Congenital Diaphragmatic Hernia: The Surgeon’s Perspective

Erik D. Skarsgard, MD* and Michael R. Harrison, MD†

OBJECTIVES
After completing this article, readers should be able to:

1. Describe other conditions that should be sought following prenatal diagnosis of congenital diaphragmatic hernia (CDH).
2. Describe the procedures that optimize the outcome for CDH upon delivery of the infant.
3. Delineate the two most significant prenatal ultrasonographic predictors of postnatal mortality from CDH.
4. Describe the standard of care for those who have CDH that can be managed without extracorporeal membrane oxygenation.
5. Delineate the overall survival rate associated with CDH diagnosed antenatally.

Introduction
Congenital diaphragmatic hernia (CDH) is a simple anatomic defect in which a hole in the diaphragm allows abdominal viscera to herniate into the thorax. The physiologic consequences of this defect may be mild and minimally symptomatic at birth, but often they are severe and may result in neonatal mortality, usually from irreversible pulmonary hypoplasia or severe persistent pulmonary hypertension. Prenatal diagnosis has facilitated the early recognition of this condition, and much has been learned about the “natural history” of fetal diaphragmatic hernia that has allowed recent identification of accurate fetal prognostic indicators of neonatal outcome.

Incidence and Associated Malformations
The incidence of CDH is estimated to be 1 per 2,000 to 5,000 births. Its incidence in stillborns is less well studied, but it is important in understanding the contribution of associated congenital defects to the so-called “hidden mortality” that is associated with prenatal diagnosis. Population-based studies of CDH among liveborn, stillborn, and spontaneously aborted fetuses suggest that approximately 30% of fetuses who have CDH will die before birth, usually from chromosomal or lethal nonpulmonary malformations. Even among those fetuses who have CDH and survive to birth, the incidence of associated life-threatening malformations is higher in those in whom the diagnosis is made antenatally, especially if it is made before 25 weeks’ gestation. The reason for this observation is unclear, but an earlier gestational event that leads to the development of CDH may contribute to malformations in other organ systems as well.

Excluding conditions that are considered to be part of the “CDH-syndrome” (pulmonary hypoplasia, patent ductus arteriosus, patent foramen ovale, and malrotation), approximately 40% of liveborn patients who have CDH have one or more associated anomalies. Approximately 60% of these anomalies are cardiac, 23% are genitourinary, 17% are gastrointestinal, 14% involve the central nervous system (CNS), and 10% are chromosomal. The most commonly recognized cardiac malformation is referred to as “heart hypoplasia” and represents a spectrum of malformation that ranges from hypoplastic left heart syndrome to a structurally normal heart that is globally hypoplastic (defined as an autopsy finding of heart weight one standard deviation below the mean of controls matched by body weight). The diagnosis of heart hypoplasia appears to be a high independent predictor of mortality, yet it is a difficult diagnosis to make other than at autopsy. Therefore, its utility as a prognostic indicator of survival in the fetus or neonate who has CDH remains unclear.

Pathophysiology
The development of a dome-shaped musculotendinous partition between the thoracic and abdominal cavities involves an incompletely understood, complex process of embryologic tissue interaction. The septum transversum is a mesodermal mass located cranial to the pericardial cavity. At approximately the fourth or fifth week of gestation, it forms an incomplete partition between the thoracic and abdominopelvic cavities and fuses dorsally with the dorsal mesentery of the esophagus. Simultaneously, the pleuroperitoneal membranes invaginate from lateral body wall mesenchyme and fuse with the mesentery of the esophagus and the septum transversum ventrally, thereby defining the pleuroperitoneal canals. The bilateral pleuroperitoneal canals remain open until the end of the sixth week, when continued pleuroperitoneal membrane growth and medial fusion with the septum

ABBREVIATIONS
CDH: congenital diaphragmatic hernia
CNS: central nervous system
CT: computed tomography
ECMO: extracorporeal membrane oxygenation
iNO: inhaled nitric oxide
LHR: lung-to-head ratio
OI: oxygenation index
PLV: partial liquid ventilation
PPHN: primary pulmonary hypertension of the newborn
TLV: total liquid ventilation
transversum obliterates these canals and completes the intact diaphragm, which subsequently becomes muscularized. During the ninth to twelfth weeks, as the pleural cavities expand, muscle from the lateral body wall invaginates into the diaphragm, forming a peripheral muscular rim.

