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Fetal Surgery for Congenital Diaphragmatic Hernia: A Surgery for the Next Millennium

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Introduction

Congenital diaphragmatic hernia (CDH) is still an unsolved problem. The disease which has been, for a long time, thought to be merely a hole in the diaphragm, appears to be an intriguing malformation with a poorly understood pathogenesis and a complex pathophysiology. CDH results in various degrees of pulmonary hypoplasia and severe persistent pulmonary hypertension of the newborn. Despite a continuous improvement in antenatal diagnosis and neonatal intensive care, the overall mortality rate for CDH is still reaching 60%. Experimental work during the past 20 years suggests that CDH is a disease of impaired lung development associated with, but not caused by, a structural defect of the diaphragm. Furthermore, there is increasing evidence that the lung in CDH is not only small in size but that it contains numerous disorders, e.g., surfactant deficiency, decreased anti-oxidant activity, increased vascular reactivity with decreased nitric oxide and increased endothelin 1 activity and left heart hypoplasia. Although an antenatal diagnosis of CDH is feasible by an ultrasound, a reliable predictor of pulmonary hypoplasia, the main prognostic factor in CDH, has to be investigated. Whilst modern therapeutic strategies such as high-frequency oscillatory ventilation, extracorporeal membrane oxygenation (ECMO), exogenous surfactant and in-

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haled nitric oxide, may be beneficial in selected subjects, most newborns with severe hypoplastic lungs will not survive despite these postnatal therapies. These newborns would gain some benefits from antenatal treatment directed to alter the lung growth early in utero to minimize pulmonary hypoplasia. Antenatal correction of congenital diaphragmatic hernia in the human fetus is an attractive theoretical possibility that might reverse pulmonary hypoplasia before it becomes too severe for post-natal survival. Factors which contribute to poor prognosis have to be established in order to identify those fetuses which are most likely to receive benefit from an antenatal therapy and those with a good prognosis in whom an antenatal surgery should not be attempted.

Antenatal ultrasonography of CDH reveals displacement of the heart towards the right and an absence of a normally positioned fluid-filled stomach on repeated examination. The peristalsis of chest contents or movements of abdominal contents into the chest on inspiration are more specific findings. A small abdominal circumference and a cystic or solid mass in the chest are only suggestive findings.[1,2]

The mortality for potentially correctable CDH diagnosed before birth ranges from 58% to 80%, despite optimal care presently available after birth including extracorporeal membrane oxygenation. This variation is attributable to an unknown magnitude of a "hidden mortality" derived from infants who die with CDH in utero or soon after birth and who have not been recognized before birth.[3,4,5]

Indications For Antenatal Therapy

Current inclusion criteria for antenatal therapy for CDH diagnosed in utero include:

1. A singleton in whom detailed sonographic examinations and a genetic study show no concomitant abnormality.[6]

2. Less than 30 weeks' gestation.[6]

3. The fetus has greatest definite risks of dying despite all conventional postnatal care, i.e.

3.1 Early diagnosis (before 25 weeks' gestation).[7,8,9]

3.2 A low lung-to-head ratio (LHR).[8,9,10] All neonates with an LHR of less than 0.6 die whereas the survival rate is 100% for those whose LHR is greater than 1.35. Those with an LHR between 0.6 and 1.35 have a survival rate of 61%.[9]

3.3 Liver herniation into the fetal thorax.[8,9,11] The ultrasonographic findings for liver herniation are bowing of the umbilical segment of the portal vein (portal sinus) to the left of the midline and coursing of portal branches to the lateral segment of the left hepatic lobe toward or above the diaphragmatic ridge.[11]

3.4 Stomach site. Babies with a thoracic stomach have a higher mortality and more frequently develop a significant persistent fetal circulation (PFC) than babies whose stomach is normally sited.[12,13]

3.5 Polyhydramnios.[3,7,13] Polyhydramnios is a common prenatal marker for CDH as well as a predictor for a poor clinical outcome.

