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Review Article

The Development of Fetal Surgery

Seok Joo Han and Eui Ho Hwang

Division of Pediatric Surgery, Department of Surgery, Yonsei University College of Medicine, Seoul, Korea.

The history of fetal surgery features an absolute dependency upon the possibility of diagnosis before birth. Powerful new imaging methods, the techniques of sampling amniotic fluid and fetal tissue, and modern molecular genetics for the prenatal diagnosis of various congenital diseases have removed the veil of secrecy from the fetus. Even though most prenatally detected congenital malformations can be managed after maternal transport, a few simple anatomic defects require fetal surgery, albeit with predictably poor results. The understanding of intrauterine physiology and pathophysiology in several congenital malformations has been worked out in animal model study, and the natural history of congenital defects revealed by prenatal observations on human fetuses. Selection criteria for intrauterine intervention have been developed. Over the last two decades, surgical techniques for open and endoscopic fetal surgery have been defined and anesthesia and tocolysis for fetal surgery improved. As we enter the 21st century, this field of surgery will surely expand.

Key Words: Fetal surgery

Until the last half of the 20th century, the fetus had remained reclusive, wrapped and hidden from view within the womb, having floated undisturbed throughout pregnancy until the time of delivery. The main reason for the longstanding sequestered life of fetus was not due to an unwillingness to accept the possibility of treatment, but rather to a lack of any sure way of observing and understanding intrauterine life. After the first report of an *in utero* ultrasonographic diagnosis of congenital anomalies in the 1970s, it became possible to define prenatal diagnoses and the intrauterine natural history of fetal diseases. Many experimental fetal surgeries have also been performed that have enabled us to understand the physiology of the normal fetus and the pathophysiology of fetal defects. During the last decade, fetal surgery pioneer groups have investigated the rationale and feasibility of human fetal surgery, and attempted intrauterine correction of specific congenital anomalies, such as congenital diaphragmatic hernia, congenital cystic adenomatoid malformation, obstructive hydronephrosis, sacrococcygeal teratoma, meningomyocele and twin-twin transfusion syndrome.

In this article, we review the history of the development of fetal surgery. A distinction will be made between experimental fetal surgery and clinical trials.

The brief summary of milestones in fetal surgery development is presented in Table 1.

THE ANCIENT FETAL MEDICINE

In attempting to explain how the fetus was related to the child, Greek and Roman scholars conceived the idea of the homunculus-a miniature man living and growing within the mother before birth (Fig. 1).[1] Aristotle (BC 384 - BC 322), a Greek philosopher and scientist, thought that a miniature man in the father's sperm grew into a baby in the mother's womb. In the absence of biologic information, the homunculus provided a very good explanation for the origin of fetus. Hippocrates (BC 460 - BC 377), a Greek physician regarded as the Father of Medicine, came to the "brilliantly intuitive" conclusion that the fetus urinates *in utero* and that amniotic fluid is largely composed of fetal urine. Celsus (BC 30? - AD 45?), a Roman physician of the first century, is said to have

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Reprint address: requests to Dr. Eui Ho Hwang, Division of Pediatric Surgery, Department of Surgery, Yonsei University College of Medicine, C.P.O. Box 8044, Seoul 120-752, Korea. Tel: 82-2-361-5544, Fax: 82-2-313-8289, E-mail: ehhwang@yumc.yonsei.ac.kr

Table 1. Milestones in the Development of Fetal Surgery

Decapitation of a fetus for the impacted transverse lie (Celsus, Roman era)
The first reported successful fetal surgery in an animal (Bors, 1925)[5]
The first direct endoscopic visualization of the fetus (Westin, 1954)[44]
Direct fetal transfusion (Lilly, 1963)[32,33]
Lamb model of congenital diaphragmatic hernia (de Lorimier et al., 1967)[17]
Lamb model of obstructive uropathy (Beck, 1971)[20]
Introduction of real-time ultrasonography (1970s)
The first successful human open fetal surgery (Harrison et al., 1983)[2]
The first successful human open fetal surgery of congenital diaphragmatic hernia (Harrison et al., 1989)[2]
Experimental fetoscopic techniques (Harrison et al, 1989)[2]
The first successful human endoscopic vesicostomy (MacMahon, 1992)[45]
The first successful FETENDO clip (Harrison et al., 1997)[2]

