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Prospects for fetal surgery

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ABSTRACT

Until about forty years ago, the womb shielded the fetus from observation and therapy. The rapid changes in the diagnosis and treatment of human fetal anatomical abnormalities are due to improved fetal imaging studies as well as fetal sampling techniques (e.g. amniocentesis, chorionic villus sampling), and a better understanding of fetal pathophysiology derived from laboratory animals. Fetal therapy is the logical culmination of progress in fetal diagnosis. In other words, the fetus is now a patient. The fetal surgical treatment of the most severe form of spina bifida – myelomeningocele (MMC) – will be used as a paradigm to illustrate progress in and future prospects for fetal surgery. This review will focus on the rationale for in utero repair in the context of pathologic observations and animal models of MMC, outcomes from human fetal MMC repair including the recently completed Management of Myelomeningocele Study (MOMS trial), and future research directions.

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1. Introduction

Accurate diagnosis of a fetal anomaly allows the physician and parents to choose the best way to manage the pregnancy. Although most prenatally diagnosed malformations are best managed by maternal transport (transport of the mother to the tertiary medical center for planned delivery), planned delivery near term, and appropriate neonatal therapy, other choices include elective abortion, a change in the timing or mode of delivery, or in utero therapy. There are some simple anatomical abnormalities with predictable and life-threatening prenatal pathophysiological consequences that may benefit from surgical correction before birth (Table 1).

In the 1960s, direct fetal exposure and catheterization of fetal vessels for exchange transfusion was unsuccessful and the procedure was abandoned. In the 1970s, experience with increasingly advanced ultrasound technology led to the accurate diagnosis before birth of many anatomical defects. In the 1980s, the rationale and feasibility of in utero repair for various fetal anomalies was explored. The steps leading from laboratory to bedside can be summarized as follows: the pathophysiology of potentially treatable fetal abnormalities was clarified in fetal laboratory animals, and experimental in utero correction was shown to be efficacious; serial sonographic study of human fetuses with anatomical lesions determined the features that affect clinical outcome and helped to devise selection criteria for prenatal intervention; and the surgical, anesthetic, and tocolytic techniques for hysterotomy and fetal surgery

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Table 1
Diseases amenable to fetal surgical intervention in selected cases.

Malformation	Effect on development	In utero treatment
Cystic adenomatoid malformation or pulmonary sequestration	Pulmonary hypoplasia, hydrops	Thoracoamniotic shunting, fetal lobectomy, steroids
Sacrococcygeal teratoma	Vascular steal, hydrops	Excision
Urethral obstruction	Renal dysplasia, pulmonary hypoplasia	Vesicoamniotic shunting, laser ablation of PUV
Laryngeal atresia	Congenital high airway obstruction syndrome, hydrops	Ex utero intrapartum therapy (EXIT procedure)
Congenital diaphragmatic hernia	Pulmonary hypoplasia, respiratory failure	Tracheal occlusion and release
Hypoplastic left heart syndrome	Inadequate cardiac growth	Increase cardiac chamber blood flow
Twin–twin transfusion & TRAP	Vascular steal, hydrops	Laser coagulation of placental vessels or umbilical cord
Amniotic bands	Limb deformity & functional loss	Lyse bands
Chorioangioma	Vascular steal, hydrops	Laser photocoagulation of placental vessels
Myelomeningocele	Damage to spinal cord, hindbrain herniation, hydrocephalus	Closure of defect

were developed in non-human primates, were shown to be safe for the mother and her future reproductive potential, and were finally introduced clinically. In the 1990s, clinical fetal surgery became more widespread, and ultrafast fetal magnetic resonance imaging (MRI) was introduced to enhance prenatal diagnosis. In the first decade of 21st century, refinements in patient selection and treatment were introduced, and randomized clinical trials elucidated the safety and efficacy of fetal surgical therapy. The indications for fetal surgery were extended to non-life-threatening but serious birth defects such as spina bifida.

