Fetal surgery continues to advance

February 16 2010

Repairing birth defects in the womb. Inserting a tiny laser into the mother's uterus to seal off an abnormal blood flow and save fetal twins. Advancing the science that may allow doctors to deliver cells or DNA to treat sickle cell anemia and other genetic diseases before birth.

These are examples of the still-emerging field of fetal surgery. "Fetal surgery is a unique field in maternal-fetal medicine," said pediatric surgeon N. Scott Adzick, M.D., medical director of the Center for Fetal Diagnosis and Treatment (CFDT) at The Children's Hospital of Philadelphia. "Detecting birth defects prenatally has allowed physicians to provide better perinatal care," said Adzick, "but many of these babies were already too sick for us to treat them successfully after they were born. This dilemma led to the development of fetal surgery."

"Some of the fetal anomalies we treat are so rare that a physician may encounter them only once or twice in a career," continued Adzick, who is surgeon-in-chief at Children's Hospital. "However, as prenatal diagnosis continues to improve, along with surgical techniques and tools of molecular biology, we have an expanded range of conditions for which we may devise ways to intervene before birth with clear benefits."

Internationally prominent as a pioneer in fetal surgery, Adzick edited the February 2010 issue of the journal *Seminars in Fetal & Neonatal Medicine*. That issue is entirely devoted to advances in fetal surgery. Adzick and other practitioners at The Children's Hospital of Philadelphia describe innovative surgeries, high-tech procedures, and the prospect of prenatal gene therapy and stem cell treatments in a collection

of articles reviewing the current state of the science in fetal therapy.

The CFDT, which marks its 15th anniversary this year, is a premier program, one of a handful worldwide to offer a full range of fetal procedures. Since the center opened in 1995, more than 10,000 parents have used its services, from all 50 U.S. states and from 46 other countries.

Open fetal surgery to remove abnormal masses or patch an opening

Open fetal surgery involves cutting into the mother's abdomen and uterus in order to operate on the fetus. In his article on open fetal surgery, Adzick describes the multidisciplinary team and sophisticated imaging technologies used to assess patients referred to the center, the only such facility that includes a Special Delivery Unit for mothers carrying babies with known birth defects. Adzick describes fetal surgeries for two life-threatening defects: lung masses, which may compress the developing heart, leading to heart failure, and sacrococcygeal teratomas, large tumors attached to the fetus's tailbone, which can lead to heart failure or a fatal hemorrhage before birth. Fetal surgery, he adds, places special demands on caregivers to ensure safety for two patients—the mother and the fetus.

Adzick's second article concerns fetal surgery for open spina bifida, referred to as myelomeningocele. A defect in which part of the spinal cord remains unprotected by skin and tissue, it may result in hydrocephalus, mental retardation, bowel and bladder problems, and lifelong paralysis. While usually non-lethal, it is a relatively common cause of major disability, affecting one in 2,000 live births.

To repair a myelomeningocele, fetal surgeons shield the developing

spinal cord by closing the defect with the fetus's own tissue. Definitive results of outcomes after fetal surgery are expected from a randomized clinical trial sponsored by the National Institutes of Health. The Management of Myelomeningocele Study (MOMS), which began in 2003, is expected to conclude treatments in the trial in 2011 at three fetal surgery centers, The Children's Hospital of Philadelphia, Vanderbilt University and the University of California-San Francisco.

Laser treatment shuts off dangerous twin-to-twin connection

Another application of fetal surgery is for twin-twin transfusion syndrome, occurring in 10 to 15 percent of identical twins. In this condition, one fetus grows at the expense of its twin because of abnormal blood vessel connections in their shared placenta. Michael Bebbington, M.D., of the CFDT, reviews current therapies for this condition, noting that the scientific evidence favors selective laser photocoagulation. In this procedure, using a viewing instrument called a fetoscope, the fetal surgeon employs a laser to seal off the blood vessels that carry hazardous blood flow between the two fetuses.

Prenatal stem cell and gene therapy moving toward clinical use

The greatest future impact of fetal treatments probably lies in non-surgical approaches—prenatal stem cell therapy and gene therapy. In contrast to the relatively rare anatomical defects addressed in fetal surgery, cell and gene therapy offer the possibility of treating many genetic diseases before birth, including sickle cell anemia, immune deficiency disorders and some types of muscular dystrophy.

These potential therapies are reviewed by Alan W. Flake, M.D., and his

colleagues at the Center for Fetal Research at Children's Hospital. Now in his third decade of investigating fetal surgery, Flake pioneered fetal bone marrow transplantation in 1996, successfully treating severe combined immunodeficiency disease (SCID) in utero.

In-utero hematopoietic stem cell transplantation (IUHCT) focuses on stem cells that develop into all the types of cells found in the blood. The keystone of this approach is the fetal immune system's unique tolerance of transplanted cells. Flake's strategy involves using prenatal stem cell transplants to achieve tolerance of foreign cells, which are incorporated into the fetal circulation. This sets the stage for postnatal transplant of therapeutic blood cells from the same donor that will not be rejected by the infant's immune system.

The specific characteristics of SCID make this disease uniquely amenable to a prenatal stem cell approach. Now, says Flake, research in animal models is progressing toward using IUHCT to treat other immune deficiency diseases, the hemoglobin disorders sickle cell anemia and thalassemia, and lysosomal storage diseases (genetic disorders in which the lack of an enzyme causes metabolic chemicals to accumulate to toxic levels in cells).

Some diseases that progress to irreversible organ damage may offer targets for prenatal gene therapy—in which physicians deliver therapeutic DNA to correct a genetic defect. Proof-of-principle studies in animals have produced preclinical successes for prenatal gene therapy in cystic fibrosis, Duchenne's muscular dystrophy, Pompe disease and the lysosomal storage disease Sly syndrome. There have also been promising animal studies in types of hemophilia. As with postnatal gene therapy, important safety issues remain to be solved before prenatal gene therapy can be offered in the clinic. "Fetal gene therapy is still in the early experimental stage," said Flake, while noting great progress in this field.

EXIT procedure—a partial delivery buys time for fetal surgery

Other articles in the special issue discuss fetal treatments for congenital diaphragmatic hernia, thoracic and bladder shunts, fetal anesthesia, and the ex-utero intrapartum therapy (EXIT) procedure. The EXIT procedure is a "partial delivery" in which the fetus is partially removed from the uterus but remains attached to the circulation carried by the umbilical cord and placenta so that surgeons can correct airway blockages before performing a full delivery. Clinicians at Children's Hospital have the world's most extensive experience in performing the EXIT procedure.

Provided by Children's Hospital of Philadelphia