Failure of formation or fusion of one of the pleuropertitoneal membranes results in a posterolateral diaphragmatic defect that often is referred to as the foramen of Bochdalek. This defect occurs five times more frequently on the left side than the right, probably because of earlier closure of the right pleuropertitoneal canal than the left. If the pleuropertitoneal canal remains open when the intestines return to the abdomen from the umbilical cord during the tenth week, the abdominal viscera move freely into the thoracic cavity. If the pleuropertitoneal canal closes but fails to become muscularized, a hernia with a sac results, as is seen in 10% to 15% of patients who have CDH.

Animal models of CDH have demonstrated that in utero compression of developing fetal lungs by herniated abdominal viscera impairs pulmonary growth and maturation, resulting in pulmonary hypoplasia, which can be quantified by histologic, biochemical, and pulmonary morphometric techniques. There is some debate about whether pulmonary hypoplasia is a secondary phenomenon caused only by visceral herniation or whether it might represent primary pulmonary maldevelopment, with the diaphragmatic hernia being a secondary phenomenon.

Whatever its cause, pulmonary hypoplasia, which usually is a bilateral process, even in unilateral CDH, results in alveolar hypoplasia and a distinctly abnormal pulmonary vascular bed. Arterial branches are reduced, and there is a medial thickening in the small preacinar and intra-acinar arterioles. The physiologic consequence of this abnormality in pulmonary vasculature is an increase in pulmonary vascular resistance, which contributes to the development of persistent pulmonary hypertension, arguably the principal determinant of mortality in CDH. Another contributing factor appears to be a hyperreactivity to known stimuli of pulmonary vasoconstriction, including hypoxia, acidosis, hypothermia, and stress. Alterations in the levels of various cellular mediators (nitric oxide, endothelins, prostaglandins, leukotrienes, catecholamines, and the renin-angiotensin system) have been implicated in this process, and it is hypothesized that the vasculature of CDH lungs have an exaggerated response to such stimuli.

Prenatal Diagnosis

CDH may be diagnosed ultrasonographically during routine obstetric screening or during investigation of polyhydramnios, which is reported to complicate up to 80% of pregnancies in which CDH occurs. The accuracy of prenatal diagnosis varies, depending on the site of the lesion and the presence of corroborating criteria such as mediastinal shift and abnormal fetal abdominal anatomy. The diagnosis is suggested strongly by the presence of a fluid-filled stomach or intestine at the level of the four-chamber view of the heart (Fig. 1). The absence of a fluid-filled stomach in the abdomen or the presence of liver (confirmed by Doppler vascular flow) in the thorax also increases the likelihood of the diagnosis.

The association of polyhydramnios with CDH is believed to result from a kinking of the distal esophagus caused by translocation of the stomach into the chest. This effectively obstructs fetal swallowing, resulting in polyhydramnios, and in some instances, a very small fetal stomach that may be difficult to see in either the chest or abdomen. Certain fetal lung lesions (sequestration, congenital cystic adenomatoid malformation) may cause a mass effect with mediastinal shift that could be difficult to differentiate from CDH, particularly if the “mass” bears a ultrasonographic similarity to echo-free bowel. Herniated abdominal contents associated with right-sided CDH can be difficult to identify because of subtle differences in echogenicity between fetal liver and lung.

Prenatal Care

Once a prenatal diagnosis of CDH has been made, other congenital anomalies, particularly those affecting the cardiovascular and central nervous systems, should be sought. Fetal karyotype should be determined by amniocentesis or chorionic
villus sampling. If the diagnosis of CDH is made before 24 weeks’ gestation, identification of a second major, life-threatening malformation or chromosomal aberration may lead the parents to consider elective termination of the pregnancy. Most centers offer antenatal counseling to assist families with decisions relating to continuation of pregnancy, ongoing prenatal and postnatal care, and occasionally consideration of fetal intervention. This involves meeting with representatives from neonatology, surgery, perinatology, and genetics and facilitation through parental education of a treatment algorithm that is appropriate for that family. For a fetus who has CDH, a plan for maternal delivery at a tertiary perinatal center offering all advanced strategies for respiratory failure, including extracorporeal membrane oxygenation (ECMO), usually is most appropriate. A spontaneous vaginal delivery should be anticipated unless obstetric issues dictate otherwise.