4. The benefits for the mother and the fetus are weighed against the risk for the mother combined with the risk of fetal loss from the procedure. Although hysterotomy for fetal surgery can be accomplished without unduly endangering the mother's life and her future reproductive potential,[14] all future deliveries have to be done by Caesarean sections.[13]

The Development of Open Fetal Surgery

In the 1980s, the developmental pathophysiology of CDH was investigated in animal models. The experimental fetal repair of CDH in lambs restored the pulmonary arterial bed to normal.[15] In the 1990s, the surgical techniques for the hysterotomy and the fetal surgery were refined.[6]

Preoperative tocolysis begins with an administration of an indomethacin suppository. Intraoperative maternal care and monitoring techniques are the same as any major operations. After the maternal abdominal incision is completed, intraoperative ultrasonography is used to confirm the placental and fetal positions. The hysterotomy is performed parallel to and at least 6 cm away from the edge of the placenta. The absorbable staples[16] are applied in order to fuse an amniotic membrane to uterine walls and provide a haemostasis. Throughout the procedure, the condition of the fetus will be monitored by a pulse oximeter and an implanted radiotelemeter which continuously records the fetal electrocardiogram and temperature.[17,18] The lateral aspect of the fetus is exposed. Simultaneous thoracic and subcostal incisions are made.[6,19] A Gortex silo is then sutured to the edge of the subcostal incision. The herniated viscera are reduced into the silo. The diaphragmatic defect is closed with another patch. The fetus is then returned to the uterus. The staple line is excised and the hysterotomy is closed with continuous sutures to ensure this watertight repair. Warm saline with antibiotics is used to replace amniotic volume. The maternal laparotomy incision is closed in layers.

Although the technique of open fetal surgery is feasible, preterm labour is the Achilles's heel of fetal therapy.[7,14] The regimen of preoperative indomethacin, intraoperative deep halogenated inhalation anesthesia and postoperative indomethacin, magnesium sulfate and betamimetics, which was worked out in monkeys, has been proven to be an inadequate tocolysis for extensive procedures in human.[13] Although intravenous nitroglycerin is used intraoperatively and postoperatively as a potent tocolytic agent, it requires careful control to avoid serious complications.[13] Although halogenated inhalation agents provide satisfactory anesthesia for the mother and the fetus and achieve an intraoperative uterine relaxation, they can produce fetal and maternal myocardial depression. Moreover, indomethacin can constrict the fetal ductus arteriosus. After the operation finishes, all vital signs of the mother and fetal well-being are meticulously monitored. Fetal well-being and uterine activity are recorded externally by a tocodynamometer and by a radiotelemeter implanted at surgery. When the labour is controlled and the fetus is stable, the mother is transferred from the intensive care unit to an obstetric ward where radiotelemeter monitoring continues until discharge (usually after 1 week). Out patient monitoring and the tocolysis continue and fetal sonograms are performed at least weekly. Caesarean delivery is performed when membranes rupture or the labour cannot be controlled, usually before 36 weeks' gestation.

The early results of CDH repair in human were frustrating.[7,20] Twenty human fetuses were operated prenatally. Eight died at operation because attempts to reduce the herniated liver compromised the umbilical venous return. Three died in utero within 48 hours of repair. One died immedi-

ately after birth. Two were delivered prematurely and died subsequently. Other two fetuses who demonstrated a rapid growth of the lung in utero after surgery, had surprisingly good lung function after birth. Unfortunately, both died of nonpulmonary problems beyond the age of two weeks. Only four from twenty recorded in these early series survived.

Fetuses with herniation of the liver through a diaphragmatic defect have a high incidence of perioperative death. Attempts to reduce a herniated liver can result in a significant distortion of the fetal vasculature, leading to fetal death.[21] Liver herniation into the fetal thorax is an absolute contraindication for this open fetal surgery.[11,21] The latest report showed that three from four fetuses with CDH without liver herniation survived.[22] Because complete repair for fetuses with congenital diaphragmatic hernia with liver herniation in utero has been unsuccessful, a strategy of a temporary tracheal occlusion has been developed to gradually enlarge these hypoplastic lungs.[8]

Plugs The Lung Until it Grows (PLUG)

Fetal lungs normally produce fluid that flows through the upper airway into the amniotic fluid. In 1994, it was shown in fetal lambs that an obstruction of the flow of lung fluid expands the developing fetal lungs and propels the viscera from the chest, alleviating the pulmonary hypoplasia.[23] Antenatal tracheal occlusion increases a volume of the total lung, a volume of the parenchyma density, airspace within the parenchyma and gas exchange surface areas and reduces the herniated viscera.[23,24] The effect is greater when tracheal occlusion is performed early rather than late in gestation.[24] Although a tracheal occlusion increases lung growth by increasing cell divisions, it decreases surfactant protein synthesis by decreasing type II pneumocytes.[25] However, the surfactant-producing system can mature and catch-up later.[26] An experimental fetal tracheal occlusion by a translaryngeal placement of a compressible, water-impermeable polymeric foam was first tested in lamb models.[27]