The promise of fetal surgery is that the earliest possible intervention for a life-threatening or disabling fetal disorder may produce the best results. Because fetal surgery jeopardizes the pregnancy and may put the mother as well as the fetus at risk, it should be considered only in centers that are committed to a program of continuing research together with circumspect clinical application (Table 2). A fetal treatment center requires the close collaboration of dedicated pediatric surgeons, perinatal obstetricians, radiologists, echocardiographers, neonatologists, geneticists, ethicists, obstetric and neonatal nurses, and a compassionate nurse coordinator. The fetal treatment team should be committed to having this innovative therapy reviewed by uninvolved professional colleagues (institutional review board), to publish all results (bad as well as good), to avoid media reports until cases are peer reviewed, and to test the validity and cost-effectiveness of this approach in properly controlled trials.

2. The vexing challenge of spina bifida

Open spina bifida or myelomeningocele (MMC) is a devastating congenital defect of the central nervous system for which there is no cure. The natural history of MMC includes a constellation of findings which correlate with the proximal anatomic extent of the defect. MMC is characterized by protrusion of the meninges and spinal cord through open vertebral arches leading to lifelong paralysis and hydrocephalus (Fig. 1). In addition, MMC patients are often limited by various degrees of mental impairment, bowel and bladder dysfunction, and orthopedic disabilities. While the etiology of MMC remains poorly understood, primary failure of neural tube closure at the caudal neuropore in the embryonic period results in exposure of the developing spinal cord to the uterine environment [1]. Without protective tissue coverage, secondary destruction of the exposed neural tissue by trauma or amniotic fluid may occur throughout gestation. Until 15 years ago, treatment of MMC consisted of surgical closure of the spinal canal at birth and lifelong supportive care. Since that time the clinical experience with midgestational human repair has been shown to improve neurologic function and reduce morbidity from hydrocephalus and the Arnold–Chiari II malformation by reversal of the hindbrain herniation component.

Advances in prenatal diagnosis now permit diagnosis of spina bifida as early as the first trimester, and extensive research into the etiology of neural tube defects has elucidated both genetic and micronutrient causes [2]. While substantial progress has been made in preventing this disorder through folic acid supplementation, the impact of this preventative approach has leveled off [3]. Consequently, spina bifida affects 1 in 2000 live births, which translates to about 1500 live births with spina bifida in the United States each year. Not included in these figures are the estimated 25–40% of MMC pregnancies in which the fetus is aborted. Mothers who choose to continue the pregnancy must prepare for a child with significant care needs and high medical expenses. Despite aggressive postnatal treatment, nearly 14% of all spina bifida neonates do not survive past 5 years of age, with the mortality rising to 35% in those with symptoms of brainstem dysfunction secondary to the Arnold–Chiari malformation. While 70% of patients have an I.Q. above 80, only half are able to live independently as adults, even with adapted accommodations. The emotional and financial impact on the family and community is enormous.

In addition to motor and sensory deficits due to the spinal cord lesion, significant complications in MMC come from hydrocephalus and the Arnold–Chiari II malformation. Hydrocephalus, defined as any enlargement of the cerebral ventricles, occurs in more than 85% of patients with MMC. More than 80% of spina bifida patients require placement of shunts to prevent the neurologic and intellectual compromise that

Table 2
Criteria for fetal surgery.

1. Accurate diagnosis possible with exclusion of associated anomalies
2. Natural history of the disease is documented, and prognosis is established
3. Currently no effective postnatal therapy
4. In utero surgery proven feasible in animal models, reversing deleterious effects of the condition
5. Interventions performed in specialized multidisciplinary fetal treatment centers within strict protocols and approval of an Institutional Oversight Board with informed consent of the mother or parents

Fetal Surgery for Myelomeningocele (MMC) – the most severe form of Spina bifida

Spina bifida affects about 1,500 babies born each year in the United States

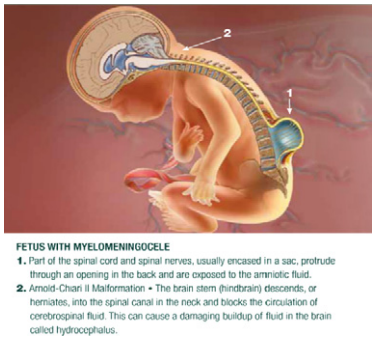

Fig. 1. The neural tube fails to close by 4–6 weeks gestation leading to spina bifida.