

## Current Management of Congenital Diaphragmatic Hernia

a report by

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### Introduction

Congenital diaphragmatic hernia (CDH) affects nearly one in 2,400 live births in the US each year.<sup>1</sup> The care of these patients who are diagnosed with CDH remains frustrating despite recent advances in medical and surgical treatment in the newborn intensive care units (ICUs). In 1984, the estimated mortality rate of infants who presented for treatment within the first 24 hours of life with CDH was estimated at approximately 50%.<sup>2</sup> Other centers report survival rates of 35% to 58%.<sup>3</sup> This high mortality has been attributed to pulmonary hypoplasia, pulmonary hypertension, surfactant deficiency, left ventricular dysfunction, congenital abnormalities, and iatrogenic lung injury associated with aggressive mechanical ventilation.<sup>4-9</sup> The annual cost of healthcare for infants with CDH has been estimated to be at least US\$230 million.<sup>10</sup> Less severely affected infants survive with modern postnatal surgical care, although infants that are severely affected often die despite all interventions.<sup>11</sup> The possibility of salvaging severely affected infants that have isolated diaphragmatic hernia using prenatal treatment has motivated decades of research aimed at better defining the natural history of CDH and determining prognostic factors for survival.

### Prenatal Diagnosis and Natural History

An accurate prenatal diagnosis of CDH and the identification of associated anomalies are essential. This must be done to optimize the possibility of *in utero* surgery, medical and surgical treatments delivered postnatally, as well as the location of delivery in a high technology tertiary center with the availability of extracorporeal membrane oxygenation (ECMO), inhaled nitric oxide (iNO), high frequency ventilation (HFOV), and surfactant replacement therapy.

Obtaining a prenatal ultrasound has evolved as the 'standard of care'. This prenatal ultrasound is usually obtained before 25 weeks of gestation and allows for an accurate diagnosis in the majority of cases. There is a dynamic variation in the amount of herniated viscera, as well as the amount of time that the intestines are present in the chest. These variables account for the spectrum of severity that is seen after birth.

The ultrasound is usually adequate to make the diagnosis of an isolated CDH. Using color flow Doppler imaging of the umbilical and portal veins can detect liver herniation *in utero* by following the vessels above the diaphragmatic defect.<sup>12</sup> This prenatal ultrasound is usually combined with amniocentesis to exclude chromosomal abnormalities. If necessary, a fetal magnetic resonance image (MRI) can be performed for confirmatory diagnosis.

Early detection of this diagnosis allows the family to make informed decisions regarding possible pregnancy interruption, performing fetal surgery, and allowing the birth to take place in an appropriate center for aggressive intervention.

### Predictors of Survival

Prenatally diagnosed CDH can be stratified into two categories by prognostic indicators. Those that are amenable to aggressive postnatal care are labeled with a 'good' prognosis and those who are unfavorable to aggressive care are labeled as 'poor' prognosis. The infants with poor prognosis were the patients who were previously felt to be potential candidates for fetal surgery.<sup>13</sup>

The two most promising prognostic indicators are the presence or absence of liver herniation into the chest across the diaphragmatic defect and sonographic measurement of the lung-to-head ratio (LHR). There is a 93% survival in the liver-down group but only a 43% survival in the liver-up group.<sup>14</sup> However, the best predictor of survival is the LHR. The LHR is determined by obtaining a transverse axial image through the chest at the level of the four-chamber view of the heart at a gestational age of 24 to 26 weeks. An LHR of <1.0 is associated with 100% mortality, whereas an LHR of greater than 1.4 is associated with no mortality. An LHR between 1.0 and 1.4 correlates with a mortality of approximately 60%. Several studies have confirmed the usefulness of the LHR in predicting postnatal survival.<sup>15,16</sup>

As the capability to make the diagnosis prenatally has improved, a number of prognostic indicators for survival have evolved. These include the presence of polyhydramnios,<sup>17</sup> prenatal diagnosis at <25 weeks



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gestation, prematurity, the presence or absence of major congenital anomalies, the presence of an intrathoracic stomach,<sup>18,19</sup> small lung to thorax transverse area ratio,<sup>20</sup> and a small left ventricular mass.<sup>21,22</sup> These have all been associated with a poor prognosis. The most widely accepted and reliable predictor remains the LHR.