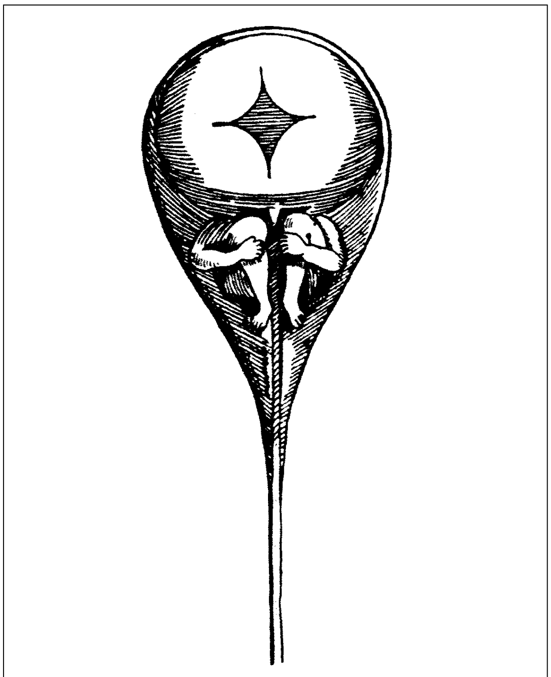

Fig. 1. A 17th Century drawing of a homunculus, a "little man" in a fetal position, living inside the head of a sperm cell (From Hartsoeker: Essai de Dioptrique, Sect. 88, Parks, 1694. In Meyer AW: The Rise of Embryology. Standford: Stanford University Press, 1939; without permission).

recommended decapitation for the impacted transverse lie. Andreas Versalius (AC 1514-1564), the Father of Modern Anatomy, made the first "truly analytic" observations on the living mammalian fetus. He pointed out that the fetus attempts to breath when exposed to air. He also noted that the fetal arteries in the umbilical cord pulsate regularly until fetal breathing begins.

THE EXPERIMENTAL FETAL SURGERY

It was not until the 19th century that experimental animal preparations were used to make physiologic observations on the living mammalian fetus. Bichat in 1803 was the first to study fetal movement. Zunt in 1877 and later Preyer in 1885, studied intact fetal guinea pigs suspended in warm saline and noted that once a fetus had been allowed to breathe, it could not be returned to its mother and survive.[2] In 1918, Mayer removed fetal guinea pigs from the uterus and placed them in the abdominal cavity.[3] Some of these fetuses survived for several days. In 1919 Wolff repeated these experiment in fetal rabbits and obtained same results.[4] In 1925 Bors reported the first successful fetal surgery procedure.[5] He amputated the limbs of guinea pig fetuses through a small uterine incision. The incision was closed and viable fetuses were eventually delivered. In same year, Nicholas also achieved survivals after ablating an eye, leg or a tail in fetal rats.[6] These procedures led to the development of techniques for the study of fetal physiology by more sophisticated ablative surgery. Hooker and Nicholas in 1930 developed a technique for spinal cord section and other investigators developed techniques for the ablation of critical fetal endocrine organs.[7] In 1939 Tobin performed fetal adrenalectomy,[8] and later Jost studied the effects of gonadectomy at various stages of fetal development,[9] and in 1946 showed that the removal of the fetal rabbit testis profoundly influenced the subsequent development of the sexual organs. In 1949 Foote and

Foote explored decapitation as a means of studying the influence of the pituitary on subsequent fetal development.[10] Domm and Leroy used a similar method of hypophysectomy in the fetal rat in 1951 to study the subsequent development of fetal organs dependent on the pituitary.[11]

The need for long-term experimentation led to the use of larger experimental animals. Sheep were probably the most widely used animals, because they were relatively cheap and had a high incidence of twinning. The other major reason for using sheep was that it has a relatively quiescent ovine uterus. The sheep uterine wall, even during pregnancy, is very thin and nowhere near as muscular or vascular as the primate uterus.

Between the late 1950s and the early 1960s, the emphasis of physiologic experimentation shifted from acute and ablative experiments to chronic experiments, using a variety of long-term catheterization techniques. Maloney studied the functional development of the respiratory system in a fetal lamb model.[12] In 1955 Louw and Barnard showed that ligation of the mesenteric vessels in the fetal puppy resulted in intestinal atresia.[13] Jackson et al. were able to create coarctation of the aorta in 1963.[14] In 1966 Holder and Aschraft[15] and Morgan et al.[16] attempted to create experimental biliary atresia.

