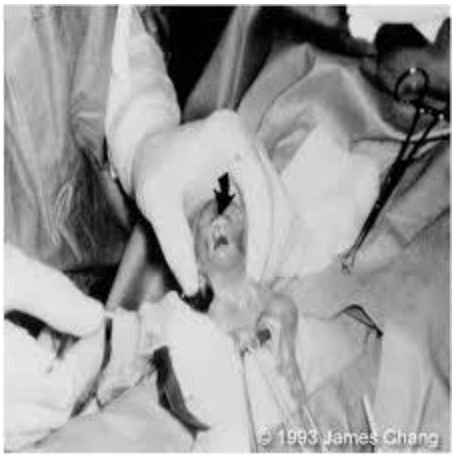

Figure 3: Intraoperative photograph of a 75 day gestation (term=165 days) fetal rhesus monkey, with a 2 mm excisional wound (arrow) made in the upper lip, which was approximated with sutures.

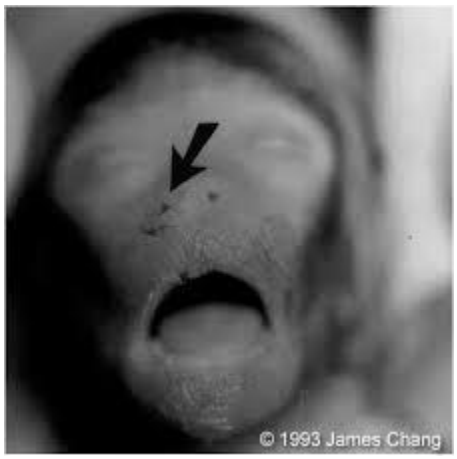

Figure 4: Same fetus as in Fig. 3, after wounding. The lip wound is not grossly visible, except for its sutures (arrows). This wound healed without scar formation.[7]

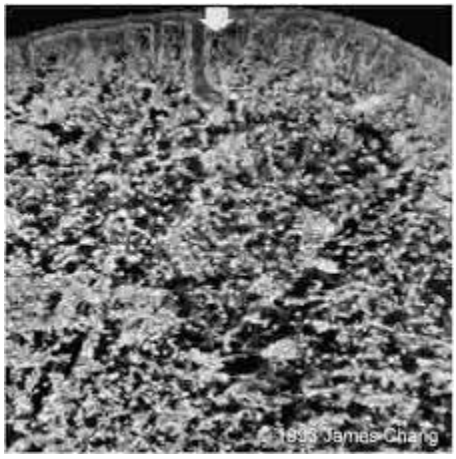

Figure 5: Immunohistochemical staining for collagen type III in an identical gestational age monkey lip wound (arrow), demonstrates scarless fetal wound repair in the non-human primate[8].

Nevertheless, much of this work has been accomplished in the sheep model because of the animal's prolonged gestation time, ease of fetal exposure and manipulation, and a relative resistance to premature labor. In fetal lambs, incisional wounds heal without scarring at 100 days gestation and begin to scar at 120 days; gestation (term pregnancy=145 days)[9]. Therefore, a transition period exists during which the fetus begins to heal in the usual adult-like manner. Using the fetal rhesus monkey model, we have determined that an intermediate "transition"

wound occurs whereby the wound heals with a normal collagen pattern but without restoration of normal hair follicle and sweat gland patterns[10].

Differences between fetal and adult wound healing

Table 1: Differences between fetal and adult healing

Intrauterine environment: amniotic fluid rich in:[9] 1 growth factors 1 hyaluronic acid 1 fibronectin
Intrauterine environment: amniotic fluid poor in: 1 oxygen (pO_2 is roughly 3-4 times less than in adults).
minimal acute inflammatory response
paucity of neutrophils
macrophages recruited to fetal wound[10]
high level of hyaluronic acid
enhanced fibronectin production

These differences include those involving the intrauterine environment where the fetus is bathed in amniotic fluid, which is rich in growth factors, hyaluronic acid, and fibronectin, and where the fetus remains relatively hypoxic. Mid-gestational fetal lamb tissue pO_2 is roughly 16 mmHg, whereas adult tissue pO_2 ranges from 45 to 60 mmHg.

