

*Medical Progress***PEDIATRIC SURGERY****Second of Two Parts**

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CHILDHOOD CANCER

Cancer is a leading cause of death in children, second only to accidental injury, and is responsible for approximately 10 percent of deaths in children. More than 10,000 new cases of childhood cancer are diagnosed each year in the United States. The rapid strides that have been made in the treatment of childhood cancer are largely the result of studies by national groups of investigators. Indeed, the Pediatric Oncology Group and the Children's Cancer Group are being consolidated into a single entity called the Children's Oncology Group, which should further facilitate cooperative trials in the treatment of pediatric cancers.

The diagnosis of many pediatric cancers now relies on molecular techniques, biologic staging, or both, and surgery is necessary to obtain tumor tissue for these evaluations. Molecular diagnosis is also an effective way to screen children for diseases that require surgery. For example, medullary thyroid carcinoma in children is usually associated with multiple endocrine neoplasia type IIA or IIB. The diagnosis of this syndrome by direct DNA testing in children from affected families allows prophylactic thyroidectomy to be performed before extensive local or metastatic medullary thyroid carcinoma can develop.⁵² Surgery plays a particularly important part in the treatment of two solid tumors of childhood: Wilms' tumor and neuroblastoma.

Wilms' Tumor

The treatment of Wilms' tumor exemplifies the effectiveness of combining surgery, chemotherapy, and radiation in the treatment of children with cancer. Wilms' tumor is the most common malignant renal tumor in children, with 450 new cases diagnosed each year in the United States. The mortality rate associated with Wilms' tumor exceeded 60 percent in the 1950s. However, as a result of a series of cooperative trials conducted by the National Wilms' Tumor Study (NWTS) Group, which began in 1969, the relapse-free survival rate at two years now exceeds 90 per-

cent.⁵³ The goals of the study group have been to improve overall survival while minimizing the morbidity associated with therapy. Risk factors for the local recurrence of Wilms' tumor include an advanced local stage (particularly as manifested by the involvement of para-aortic lymph nodes), unfavorable histologic features, and spillage of tumor cells at the time of resection.⁵⁴ The NWTS is now recruiting patients for the fifth cooperative clinical trial. The goal of NWTS-5 is to determine the value of tumor markers as prognostic factors in children with tumors that have favorable histologic features, as well as to compare therapeutic regimens.

The treatment of bilateral Wilms' tumor has focused on nephron-sparing procedures. Substantially more renal mass has been preserved in patients treated initially with biopsy, followed by chemotherapy and delayed definitive resection, than in those who undergo an initial radical resection followed by chemotherapy.⁵⁵ The NWTS-4 trial included 98 patients with synchronous bilateral Wilms' tumor who underwent renal salvage therapy.⁵⁶ The treatment included partial nephrectomy or enucleation of tumor nodules either before or after chemotherapy. The survival rate at four years was 82 percent, with a local-recurrence rate of 8 percent. More than half the renal mass was preserved in 64 percent of the patients treated with salvage techniques.

Neuroblastoma

Neuroblastoma is the most common extracranial solid tumor in infants and children, with about 600 new cases diagnosed annually in the United States. This tumor has interested investigators because of its ability to regress spontaneously or to assume a benign histologic appearance. The former is more common in infants, whereas differentiation into a benign ganglioneuroma is more common in children over the age of one year. Unfortunately, the majority of children over the age of one year have metastatic disease at the time of diagnosis, with a poor outcome despite aggressive multimodal therapy.

A number of biologic features of the tumor have prognostic importance, such as the number of copies of *N-myc*, ploidy, deletions of chromosome 1p, additional copies of chromosome 17q, the level of expression of *TRKA* (the gene for the receptor of the neurotrophin nerve growth factor), and specific histologic features.⁵⁷ Studies of treatment in children with neuroblastoma have been aided by the widespread use of the International Neuroblastoma Staging System. This classification helps discriminate among low-, intermediate-, and high-risk patients, which is critical in choosing an individual therapeutic strategy, and it is both a clinical and a surgical staging system. The role of surgery may be to obtain tissue for histologic studies that establish the diagnosis and determine biologic markers, to allow further assessment

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of the stage of the tumor, or to provide definitive therapy for localized disease.

