The Fetus as a Patient

Surgical Considerations

MICHAEL R. HARRISON, M.D., and N. SCOTT ADZICK, M.D.

From the Fetal Treatment Program and the Department of Surgery, University of California, San Francisco, California

The diagnosis and treatment of human fetal defects has evolved rapidly over the past decade due to improved fetal imaging techniques and better understanding of fetal pathophysiology derived from animal models. The detection of a fetal anomaly may now lead to a change in the timing of delivery, a change in the mode of delivery, or prenatal treatment. Because most therapeutic maneuvers involve some risk to the fetus and mother, there must be a reasonable expectation that the procedure is feasible, safe, and effective before it can be attempted in humans. This requires reliable information about the pathophysiology and natural history of the disease process, the efficacy of fetal surgical intervention in ameliorating the disease, and the feasibility and safety of the proposed intervention. This paper focuses on the rationale and initial clinical experience with fetal surgery for a variety of life-threatening fetal anatomic defects.

PRENTAL DIAGNOSIS HAS undergone an explosion of growth in the past decade. The primary impetus for this rapid expansion has come from the widespread use of prenatal ultrasonography. After the first reports of *in utero* ultrasonographic diagnosis of congenital anomalies in the 1970s, increasingly sophisticated equipment and experience in interpretation led to the accurate prenatal diagnosis of a growing number of surgical lesions.[1]

Prenatal diagnosis and serial sonographic study of fetuses with anatomic lesions now makes it possible to define the natural history of these abnormalities, determine the pathophysiologic features that affect clinical outcome, and formulate management based on prognosis. Prenatal diagnosis has defined a 'hidden mortality' for some lesions such as congenital diaphragmatic hernia, bilateral hydronephrosis, sacrococcygeal teratoma, and cystic adenomatoid malformation of the lung. These lesions, when first evaluated and treated after birth, demonstrate a favorable selection bias. The most severely affected fetuses often die *in utero* or immediately after birth.[2]

Routine obstetric sonography changed the surgical management of many congenital anomalies. Most correctable malformations that can be diagnosed *in utero* are best managed by appropriate medical and surgical therapy after maternal transport and planned delivery at term. Prenatal diagnosis may influence the timing (Table 1) or the mode (Table 2) of delivery. In rare cases, various forms of *in utero* therapy may be possible either now or in the future (Table 3). For instance hematopoietic stem cell and hepatic enzyme deficiencies may be treated by *in utero* stem cell and hepatocyte transplantation in the near future.[3]

The possibility of open fetal surgical intervention, although a formidable undertaking, may be the only solution for some fetal problems. Fetal surgery is only justifiable, however, if (1) the natural history and pathophysiology of the disease is well understood; (2) the prenatal diagnosis is accurate, capable of excluding other anomalies, and able to predict which fetuses have a sufficiently bad prognosis to justify *in utero* intervention; (3) if *in utero* correction is shown to be efficacious in animal models; and (4) if maternal risk is proved to be acceptably low.

In the past decade, we investigated the rationale and feasibility of *in utero* repair for a number of fetal anomalies, including congenital hydronephrosis, congenital diaphragmatic hernia, sacrococcygeal teratoma, cystic adenomatoid malformation, chylothorax, and simple types of congenital heart disease. In addition some recent experimental studies delineating the ability of the fetus to heal without scarring may have implications for all surgeons.[4–6] This review will focus on our experimental and clinical experience with open fetal surgery for prenatally diagnosed life-threatening anatomic anomalies.

Supported by NIH grants HL39875 and HD25505, and an American College of Surgeons Fellowship.

Address reprint requests to Michael R. Harrison, M.D., The Fetal Treatment Program, Room 585-HSE, University of California, San Francisco, CA 94143-0570.

Accepted for publication January 10, 1990.

TABLE 1. *Defects that May Lead to Induced Preterm Delivery for Early Correction* Ex Utero

Obstructive hydronephrosis
Gastroschisis or ruptured omphalocele
Intestinal ischemia and necrosis secondary to volvulus, meconium ileus, and so on
Amniotic band malformation complex

Management of the Fetus with Congenital Hydronephrosis

Unrelieved urinary tract obstruction interferes with fetal development. The severity of damage at birth depends on the type, degree, and duration of the obstruction.[7,8] Although children born with partial bilateral obstruction may have only mild hydronephrosis that is reversible with decompression after birth, children born at term with high-grade obstruction may already have advanced hydronephrosis and renal dysplasia that is incompatible with life. In addition oligohydramnios secondary to decreased fetal urine output produces pulmonary hypoplasia, which often is fatal at birth.

It is possible that the life-threatening problems of respiratory and renal insufficiency may be ameliorated if the obstruction is relieved early enough in gestation to allow normal development to proceed. Optimal clinical management of both patients, mother and fetus, depends on a thorough understanding of the pathophysiology of fetal obstructive uropathy and its sequelae on the developing fetus.

The approach to fetal hydronephrosis developed in the last decade is a paradigm for fetal treatment in general. In this short period, the management of fetal hydronephrosis advanced dramatically due to multiple studies defining the natural history and pathophysiology of fetal urinary tract obstruction and to an intensive search for ways to assess fetal renal function and improve selection for treatment. From this large body of experimental and clinical work, for any individual case, the family can be counseled about the prognosis and options in management, ranging from termination of a hopeless pregnancy to prenatal intervention for those few fetuses whose renal and pulmonary development is threatened.

Development of the Fetal Lamb Model

To study the pathophysiology of fetal urethral obstruction and the efficacy and feasibility of correction *in utero*, it was necessary first to develop an animal model. Studies using fetal lambs evaluated the effect of obstruction and its subsequent correction on pulmonary and renal development.[9,10] We produced an accurate model of severe bilateral hydronephrosis in the fetal lamb by ligating the urachus and occluding the urethra with an ameroid constrictor or a ligature at 95 to 105 days gestation (full term is 145 days). Then we decompressed some of the obstructed fetuses by performing a suprapubic cystostomy at a second fetal operation about 3 weeks later and compared obstructed, decompressed, and control lambs at birth (Fig. 1). Uncorrected lambs did poorly; one half of them were stillborn. Liveborn obstructed lambs had severe respiratory insufficiency and only one survived the newborn period. The lungs were hypoplastic by weight and volume compared to corrected animals. The bladder, ureters, and renal pelves were dilated severely, mimicking the morphologic disease in human neonates. In contrast, the corrected lambs fared much better. Seven of nine lambs diverted *in utero* were liveborn, with resolution of the urinary tract dilatation and with far less respiratory difficulty. Relatively late obstruction in the fetal lamb (100 days), however, did not produce the typical cystic and dysplastic changes seen in human urinary tract malformations. To address the relationship between obstruction and renal dysplasia, an earlier gestational model was developed.

To test whether obstruction earlier in fetal life leads to renal dysplasia, we produced complete unilateral ureteral obstruction in fetal lambs at the beginning of the second trimester (55 to 65 days gestation). We documented that the kidney obstructed at this early stage was both hydronephrotic with ureteral and calyceal dilation proximal to the ligation, and dysplastic when examined at term.[11] This model then was used to determine whether renal dysplasia associated with fetal urinary tract obstruction was preventable by *in utero* decompression.

Following early second trimester unilateral ureteral ligation in 25 fetal lambs, the fetuses underwent reoperation and ureterostomy of the obstructed ureter after three predetermined time intervals (3, 6, or 9 weeks).[12] The fetus was returned to the uterus and subsequently delivered at term by Cesarean section. Each newborn had the function and morphology of the previously obstructed kidney compared to the contralateral control kidney. This study demonstrated that ureteral obstruction in the early midtrimester with subsequent decompression before term prevented renal dysplasia. Urinary tract decompression reversed the obstructive changes and the degree of pathologic and functional impairment seen in the obstructed kidney was proportional to the duration of obstruction. Other studies in fetal lambs have shown that the oligohydramnios-induced pulmonary hypoplasia associated with obstructive uropathy is similar to that seen in human

TABLE 2. *Defects that May Lead to Cesarean Delivery*

Giant omphalocele
Large sacrococcygeal teratoma, cervical hygroma, cervical teratoma
Malformations requiring preterm delivery in the presence of inadequate labor or fetal distress