Intrinsic differences also exist between fetal and adult tissue. Notably, in fetuses, there is a minimal acute inflammatory response with a paucity of neutrophils[7]. In addition, recent data from our research group suggests that macrophages are recruited to fetal wounds and express several types of growth factors (transforming growth factor, tumor necrosis factor) which may regulate tissue repair)[11]. It appears that fetal wound healing utilizes different and perhaps more selective cellular mechanisms of tissue repair. Other considerations in fetal versus adult tissue repair include a fetal wound matrix rich in hyaluronic acid (a major glycosaminoglycan that facilitates cell migration), the explosive growth and synthetic potential of fetal fibroblasts with organized collagen deposition, and enhanced fibronectin production during embryogenesis[7].

Animal Models

Several animal models of fetal plastic surgery have been established to investigate these issues. To date, almost all animal models have involved the creation and repair of cleft lips, which are technically the easiest fetal congenital lesion to repair. In 1985, Hallock played a pioneering role in this new field by describing a fetal cleft lip model in mice, where Dilantin- induced lip clefts were successfully repaired on day 17 of the usual 19-day gestation[12]. His further work has involved repairing a surgically divided lip in the fetal rhesus monkey[13]. A cleft lip model in fetal rabbits was previously established[14]. As expected, the fetal rabbits healed without histologic evidence of scarring. More importantly, cephalometric measurements after successful lip repair in these rabbits exhibited normal maxillary length and width[15-17]. These data supported the hypothesis that scarless repair would allow subsequent normal facial growth.

The sheep model has provided valuable information regarding in utero repair of cleft lips.

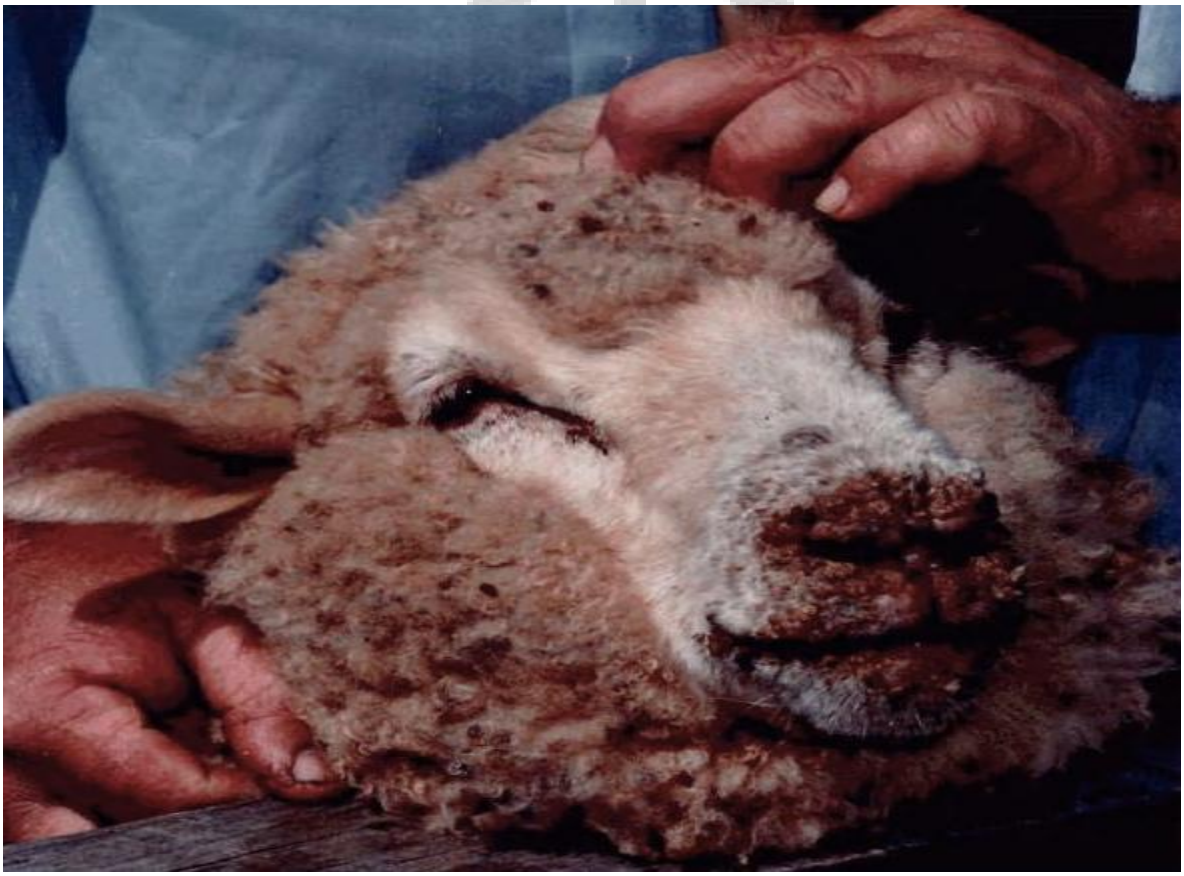

Figure 6. Sheep Model for Fetal Surgery[16]

