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Fetal Surgery for Congenital Diaphragmatic Hernia: The North American Experience

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The role for fetal surgery in treating fetuses with congenital diaphragmatic hernia (CDH) is unclear. Two decades of investigation have improved our understanding of the prenatal natural history, pathophysiology, and outcomes of these patients. During this same period, there have been advances in fetal surgery techniques including improvements in fetal monitoring, maternal–fetal anesthesia, tocolysis, and improved instrumentation to permit increased application of videoscopic approaches. Because of technical challenges, open fetal repair of CDH has been abandoned. Fetal tracheal ligation has shown promise, but a recently published prospective, randomized trial failed to show a benefit of fetoscopic tracheal ligation compared with expert postnatal treatment. Although there is evidence that postnatal outcomes for infants with this disease have improved with the adoption of gentilation ventilator management, high-frequency ventilation, and ECMO, there continues to be a subset of infants with severe CDH that die or suffer serious long-term morbidity despite advanced surgical care. The purpose of this article is to review issues related to prenatal diagnosis, patient selection, and outcomes for fetal surgery; and ultimately to assess whether there is a role for fetal surgery in treating fetuses with CDH.
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Congenital diaphragmatic hernia (CDH) remains a vexing clinical problem for all who care for these complex patients. It is one of the more common major birth defects: it is more than twice as common as childhood cancers, and 10 years ago had estimated annual health care costs that exceeded $230 million.[1-7] Despite significant advances in neonatal surgical care, the mortality and morbidity associated with this condition remain high.[1,3,5,8] It is frustration with these poor outcomes that has led to development of prenatal treatment strategies for this disease.

In one sense, the anatomic defect found in CDH is simple. Unfortunately, this hole allows the stomach, spleen, liver, and midgut to herniate into the chest and results in life-threatening pulmonary hypoplasia and pulmonary hypertension. Most evidence suggests that it is the viscera in the chest that causes these devastating effects in the developing lungs. Although the pathogenesis of this condition may be more complex with the diaphragm hole and pulmonary hypoplasia occurring as independent events, it is clear that reduction of the viscera and repair of the diaphragm defect is critical to improvement in pulmonary function and eventual survival.[9,10]

Theoretically, fetal surgery for this disease makes sense. If the viscera can be removed from the chest, and if the fetal lungs can be stimulated to grow at a time when the fetus depends on the placenta for gas exchange, then perhaps the outcome for this condition can be improved. There has been extensive experimental work which has proven the rationale and feasibility of in utero interventions for this condition. However, results from recent clinical trials have raised doubts as to what the role of fetal therapy for CDH should be.[11,12] The purpose of this article is to review the issues involved in prenatal treatment of CDH.

Prenatal Diagnosis and Stratification of Severity

To consider any fetal therapy, it is critical that: (1) we can accurately diagnose the condition and any associated anomalies that may have an impact on outcome; (2) we can reliably

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predict which individual fetuses will die or suffer serious long-term morbidity without fetal intervention; and (3) the procedure improves the outcome of the fetus with little to no maternal risk.

Since the late 1970s, CDH has been diagnosed before birth.[13] Before advances in ultrasound, amniography played a role in the diagnosis of this condition.[13-15] In today's practice, more than half of the infants with CDH are diagnosed before birth, and there are few false-positive diagnoses.[1,16-18] Delayed or intermittent herniation of viscera, lack of access to prenatal care, variability in prenatal ultrasound rates, and differences in ultrasound technique contribute to the lack of fetal diagnosis in some patients. At times it may be difficult to distinguish CDH from a cystic lung mass or other cystic lesions. In these patients, fetal MRI has been useful to enhance diagnostic accuracy and to further exclude associated anomalies.[19,20]