In low-risk patients, surgical treatment alone, with close clinical follow-up, results in a survival rate that exceeds 95 percent. Intermediate-risk patients generally require surgical resection, with chemotherapy and, occasionally, radiation therapy for residual disease, which results in a survival that is generally greater than 80 percent. Patients with neuroblastoma in the high-risk group have a poor prognosis. Aggressive therapeutic strategies are being used in an effort to improve the outcome. Recent strategies have included a greater dose intensity of chemotherapeutic regimens and aggressive surgical resection with myeloablative therapy followed by allogeneic bone marrow transplantation. Despite such aggressive therapies, the survival rate has been only 20 to 40 percent. The additional use of biologic agents such as 13-*cis*-retinoic acid may improve the long-term outcome for high-risk patients.⁵⁸

TRANSPLANTATION

Several major medical centers have programs for kidney, liver, heart, lung, and bowel transplantation in children. On the basis of data from the United Network for Organ Sharing, approximately 450 to 500 children received liver transplants each year over the past decade, and the most common indication for transplantation was biliary atresia.⁵⁹ The difficulty of obtaining grafts of the appropriate size for transplantation in children, particularly young children, has stimulated efforts to use split-liver and reduced-size grafts from cadaveric donors, as well as grafts from living donors. From 1990 to 1996, there was a 300 percent increase in the use of grafts from living donors and a 50 percent increase in the use of both split-liver and reduced-size grafts. The use of whole-liver grafts from cadaveric donors decreased proportionately so that the total number of transplantations each year was unchanged. The rate of graft survival at one year was higher for grafts from living donors (75.6 percent) than for whole-liver grafts, split-liver grafts, and reduced-size grafts from cadaveric donors (70.9, 60.3, and 61.1 percent, respectively); the corresponding survival rates for patients at one year were 88.4, 82.6, 82.0, and 74.4 percent.

Goss et al. have reported the long-term results of liver transplantation in children.⁶⁰ Among 440 children who underwent 569 transplantations at the University of California, Los Angeles, Medical Center, the graft-survival and patient-survival rates at 10 years were 54 percent and 76 percent, respectively. In 1994, a tacrolimus-based immunosuppressive regimen was introduced, with a subsequent decrease in the rate of corticosteroid-resistant rejection. Since 1993, the survival rate for children who were less than one year old at the time of transplantation has exceeded 80 percent. This degree of success, which has also been

achieved at other centers dedicated to pediatric transplantation, may be due in part to improvements in perioperative management, surgical experience, and the introduction of microvascular techniques to reduce the incidence of hepatic-artery thrombosis. The report by Goss et al. confirms the durable benefit of transplantation as a treatment for liver failure in children.

The use of split-liver grafts has evolved from *ex vivo* techniques, in which the liver is divided after its removal from the cadaveric donor, to *in situ* techniques, in which the liver is split before it is removed from the donor, while the heart is still beating, a technique that results in two functioning grafts for transplantation in two recipients.⁶¹ The graft-survival and patient-survival rates at two years with the *in situ* approach are 80.5 percent and 90.7 percent, respectively. *In situ* preparation adds an additional 1.0 to 1.5 hours to the time required to remove the liver but markedly decreases the cold-ischemia time, which can improve the functioning of the graft. Despite the options now available for obtaining grafts, the mortality rate among patients awaiting suitable donors approaches 10 percent.

The registry of the North American Pediatric Renal Transplant Cooperative Study includes data on 4329 renal transplants received by children between 1987 and 1996.⁶² Obstructive uropathy was the most common underlying cause of renal failure, accounting for 16.4 percent of the transplantations. Forty-seven percent of the transplanted organs were from living donors. A total of 1170 grafts failed, with 50 percent of the failures due to acute or chronic rejection. The rate of graft survival at five years was 76.2 percent for organs from living donors and 60.3 percent for cadaveric organs. There were 214 deaths, with infection the most common cause of death.

Infants with renal failure are particularly prone to severe growth retardation and neurocognitive deficits. However, the potential for catch-up growth is greater in infants than in older children, so early transplantation is probably warranted.⁶³ Transplantation in infants has been limited by ethical and technical considerations, as well as the restricted availability of donors. Currently, there is an inverse relation between age and the risk of graft failure (for both cadaveric grafts and those from living donors). In addition, although the incidence of rejection is lower in infants than in older children, the risk of bacterial infection is greater in infants.⁶⁴ Improved techniques of transplantation, the use of organs from adult donors, and aggressive intravenous volume loading have resulted in improved rates of graft survival.⁶⁵ Overall, the rate of graft survival at four years in children who undergo transplantation before the age of one year is 75 percent for grafts from living donors and 45 percent for grafts from cadaveric donors.⁶²