Longaker and colleagues recently reported a fetal cleft lip repair model in lambs, also documenting scarless healing of the cleft lip without secondary mid-face growth retardation[18]. The most exciting innovation, however, has been the use of endoscopic technology. Estes and colleagues were able to create and repair a cleft lip in fetal lambs using small endoscopic ports rather than the conventional large hysterotomy incision. The authors suggested that these small incisions may allow for surgical repair earlier in gestation and may prevent the postoperative difficulties with preterm labor that have hindered human fetal surgery thus far[19].

Potentially Treatable Lesions

Having discussed human fetal surgery, laboratory observations of scarless fetal wound healing, and the various animal models established, which craniofacial anomalies and congenital deformities would be candidates for in utero repair in future (Table 2).

Table 2: Potentially Treatable Lesions[20]

cleft lip
cleft palate
craniofacial clefts
Treacher-Collins syndrome
craniofacial microsomia
craniosynostosis with resultant skull deformities
hyper- and hypotelorism
Pierre-Robin syndrome
syndactyly
amniotic band syndromes

Cleft lip is the most likely lesion to be repaired in utero because the operation would be technically least difficult. Other more complicated craniofacial anomalies which could be prenatally diagnosed by ultrasound include: cleft palate; centric and acentric craniofacial clefts, including Treacher-Collins syndrome; craniofacial microsomia; craniosynostosis with resultant skull deformities; orbital hypertelorism and hypotelorism; and Pierre-Robin syndrome. Aside from craniofacial defects, syndactyly and amniotic band syndromes are other congenital lesions

that would be potential candidates for in utero repair[21-23]. All of these complicated defects will require the development of reliable animal models prior to consider prenatal repair. By studying the natural history and developmental pathophysiology of these resultant defects, surgeons will learn when to best intervene. Furthermore, the operations for these more complicated defects may prove to be extremely demanding relative to correct cleft lips in utero and may require substantial training before they can be performed on humans.

Prenatal Surgery: Helping Babies before Birth

Operating on a baby before birth may seem like science fiction, but prenatal surgery is becoming more and more common in special pediatric programs throughout the United States.

Since prenatal surgery was first pioneered in the 1980s, it has become an important way to correct certain birth defects that could be severe (and in some cases fatal) if babies were born with them unrepaired.

Prenatal surgery (also called fetal surgery or fetal intervention) most often is done to correct serious problems that can't wait to be fixed, like certain heart defects, urinary blockages, bowel obstructions, and airway malformations.

Some of the greatest successes have come from correcting spina bifida (an often disabling spinal abnormality in which the two sides of the spine fail to join together, leaving an open area). A recent landmark study reports that kids with spina bifida who received fetal surgery typically are more likely to walk, less likely to have serious neurological problems, and less likely to need a shunt to drain brain fluid[24].

The most common types are:

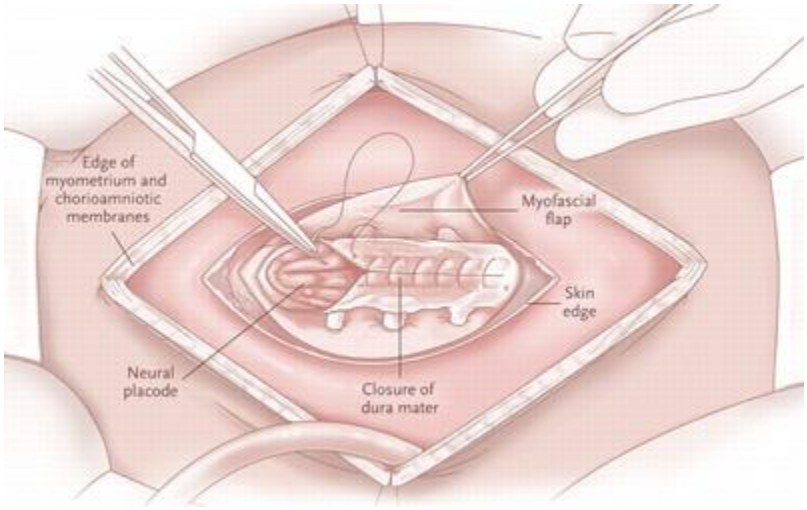

Figure 7. Open Fetal Surgery[25]

In open fetal surgery, the mother is placed under general anesthesia and given an epidural to help with pain control. The fetus is also given medications as needed for pain control and to prevent movement.