TABLE 3. *Defects That May Require* In Utero *Treatment*

Malformation	Effect on Development	*In Utero* Treatment
Urethral obstruction	Hydronephrosis, lung hypoplasia → renal, respiratory failure	Vesicostomy
Congenital diaphragmatic hernia	Pulmonary hypoplasia → respiratory failure	CDH closure
Fetal chylothorax	Pulmonary hypoplasia → respiratory failure	Thoracoamniotic shunt
Sacrococcygeal teratoma	Massive arterio-venous shunting → placentomegaly, hydrops	Excision
Cystic adenomatoid malformation of the lung	Pulmonary hypoplasia, hydrops	Excision

fetuses and that decompression of the obstructed urinary tract permits restoration of amniotic fluid volume and compensatory lung growth.[13,14]

There are several lines of evidence that suggest that pulmonary hypoplasia is the result of simple compression of the fetal lung.[15–17] In cases of congenital hydronephrosis, the massively distended urinary tract elevates the diaphragm and the oligohydramnios results in a small intrauterine cavity that compresses the fetal thorax. If the lung changes are secondary to compression and are not due to a primary pulmonary malformation, restoration of normal amniotic fluid volume by fetal urinary tract decompression would reverse the constraint on normal lung growth. The lamb studies support this hypothesis. Lambs born after correction of urinary tract obstruction *in utero* fared much better, and the improvement correlated roughly with larger lungs. In addition we demonstrated in a fetal rabbit model that decompressing the lungs by restoration of amniotic fluid volume or by reducing pressure on the diaphragm allows the lungs to grow.[18] Further studies in the same experimental preparation suggest that the loss of the internal stenting force of fetal lung fluid is an important etiologic factor.[19]

The Problem of Selection: Assessment of Fetal Renal Function

A major problem in management of the fetus with hydronephrosis is determining how to select from a large number of fetuses with dilated urinary tracts only those with obstruction severe enough to compromise renal and pulmonary function at birth, yet not so severe that renal function cannot be salvaged even with *in utero* decompression. The fetus with a dilated low-pressure system who continues to have good urine output and adequate amniotic fluid volume requires no intervention. At the other end of the spectrum, the fetus with severe renal dysplasia that is not reversible, even with decompression, clearly should not be treated. The fetus with unilateral disease of any type with a normally functioning contralateral kidney can be managed conservatively because the disease is not life threatening. But the fetus with bilateral

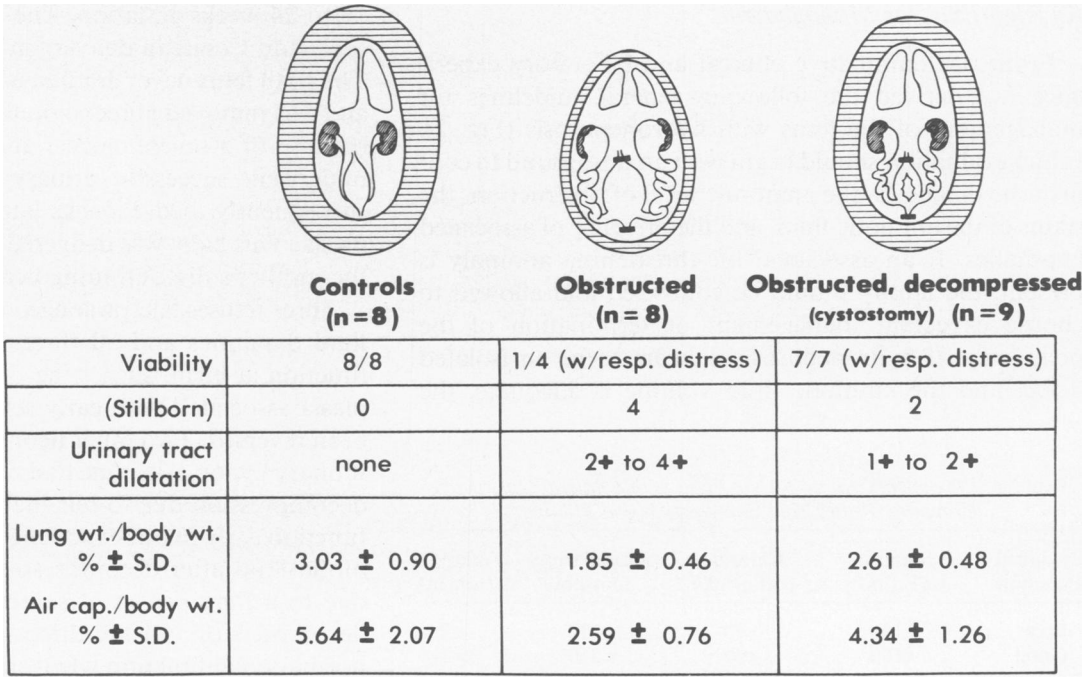


FIG. 1. Summary of data. Obstructed lambs had a high mortality rate, small lungs, and grossly dilated urinary tracts. Decompression *in utero* significantly improved survival, lung size, and urinary tract dilation. Four obstructed lambs and two decompressed lambs were delivered vaginally before planned ceasarean delivery, so viability could not be assessed (reprinted with permission).

hydronephrosis and unknown renal functional potential who might be a candidate for intervention requires renal function assessment.

The presence of oligohydramnios is a critical determinant of death.[20] Fetuses identified with oligohydramnios in the early second trimester have a mortality rate in excess of 90%.[21,22] We tried to define criteria to predict which of these fetuses would be salvageable. To be a candidate for fetal intervention, the affected fetus must have good residual renal function at the time of diagnosis, despite oligohydramnios. The ultrasound appearance of the fetal kidneys provides valuable prognostic information if the renal parenchyma shows increased echogenicity or cystic changes, but is less predictive in their absence.[23]

We reviewed our experience with 20 fetuses with congenital bilateral hydronephrosis referred for treatment to determine the prognostic value of various criteria used to assess renal functional potential.[24] Based on these results, six prognostic criteria to identify the fetus with 'good function' and 'poor function' were generated (Table 4). Although these results are based on a retrospective analysis, the utility of these parameters was confirmed in recent prospective and retrospective studies.[21,22] The development of prognostic criteria that predict the potential for recovery greatly simplified counseling of the families and selection of appropriate management. The prognostic criteria (urine Na <100 mEq/L, Cl <90 mEq/L, Osm <210 mosm, and normal fetal kidneys by ultrasound) have proved to predict reliably neonatal and long-term outcome after *in utero* urinary tract decompression, and the urine studies can be obtained by a single fetal bladder aspiration under ultrasound guidance.

An Algorithm for Management

From our cumulative clinical and laboratory experience, we derived the following general guidelines for management of the fetus with hydronephrosis (Fig. 2). Initial evaluation should begin with an ultrasound to confirm the diagnosis, the anatomic level of obstruction, the status of the amniotic fluid, and the presence of associated anomalies. If an associated life-threatening anomaly is present, the family should be counseled and allowed to choose expectant management or termination of the pregnancy. If hydronephrosis appears to be an isolated defect and the amniotic fluid volume is adequate, the mother should be followed by serial ultrasound. If amniotic fluid volume remains adequate, then the mother should receive routine obstetric care, and the fetus can be treated after birth. If moderate-to-severe oligohydramnios develops, the fetus should undergo a complete prognostic evaluation to determine the fetus's potential for normal renal and pulmonary function at birth. For the fetus with predicted renal dysplasia, aggressive obstetric care or *in utero* decompression is not indicated. For the fetus with predicted preserved renal function, there are two management options depending on fetal lung maturity. For the fetus with mature lungs, immediate delivery and *ex utero* decompression is indicated, and for the fetus with immature lungs, *in utero* decompression is recommended. For open fetal surgery, the gestational age at diagnosis should be less than 28 weeks, as successful decompression sometimes can be performed after this time with a percutaneously placed fetal vesicoamniotic shunt catheter. Before 28 weeks gestation, fetal catheter placement has been unsuccessful largely due to frequent catheter obstruction and dislodgement.[25]

TABLE 4. *Prognostic Criteria for the Fetus with Bilateral Obstructive Uropathy: Fetal Urine Composition and Volume*

Predicted Function	Sodium (mEq/mL)	Chloride (mEq/mL)	Osmolarity mosmol	Output (mL/hr)
Poor	>100	>90	>210	<2
Good	<100	<90	<210	>2

The Evolution of Open Fetal Surgery for Hydronephrosis

The criteria for attempting open fetal surgery were satisfied by our group in the early 1980s. The first open case for hydronephrosis was performed in 1981,[26] and six others have been performed since then. It is important to remember that only 7 of more than 200 cases of bilateral hydronephrosis referred for management during the last decade were deemed appropriate for open fetal surgery.[25,27] The first fetus had bilateral ureterostomies and the subsequent six had marsupialization of the bladder at 18 to 24 weeks gestation. The first five pregnancies proceeded to Cesarean delivery at 32 to 35 weeks gestation. The sixth fetus never drained urine well after vesicostomy and was removed at reexploration by the parent's request because of a severe cloacal anomaly. The seventh fetus underwent successful urinary tract decompression but subsequently died 2 weeks later from pulmonary hypoplasia. This baby was delivered prematurely as a result of the mother's discontinuing her oral tocolytic therapy.