Outcomes for patients with CDH vary widely depending on when the disease is examined. Fetuses with CDH have lower survival rates than those for live born infants, or for infants presenting to a neonatal surgical center. This paradigm has been termed the "hidden mortality" by Harrison and colleagues,[21] and has been confirmed by multiple investigators.[1,3,5,8,17,22] Dillon and colleagues reviewed the outcomes from a large series of fetuses with CDH registered in the Northern Region Congenital Abnormality Survey in the United Kingdom.[3] Between 1985 and 1997, 201 fetuses were evaluated for diaphragmatic problems, of which 187 had congenital diaphragmatic hernia (14 had diaphragm eventration). From this cohort, 38 pregnancies were terminated, 26 of which had "multiple abnormalities," and 14 pregnancies (7%) were complicated by spontaneous miscarriage or stillbirth. The overall 1-year survival for this group of fetuses was 37%, but for live born fetuses the survival was 50%. Furthermore, for those live born babies with isolated CDH, the overall survival was 59%. In 2005, the same 59% survival was reported for a group of 22 fetuses with isolated CDH treated at a single obstetric and neonatology unit in Germany.[23] In addition, Cohen and colleagues from the Center for Fetal Diagnosis and Treatment at the Children's Hospital of Philadelphia (CHOP) reported 58% survival for a large group of live born fetuses with isolated CDH treated at that center. In that report, 174 patients with CDH, most of whom had prenatal diagnosis, were treated between 1996 and 2000. The overall survival, including fetuses with associated anomalies, was 43%. For those fetuses with isolated CDH ($n = 143$), the survival was 48.3%, and when the fetal deaths were excluded, the survival was 58%. For the 81 patients with isolated CDH that underwent surgical repair at this institution, the survival was 85%, thus confirming this notion of "hidden mortality."

The key to choosing appropriate patients for fetal intervention is to identify those that would not survive with postnatal therapy alone. There are multiple factors that have been proposed to correlate with the degree of pulmonary hypoplasia and poor fetal outcome, including reduced lung:thoracic transverse area ratio,[24] smaller lung size on fetal ultrasound,[16] abnormal fetal breathing characteristics based on nasal fluid flow parameters,[25,26] the degree of left ventricular hypoplasia,[27-34] or abdominal circumference below the third percentile.[35] Although polyhydramnios may be an indicator of worse outcome, it usually does not develop until later in gestation, at which time it is too late to consider alternative approaches.[3,36,37] Mediastinal shift and the presence of the stomach in the chest has been suggested as a poor prognostic indicator, but merely indicates left visceral herniation and does not necessarily prejudice survival.[8,38-40] Earlier prenatal identification of CDH may lead to an increase in the termination rate, but likely is not an important predictor of outcome.[28,37,41,42] In some fetuses with smaller diaphragm defects, the abdominal viscera may not herniate until later in pregnancy or even later in postnatal life. These babies appear to have decreased risk of pulmonary hypoplasia and better chance of survival. Although delayed herniation is one reason there is failure of ultrasound to identify CDH before 25 weeks gestation,[43,44] failure is more commonly due to inadequate equipment performance or scanning technique.[45]

It is clear that the prenatal detection of other major anomalies is associated with significantly worse outcome for fetuses with CDH, particularly if there are cardiac anomalies.[46-49] In one large series, 31 of 174 infants with CDH had major cardiac anomalies, including VSD ($n = 9$), isolated arch obstruction ($n = 4$), hypoplastic heart syndrome ($n = 4$), Tetralogy of Fallot ($n = 4$), transposition of the great arteries ($n = 2$), and others. Of this group, 7 (23%) suffered fetal demise, and the postnatal survival for live born infants was only 17% (4 of 24). Aside from the presence of chromosomal abnormalities on amniocentesis, the finding of cardiac defects, intrauterine growth retardation, renal hypoplasia, cystic hygroma colli, craniofacial abnormalities, and elevated amniotic fluid alpha-fetoprotein are suggestive of an associated syndrome. Nearly all patients with syndromic CDH die, and those that may survive usually have very poor developmental outcome.[49,50]

At present the best prognostic indicators for CDH are the presence or absence of liver herniation into the chest across the diaphragmatic defect ("liver up" versus "liver down" CDH) and sonographic measurement of the lung/head ratio. In a prospective study, the absence of liver herniation (liver-down) predicted 75% to 80% survival with either fetal or postnatal treatment[51] compared with historical survival of only 20% to 27% for fetuses with prenatally diagnosed CDH.[28,37] Moreover, a retrospective review of 48 patients with prenatally diagnosed CDH found 93% survival in the liver-down group versus 43% survival in the liver-up group.[52] These data suggest that the absence of liver herniation predicts a favorable prognosis, and most of these infants should do well with intensive postnatal therapy.

The right lung area-to-head circumference ratio (LHR) has been validated as a useful prognostic indicator, particularly in those fetuses with liver-up CDH.[46,53-55] It was described as an estimate of right lung area for fetuses with left-sided diaphragmatic hernia and is an estimate of the degree of pulmonary hypoplasia. LHR is determined on a transverse scan of the fetal thorax at the level of the four-chamber view of the fetal heart. It is calculated by multiplying the longest two