The tracheal occlusion strategy requires the development of techniques to safely reverse the obstruction at birth. The Ex Utero Intrapartum Tracheoplasty (EXIT) is a technique in which the principles of fetal surgery (anesthesia for the mother and the fetus and maintenance of an umbilical circulation to support the fetus) are used during Caesarean delivery to allow the airway to be secured while the fetus remains on the maternal bypass.[13,28]

The first human temporary tracheal occlusion series was 8 CDH fetuses with liver herniation at 25 to 28 weeks' gestation.[28] Two patients received internal plugs and the other six had external clip applied. Although five showed a dramatic lung growth in utero with reversal of pulmonary hypoplasia documented after birth, four of them died of nonpulmonary causes. Only one from eight survived. A case has been reported of a human fetus with congenital diaphragmatic hernia who developed a hydrop fetalis from the profound increased intrathoracic pressure following a tracheal occlusion and died subsequently.[29]

Fetal Endoscopic ("Fetendo") Surgery

Despite recent advances in fetal surgery, preterm labour remains a major problem directly related to the large uterine incision required for fetal

exposure. Fetal endoscopic surgery ("Fetendo") obviates the need for a large uterine incision and may reduce the overall risks of fetal surgery by causing less uterine trauma and ultimately less preterm labour.[30] Adaptation of this current, minimally invasive surgical technique to the PLUG technique allows the treatment of CDH without opening the uterus. In 1996, the video-fetoscopic, intrauterine technique of tracheal occlusion (called Fetendo-PLUG) was first developed in four fetal lambs[31] and one year later, a 30-week-old human fetus with congenital diaphragmatic hernia was the first to be managed with this method.[32]

The concise technique of Fetendo-PLUG will be described.[31,32] After maternal laparotomy is performed and the uterus is exposed, a 5-mm balloon-cuffed trocar is introduced through a uterine puncture directly into the fetal oral cavity. A bronchoscope (with an instrument channel) is used to endoscopically intubate the trachea through the trocar. The trocar is advanced over the bronchoscope and its balloon is inflated to provide secure tracheal access below the vocal cords. Subsequently, a 10-mm trocar is placed directly over the fetal neck and the amniotic space is expanded with warm saline. Another 5-mm laparoscope is introduced. Under simultaneous, dual video-fetoscopic (endotracheal and endoamniotic) visualization, a 1-mm nephrostomy puncture wire is advanced along the instrument channel of the bronchoscope, through the anterior wall of the trachea and fetal neck into the amniotic space, then through the uterine wall to the outside. Withdrawal of the bronchoscope over the wire leaves a 5-mm endotracheal "trocar channel" in place. A compressed, gelatin-encapsulated, polymeric foam (outer diameter 4.8 mm) will be delivered by a suture attachment to the guide wire and inserted along this trocar channel. Once the foam is in its final endotracheal position, dissolution of the gelatin membrane allows the expansion of the foam to produce a water impervious tracheal occlusion.[31]

Harrison, et al,[8] compared the outcome of the poor-prognosis patients (liver herniation and a low LHR) treated by one of three methods: (1) standard postnatal care, (2) fetal tracheal occlusion via open hysterotomy and (3) the video-fetoscopic (Fetendo) technique of tracheal occlusion without hysterotomy. Thirteen fetuses receiving a standard postnatal treatment including extracorporeal membrane oxygenation had a survival of 38%. The survival rate for 13 open fetal tracheal occlusion patients was 15% whereas eight who underwent fetoscopic tracheal occlusion had a survival of 75%. All but one Fetendo clip patients had their lungs enlarged. In contrast, only 5 from 13 fetuses who received an open tracheal occlusion demonstrated lung growths.

Antenatal Dexamethasone

Antenatal glucocorticoid therapy increases lung maturation[33] and prevents pulmonary artery structural changes[34,35] in rats with nitrofen-induced congenital diaphragmatic hernia. However, there is no experimental studies in human subjects.

Surgical treatment of human congenital diaphragmatic hernia is currently at a stage similar to that of the orthotopic liver transplantation before the availability of cyclosporin. More basic and clinical research has to be done to improve the survival of these antenatally treated fetuses.

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