Three fetuses had prolonged return of normal amniotic fluid dynamics and all three had adequate pulmonary function at birth, suggesting that fatal pulmonary hypoplasia associated with early severe oligohydramnios had been reversed. Two other neonates died at birth with pulmonary hypoplasia. One had no amniotic fluid even after decompression due to our inability to predict fetal renal function early in our experience. The other had some amniotic fluid after decompression but a tiny chest cavity due to a long period of severe oligohydramnios before decompression. Of the three surviving infants, one had normal renal function when she died of unrelated causes

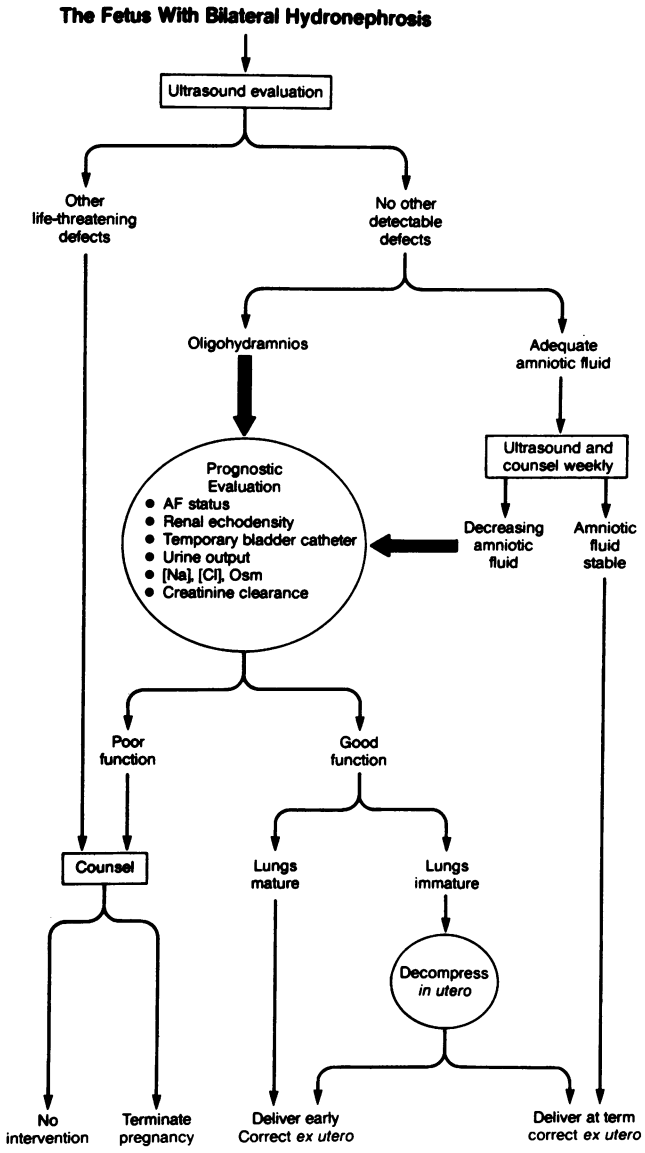


FIG. 2. Management scheme for the fetus with bilateral hydronephrosis.

at 9 months of age. One has normal renal function at age 3 years. The third developed failing renal function by 3 years, has grown and developed normally, and subsequently received a successful kidney transplant. Our current selection criteria would accurately exclude from treatment the two fetuses who died of pulmonary hypoplasia.

Throughout this initial period of performing fetal surgery, our selection criteria have been evolving. Improvements in selection now make it possible to avoid intervention in hopeless cases. This small series of human cases confirms that the development of fatal pulmonary hypoplasia can be prevented if amniotic fluid dynamics can be restored by decompression of the obstructed urinary tract. It is still unclear if *in utero* intervention arrested or reversed cystic dysplastic changes caused by obstructive uropathy because it is possible that the dysplastic changes initiated *in utero* will compromise renal function progressively as functional demand increases with growth. We believe, however, that relief of obstruction during the most active phase of nephrogenesis, between 20 and 30 weeks gestation, may obviate further damage and allow nephrogenesis to proceed normally.[24] Further experience and long-term follow-up are necessary to determine the effectiveness of *in utero* decompression in reversing or arresting renal damage caused by obstruction.

Management of the Fetus with Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) is an anatomically simple defect that is correctable easily by removing the herniated viscera from the chest and closing the diaphragm.[28] However many infants with CDH die of pulmonary insufficiency despite optimal postnatal care because their lungs are too hypoplastic to support extrauterine life. The pulmonary hypoplasia seen with CDH has been well documented clinically and experimentally; it appears to be caused by compression of the developing fetal lung by herniated bowel. In this section, the evolution of *in utero* therapy for CDH will be described. As was the case for bilateral hydronephrosis, 10 years of experimental and clinical work that supports the pathophysiologic rationale for correction of CDH *in utero* will be reviewed.

The Fetal Lamb Model

To study the pulmonary hypoplasia that accompanies CDH and the possibility of reversing these changes by correcting the CDH *in utero*, a model was developed in which a conical, silicone-rubber balloon was inflated progressively in the left hemithorax of fetal lambs over the last trimester to simulate compression of the growing fetal lung by abdominal viscera.[29] Lambs with inflated intrathoracic balloons deteriorated rapidly at term delivery and died of respiratory insufficiency despite maximal resuscitation and ventilatory support. Deflation of the balloon midway through the third trimester (simulated 'correction') allowed sufficient lung growth to alleviate respiratory insufficiency and to assure survival in five of five lambs delivered by Cesarean section.[30] Simulated correction produced a significant increase in lung weight, air capacity, compliance, and area of the pulmonary vascular bed (Fig. 3).

Although the balloon model established the efficacy of *in utero* repair, it could not be used to study the feasibility of correction or to develop the surgical techniques necessary for actual successful fetal surgical repair. For this purpose we had to create and then attempt to repair surgically actual fetal diaphragmatic hernias. We created

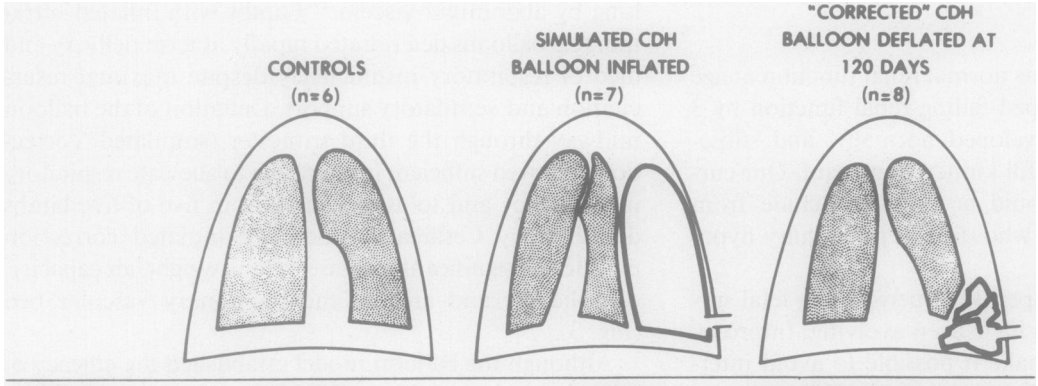
diaphragmatic hernias in fetal lambs by making a hole in the left diaphragm and demonstrated that herniated viscera produced pulmonary hypoplasia comparable to that produced by the balloon. We then tried to repair the CDH surgically at a second operation.[31]

The first attempts at repair were unsuccessful because increased intra-abdominal pressure secondary to replacement of the viscera into the abdomen resulted in severely compromised umbilical venous blood flow. It became clear that the abdominal cavity would need to be enlarged to prevent increased intra-abdominal pressure after CDH repair. Incorporating a piece of silastic into the abdominal wall proved to be a satisfactory solution allowing the abdominal contents to be accommodated without increased pressure. When we used these techniques for repair of fetal CDH, the lambs survived at term and when they were killed the lungs were well expanded, histologically mature, and much larger than those of uncorrected animals.[31] These findings were confirmed by others using a similar fetal lamb model.[32] Subsequent pulmonary morphometric studies showed that an early gestational CDH lamb model simulates the morphologic features that correlate with fatal outcome for human neonates with CDH and persistent fetal circulation, and that fetal surgical repair ameliorates these vascular changes and permits compensatory lung growth and development.[33]