### Fetal Surgery

Repair of the CDH with a two-step fetal procedure relied on an open hysterotomy that led to significant morbidity and mortality. The incidence of pre-term labor and delivery with a hysterotomy were unaccepted. This prompted years of research into techniques for placement of devices that were less traumatic to the gravid uterus.

One such device was video-assisted fetal endoscopy (FETENDO) that allowed tracheal occlusion to be performed endoscopically without the need for a maternal hysterotomy. The pediatric surgeons initially used two titanium clips to completely occlude the trachea. This procedure required long operative times and many ports. This technique proved too damaging to the trachea and has been abandoned.<sup>23</sup> The most recent approach involves placement of an intratracheal balloon. Removal of the balloon and delivery of the fetus is performed using the *ex utero* intrapartum treatment (EXIT) strategy.<sup>24</sup> The length of time that the trachea needs to be occluded is still in question.

After a retrospective analysis of the patients who had received temporary tracheal occlusion to enlarge the hypoplastic lung, a decision was made to evaluate this new therapy in a National Institutes of Health (NIH)-sponsored prospective, randomized trial. This trial took place at the University of San Francisco (UCSF) and the Children's Hospital of Philadelphia (CHOP). Inclusion criteria included women carrying fetuses that were between 22 and 27 weeks of gestation and that had severe, left-sided congenital diaphragmatic hernia with liver herniation and an LHR below 1.4. The randomized fetuses had no other detectable anomalies and were randomly assigned to fetal endoscopic tracheal occlusion or standard care. The primary outcome was survival at the age of 90 days. Secondary outcomes were measures of maternal and neonatal morbidity.<sup>25</sup>

After randomization of 24 women, enrollment was stopped because of the unexpectedly high survival rate with standard care and the conclusion of the data safety monitoring board that further recruitment would not result in significant differences between the groups. Eight of 11 fetuses (73%) in the tracheal-occlusion group and 10 of 13 (77%) in the group that received standard care survived to 90 days of age ( $p=1.0$ ). Premature rupture of the membranes and pre-term

delivery were more common in the group receiving intervention than in the group receiving standard care. The gestational age of the intervention group was  $30.8 \pm 2$  weeks versus  $37.0 \pm 1.5$  weeks ( $p=0.001$ ). The rate of neonatal morbidity did not differ between the groups.<sup>25</sup> Therefore, this NIH trial was stopped in the early phase of enrollment.

Two potential explanations for the high survival rate in the control group are proposed. One reason is the almost universal screening of pregnant women with prenatal ultrasounds that would identify all CDHs prenatally and lead to their delivery at selected tertiary care centers – therefore improving these selected tertiary centers' overall survival statistics.<sup>26</sup> Another potential reason why antenatal intervention may not result in a better outcome than conventional therapy is that any potential benefit may be negated by substantial fetal morbidity associated with the surgical procedure itself. Most pregnancies subjected to antenatal fetal surgery end in significantly pre-term delivery of infants who could not be placed on ECMO. pre-term delivery usually occurs within six weeks after the procedure.<sup>26</sup> Indeed, there may be a group of fetuses that might benefit from antenatal therapy, but such a group cannot be reliably identified. To improve survival, new therapies need to be developed.

### New Therapies

This improvement in survival is related to decreasing iatrogenic injury to the respiratory epithelium. Some centers in the US have adopted similar ventilator strategies, which minimizes volutrauma. In these centers, the premise of ventilator management is 'low rate' ventilation as the first mode of ventilation. An example of initial settings are  $FiO_2=1.0$ ; intermittent ventilatory rate (IMV)=40; peak inspiratory pressure (PIP)=20; positive end expiratory pressure (PEEP)=5; flow=5–7l/minute; and inspiratory time (IT)=0.5 seconds. The ventilation is not synchronized. If this is unsuccessful, a high frequency positive pressure ventilation is used with the following settings: IMV=100; IT=0.3 seconds; gas flow=10–12l/minute; and PEEP=0.

The goals of this strategy are to avoid paralysis, use minimal sedation, and avoid hyperventilation to induce a respiratory alkalosis. Other useful caveats are the weaning of pressure and rate as oxygenation and carbon dioxide improve. Infants on a rate of 100 breaths per minute (BPM) are weaned directly to a rate of 40 and extubation occurs at a rate of 10 BPM. The PIP is adjusted as needed based on chest excursion – never to exceed 25cm of water pressure. Each ventilator change is given 30 minutes to evaluate the success of the maneuver. The survival rates using these ventilatory strategies are between 85% and 93%.<sup>27</sup> If conventional

mechanical ventilation is unsuccessful, HFOV is initiated. Lack of a response would lead to the use of iNO and preparation for ECMO.