De Lorimier's group developed a model for studying the diaphragmatic hernia in the fetal lamb,[17,18] and between 1970 and 1973, Beck,[19,20] Tanagho,[21-23] and Javadpour et al.[24] developed models for studying obstructive uropathy in sheep. Kent et al.[25] and Burington and Olley[26] studied the physiology of the circulation in lambs with diaphragmatic hernia. In these studies, the diaphragmatic hernia was created by fetal surgery relatively early in gestation. Starrett and de Lorimier reported similar results in lambs in which the diaphragmatic hernia was created much later in fetal life.[27]

The use of primates as a model for fetal surgery has been relatively restricted. Primates are expensive and the pregnancies are more difficult to maintain. However, many models for fetal surgery have been developed exclusively for primates. In the late 1960s, Chez conducted experiments observing renal function in a variety of monkey models.[28,29] These were relatively short-term catheterization studies. In 1969, Parshall and Silverstein reported upon the utilization of fetal Rhesus monkeys for immunologic studies, including skin graft, splenectomy and thymectomy.[30] These investigators operated on the same fetus, as many as four times, with no increase in either maternal or fetal morbidity. About the same time, Myers studied the results of carotid and internal jugular vein ligation in the development of the fetal brain.[31] These investigators were able to totally exteriorize the fetus in rhesus monkeys, while carefully maintaining the umbilical cord.

During this period, fetal surgery was used in animal experimental research to observe the normal development and physiology of the fetus and to investigate the pathophysiology of congenital anomaly.

After the introduction of ultrasonography for the *in utero* diagnosis of human congenital anomalies in the 1970s, it became possible to start work on the intrauterine correction of human fetal diseases.

THE THERAPEUTIC FETAL SURGERY

Therapeutic fetal surgery could not begin until the means were available to diagnose fetal disease.

In the 1950s and early 1960s, Rh incompatibility was a major problem in obstetrics, its most severe expression was erythroblastosis fetalis. Liley showed that direct fetal transfusions, utilizing the peritoneal cavity, were technically successful in three cases.[32,33] Later that same year, Freda and Adamsons carried out an open exchange transfusion in a fetus of about 28 weeks gestation over a two-hour period, utilizing a cutdown on the fetal femoral artery.[34] In 1966, Asensio et al. carried out a similar open exchange transfusion by using the saphenous vein at 31 weeks gestation.[35] The baby was delivered three weeks later and survived. The introduction of Rh_0 (D) immune globulin resulted in a dramatic decrease in the incidence of Rh sensitized mothers and a corresponding drop in the frequency of the fetal transfusion procedure.

In recent years, ultrasound has been the mainstay of antenatal diagnosis, and is currently used in some countries to check almost every pregnant woman. From the pediatric surgeons' point of view, ultrasound allows the antenatal diagnosis of major congenital anomalies, at pediatric surgical centers before birth rather than after. Fetal magnetic resonance imaging (MRI) is a recently developed diagnostic modality (Fig. 2), which has several advantages for fetal surgery over obstetric ultrasound, such as its large field of view, superior soft-tissue contrast, more precise volumetric measurements, and its greater accuracy in terms of demonstrating intracranial abnormalities.[36]

The ability to diagnose congenital anomalies before birth has resulted in a marked interest in the possibilities of *in utero* surgery as a means of correcting such defects. Harrison et al. reviewed the management options available in the case of a fetus with a correctable defect,[37] and pointed out that selective termination of the pregnancy presents a reasonable option for some uniformly fatal