The Natural History of Congenital Diaphragmatic Hernia

Survey data derived from neonatal centers underestimate the incidence and mortality rate of CDH because the more severely affected infants often die before the anomaly is recognized. Minimum incidence figures derived from various sources range from 1 in 2400 to 1 in 5000 live births; the true incidence, including stillborn fetuses, is probably about 1 in 2200 births.[2,34–36] Paradoxically the mortality rate of infants with CDH reported from major neonatal centers has not improved with the recent improvements in neonatal transport and intensive care. Earlier reported series quoted mortality rates of about 50% for postnatally detected CDH but included only the most favorable cases, those that survived to be transferred to the major referral center. The most severely affected infants died before they came to the attention of the referral center, accounting for a significant 'hidden mortality,'[2] a situation directly analogous to that seen with prenatally diagnosed bilateral hydronephrosis. With improved neonatal transport and respiratory support, some of these desperately ill infants now survive long enough to be treated. Because the mortality rate is extremely high in this group, recent series from highly capable centers often show dismal results.[37]

Management of the fetus with prenatally diagnosed CDH depends on an understanding of the natural history, pathophysiology, and prognostic factors affecting outcome. It would seem that prenatal diagnosis of CDH would result in immediate postnatal repair and survival. However our initial reported experience with fetal CDH was very disappointing—there were no survivors of seven fetuses prospectively diagnosed before birth.[38] This led to a multicenter survey that documented the natural history and clinical outcome of fetal CDH in 94 cases.[39] This study demonstrated that the prenatal sonographic diagnosis was accurate, the mortality rate was high (80%), and polyhydramnios was a prenatal predictor of poor clinical outcome. A subsequent study of 38 prenatally diagnosed cases from a single medical center permitted a detailed assessment of prognostic factors and evaluation of the impact of extracorporeal membrane oxygenation (ECMO) on outcome.[40] This study found that survival was poor despite optimal postnatal therapy, including ECMO, and



VIABILITY	6/6 LIVED	6/6 DIED	5/5 LIVED (with resp. distress)
Lung Weight	123.2±25.4	49.6±6.6	79.1±6.0
Lung Wt./Body Wt.	3.42±0.30	1.71±.03	2.26±.14
Air Capacity	222.5±47.9	58.8±7.6	151±10.0
Air Cap./Body Wt.	6.24±0.84	2.37±0.12	4.55±0.32

FIG. 3. Summary of data for lambs with simulated CDH (reprinted with permission).

that both polyhydramnios and an early gestational diagnosis were associated with a dismal outcome. Thus the severity of a fetal CDH can be judged by the timing of herniation, the degree of pulmonary compression (lung-to-thorax ratio at the level of a four chamber view of the heart), and the presence of polyhydramnios.

Initial Experience with Repair In Utero

We obtained the approval of the Committee on Human Research in 1983 for open fetal surgery for CDH. Only eight cases in 7 years have met our stringent selection criteria. In addition it has been imperative that the families understand the risks of fetal surgery and be willing to travel to San Francisco. Finances were a major stumbling block because insurance companies refused to cover any expenses associated with this experimental procedure. Although there were no professional fees, the cost of the procedures and hospitalization had to be borne by the investigating institution. Although we were contacted by telephone about a large number of fetuses with CDH, only a fraction (less than 1 in 10) was even a candidate to come to San Francisco for further evaluation. Of the potential candidates, at least one half were excluded by social and financial considerations.

After extensive experimental work demonstrated the efficacy, feasibility, and safety of repair *in utero*, we tried to salvage eight highly selected fetuses with severe CDH by open fetal surgery.[41] The experience with these very severe cases initially was discouraging, but each of these cases contributed to invaluable knowledge and experience that eventually led to the first clinical success. The first three fetuses died at operation because attempts to reduce the friable incarcerated liver from the fetal chest were unsuccessful. In the fourth case, a Gore-Tex diaphragm was constructed around the liver but lung decompression was ineffective and the baby died at birth. The last four fetuses were repaired successfully and the technical problem with mildly herniated liver proved to be surmountable. All four demonstrated rapid growth of the lung *in utero* and had surprisingly good lung function after birth. Two subsequently died of nonpulmonary problems (an unrelated nursery accident in one and intestinal complications in the other), but the last two babies have done well.[42]

An Algorithm for Prenatal Management of CDH

Figure 4 shows our proposed algorithm for management. Once a diaphragmatic hernia is diagnosed by ultrasound, the patient should be referred for chromosomal analysis by amniocentesis (results in about 2 weeks) or percutaneous umbilical blood sampling (results in about 2 days), screening for other anatomic abnormalities by an experienced obstetric sonographer, and evaluation for cardiac abnormalities by fetal echocardiography. When

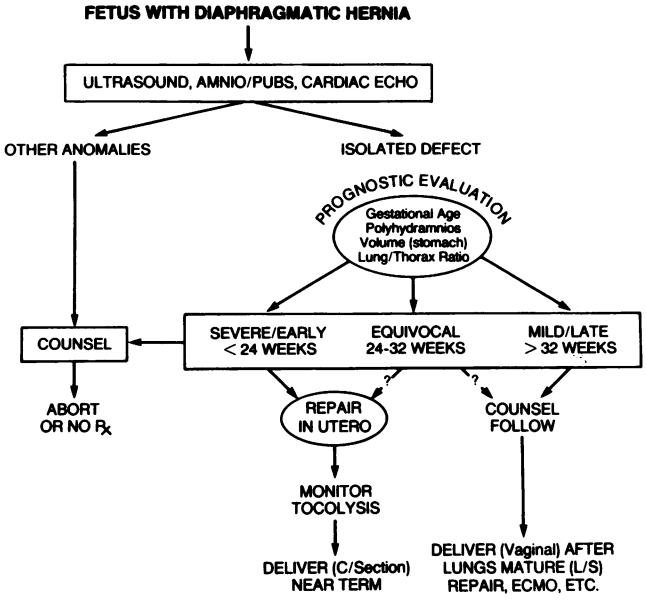


FIG. 4. Algorithm for management of the fetus with CDH (reprinted with permission).

associated serious anomalies are discovered, the family may choose to terminate the pregnancy.

There is a wide spectrum of severity in CDH. Some mildly affected fetuses will be detected later in gestation, develop polyhydramnios later or not at all, and have a smaller volume of viscera in the chest. These fetuses should be followed by sonogram and delivered at an appropriate tertiary perinatal center after the lungs are mature. Unfortunately most fetuses are on the severe end of the spectrum and will not survive even with optimal conventional pre- and postnatal management. In general these fetuses will be detected earlier, develop polyhydramnios earlier, and have a larger volume of viscera in the chest (dilated stomach, impressive mediastinal shift, little lung visible in either thorax). Every effort should be made to determine if the liver is herniated into the chest because this affects prognosis and the technical difficulty of repair before birth. Between 20 and 30 weeks, the family can choose between conventional management or fetal repair depending on assessment and their personal attitude. After 30 weeks the only option is conventional management aimed at maximizing postnatal care. Although fetal repair theoretically is possible until 32 weeks, it is probably best performed before 30 weeks for two reasons. First the longer the decompressed lung has to grow before it is required to support life at birth, the better (and preterm labor associated with hysterotomy may shorten the remaining gestation). Second it is our impression that the risk of inducing preterm labor is greater when the procedure is performed later in gestation. Although it would seem technically advantageous to operate on a larger fetus with more mature tissues, surgical procedures have proved

feasible in fetuses as young as 18 weeks. Now we will consider fetuses between 20 and 30 weeks gestation for *in utero* repair.

Management of Fetal Chylothorax

Congenital pleural effusions often are due to fetal chylothorax (FCT) and can be diagnosed as early as 16 weeks gestation.[43] Small effusions may be harmless, while large effusions may result in pulmonary compression, pulmonary hypoplasia, and hydrops. We recently reported a series of 32 cases.[44] The overall mortality rate was 53%. Polyhydramnios was present in 22 cases and was not associated with a higher mortality rate. Early diagnosis (less than 32 weeks gestation) and hydrops were associated with a higher mortality rate. Pleural fluid was available in 12 patients, all of whom had more than 80% lymphocytes on cell count, which confirmed the diagnosis of FCT.