During the surgery, the surgeon makes a 10-inch incision into the mother's abdomen and a 4 to 5-inch incision into the uterus using a special device that helps to control bleeding and membrane separation[25]. Warmed fluids are continuously infused into the uterus to keep the amniotic fluid level safe for the mother and baby. The surgery is performed on the baby while still in the womb, and then the uterus is closed.

After open surgery, physicians require mothers to stay in the hospital for 4 to 5 days or until any complications are ruled out. Then they ask mothers to remain on modified bed rest to decrease the risk of preterm delivery for the rest of the pregnancy (no heavy lifting, only light activity).

If a mother is from out of town, they ask that she remain in St. Louis for two weeks following fetal surgery with a dedicated caregiver. Medications are also used for the remainder of the pregnancy to decrease the chance of any preterm labor[26]. Although many mothers can carry the pregnancy to term, most deliver their babies early, at an average of 34 to 35 weeks.

Because the uterine incision for open fetal surgery does not heal as well as that for a cesarean section, our open fetal surgery mothers cannot labor in the current and future pregnancies. All future deliveries should be by cesarean section[26].

Open Fetal Surgery may be used for several conditions:

- Open fetal repair for myelomeningocele
- Resection of a chest or neck mass
- Resection of a sacrococcygeal teratoma[27]

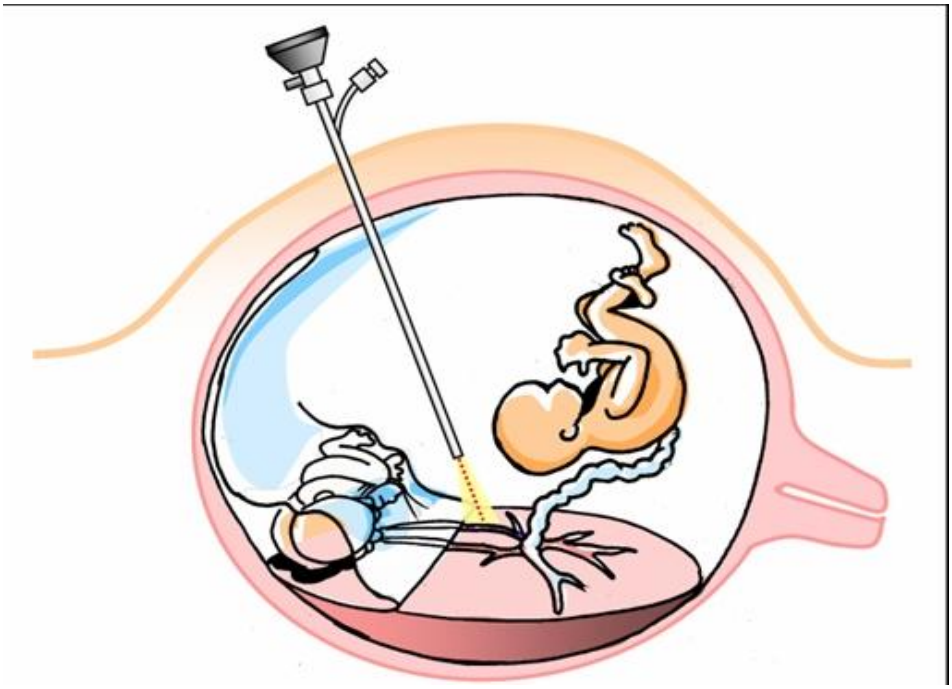

Figure 8. Minimally Invasive Fetoscopic Surgery[28]

In minimally invasive fetoscopic surgery, the surgeon makes a pencil-tip-sized incision and inserts a small telescope called a fetoscope into the uterus. The fetoscope allows for a telescopic view into the uterus. Ultrasound technology helps to guide the fetoscope throughout the uterus.

Fetoscopic surgery is much less invasive than open fetal surgery, thus decreasing the risk of preterm labor. Mothers are given anesthesia during the procedure to help with pain control and anxiety. The fetus is also given medication to decrease movement and prevent pain[28].