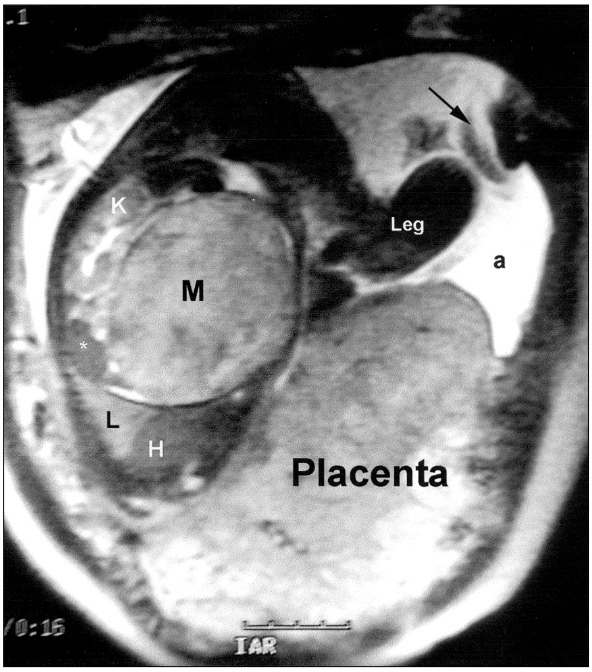

Fig. 2. A fetal MRI taken at 35 weeks of gestation shows a very large mass originating from the left lobe of liver. The prenatal MRI diagnosis was infantile hepatic hemangioendothelioma compressing the diaphragm. The baby underwent emergency surgical resection of hepatic mass after birth for a life-threatening respiratory difficulty and Kasabach-Merritt syndrome. The pathologic diagnosis was hepatic hemangioendothelioma. Abbreviations: Amniotic fluid (a), left kidney (K), lung (L), mass (M), heart (H), liver (*) and umbilical cord (arrow).

lesions, such as, anencephaly or bilateral renal agenesis. Other lesions, such as atresia of the gastrointestinal tract, would be best managed by allowing the pregnancy to proceed to term, in order to allow neonatal correction of the defect. Some lesions, such as obstructive uropathy or some cases of hydrocephalus may require induced preterm delivery, whilst other lesions, such as conjoined twins or large sacrococcygeal teratoma may require cesarean section. The list of anomalies that may require *in utero* therapy is short, and the only surgical lesions listed for human fetal surgery were bilateral hydronephrosis, diaphragmatic hernia, obstructive hydrocephalus, large sacrococcygeal teratoma, congenital cystic adenomatoid malformation of lung, meningomyocele and twin-twin transfusion syndrome.

Fetal intervention is only justified in the face of a progressive disorder that is likely to be fatal in the absence of treatment. By necessity, operating on the fetus involves a surgical procedure on the mother. Maternal morbidity will restrict fetal surgery to major life-threatening anomalies for the foreseeable future. The basic idea of fetal surgery is that the disordered development of an fetal organ can be normalized, possibly even completely restored, if a corrective procedure is carried out early enough in fetal life.

In 1980s, the experiences of many years of work in the animal laboratory were translated to the operating room, and open fetal surgery was first performed on humans. Much of this work was performed at the University of California, Fetal Treatment Center at the San Francisco under the direction of Michael Harrison.[38,39] The surgical, anesthetic and tocolytic techniques for fetal surgery were developed in nonhuman primates and were applied clinically, in otherwise lethal conditions. For each birth defect, the steps included:- the clarification of the relevant pathophysiology in fetal laboratory animals, the demonstration of the efficacy of fetal intervention in laboratory animals, the definition of the anatomic substrate using ultrasonography in humans by serial study of human fetuses, the development of appropriate selection criteria for prenatal intervention, and only when these prerequisites were satisfied, were the techniques applied to the human fetus.[38,39]

Open fetal surgery has been performed in several centers during the past decade. The surgical procedures most commonly performed in the fetus include:- the correction of congenital diaphragmatic hernia, the resection of cystic adenomatoid malformation of the lung, vesicostomy for obstructive hydronephrosis, the repair of meningomyocele, and the excision of large sacrococcygeal teratomas.[40] However, this open procedure suffers from the major disadvantage of performing surgery on a stressed fetus, as the amniotic fluid is removed and the fetus is exposed to the operating theatre environment. Consequently, the attendant fetal mortality following open fetal surgery is high, and can reach 50%.[38] The Fetal Treatment Center in San Francisco has the widest experience, and after 20 years of open surgery, they are now abandoning most open fetal operations.[40-42] Maternal morbidity related to a large hysterotomy is high.[42] Moreover, premature labor, which occurs in virtually all cases is often difficult to control. Long term follow up of survivors of open fetal surgery has shown a 21% incidence of severe central nervous system injuries in babies, which may be attributed to hypotension during the surgical intervention, fetal exposure during the operation, or to drug treatment given to the mother.[43]

More recently, the merging of fetoscopy and advanced video-endoscopic surgery has become the basis of endoscopic fetal surgery. Direct endoscopic visualization of the fetus was first described by Westin in 1954.[44] The main problem is the limited vision allowed by the viscous and debris-filled amniotic fluid. MacMahon et al. performed the first endoscopic vesicostomy in 1992.[45] At 17.5 weeks of gestation, he was able to undertake a functional vesicostomy using a 3 mm endoscope and a Nd:YAG laser fiber.

Successful fetoscopic clipping of the fetal trachea to accelerate the lung growth in the congenital diaphragmatic hernia has been reported in six human cases.[46] Four out of six survived, and once again, the fetoscopic modification of the procedures seemed to reduce the need for tocolytics for the same procedure by hysterotomy. Although it remains in its early clinical phase, endoscopic fetal surgery offers new hope for surgical fetal therapy.