Small effusions diagnosed late in gestation often have a satisfactory outcome without prenatal treatment and some resolve spontaneously. In these cases, serial ultrasound examinations should be performed with appropriate postnatal follow-up. For large effusions causing hydrops, *in utero* decompression may offer the only hope for survival. Although success with repeated percutaneous thoracenteses *in utero* has been reported, we recently used a thoracoamniotic shunt to decompress successfully the FCT after multiple attempts at aspiration failed to drain permanently the fetal chest. Rodeck[45] reported the successful placement of a thoracoamniotic shunt in eight fetuses with massive FCT. Six of these infants survived, five without respiratory difficulty after birth. Lung reexpansion was seen in all of the survivors, but not in the two who died.

Management of Fetal Tumors

Sacrococcygeal Teratoma

Most babies with sacrococcygeal teratoma (SCT) are diagnosed as newborns when the malignant potential is low and the prognosis is good. However prenatal diagnosis identified fetuses with SCT who die *in utero*. The gestational age has important prognostic significance. We reported a series in which six of eight fetuses survived when the diagnosis was made after 30 weeks gestation, but only 1 of 14 fetuses survived when the diagnosis was made before 30 weeks gestation.[46] When diagnosed before 30 weeks gestation, invariably there has been development of massive tumor enlargement, fetal hydrops, and placentomegaly. In each of six fetuses diagnosed at 14 to 23 weeks gestation, the mothers developed 'mirror syndrome' with vomiting, hypertension, edema, and proteinuria. Two of the six affected mothers required treatment in the intensive care unit for pulmonary edema.

We recently demonstrated by Doppler ultrasound that the tumor in these severe cases behaves as a large arteriovenous fistula with markedly increased distal aortic blood flow and shunting of blood away from the placenta.[47] Fetal demise presumably occurs because of high-output cardiac failure with the development of hydrops.

These findings have important implications for management. Fetuses with lesions larger than 5 cm should be delivered by Cesarean section to avoid dystocia, tumor rupture, or hemorrhage into the tumor, which may occur with vaginal delivery.[46] Cases with hydrops diagnosed after 30 weeks gestation should be delivered when pulmonary maturity is attained. Lesions diagnosed before 30 weeks gestation usually have a poor outcome and may require surgical excision *in utero*.

Congenital Cystic Adenomatoid Malformation

Congenital cystic ademomatoid malformation (CCAM) can present as a fatal lesion in a fetus or neonate, or as a relatively mild lesion causing respiratory difficulty or recurrent infections in an infant or child. It represents a spectrum of disease characterized by cystic lesions of the lung. The macrocystic type has cysts that grow to several centimeters in diameter. Microcystic disease has multiple cystic lesions less than 5 mm in diameter. Prenatal ultrasound generally can distinguish individual cysts in macrocystic disease while microcystic lesions usually have the appearance of an echogenic, solid lung mass.[48]

Differences in survival rate of patients with CCAM have been ascribed previously to the histologic type of the lesion, but our experience and that of others demonstrates that an unfavorable outcome is associated most closely with hydrops. Hydrops probably is secondary to vena cava obstruction or cardiac compression from the extreme mediastinal shift caused by these lesions, and hydrops has been associated with other space-occupying thoracic lesions.[49] The invariably fatal outcome seen with large CCAM lesions is related to several factors, including development of hydrops, hypoplasia of normal lung tissue secondary to prolonged compression *in utero*, and lack of early diagnosis and immediate postnatal surgery. Macrocystic lesions may resolve spontaneously when followed by serial ultrasound throughout the course of pregnancy.[50]

It is possible that *in utero* surgical decompression or removal of the CCAM will reverse the hydrops and allow sufficient lung growth to permit survival in these severe cases. We demonstrated experimentally that *in utero* pulmonary resection is feasible and that compensatory lung growth of the opposite lung occurs.[51] Thoracentesis of macrocystic lesions *in utero* does not provide lasting decompression of normal lung tissue.[48] However percutaneous placement of a double pigtail catheter shunt between a large lung cyst and the amniotic space in a fetus with CCAM at 20 weeks gestation resulted in sustained

cyst decompression and resolution of hydrops, with delivery 17 weeks later and successful postnatal surgery.[52]

Maternal Mirror Syndrome: An Unsolved Problem After Resection of Fetal Tumors

Large fetal tumors may result in placentomegaly, hydrops, and fetal death. The 'maternal mirror syndrome' (MMS) is a hyperdynamic state in which the maternal physiology 'mirrors' that of the hydropic fetus with hypertension, peripheral and pulmonary edema, and gastrointestinal and renal dysfunction. Maternal mirror syndrome is associated with severe Rh disease and other fetal conditions that cause placentomegaly and complicates control of preterm labor.[53] We encountered this syndrome twice after resection of large tumors in hydropic moribund fetuses.

The first case was a fetus at 21 weeks gestation referred with a huge sacrococcygeal teratoma, placentomegaly, and hydrops due to massive arteriovenous shunting through the tumor.[47] Successful complete resection of the tumor *in utero* led to marked improvement in the fetal hydrops. The second case was a fetus at 27 weeks gestation referred with a giant congenital cystic adenomatoid malformation with massive mediastinal shift, hydrops, and placentomegaly. A thoracoamniotic shunt was not possible because the lung lesion was microcystic. The mass was resected successfully *in utero* by right middle lobectomy with consequent improvement in the fetal pathophysiology.[54] In both cases placentomegaly persisted after operation and the mothers developed progressive MMS that prevented adequate tocolysis despite fetal improvement. A Cesarean section was performed for maternal safety in the first case after 12 days and the second case after 6 days, and the MMS resolved quickly. The premature infants died soon after delivery from respiratory insufficiency.

Although fetal tumor excision is technically feasible, reversal of the fetal pathophysiology did not rapidly correct the placentomegaly or resolve the MMS. Maternal mirror syndrome may be caused by placental release of vasoactive compounds resulting in a severe pre-eclamptic state. Until the MMS riddle is solved, earlier intervention before the onset of placentomegaly and hydrops may be the only approach to salvage these doomed fetuses.

Recently successful *in utero* resection of a large CCAM was performed in a 23-week-old fetus with ascites but no placentomegaly. After tumor resection, the ascites resolved and good lung growth occurred *in utero*. That child is thriving at 8 months of age.[54] In that case the early diagnosis, the large size of the tumor, and the early onset of hydrops indicated a dismal prognosis, which led us to consider prenatal intervention as the only hope for a successful outcome. We can now add appropriately selected cases of CCAM to the list of congenital lesions that are amenable to fetal surgical therapy.

Congenital Heart Disease

Many types of congenital cardiac disease now can be diagnosed readily *in utero* with a high degree of accuracy.[55] Prenatally diagnosed complete heart block (CHB) can occur without associated cardiac anomalies, is often refractory to attempts to increase heart rate and cardiac output by medical therapy, and results in fetal demise.[56] We developed a model of CHB in fetal lambs and have demonstrated the feasibility of epicardial ventricular or atrioventricular pacing to increase cardiac output. The model may facilitate the development of new clinical therapies to salvage refractory cases of fetal CDH.[57] Another group of investigators has tried percutaneous transthoracic pacing in a hydropic fetus with CHB, but this effort failed for technical reasons.[58]

Although the *in utero* pathophysiology of congenital cardiac lesions is not understood completely, it appears that decreased blood flow during fetal life can result in secondary hypoplasia of vessels or cardiac chambers.[59] Experimental intrauterine repair of pulmonary artery stenosis is feasible without cardiac bypass[60,61] and hypothermia or bypass techniques may make open fetal cardiac surgery possible in the future.[62,63]

Maternal Management and Risk

Maternal safety is the paramount consideration in fetal surgery. A series of 102 fetal operations in 94 monkeys permitted us to develop anesthetic, surgical, and tocolytic regimens for fetal surgery and demonstrate satisfactory maternal safety.[64–66]

Clinical Experience: Operative Technique

Perioperative clinical management principles are based directly on the experimental nonhuman primate work. Maternal preparation begins with a 100-mg suppository of indomethacin before operation and placement of an epidural catheter for postoperative analgesia. During operation halothane is used for uterine relaxation and for fetal and maternal anesthesia. After operation ritodrine, magnesium sulfate, and indomethacin are used for tocolysis. Maternal intraoperative monitoring includes a blood pressure cuff, large-bore intravenous catheters, a bladder catheter, electrocardiographic leads, and a transcutaneous pulse oximeter (Fig. 5).