Because the uterine incision for fetoscopic surgery is very small, it heals well. Mothers can labor in the current and future pregnancies, and can plan on a vaginal delivery. Based on current research, we do not think that fetoscopic surgery will affect future pregnancies.

Fetoscopic surgery may be performed for several conditions:

Laser ablation of placental vessels for twin-twin transfusion syndrome, where the surgeon uses a laser, inserted into the uterus through the fetoscope, to eliminate communicating blood vessels in the placenta between twin fetuses[29].

Laser ablation of lesions, where the surgeon uses a laser inserted into the uterus through the fetoscope to eliminate the area causing complications, such as a posterior urethral valve in bladder outlet obstruction or amniotic band constricting a limb[29].

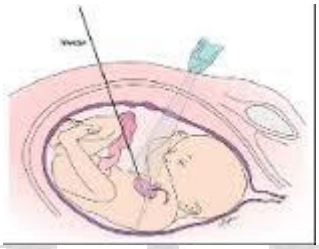

Figure 9. Fetal Image Guided Surgery[30]

Some fetal surgery is done without an incision to the uterus or use of an endoscope. Doctors use ultrasound to guide them as they perform "fetal manipulations," such as placing a catheter in the bladder, abdomen, or chest. The least-invasive form of fetal surgery, it's not used for serious conditions that require open surgery[30].

Needle Based Ultrasound Guided Procedures:

In needle based ultrasound guided procedures**,** the physician provides fetal intervention through ultrasound guidance and needle based therapy. This is less invasive than open or fetoscopic fetal surgery to the mother and baby, and usually does not require an overnight stay in the hospital.

However, physicians require the mother to stay for several hours after the procedure to rule out any complications. Needle based therapy may be used for several conditions:

- Amnioreduction/ Amnioinfusion, where a needle is placed into the uterus and amniotic fluid is either removed due to polyhydramnios (too much amniotic fluid) or warmed fluid is infused due to oligohydramnios (too little amniotic fluid)[31].

- Fetal transfusion or fetal blood sampling, where the surgeon places a needle into the baby's umbilical cord either provide donor blood to the baby or to remove fetal blood for sampling.

- Fetal shunt placement, where the surgeon places a small tube between the chest or bladder and the amniotic fluid to drain excess fluid[31].

Rationale for Fetal Surgery

All conventional postnatal plastic surgery falls short of truly optimal repair either due to the remaining functional deficit or subsequent scarring. Based on the animal models described above, it is clear that correctly timed fetal repair of surgically created cleft lips results in normal aesthetic facial morphology. Therefore, the rationale for operating in utero would be to intervene at an early stage of development, preventing the devastating developmental sequelae evident at birth, and to allow fetal wound healing capabilities to optimize tissue repair[32]. While some critics argue that fetal plastic surgery would be too costly, one must take into account the considerable time and expense involved in conventional postnatal craniofacial surgery. For example, reconstructive surgery for young patients with Treacher-Collins syndrome or even cleft palate may require multiple operations as well as years of orthodontic and speech therapy[32].

Guidelines for Fetal Surgery for Myelomeningocele:

Fetal surgery for myelomeningocele may be offered in the following circumstances:

- Myelomeningocele at level T1 through S1 with hindbrain herniation. The lesion can extend below S1, but the highest level cannot be outside the T1-S1 range. Lesion level and hindbrain herniation will be confirmed by ultrasound and MRI[33].
- Gestational age at the time of fetal surgery for myelomeningocele must be not greater than 25 weeks 6 days.
- Maternal age ≥ 18 years
- Singleton pregnancy
- Written confirmation of normal karyotype, elevated AFAFP and positive acetycholinesterase (ACHE)

Fetal surgery for myelomeningocele will not be offered if the mother has any of the following conditions:

- Insulin-dependent pregestational diabetes[33]
- Fetal anomaly not related to myelomeningocele — such as a cardiac defect or intracranial hemorrhage[34]
- Fetal kyphosis of 30 degrees or more at the level of the myelomeningocele lesion determined by MRI and ultrasound at CHOP
- Cerclage or documented history of incompetent cervix
- Placenta previa
- Placental abruption — a suggestion of a recent abruption or chronic placental edge bleeding (marginal abruption)
- A history of vaginal bleeding will be evaluated before fetal surgery will be offered.
- Short cervix (< 20 mm) based on the measurement taken at the time of evaluation.
- BMI greater than 35.
- Previous spontaneous delivery prior to 37 weeks — If membranes were intact and labor was induced, this is not considered spontaneous.[34]
- Maternal-fetal Rh isoimmunization, Kell sensitization or a history of neonatal alloimmune thrombocytopenia.
- Maternal HIV or Hepatitis-B status positive
- Maternal Hepatitis-C status positive
- Uterine anomaly such as multiple fibroids, Mullerian duct abnormality, bicornuate or unicornuate uterus, uterine septum, and double uterus. Any patient with a previous hysterectomy in the active segment of the uterus (whether from a previous classical caesearean, uterine abnormality such an arcuate or bicornuate uterus, myomectomy, or previous fetal surgery).
- Maternal hypertension would increase the risk of preeclampsia or preterm delivery (including, but not limited to: uncontrolled hypertension, chronic hypertension with end organ damage and new onset hypertension in current pregnancy)[34].
- Other maternal medical condition which is a contraindication to surgery or general anesthesia, such as some cases of asthma, cardiac disease or the refusal of a blood transfusion. Examples of medical conditions that are not exclusionary: epilepsy, abnormal pap results and thyroid nodules.
- No support person.

- Inability to comply with the travel and follow up requirements after fetal surgery.
- Patient does not meet other psychosocial criteria as evaluated by our social worker.

Fetal Surgery—An Exciting New Option for Spina Bifida:

A landmark study, co-led by experts at Vanderbilt University Medical Center, proves that babies who have surgery to repair spina bifida while still in the womb have better outcomes than babies who have surgery after birth. The positive outcomes include a decreased risk of death or need for shunt placement in the brain by the age of 12 months, plus improved mental and motor function[35].

Members of the fetal surgery team at Vanderbilt pioneered the innovative surgical procedure to repair myelomeningocele, the most serious form of spina bifida. Surgeons at Vanderbilt performed the first ever in utero repair for myelomeningocele in 1997 on Corey Meyer and her unborn son Daniel. Since those early procedures, Noel Tulipan, M.D., internationally renowned neurosurgeon and director of pediatric neurosurgery, has performed more than 200 prenatal surgeries to repair the spina bifida defect[36].

Vanderbilt University Medical Center is one of only three centers in the U.S. who participated in the National Institutes of Health (NIH) funded Management of Myelomeningocele Study (MOMS), a clinical trial comparing the two methods of treatment for babies with spina bifida; fetal surgery before birth and surgical closure after birth[37]. The results of the seven year study show that repairing the fetal defect, typically between 19 and 26 weeks of gestation, improves the health of children with spina bifida.

Limits

At the present time, fetal plastic surgery is limited by several issues. First of all, surgeons must continue to develop safe operative techniques for fetuses with life-threatening malformations. Obviously, until such operations are routinely successful, it is too much early to attempt human fetal surgery for non-life-threatening malformations such as cleft lip or craniosynostosis[38,39,40]. To the date much of the experimental work has focused on cleft lip, considerably more experience in animal models is necessary to determine which other congenital anomalies may also be treated by fetal surgery. The development of fetal wound healing has offered plastic

surgeons the possibility for scarless repair. It should be continued to advocate caution in this field[41] but, at the same time, hope that scientists will further provide both molecular answers and animal models for this fascinating phenomenon.

Future Development

What lies in the future for fetal plastic surgery? We certainly do not advocate plastic surgery on the fetus at this point, but instead offer a preview of a field that may one day develop[42].

CONCLUSION

Fetal surgery is a new field that is expanding rapidly. Currently, it is being done only in few centers in the world. This is a rapidly evolving field and some controversies still need to be resolved. Standardized assessment tools and blood micro sampling techniques for the fetus need to be developed to allow further development of clinical protocols. Questions regarding fetal stress and optimal drug dosing in the fetus remain open to speculation until these techniques evolve to answer our questions. In line with the trend in the adult, neonatal minimally invasive congenital heart surgery has become an important area of interest.