### Long-term Outcomes

There are many reports regarding adverse long-term outcomes in patients with CDH. Adverse outcomes include neurocognitive and neuromotor developmental delays, gastroesophageal reflux disease (GERD), chronic lung disease (CLD), hypoplastic left heart syndrome (HLHS) and right ventricular hyperplasia, failure to thrive, reherniation, and scoliosis, as well as chest wall abnormalities.

The most common neurocognitive and neuromotor deficits are cerebral palsy, mental retardation, and developmental delays. Some factors that may contribute to these problems include variable degrees of perinatal asphyxia, additional hypoxic insults, toxic medications, iatrogenic factors, i.e. use of ECMO, paralysis, and hyperventilation to induce a respiratory alkalosis.

There is a situation of the gastroesophageal angle and partial malrotation with duodenal-jejunal ectasias and associated motility disorders with GERD and delayed gastric emptying. The incidence is not known but estimated to range from 20% to 89%.

Some pediatric surgeons do not feel that many of these infants need surgery since it is not primarily a problem of reflux and they can be managed medically. They also doubt that many of these patients need a gastrostomy tube or an anti-reflux procedure such as a Nissen or THAL procedure. Many of these infants need evaluation with a 24-hour pH probe and some will develop Barrett's esophagitis.

A small number of the infants with CDH who require continuous ventilator support will survive. Despite postnatal growth of the alveoli in the lungs and associated blood vessels, it is a slow and insidious process. The major pulmonary problem seen in infants with CDH is chronic lung disease (CLD) with a reported 62% incidence. CLD may be secondary to a combination of the effects of primary lung hypoplasia, dysplasia from barotraumas/volutrauma and oxygen toxicity, chronic aspiration, and the development of reactive airway disease. Cardiac function usually returns to normal by the time the infant is ready for discharge. Those infants with residual oxygen requirement probably have some degree of pulmonary hypertension and that is a poor prognostic sign for survival.

Somatic growth failure results in failure-to-thrive (FTT) of the infant. This phenomenon is an increasingly recognized morbidity of CDH. This may

start *in utero* and is related to the cardiovascular insufficiency or other compressive phenomena. Also, it is very difficult to achieve adequate caloric support in the face of GERD and CLD.

Other potential neurodevelopmental morbidities include sensorineural hearing impairment that has been reported as high as 21%. Passing the initial hearing screen, whether automated auditory brainstem response or otoacoustic emissions, is only the first step in the evaluation of these infants' hearing. They must be followed for the development of progressive hearing impairment.

### Potential Therapies

Potential therapies for the future include partial liquid ventilation. The use of perfluorocarbons for lung distension in cases of severe CDH with superimposed conventional gas ventilation is one such therapy. Because of the US Food and Drug Administration (FDA) ban on trials in the US using perfluorocarbons, studies are on-going in Scotland. Dr Walker et al. used perfluorodecalin in six infants being treated with ECMO. They report an increase in the size of the affected lung by 272% radiographically. There was also an increase in the size of the contralateral lung by 51%. All patients were repaired on ECMO and all survived.<sup>29</sup>

In the future, routine use of fetal MRI for stratification may become the standard-of-care in order to prepare the family for the difficult decisions that lie ahead. Strong consideration should be given to the use of antenatal steroids at 37.5 weeks to assure an adequate surfactant pool. Many lung growth factors may become available in the future such as growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), and transforming growth factor beta (TGF- $\beta$ ).

### Conclusions

There are many surgical approaches to the repair of CDH including fetal surgery, minimally invasive surgery, delayed repair, and the appropriate use of ECMO to support CDH patients until the operative procedure. However, fetal surgery is currently not the answer as accurate predictors of survival have not been identified. Aggressive over-ventilation is lethal to these patients and should be avoided if possible. Lung protection from barotraumas/volutrauma is paramount and can improve survival statistics and decrease morbidities. If the CDH team accepts this standardized approach to the use of conventional mechanical ventilation, hope exists for improved outcomes until new therapies are evaluated and accepted for general use. There are many surgical approaches to the repair of CDH including fetal surgery, minimally invasive surgery, delayed repair, and the appropriate use of ECMO to support CDH. ■

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