The mother is positioned supine with towels placed under the right side to lift her uterus off of the inferior cava to avoid compromise of venous return. The uterus is exposed through a low transverse abdominal incision and delivered into the operative field. A large abdominal ring retractor is used to maintain exposure. Sterile intraoperative ultrasound is used to confirm the fetal position and placental location. The position and orientation of the hysterotomy is planned to stay as far away from the

placenta as possible and still allow exposure of the appropriate part of the fetus. Excess amniotic fluid is aspirated with a trocar and kept warm. The hysterotomy can be performed with an absorbable stapler that is fast and hemostatic.[67] An alternative method to minimize blood loss during hysterotomy is by manual compression on either side of the proposed hysterotomy: the uterine incision then is made between the assistant's hands using electrocautery. Immediately thereafter specially designed compression clamps are placed around the edge of the uterine incision to prevent bleeding.

For urinary tract decompression,[25-27] the lower extremities of the fetus are exteriorized and a transcutaneous pulse oximeter is placed around the fetal thigh. A midline suprapubic incision is made through the fetal abdominal wall exposing the thick-walled and distended bladder. The bladder is then opened and marsupialized to the abdominal wall using interrupted 4-O silk sutures (Fig. 6).

For diaphragmatic hernia,[41,42] the left arm of the fetus is exteriorized for monitoring and the left side of the chest and upper abdomen is stabilized by placing a Babcock clamp onto the costal margin (Fig. 7). The diaphragm is repaired with a Gore-Tex patch through a subcostal incision and the abdomen is enlarged to accommodate the viscera using another synthetic patch (Fig. 8).

The fetus is returned to the uterine cavity and the amniotic fluid is restored with either warm normal saline or warm amniotic fluid containing 500 mg nafcillin. The uterus is closed with three layers of absorbable sutures and fibrin glue. The low transverse abdominal incision is closed in layers using running 0-PDS suture and the skin is closed with a subcuticular suture. Beyond these technical points, we have learned that, as a general principle, fetal surgery should be 'all or none,' *i.e.*, the fetal repair should be complete and adequate to ensure a good chance for fetal survival, or else the otherwise doomed fetus should be removed. A partial or inadequate repair presents an ongoing threat to the mother for little potential benefit.

Postoperative Management

Premature labor remains the largest obstacle to a successful outcome in the postoperative course. After operation uterine contractions and fetal heart rate are monitored and tocolytic therapy with betamimetics, magnesium sulfate, and prostaglandin synthetase inhibitors is adjusted accordingly. Once the initial period of uterine contractions has subsided (usually within 5 days), oral tocolytics gradually are substituted for intravenous drugs and then continued throughout the remainder of the pregnancy. Perioperative antibiotics, generally a cephalosporin, are continued for 3 days after operation. The patient is kept at bedrest for at least 3 days following surgery and then begins a progressive ambulation program. Postoperative adynamic ileus is common for 2 or 3 days, and oral intake resumes with the return of bowel function. Generally the patient is discharged on only oral tocolytic therapy within 10 days of the procedure.

Maternal Outcome

Between 1981 and 1989, 18 women have undergone open fetal surgery in the Fetal Treatment Program at

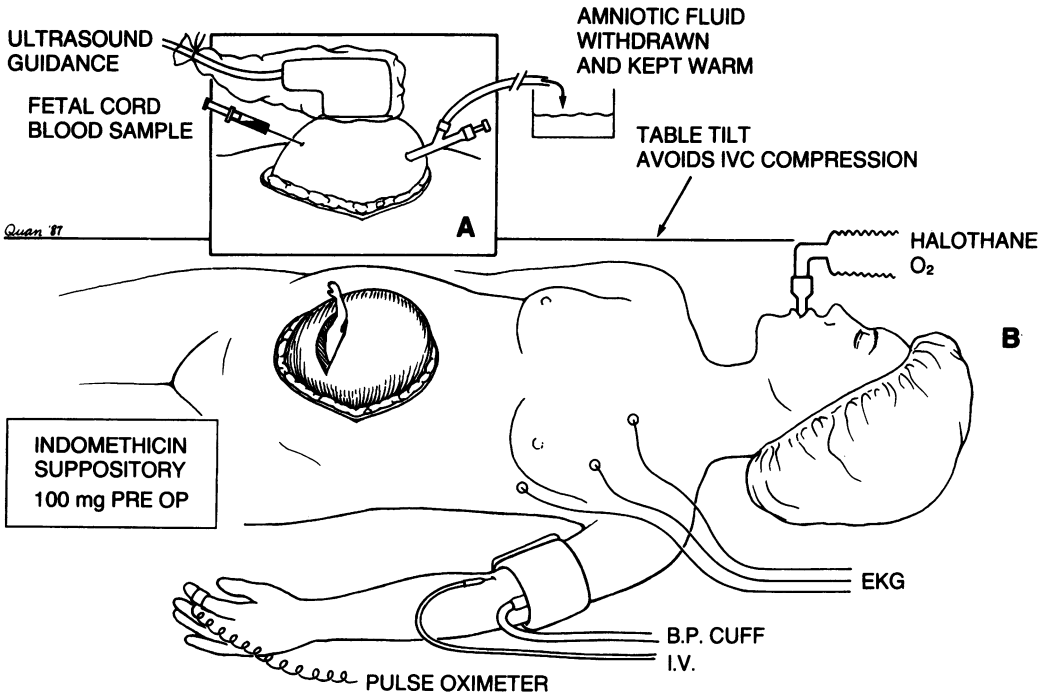


FIG. 5. Drawing of maternal positioning and monitoring for open fetal surgery.

UCSF. The operations were performed for four indications: bladder outlet obstruction, congenital diaphragmatic hernia, sacrococcygeal teratoma, and congenital cystic adenomatoid malformation. Fifteen of the procedures were technically successful, resulting in a viable fetus after operation. In three cases the fetal anatomic problem proved to be irreparable at the time and the fetus was removed. Women with continuing pregnancies are committed to Cesarean section at the time of delivery.

Obviously maternal safety is the first priority in all cases. There have been no maternal deaths and few maternal complications. There was one case of mild antibiotic-associated pseudomembranous colitis that responded to oral vancomycin. One patient developed a small amniotic fluid leak from the hysterotomy site causing abdominal pain several weeks after she returned home. This was stopped easily during reoperation with a single suture and has not happened again since we changed our method of hysterotomy closure to three layers. The maternal mirror syndrome developed in two mothers after resection of fetal tumors as described above. This complication made control of preterm labor difficult and finally necessitated Cesarean delivery. Finally poor patient compliance occurred in one case—the mother stopped her oral tocolytics and promptly went into premature labor and delivered vaginally.

Effect on Reproductive Potential

One of the principal concerns following fetal surgery is the ability of the mother to carry further pregnancies. We first evaluated the potential for future reproduction after fetal surgery in a large series of nonhuman primates.[66] Computed medical records are maintained for each primate at the California Primate Research Center, Davis, California. This database provided reliable information regarding subsequent breeding and contraception and permitted comparison of our experimental fetal surgery group with the normal breeding colony. We found that in animals that had uterine closure with absorbable sutures, fetal surgery did not interfere with subsequent fertility.[62] However animals that had metal staple hysterotomy closure had a markedly decreased fertility rate. It is now clear that metal staples migrate through the uterine wall and we speculate that exposure of the endometrial cavity to permanent foreign body hinders fertility. Based on this experience, we no longer use the metal stapler for uterine closure and subsequently developed a stapler for hysterotomy that uses absorbable staples.[67]

Uterine rupture is a dreaded complication during labor following previous Cesarean section and it occurs more commonly after a classic Cesarean section than after a

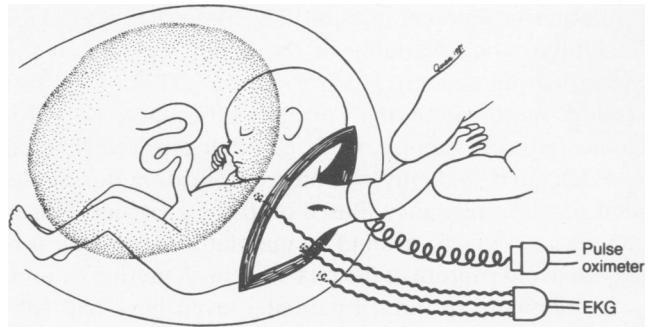


FIG. 7. Left arm and chest exteriorized and monitors placed with subcostal incision shown. A miniaturized radiotelemetry device can be placed subcutaneously for perioperative fetal EKG, temperature, and activity monitoring (reprinted with permission).