REFERENCES

1. Ashburn DA, Blackstone EH, Wells WJ, et al. Determinants of mortality and type of repair in neonates with pulmonary atresia and intact ventricular septum. *J Thorac Cardiovasc Surg*. 127(4):1000–1007. discussion 1007–1008. 2004 Apr
2. Shinebourne EA, Rigby ML, Carvalho JS. Pulmonary atresia with intact ventricular septum: from fetus to adult: congenital heart disease. *Heart.* ;94(10):1350–1357. 2008 Oct
3. Tulzer G, Arzt W, Franklin RC, et al. Fetal pulmonary valvuloplasty for critical pulmonary stenosis or atresia with intact septum. *Lancet.* 16;360(9345):1567–1568. 2002 Nov
4. Mizrahi-Arnaud A, Tworetzky W, Bulich LA, et al. Pathophysiology, management, and outcomes of fetal hemodynamic instability during prenatal cardiac intervention. *Pediatr Res.*62(3):325–330.2007 Sep
5. McElhinney DB, Marshall AC, Wilkins-Haug LE, et al. Predictors of technical success and postnatal biventricular outcome after in utero aortic valvuloplasty for aortic stenosis with evolving hypoplastic left heart syndrome.*Circulation.*;120(15):1482–1490. 2009 Oct
6. McElhinney DB, Benson CB, Brown DW, et al. Cerebral blood flow characteristics and biometry in fetuses undergoing prenatal intervention for aortic stenosis with evolving hypoplastic left heart syndrome. *Ultrasound Med Biol.* ;36(1):29–37. 2010 Jan
7. Wilkins-Haug LE, Tworetzky W, Benson CB, et al. Factors affecting technical success of fetal aortic valve dilation.*Ultrasound Obstet Gynecol.* ;28(1):47–52. 2006 Jul
8. Marshall AC, Tworetzky W, Bergersen L, et al. Aortic valvuloplasty in the fetus: technical characteristics of successful balloon dilation. *J Pediatr*;147(4):535–539. 2005 Oct

9. Tworetzky W, Wilkins-Haug L, Jennings RW, et al. Balloon dilation of severe aortic stenosis in the fetus: potential for prevention of hypoplastic left heart syndrome: candidate selection, technique, and results of successful intervention. *Circulation.* 12;110(15):2125–2131. 2004 Oct
10. Kohl T, Sharland G, Allan LD, et al. World experience of percutaneous ultrasound-guided balloon valvuloplasty in human fetuses with severe aortic valve obstruction. *Am J Cardiol.* 15;85(10):1230–1233.2000 May
11. Maxwell D, Allan L, Tynan MJ. Balloon dilatation of the aortic valve in the fetus: a report of two cases. Br Heart J.;65(5):256–258. 1991 May
12. Marshall AC, van der Velde ME, Tworetzky W, et al. Creation of an atrial septal defect in utero for fetuses with hypoplastic left heart syndrome and intact or highly restrictive atrial septum. *Circulation.* 20;110(3):253–258. 2004 Jul
13. Marshall AC, Levine J, Morash D, et al. Results of in utero atrial septoplasty in fetuses with hypoplastic left heart syndrome. *Prenat Diagn*. ;28(11):1023–1028. 2008 Nov
14. Allan LD, Maxwell DJ, Carminati M, et al. Survival after fetal aortic balloon valvoplasty. *Ultrasound Obstet Gynecol.* ;5(2):90–91. 1995 Feb
15. Hospital stays, hospital charges, and inhospital deaths among infants with selected birth defects—United States, 2003. *MMWR Morb Mortal Wkly Rep.* 19;56(2):25–29. 2007 Jan
16. National Center on Birth Defects and Developmental Disabilities. Metropolitan Atlanta Congenital Defects Program 2004 Annual Report. Atlanta, GA: Centers for Disease Control and Prevention; 2004.
17. Quintero RA, Huhta J, Suh E, et al. In utero cardiac fetal surgery: laser atrial septotomy in the treatment of hypoplastic left heart syndrome with intact atrial septum. *Am J Obstet Gynecol.*;193(4):1424–1428.2005 Oct
18. Glatz JA, Tabbutt S, Gaynor JW, et al. Hypoplastic left heart syndrome with atrial level restriction in the era of prenatal diagnosis. *Ann Thorac Surg.*;84(5):1633–1638. 2007 Nov
19. Rudolph CD, Rudolph AM, Hostetter MK, et al., editors. Rudolph's pediatrics. New York: *McGraw-Hill Medical Pub* Div; 2003.
20. Butler N, Claireaux AE. Congenital diaphragmatic hernia as a cause of perinatal mortality. *Lancet.* 31;1(7231):659–663.1962 Mar
21. Cortes RA, Keller RL, Townsend T, et al. Survival of severe congenital diaphragmatic hernia has morbid consequences. *J Pediatr Surg*;40(1):36–45. discussion 45–46. 2005 Jan
22. Deprest J, Gratacos E, Nicolaides KH. Fetoscopic tracheal occlusion (FETO) for severe congenital diaphragmatic hernia: evolution of a technique and preliminary results. *Ultrasound Obstet Gynecol.* 24(2):121–126.2004 Aug
23. Flake AW, Crombleholme TM, Johnson MP, et al. Treatment of severe congenital diaphragmatic hernia by fetal tracheal occlusion: clinical experience with fifteen cases. *Am J Obstet Gynecol*;183(5):1059–1066.2000 Nov
24. Gibbs DL, Piecuch RE, Graf JL, et al. Neurodevelopmental outcome after open fetal surgery. *J Pediatr Surg.* ;33(8):1254–1256. 1998 Aug
25. Harrison MR, Adzick NS, Bullard KM, et al. Correction of congenital diaphragmatic hernia in utero VII: a prospective trial. *J Pediatr Surg*;32(11):1637–1642. 1997 Nov
26. Harrison MR, Adzick NS, Flake AW, et al. Correction of congenital diaphragmatic hernia in utero: VI. Hard-earned lessons. *J Pediatr Surg*;28(10):1411–1417. discussion 1417–1418. 1993 Oct
27. Harrison MR, Adzick NS, Flake AW, et al. Correction of congenital diaphragmatic hernia in utero VIII: Response of the hypoplastic lung to tracheal occlusion. *J Pediatr Surg*;31(10):1339–1348. 1996 Oct
28. Harrison MR, Albanese CT, Hawgood SB, et al. Fetoscopic temporary tracheal occlusion by means of detachable balloon for congenital diaphragmatic hernia. *Am J Obstet Gynecol*;185(3):730–733. 2001 Sep
29. Harrison MR, Keller RL, Hawgood SB, et al. A randomized trial of fetal endoscopic tracheal occlusion for severe fetal congenital diaphragmatic hernia. *N Engl J Med.* 13;349(20):1916–1924. 2003 Nov
30. Harrison MR, Langer JC, Adzick NS, et al. Correction of congenital diaphragmatic hernia in utero, V. Initial clinical experience. *J Pediatr Surg*;25(1):47–55. discussion 56–57. 1990 Jan