The role of in utero surgery for CDH remains controversial. However, the recent identification of new and reliable ultrasonographic predictors of postnatal mortality and the evolution of a minimally invasive surgical technique justifies in utero surgery for CDH as a reasonable treatment option for select fetuses who have essentially no chance of survival despite optimal postnatal care.

**Postnatal Diagnosis**

The presentation of CDH after birth is determined primarily by the severity of the pulmonary hypoplasia and pulmonary hypertension. The most severely affected babies will be symptomatic with their first breath, and most infants will develop symptoms within the first 24 hours of life. Classically, these babies are born with a scaphoid abdomen and develop progressive respiratory distress as swallowed air causes intestinal distension and worsening lung compression and mediastinal shift. If the mediastinal compression is severe enough to compromise venous return, they may develop poor perfusion and hypotension. The diagnosis is confirmed by a chest radiograph that demonstrates bowel loops within the chest (Fig. 2). A nasogastric tube should be placed immediately to locate the gastric bubble and decompress the intestines.

Occasionally, a large, basal multicystic lung lesion such as a congenital cystic adenomatoid malformation will have the appearance of a CDH on plain radiography. In these instances, ultrasonographic visualization of an intact diaphragm or computed tomographic (CT) scan of the chest may be necessary. Diaphragmatic eventration may be associated with birth trauma or anterior horn cell neuropathy (Werdnig-Hoffman disease) and can be diagnosed by ultrasonography or fluoroscopic demonstration of paradoxical diaphragmatic excursion.

Once the diagnosis of CDH has been confirmed, a careful search for associated anomalies should be performed with renal and cranial ultrasonography, echocardiography, and karyotyping.

Although most patients who have CDH present within the first day of life, 10% to 20% present later with recurrent respiratory distress, chronic pulmonary infection, or acute gastrointestinal symptoms caused by gastric volvulus or intestinal obstruction.

**Preoperative Care**

The basic tenet on which postnatal care for CDH is based is the understanding that pulmonary hypoplasia and pulmonary hypertension caused by CDH represent a physiologic emergency, not a surgical one. Initial therapy should be directed toward hemodynamic stabilization and respiratory support, with avoidance of hypoxemia and acidemia and minimization of iatrogenic lung injury.

**RESUSCITATION AND MONITORING**

Endotracheal intubation should be performed routinely on all patients who have CDH diagnosed prenatally and in all but the least symptomatic of patients presenting after birth. A nasogastric tube should be placed to minimize intestinal distension within the thoracic cavity. Arterial and venous access should be achieved through the umbilicus, and fluids (crystalloid, colloid, and...
blood) and inotropes (dopamine or dobutamine) administered to support blood pressure and perfusion.

In addition to the umbilical arterial line, which is postdural, it is useful to have a preductal monitor (either a right radial arterial line or right upper extremity pulse oximeter probe) as well. The oxygen saturation gradient allows trending of the right-to-left shunt fraction and offers an estimate of the severity of pulmonary hypertension. The preductal blood gas measurement may offer some prognostic information about the severity of pulmonary hypoplasia by reflecting the capacity of the lung to exchange gas. It has been suggested that babies who have CDH and cannot achieve fully saturated preductal blood and a P\textsubscript{a}CO\textsubscript{2} of less than 50 torr in the setting of optimal conventional ventilatory therapy have pulmonary hypoplasia that is incompatible with life. It is very important to avoid systemic hypotension, which may lead to right-to-left shunting in the presence of pulmonary hypertension.