FETAL SURGERY IN FUTURE

Preterm labor remains the Achilles heal of all fetal surgery. It has been said that effective tocolysis would be to fetal surgery what immune suppression was to organ transplantation. If more effective tocolysis can reduce maternal and fetal risk, fetal surgery may potentially offer alternatives to the present "search and destroy" approach to prenatal diagnosis.

Developments of artificial placentas may facilitate fetal support until term, without any risk of preterm labor after fetal surgery.[47] Sometime in the future, the mother may be confronted by her future baby floating in the amniotic fluid of an artificial placental machine after fetal surgery.

Robotic surgery is another attractive enterprise in future fetal surgery. A miniature robotic submarine might swim in the amniotic fluid, enter the fetal trachea and occlude the trachea with a balloon to accelerate lung growth in the case of congenital diaphragmatic hernia. After the completion of its first mission, it might transmit monitored intra-tracheal luminal pressure, fetal heart rate and intra-amniotic fluid pressure.

Science fiction will become science fact in fetal surgery.

REFERENCES

1. Harrison MR. Unborn: Historical perspective of the fetus as a patient. Pharos 1982;19-24.
2. Harrison MR. Historical Perspective. In: Harrison MR, Enans MI, Adzick NS, Holzgreve W, editors. The Unborn patients: the art and science of fetal therapy. 3rd ed. Philadelphia: W.B. Sainders Company; 2001. p.11-8.
3. Mayer A. Uber die Moglichkeit operativer Eingriffe beim lebenden Saugetierfotus. Zentralb Gynak 1918;42: 773-83.
4. Wolff B. Experimentelle Untersuchungen uber die Entstehung extrauteriner Schwangerschaften und Uber die Moglichkeit operative Eingriffe beim lebenden Saugetierfetus. Beitr Path Anat 1919;65:423-32.
5. Bors E. Die Methodik der interuterine Operation am űberlebenden Säugetierfőetus. Arch Entwichl-Mech Org 1925;105:655-66.
6. Nicholas JS. Notes on the application of experimental methods upon mammalian embryos. Anat Rec 1925;31: 385-96.
7. Hooker D, Nicholas JS. Spinal cord section in rat fetuses