31. Harrison MR, Adzick NS, Longaker MT, et al : Repair of a congenital diaphragmatic hernia in utero. *N Engl J Med* 322: 1582-1584, 1990.
32. Longaker MT, Golbus MS, Filly RA, et al: Maternal outcome with open fetal surgery: Analysis of the first 17 cases. *JAMA* 265: 737-741, 1991.
33. Longaker MT, Adzick NS: The biology of fetal wound healing: A review. *Plast Reconstr Surg* 87: 788-798, 1991.
34. Adzick NS, Longaker MT: Animal models for the study of tissue repair. *J Surg Res* 51: 216-222, 1991.
35. Longaker MT, Whitby DJ, Adzick NS, et al: Studies in fetal wound healing, VI. Second and early third trimester fetal wounds demonstrate rapid collagen deposition without scar formation. *J Pediatr Surg* 25: 63-69, 1990.
36. Lorenz HP, Whitby DJ, Longaker MT, Adzick N S.: Fetal wound healing: The ontogeny of scar formation in the nonhuman primate. *Ann Surg* 217:391-6, 1993.
37. Longaker MT, Bouhana KS, Roberts AB, Harrison MR, Adzick NS, Banda MJ: Regulation of fetal wound healing. *Surg Forum* 42: 654-655, 1991.
38. Hallock GG. In utero cleft lip repair in A/J mice. *Plast Reconstr Surg.* 75: 785-790, 1985.
39. Hallock GG, Rice DC, McClure HM. In utero lip repair in the rhesus monkey: an update. *Plast Reconstr Surg* 80: 855-858, 1987.
40. Longaker MT, Dodson TB, Kaban LB: A rabbit model for fetal cleft lip repair. *J Oral Maxillofac Surg* 48: 714-719, 1990.
41. Dodson TB, Schmidt B, Longaker MT, et al: Fetal cleft lip repair in rabbits: postnatal facial growth after repair. *J Oral Maxillofac Surg* 49:603-611, 1991.
42. Kaban LB, Longaker MT, Stern M, et al: Wound healing and facial growth after fetal cleft lip and palate repair. *Oral Maxillofac Surg Clin North Am* 3: 735-746, 1991.