Acidemia is predominantly metabolic (related to hypoperfusion) and should be corrected with administration of fluids and bicarbonate. Stress is considered a stimulus of pulmonary hypertension. The right-to-left shunting in the presence of hypotension, which may lead to right-to-left shunting in the presence of pulmonary hypertension.

The fundamental question appears to be whether nearly term hypoplastic CDH lungs mimic premature lungs in terms of endogenous surfactant phospholipid secretion and maturation and in their response to the administration of exogenous surfactant.

Data from sheep and rat models of CDH suggest that these lungs are deficient in surfactant, but human studies of surfactant phospholipids in amniotic fluid yield conflicting data regarding fetal lung maturity. A recent study of surfactant composition of bronchoalveolar lavage fluid failed to demonstrate a difference between infants who had CDH and were ventilated, those who received ECMO, and age-matched controls. Reports of empiric exogenous surfactant therapy for CDH are anecdotal and without demonstrated benefit.

There is some evidence that infants who have CDH and receive ECMO may develop a secondary surfactant deficiency compared with those who do not have CDH, which may justify delaying administration of exogenous surfactant until after ECMO therapy.

**SURFACTANT**

The therapeutic role of exogenous surfactant in the postnatal management of respiratory failure associated with CDH remains uncertain. The fundamental question appears to be whether nearly term hypoplastic CDH lungs mimic premature lungs in terms of endogenous surfactant phospholipid secretion and maturation and in their response to the administration of exogenous surfactant.

**SURVEY STRATEGIES**

The goals of ventilation for the infant who has CDH are to: 1) achieve acceptable postductal oxygen saturation to meet the tissue’s metabolic needs, 2) avoid severe hypercarbia and respiratory acidosis, and 3) avoid iatrogenic lung injury. The level of ventilatory support needed is determined largely by the pre-existing pulmonary hypoplasia and, to a lesser degree, by pulmonary vascular reactivity.

A standard approach is to begin with pressure-limited conventional mechanical ventilation using a combination of high rate and modest mean airway pressure in an attempt to achieve postductal blood gases that have near-normal pH and P\textsubscript{a}CO\textsubscript{2} measurements and a P\textsubscript{a}O\textsubscript{2} of 50 torr. Although the favorable effects of hypocarbia and alkalemia on pulmonary vascular tone are well known, many centers have adopted ventilatory strategies that avoid extreme hyperventilation in attempts to induce hypocarbia and alkalemia because of the risks of iatrogenic lung injury. If conventional ventilation fails to meet the goals of oxygenation and ventilation, high-frequency techniques using either jet ventilation or high-frequency oscillatory ventilation may be required. Both modalities are effective at removing CO\textsubscript{2} with reduced risk of barotrauma, although neither has been shown to be effective in improving the overall outcome of neonates who have CDH.

**NITRIC OXIDE**

Nitric oxide mediates smooth muscle relaxation by liberating cyclic guanosine monophosphate (cGMP) from vascular endothelium. Because of its diffusion characteristics, it is delivered easily to the pulmonary vasculature via blending with the inspired gases of a ventilator circuit and, therefore, theoretically would appear to be an ideal therapy for pulmonary hypertension associated with the pulmonary hypoplasia of CDH. Inhaled nitric oxide (iNO) has been evaluated clinically, and its ability to improve and sustain oxygenation in pulmonary hypertension appears to be disease-related, with the best results observed in patients who have primary pulmonary hypertension of the newborn (PHPH). The responsiveness of infants who have CDH to iNO has been generally disappointing, with only anecdotal success reported.

**EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)**

ECMO, which has been used to treat neonatal respiratory failure since the early 1980s, remains the cornerstone of rescue therapy for infants who have CDH and respiratory failure refractory to conventional and high-frequency modes of ventilatory support. It is important to remember that ECMO provides a means of maintaining oxygen delivery only temporarily, and its salvage rate depends on the reversibility of the pathologic factors that led to respiratory failure within the time frame that ECMO can be used. Although the pulmonary hypoplasia associated with CDH can be “outgrown”, the time required for this adaptive process often exceeds that provided by ECMO bypass. This accounts for the significant differences in survival observed between patients who have CDH and those who have more rapidly reversible causes of respiratory failure, including PPHN, meconium aspiration syndrome, and sepsis.