Intestinal transplantation in children has not been as successful as renal and hepatic transplantation. One

reason is the technical challenges of intestinal transplantation, but a more important reason is the presence of complex immunologic barriers, which have been difficult to overcome. In a review of the international experience with small-bowel transplantation, which included data on 180 transplantations, two thirds of the transplant recipients were children, and 78 percent of the overall group of survivors were no longer dependent on intravenous hyperalimentation.⁶⁶ In the largest study performed at a single center, 55 children (median age, 3.2 years) received a small-bowel graft alone, a small-bowel graft plus a liver graft, or a multivisceral graft.⁶⁷ At three years, the overall rate of survival among the children was 55 percent, and the rate of graft survival was 48 percent. Children over the age of 10 years had the highest survival rate (89 percent). Complications were common; there was a 90 percent incidence of graft rejection and a 29 percent incidence of post-transplantation lymphoproliferative disease. These results offer hope for the future, but as with most types of transplantation, the availability of grafts is limited, and many children die before transplantation can be performed.⁶⁸ In an attempt to overcome this obstacle, a small-bowel graft from a living related donor was transplanted in a two-year-old boy.⁶⁹ Unfortunately, the child died from *Pneumocystis carinii* pneumonia 16 months after receiving the transplant.

Despite improved surgical techniques and better protection against organ rejection, the scarcity of grafts has precluded the use of organ transplantation in some children. Recent advances in tissue engineering that permit the creation of artificial organs may help solve the problem of a shortage of grafts.⁷⁰ Investigators have successfully grown cells on biodegradable polymer scaffolds. This method has been used to fabricate liver, bowel, bladder, and skin tissue; blood vessels; and cartilage and bone. Until these techniques have been perfected, allogeneic tissues must be used for transplantation, and their limited availability remains a major obstacle to pediatric transplantation.

TRAUMA

Trauma is the leading cause of death in children, and blunt trauma, such as that caused by motor vehicle collisions and falls, is the most common type of trauma in children. Child abuse is prevalent in children under the age of four years and must be considered in all children with injuries that do not appear to be consistent with the reported cause. Awareness of the possibility of child abuse and a better understanding of biomechanics of injuries (e.g., in the "shaking-impact syndrome") may improve the recognition and outcome of child abuse.⁷¹ In the past decade there has been an epidemic of penetrating injuries in children and young adults. In fact, homicide is the leading cause of death in black boys and men between the ages of 15 and 24 years. Head injuries

(both blunt and penetrating) are the most common fatal injuries in children.

Because of the prevalence of traumatic injury in children, the need for specialty care for injured children often far exceeds the resources of local hospitals. Trauma centers have been established to centralize the necessary resources and optimize the care of injured children. Recent modifications in the guidelines of the American College of Surgeons' Committee on Trauma eliminated the designation of regional pediatric trauma center. Adult trauma centers (levels 1 and 2) that care for children are required to provide the specialized services and resources that injured children often need (a pediatric intensive care unit, emergency room equipment, and services by medical specialists). If an injured child is brought to a trauma center that does not provide care for children, the center must be capable of initiating and maintaining resuscitation efforts until a transfer to an appropriate facility can be arranged.⁷² Pediatric institutions that want to be designated as trauma centers must provide the same commitment of services and resources as adult trauma centers and must maintain a close relation with the hospitals in the region that provide pediatric care.

Prevention of Injury

Much of the progress in the care of children with trauma has been in the prevention rather than the management of injury, with dramatic results. The use of safety helmets decreases the severity of head injuries from bicycle crashes and the associated mortality rate. In a review of 81 fatal injuries in children that were caused by bicycle crashes, 72 were head injuries; none of the 81 children were wearing safety helmets when they were injured.⁷³ Community and school-based educational programs have been initiated to emphasize the importance of wearing protective headgear. Many communities have enacted legislation mandating helmet use by children. According to one report, a community education program and state legislation mandating the use of safety helmets resulted in a 13-fold increase in the use of helmets among children who were hospitalized because of injuries involving bicycle crashes, with a dramatic decrease in the severity of head injuries.⁷⁴

Despite the proven efficacy of air bags in automobiles for the prevention of injuries in adults, there have been reports of children who died as a result of air-bag deployment.⁷⁵ A careful review of these incidents showed that either car seats were not used or they were used improperly in the front passenger seat (Fig. 5). This information has led the Centers for Disease Control and Prevention and the National Highway Traffic Safety Association to issue recommendations for the appropriate use of car seats to prevent further air bag-related fatalities. Similarly, inadequate or improper restraint of children in automobiles has led to

preventable injuries. Despite the clear lifesaving benefit of using restraint devices (car seats for infants and seat belts with booster seats for older children), the estimated rate of use ranges from 41 percent for toddlers to 76 percent for infants.⁷⁶ The most important risk factor for the injury of a child in a motor vehicle accident is nonuse or improper use of a car seat or seat belt.