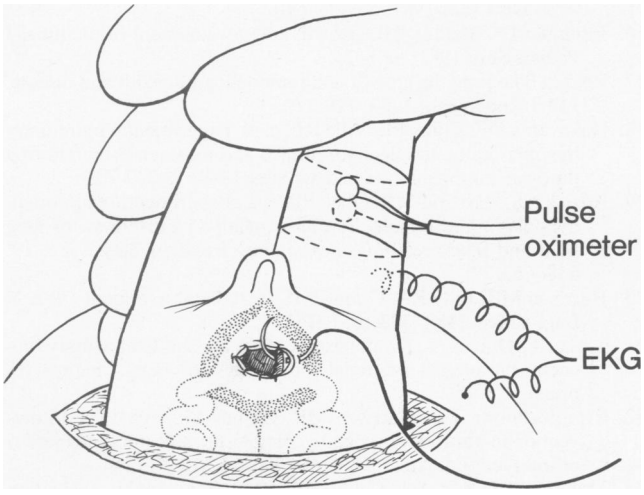


FIG. 6. Diagram of intraoperative appearance of bladder marsupialization to the fetal abdominal wall to create a vesicoamniotic fistula (reprinted with permission).

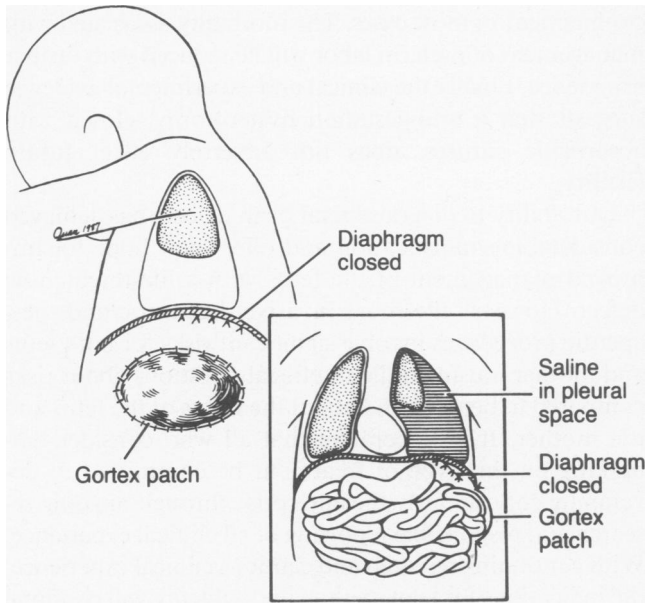


FIG. 8. Diaphragm closed. Abdomen enlarged with patch to accommodate viscera without increasing intra-abdominal pressure (reprinted with permission).

lower uterine segment incision. The hysterotomy used for fetal surgery is invariably in the upper segment of the uterine corpus and thus is comparable to a classic Cesarean section. In our nonhuman primate series there were five cases of uterine rupture, while 62 other primates labored and delivered vaginally without complication during the fetal surgery pregnancy. Based on this experience, Cesarean section delivery should be mandatory after fetal surgery to avoid rupture of the relatively fresh uterine wound.

In follow-up of our 18 patients, seven have had subsequent pregnancies, and all deliveries were by repeat Cesarean section with good outcome. The first patient has had two normal pregnancies. The remaining women are too close to their operative date to assess for fertility after fetal surgery.

From our experience in animals and in our initial clinical experience with open fetal surgery, we conclude that the anesthetic regimen first developed in the nonhuman primate model has been used successfully in humans, with an acceptable perioperative risk. The paucity of complications in the first 18 patients with open fetal procedures is a direct result of our extensive preparation in experimental fetal animals, which should be a prerequisite for anyone contemplating these procedures. We know of only one other human open fetal surgical case that was performed at a medical center where the investigators chose not to do preparatory work in nonhuman primates, and that procedure failed.

The uterine irritability induced by hysterotomy can be suppressed successfully during operation with halothane anesthesia and after operation with intravenous and oral tocolytic agents, but premature labor remains a serious and frequent problem with fetal surgery, requiring early confinement in most cases. The morbidity associated with management of preterm labor will be reduced with further experience. Finally the clinical and experimental evidence suggests that a mid-gestation hysterotomy, closed with absorbable sutures, does not adversely effect future fertility.

Our ability to diagnose fetal birth defects has achieved considerable sophistication and offers new hope for improved management of the fetus with a life-threatening defect. However the more invasive diagnostic and therapeutic procedures involve significant risks for both fetus and mother, raising difficult ethical questions about risks compared to benefits and about the rights of the fetus and the mother. It is imperative that all who consider embarking on this type of treatment be committed to developing continuously the enterprise through ongoing research and responsible reporting of all clinical experience. With continuing research and cautious clinical experience, the indications for fetal therapy undoubtedly will continue to expand.

References

1. Harrison MR, Golbus MS, Filly RA. The Unborn Patient, 2nd Edition. Philadelphia: WB Saunders, 1990.
2. Harrison MR, Bjordal RI, Landmark F, et al. Congenital diaphragmatic hernia: the hidden mortality. J Pediatr Surg 1979; 13:227–231.
3. Flake AW, Harrison MR, Adzick NS, et al. Transplantation of fetal hematopoietic stem cells in utero: the creation of hematopoietic chimeras. Science 1986; 233:766–778.
4. Adzick NS, Harrison MR, Glick PL, et al. Comparison of fetal, newborn, and adult wound healing by histologic, enzyme-histochemical, and hydroxyproline determination. J Pediatr Surg 1985; 20:315–319.
5. Krummel TM, Nelson JM, Diegelmann RF, et al. Fetal response to injury in the rabbit. J Pediatr Surg 1987; 22:640–644.
6. Longaker MT, Chiu ES, Harrison MR, et al. Studies in fetal wound healing IV: Hyaluronic acid stimulating activity distinguishes fetal wound fluid from adult wound fluid. Ann Surg 1989; 210:667–672.
7. Harrison MR, Filly RA, Parer JRT, et al. Management of the fetus with a urinary tract malformation. JAMA 1981; 246:635–639.
8. Harrison MR, Golbus MS, Filly RA. Management of the fetus with a correctable congenital defect. JAMA 1981; 246:774–777.
9. Harrison MR, Ross NA, Noall R, et al. Correction of congenital hydronephrosis in utero. I. The model: fetal urethral obstruction produces hydronephrosis and pulmonary hypoplasia in fetal lambs. J Pediatr Surg 1983; 18:247–256.
10. Harrison MR, Nakayama DK, Noall R, et al. Correction of congenital hydronephrosis in utero. II. Decompression reverses the effects of obstruction on the fetal lung and urinary tract. J Pediatr Surg 1982; 17:965–974.
11. Glick PL, Harrison MR, Noall R, et al. Correction of congenital hydronephrosis in utero. III. Early mid-trimester urethral obstruction produces renal dysplasia. J Pediatr Surg 1983; 18:681–687.
12. Glick PL, Harrison MR, Adzick NS, et al. Correction of congenital hydronephrosis in utero. IV. In utero decompression prevents renal dysplasia. J Pediatr Surg 1984; 19:649–657.
13. Adzick NS, Harrison MR, Hu L, et al. Pulmonary hypoplasia and renal dysplasia in a fetal lamb urinary tract obstruction model. Surg Forum 1987; 38:666–668.
14. Docimo SG, Luetic T, Crone RK, et al. Pulmonary development in the fetal lamb with severe bladder outlet obstruction and oligohydramnios: a morphometric study. J Urol 1989; 142:657–660.
15. Wigglesworth JS, Desai R, Guenini P. Fetal lung hypoplasia: biochemical and structural variations and their possible significance. Arch Dis Child 1981; 56:606–610.
16. Inselman LS, Mellins RB. Growth and development of the lung. J Pediatr Surg 1981; 98:1–7.
17. Reid L. The lung: Its growth and remodeling in health and disease. Am J Roentgenol 1977; 129:777.
18. Nakayama DK, Glick PL, Villa RL, et al. Experimental pulmonary hypoplasia due to oligohydramnios and its reversal by relieving thoracic compression. J Pediatr Surg 1983; 18:347–353.
19. Adzick NS, Harrison MR, Glick PL, et al. Experimental pulmonary hypoplasia and oligohydramnios: relative contribution of lung fluid and fetal breathing movements. J Pediatr Surg 1984; 19: 658–663.
20. Harrison MR, Filly RA, Golbus MS, et al. Fetal treatment 1982. N Engl J Med 1982; 307:1651–1652.
21. Muller F, Dumez Y, Dommergues M, et al. Can fetal urinary biochemistry predict postnatal renal function? Fetal Therapy (In press).
22. Crombleholme TM, Harrison MR, Golbus MS, et al. Fetal intervention in obstructive uropathy: prognostic indicators and efficacy of intervention. Am J Ob Gyn 1990; 162:1239–1244.
23. Mahoney BS, Filly RA, Callen PW, et al. Sonographic evaluation of fetal renal dysplasia. Radiology 1984; 152:143–146.