J Comp Neurol 1930;50:413-21.
8. Tobin CE. The influence of adrenal destruction on the prenatal development of the albino rat. Am J Anat 1939;65:151-66.
9. Jost A. Sur la differenciation sexulle de l'embryo de lapin I. Remarques au sujet de certaines operations chirurgicales sur L'embryon II. Experiences de parabiose. Societe de Biologie: Compte Rendus 1946;140: 461-4.
10. Foote CL, Foote FM. Changes in the thyroid gland of hamster embryos hypophysectomized by decapitation. Anat Rec 1969;105:79-91.
11. Domm LV, Leroy P. A method for fetal hypophysectomy by decapitation in the rat. Anat Rec 1951;109: 395-409.
12. Maloney JE. Review of experimental studies on the functional development of the respiratory system in the foetal lamb. Aust J Biol Sci 1983;36:1-14.
13. Louw JH, Barnard CN. Congenital intestinal atresia-observations on its origin. Lancet 1955;19:1065-7.
14. Jackson BT, Piasecki GJ, Egdahl RH. Experimental production of coarctation of the aorta *in utero* with prolonged postnatal survival. Surg Forum 1963;14:290-1.
15. Holder TM, Aschraft KW. Production of experimental biliary atresia by ligation of the common bile duct in the fetus. Surg Forum 1966;17:356-7.
16. Morgan WW, Rosenkrantz JG, Hill RB Jr. Hepatic arterial interruption in the fetus-an attempt at simulating biliary atresia. J Pediatr Surg 1966;1:342-6.
17. deLorimier AA, Tierney DF, Parker HR. Hypoplastic lungs in fetal lambs with surgically produced congenital diaphragmatic hernia. Surgery 1967;62:12-21.
18. deLorimier AA, Manus AG, Tyler WS. Morphometry of normal and hypoplastic lungs in newborn lambs. Curr Top Surg Res 1969;1:431-8.
19. Beck D. Intrauterine renal surgery: Techniques for exposing the fetal kidney during the last two-thirds of gestation. Invest Urol 1970;8:182-7.
20. Beck AD. The effect of intrauterine urinary obstruction upon the development of the fetal kidney. J Urol 1971; 105:784-91.
21. Tanagho EA. Surgically induced partial urinary obstruction in the fetal lamb. I. Technique. Invest Urol 1972;10:19-24.
22. Tanagho EA. Surgically induced partial urinary obstruction in the fetal lamb. II. Urethral obstruction. Invest Urol 1972;10:25-34.
23. Tanagho EA. Surgically induced partial urinary obstruction in the fetal lamb. III. Ureteral obstruction. Invest Urol 1972;10:35-52.
24. Javadpour N, Graziano MF, Terrill R. Experimental induction of patent allantonic duct by intrauterine bladder outlet obstruction. J Surg Res 1974;17:341-5.
25. Kent GM, Olley PM, Creighton RE, Dobbinson T, Bryan MH, Symchych P, et al. Hemodynamic and pulmonary changes following surgical creation of a diaphragmatic hernia in fetal lambs. Surgery 1972;72:427-33.
26. Burrington JD, Olley PM. Experimental diaphragmatic hernias in fetal lambs. 17th Annual Meeting of Western Society for Pediatric Research [abstract]. Clin Res 1970; 18:198.
27. Starret RW, de Lorimier AA. Congenital diaphragmatic hernia in lambs: Hemodynamic and ventilatory changes with breathing. J Pediatr Surg 1975;10:575-82.
28. Chez RA, Smith FG, Hutchinson DL. Renal function in the intrauterine primate fetus. I. Experimental technique; rate of formation and chemical composition of urine. Am J Obstet Gynecol 1964;90:128-35.
29. Chez RA, Hutchinson DL. The use of experimental surgical techniques in the pregnant Macaca mulatta Ann NY Acad Sci 1969;162:249-53.
30. Parshall CJ, Silverstein AM. Surgical approach to the study of fetal immunology in primate animals. Ann NY Acad Sci 1969;162:256-62.
31. Myer RE. Brain pathology following fetal vascular occlusion: An experimental study. Invest Ophthalmol Vis Sci 1969;8;41-8.
32. Lilly AW. Error in the assessment of hemolytic diseases from amniotic fluid. Am J Obstet Gynecol 1963;86:485-93.
33. Lilly WA. Intrauterine transfusion of foetus in haemolytic disease. Br Med J 1963;2:1107-9.
34. Freda VJ, Adamsons K. Echange transfusion *in utero*. Report of a case. Am J Obstet Gynecol 1964;89:817-23.
35. Asensio SH, Figueroa-Longo JG, Pelegrina IA. Intrauterine exchange transfusion. Am J Obstet Gynecol 1966; 95:1129-33
36. Coakley FV. Role of magnetic resonance imaging in fetal surgery. Top Magn Reson Imaging 2001;12:39-51.
37. Harrison MR, Golbus MS, Filly RA, Nakayama DK, deLorimier AA. Fetal surgical treatment. Pediatr Ann 1982;11:896-9, 901-3.
38. Adzick N, Harrison M. Fetal surgical therapy. Lancet 1994;343:897-902.
39. Harrison MR, Adzick NS. The fetus as a patient: Surgical considerations. Ann Surg 1990;213:279-91.
40. Harrison MR. Fetal Surgery. West J Med 1993;159:341-9.
41. Sullivan KM, Adzick NS. Fetal surgery. Clin Obstet Gyneacol 1994;37:355-71.
42. Flake AW, Harrison MR. Fetal surgery. Annu Rev Med 1995;46:67-78.
43. Bealer JF, Raisanen J, Skarsgard ED, Long SR, Wang K, Filly RA, et al. The incidence and spectrum of neurological injury after open fetal surgery. J Pediatr Surg 1995;30:1150-4.
44. Westin B. Hysteroscopy in early pregnancy. Lancet 1954;11:872-5.
45. MacMahon RA, Renou PMM, Shekelton PA, Paterson PJ. *In utero* cystostomy. Lancet 1992;340:1234.
46. Mychaliska G, Graft J, Filly R, Levine A, Farrell J, Jennings R, et al. Endoscopic fetal tracheal occlusion for treatment of CDH: technical innovation and clinical

outcomes. Presented at the 16th Annual Meeting of the International Fetal Medicine and Surgical Society, 1-5 June, Alyeska Resort, Alaska, USA, 1997.
47. Sakata M, Hisano K, Yasufuku M. A new artificial placenta with a centrifugal pump; long-term total extrauterine support of goat fetuses. J Thorac Cardiovasc Surg 1998;115:1023-31.