Baby walkers are responsible for nearly 25,000 injuries per year.⁷⁷ The majority of the serious injuries are the result of falls down stairs, which cause lacerations, contusions, and head injuries. The Consumer Product Safety Commission has recommended that baby walkers be wider than the standard 36-inch doorway opening or have a special mechanism that stops the baby walker on the top step. Implementation of these recommendations is likely to result in a dramatic decrease in the numbers of injuries associated with baby walkers.

There is an epidemic of violence involving guns in the United States, and children are affected by it. In the past 10 years, there has been an increase in the number of children with gunshot wounds, as well as an increase in the frequency of violent circumstances surrounding these injuries.⁷⁸ Despite their lethal nature, firearms are not currently regulated by the Consumer Product Safety Commission. Children stand

to benefit greatly from legislative efforts aimed at gun safety.

Injuries of Abdominal Solid Organs

Since the reports in the 1970s of successful nonoperative management of splenic injuries in children, the treatment of solid-organ injuries in children has changed dramatically.⁷⁹ Subsequent studies have confirmed the efficacy and safety of a nonoperative approach. Improvements in diagnostic imaging, notably the higher resolution and more rapid acquisition of computed tomographic scans, have led to a more accurate assessment of the severity of injuries to the abdominal solid viscera. Nonoperative approaches are also being used to treat hepatic, renal, and pancreatic injuries. The rate of success of nonoperative therapy has been reported to be as high as 97.4 percent for hepatic and splenic injuries.⁸⁰ Nonoperative management of hepatic and splenic injuries is also safe in children with associated head injuries.⁸¹

A recent study showed that a 4-day hospital stay (24 hours in the intensive care unit and 3 days on a medical ward) was adequate for the management of most splenic injuries.⁸² The authors recommended a three-week period of limited activity at home after discharge, with no participation in contact sports for three months. There were no adverse outcomes noted