24. Glick PL, Harrison MR, Adzick NS, et al. Management of the fetus with congenital hydronephrosis. II. Prognostic criteria and selection for treatment. J Pediatr Surg 1985; 20:376–387.
25. Crombleholme TM, Harrison MR, Langer JC, et al. Early experience with open fetal surgery for congenital hydronephrosis. J Pediatr Surg 1988; 23:1114–1116.
26. Harrison MR, Golbus MS, Filly RA, et al. Fetal surgery for congenital hydronephrosis. N Engl J Med 1982; 306:591–593.
27. Harrison MR, Golbus MS, Filly RA, et al. Management of the fetus with congenital hydronephrosis. J Pediatr Surg 1982; 17:728–742.
28. Harrison MR, deLorimier AA. Congenital diaphragmatic hernia. Surg Clin North America 1981; 61:1023–1028.
29. Harrison MR, Jester JA, Ross NA. Correction of congenital diaphragmatic hernia in utero. I. The model: intrathoracic balloon produces fatal pulmonary hypoplasia. Surgery 1980; 88:174–182.
30. Harrison MR, Bressack MA, Churg AM. Correction of congenital diaphragmatic hernia in utero. II. Simulated correction permits fetal lung growth with survival at birth. Surgery 88:260–268, 1980.
31. Harrison MR, Ross NA, deLorimier AA. Correction of congenital diaphragmatic hernia in utero. III. Development of a successful surgical technique using abdominoplasty to avoid compromise of umbilical blood flow. J Pediatr Surg 1981; 16:934–942.
32. Soper RT, Pringle KC, Scofield JC. Creation and repair of diaphragmatic hernia in the fetal lamb: technique and survival. J Pediatr Surg 1984; 19:33–37.
33. Adzick NS, Outwater KM, Harrison MR, et al. Correction of congenital diaphragmatic hernia in utero IV. An early gestational model for pulmonary vascular morphometric analysis. J Pediatr Surg 1985; 20:673–680.
34. Fitzgerald RJ. Congenital diaphragmatic hernia as a cause of perinatal mortality. Ir J Med Sci 1979; 146:280–284.
35. Butler N, Claireaux AE. Congenital diaphragmatic hernia as a cause of perinatal mortality. Lancet 1962; i:659–665.
36. Puri P, Gorman F. Lethal nonpulmonary anomalies associated with congenital diaphragmatic hernia: implications for early intrauterine surgery. J Pediatr Surg 1984; 19:29–35.
37. O'Rourke PP, Vacanti JP, Crone RK, et al. Use of the postductal PaO_2 as a predictor of pulmonary vascular hypoplasia in infants with congenital diaphragmatic hernia. J Pediatr Surg 1989; 23: 904–907.
38. Nakayama DK, Harrison MR, Chinn DH, et al. Prenatal diagnosis and management of the fetus with a congenital diaphragmatic hernia: initial clinical experience. J Pediatr Surg 1985; 20:118–122.
39. Adzick NS, Harrison MR, Glick PL, et al. Diaphragmatic hernia in the fetus: prenatal diagnosis and outcome in 94 cases. J Pediatr Surg 1985; 20:357–361.
40. Adzick NS, Vacanti JP, Lillehei CW, et al. Fetal diaphragmatic hernia: Ultrasound diagnosis and clinical outcome in 38 cases from a single medical center. J Pediatr Surg 1989; 24:654–658.
41. Harrison MR, Langer JC, Adzick NS, et al. Correction of congenital diaphragmatic hernia in utero V. Initial clinical experience. J Pediatr Surg 1990; 25:47–57.
42. Harrison MR, Adzick NS, Longaker MT, et al. Successful repair in utero of a fetal diaphragmatic hernia after removal of herniated viscera from the left thorax. N Engl J Med 1990, 322:1582–1584.
43. Benacerraf BR, Frigoletto FD, Wilson M. Successful midtrimester thoracentesis with analysis of the lymphocyte population in the pleural effusion. Am J Obstet Gynecol 1986; 155:398–399.
44. Longaker MT, Laberge JM, Dansereau J, et al. Primary fetal hydrothorax: natural history and management. J Pediatr Surg 1989; 24:573–576.
45. Rodeck CH, Fisk NM, Fraser DI, et al. Long-term in utero drainage of fetal hydrothorax. N Eng J Med 1988; 319:1135–38.
46. Flake AW, Harrison MR, Adzick NS, et al. Fetal sacrococcygeal teratoma. J Pediatr Surg 1986; 21:563–566.
47. Langer JC, Harrison MR, Schmidt KG, et al. Fetal hydrops and demise from sacrococcygeal teratoma: rationale for fetal surgery. Am J Obstet Gynecol 1989; 160:1145–1150.
48. Adzick NS, Harrison MR, Glick PL, et al. Fetal cystic adenomatoid malformation: prenatal diagnosis and natural history. J Pediatr Surg 1985; 20:483–488.
49. Golladay ES, Mollitt DL. Surgically correctable fetal hydrops. J Pediatr Surg 1984; 19:59–64.
50. Saltzman DH, Adzick NS, Benacerraf BR. Fetal cystic adenomatoid malformation of the lung: apparent improvement in utero. Obstet Gynecol 1988; 71:1000–1003.
51. Adzick NS, Harrison MR, Hu LM, et al. Compensatory lung growth after pneumonectomy in fetal lambs: a morphometric study. Surg Forum 1986; 37:309–314.
52. Clark SL, Vitale DJ, Minton SD, et al. Successful fetal therapy for cystic adenomatoid malformation associated with second trimester hydrops. Am J Obstet Gynecol 1987; 157:294.
53. Nicolay KS, Gainey HL. Pseudotoxemic state associated with severe Rh-isoimmunization. Am J Ob Gyn 1964; 89:41–43.
54. Harrison MR, Adzick NS, Jennings RW, et al. Antenatal intervention for congenital cystic adenomatoid malformation. Lancet 1990; 336:965–967.
55. Kleinman CS, Hobbins JC, Jaffe CC, et al. Echocardiographic studies of the human fetus: prenatal diagnosis of congenital heart disease and cardiac dysrhythmias. Pediatrics 1980; 65:1059–1066.
56. Taylor PV, Scott JS, Garlis LM, et al. Maternal antibodies against fetal cardiac antigens in congenital complete heart block. N Engl J Med 1986; 315:667–772.
57. Crombleholme TM, Longaker MT, Langer JC, et al. Complete heart block and AV-sequential pacing in fetal lambs: the atrial contribution to cardiac output in the fetus. Surg Forum 1989; 40:268–270.
58. Carpenter RJ, Strasburger JF, Garson A, et al. Fetal ventricular pacing for hydrops secondary to complete atrioventricular block. J Am Coll Cardiol 1986; 8:1434–1436.
59. Fishman NH, Hof RB, Rudolph AM, et al. Models of congenital heart disease in fetal lambs. Circulation 1978; 58:354–364.
60. Becal O, Gallix P, Toussaint M, et al. Intrauterine creation and repair of pulmonary artery steonosis in the fetal lamb. J Thorac Cardiovasc Surg 1987; 93:761–766.
61. Slate RK, Stevens MB, Verrier ED, et al. Intrauterine repair of pulmonary stenosis in fetal sheep. Surg Forum 1985; 36:246–248.
62. Adzick NS, Harrison MR, Slate RK, et al. Surface cooling and rewarming the fetus: a technique for experimental fetal cardiac surgery. Surg Forum 1984; 35:313–316.
63. Richter RC, Slate RK, Rudolph AM, Turley K. Fetal blood flow during hypothermic cardiopulonary bypass in utero. J Cardiovasc Surg 1985; 26:86.
64. Harrison MR, Anderson J, Rosen M, et al. Fetal surgery in the primate I. Anesthetic, surgical, and tocolytic management to maximize fetal-neonatal survival. J Pediatr Surg 1982; 17:115–122.
65. Nakayama DK, Harrison MR, Seron-Ferre M, et al. Fetal surgery in the primate II. Uterine electromyographic response to operative procedures and pharmacologic agents. J Pediatr Surg 1984; 19: 333–339.
66. Adzick NS, Harrison MR, Anderson JV, et al. Fetal surgery in the primate. III. Maternal outcome after fetal surgery. J Pediatr Surg 1986; 21:477–480.
67. Adzick NS, Harrison MR, Flake AW, et al. Automatic uterine stapling device in fetal surgery: experience in a primate model. Surg Forum 1985; 36:479–480.