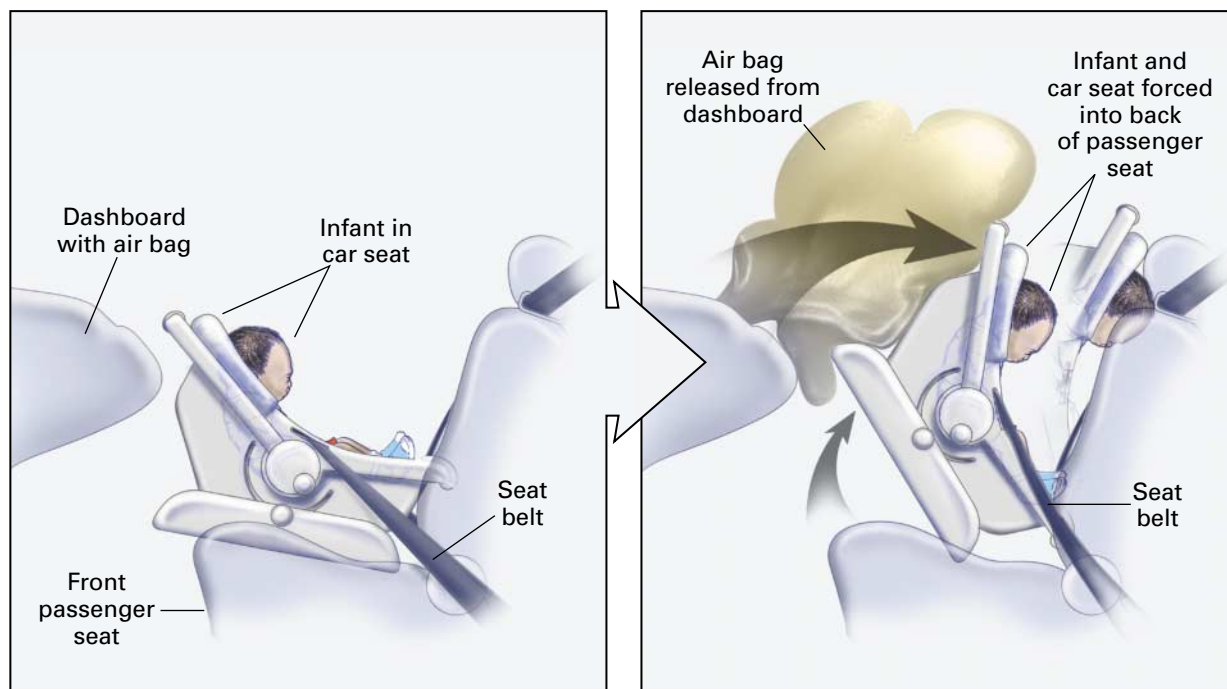


Figure 5. Mechanism of Injury in an Infant Inappropriately Restrained in the Front Passenger Seat. The release of the air bag drives the infant into the back of the seat.

in this study. A study sponsored by the Committee on Trauma of the American Pediatric Surgical Association to determine the optimal length of stay for children with solid-organ injuries is ongoing.

Pancreatic injuries, which pose the greatest challenge to trauma surgeons, may also be amenable to a nonoperative approach. Such an approach was successful in 79 percent of patients with low-grade pancreatic injuries (those that did not affect the major duct).⁸³ The role of nonoperative management in cases of pancreatic injury and possible ductal disruption remains controversial.⁸⁴

PRENATAL DIAGNOSIS AND FETAL SURGERY

Most of the congenital defects that pediatric surgeons treat can be detected before birth with ultrasonography, and new techniques such as color Doppler ultrasonography and ultrafast fetal magnetic resonance imaging have enhanced the accuracy of prenatal evaluation⁸⁵ (Fig. 6). Frequently diagnosed anomalies include abdominal-wall defects (omphalocele and gastroschisis), bowel obstruction, diaphragmatic hernia, lung lesions, obstructive uropathy, neural-tube defects, neck masses, sacrococcygeal teratoma, and adrenal neuroblastoma. Prenatal detection and serial ultrasonographic evaluation of anatomical malformations have resulted in an understanding of the natural history of these lesions, the identification of pathophysiologic features that affect the clinical outcome, and the formulation of treatments based on the prognosis. Pediatric surgeons familiar with the management of congenital defects before and after birth participate in decisions about treatment and family counseling, along with obstetricians, neonatologists, geneticists, and other specialists. Most correctable anomalies are best managed with the use of appropriate medical and surgical therapy after delivery at term. Prenatal diagnosis may also influence the timing or mode of delivery (cesarean section or vaginal delivery) and, in some cases, may lead to elective termination of the pregnancy.

If a malformation is life-threatening, fetal surgery may be performed. Fetal surgery has required the development of surgical, anesthetic, and tocolytic techniques, as well as the resolution of such ethical issues as the safety of the mother and her future reproductive potential.^{86,87} Fetal surgery is offered at only a small number of highly specialized centers throughout the world. Standards for the use of fetal surgery and for long-term follow-up are evolving.

The most severe cases of congenital diaphragmatic hernia involve herniation of the liver into the fetal chest (Fig. 6) as well as ultrasonographic signs of severe pulmonary hypoplasia. The original approach of complete in utero repair of congenital diaphragmatic hernia was unsuccessful, because abrupt movement of the liver from the fetal chest into the abdomen led to

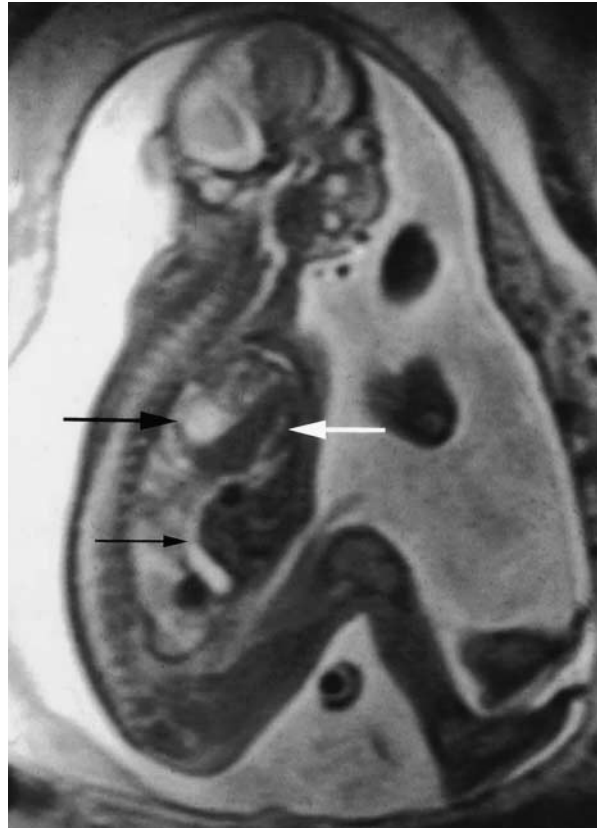


Figure 6. Ultrafast Magnetic Resonance Image of a 22-Week-Old Fetus with a Left-Sided Congenital Diaphragmatic Hernia. A sagittal view shows the herniated stomach (larger black arrow), herniated liver (white arrow), and portal vein (smaller black arrow).

compromised umbilical venous flow, resulting in fetal bradycardia and death.⁸⁸ Temporary in utero tracheal occlusion (performed with an open procedure or fetoscopically) can prevent the normal outflow of fetal lung fluid, which in turn enhances the growth of the lungs.^{89,90} Early results suggest that this approach prolongs survival.

As an outgrowth of the fetal-intervention efforts, ex utero intrapartum therapy was devised to treat fetal airway obstruction due to large neck masses or intrinsic airway problems.⁹¹ This approach involves a planned cesarean section with preservation of the maternal–fetal placental circulation for oxygenation of the fetus, which allows time for direct laryngoscopy, bronchoscopy, endotracheal intubation, or tracheostomy to establish the airway. The umbilical cord is then divided, and the fetus delivered.

Myelomeningocele, which occurs in about 1 of every 2000 live births, can result in severe lifelong disabilities, including paraplegia, hydrocephalus, incontinence, sexual dysfunction, skeletal deformations, and

mental impairment.⁹² Myelomeningocele was the first nonlethal anomaly to be treated by fetal surgery. Studies in animals provide compelling evidence that the primary cause of the neurologic deficit associated with myelomeningocele is not simply incomplete neurulation but rather chronic mechanical injury and amniotic-fluid-induced chemical trauma that progressively damages the exposed neural tissue during gestation.⁹³ Early results indicate that the surgical repair of myelomeningocele before 25 weeks of gestation can preserve neurologic function, reverse the hindbrain herniation of the Arnold–Chiari malformation, and obviate the need for postnatal placement of a ventriculoperitoneal shunt.^{94–96} Experience with this type of fetal surgery is limited, and long-term follow-up will be required to determine whether the benefits are sustained.

Other simple anatomical problems are amenable to repair before birth. Congenital cystic adenomatoid malformation is a benign cystic lung mass. A large mass can cause mediastinal shift, hypoplasia of normal lung tissue, polyhydramnios, and cardiovascular compromise, leading to fetal hydrops and death. These lesions can be resected in utero if they are predominantly solid or multicystic.⁹⁷ Percutaneous thoracoamniotic shunting is effective if the fetus has a single large cyst.

Sacroccygeal teratoma is the most common neonatal tumor, with an incidence of 1 in 35,000 live births. In some fetuses with large teratomas, high-output cardiac failure and hydrops develop and lead to death in utero — a sequence that can be reversed by removing the tumor before birth.^{98,99}

Fetal urethral obstruction interferes with the development of the kidneys and lungs. The natural history of fetal urinary tract obstruction has been well documented by ultrasonographic follow-up studies of untreated cases, and criteria for fetal treatment have been developed on the basis of the ability to predict renal function according to fetal urine electrolyte levels and the ultrasonographic appearance of the kidneys.¹⁰⁰ Although most cases do not require prenatal intervention, a fetus with bilateral hydronephrosis due to urethral obstruction in whom oligohydramnios develops may benefit from in utero decompression with the percutaneous placement of a catheter shunt under ultrasonographic guidance.¹⁰¹

Minimally invasive or fetoscopic procedures will have a greater therapeutic role in the future, as indications, instruments, and techniques are refined.¹⁰² Fetoscopic treatment may be used for abnormalities of monochorionic twin pregnancies that involve an imbalance of blood flow in the placental chorionic vessels connecting the circulations of the twins, resulting in changes in the volume of amniotic fluid, retarded growth, and hydrops. In cases of acardiac twin pregnancies, fetoscopic bipolar coagulation has been used to occlude the umbilical circulation of the abnormal

twin and save the normal twin. For the twin–twin transfusion syndrome, a fetoscopically directed laser can be used to divide the vessels.¹⁰³

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