Two types of ECMO bypass can be achieved by surgery performed in the neonatal intensive care unit. Venoarterial ECMO requires placement of an arterial inflow cannula into the transverse aortic arch via the right common carotid artery and a venous outflow cannula into the right atrium via the right internal jugular vein (Fig. 3). With this tech-
Circuit pump.

Systemic oxygen delivery is facilitated through the carotid cannula, and warmed and returned to the infant by gas exchange. The saturated blood is circulated through a membrane lung for oxygenation and a conversion to peripheral oxygenation, and recirculation within an atrium that is deformed and angulated by mediastinal shift, which leads to inadequate oxygenation and a conversion to venoarterial bypass. However, as experience with this technique has increased, the conversion rate within ECMO centers dedicated to venovenous bypass has decreased to acceptable levels.

It is difficult to identify uniform criteria for initiation of bypass in infants who have CDH and respiratory failure because of the inherent nonuniformity of “failed conventional mechanical ventilation” between institutions. It is perhaps easier to acknowledge a few exclusion criteria for ECMO. Most centers would agree that infants who have CDH and other major congenital anomalies (cardiovascular, CNS, chromosomal), gestational age less than 32 weeks, or a pre-existing hemorrhagic CNS injury should not be offered ECMO. The issue of differentiating those who have CDH and pulmonary hypoplasia that is not compatible with survival from those who have severe (but survivable) pulmonary hypertension is a topic of frequent debate. Some authors have hypothesized that an inability to achieve 100% oxygen saturation of preductal blood argues against the infant having survivable pulmonary hypoplasia, and on this basis, ECMO therapy should be offered selectively. Most centers have adopted inclusion criteria for ECMO that consider the infant’s postductal PO₂ measurement (Pao₂) relative to the mean airway ventilatory pressures (MAP) and inspired oxygen concentration (FIO₂) necessary to achieve that Pao₂. The oxygenation index (OI) is computed according to the formula:

\[ OI = \frac{(MAP \times F_{IO_2} \times 100)}{Pao_2} \]

An OI of greater than 40 on consecutive blood gas determinations generally is considered an indication for ECMO cannulation.

**Surgery**

**TIMING OF REPAIR**

As our understanding of pulmonary hypoplasia and pulmonary hypertension has evolved, CDH has become a physiologic emergency rather than a surgical one. Historically, infants who had CDH were rushed to the operating room under the (false) belief that decompression of the lungs by reduction of the abdominal viscera offered the greatest chance for survival. Usually, after a brief “honeymoon” period, progressive hypoxemia would develop as increased pulmonary vascular resistance led to right-to-left vascular shunting and accelerated respiratory deterioration. The realization that early surgical repair was associated with unfavorable changes in lung compliance and gas exchange resulted in the rationale for a period of preoperative stabilization and delayed surgical repair.

The data supporting delayed surgical repair of CDH are not uniform. A number of centers have reported improved survival rates following adoption of this approach compared with historical “early surgery” controls; others have reported no difference. Two prospective randomized studies have failed to demonstrate a survival advantage to delayed repair. It is important to note, however, that because no study has demonstrated a decrease in survival associated with delayed surgery, this approach (with its potential physiologic merit) should be adopted.

The optimal timing of surgery for delayed repair is unknown. Initial reports advocated a delay of up to 24 hours, but delays of up to 360 hours have been reported. A recent report from the CDH Study Group, which included data from 62 centers in North America, Europe, and Australia, indicated that the mean age at surgery in patients not treated with ECMO was 73 hours.
This practice of delaying repair beyond just a few hours may facilitate the pulmonary vascular remodeling purported to occur much more slowly in CDH lungs than normal lungs and may decrease the sensitivity of these vessels to vasoconstrictive stimuli, including surgical stress.

SURGICAL TECHNIQUE
The diaphragmatic defect usually is approached through a subcostal incision (Fig. 4). The viscera are reduced gently from the chest and eviscerated from the abdomen, and the defect is visualized. Approximately 20% of patients have a hernia sac, which should be excised. Usually there is a relatively adequate anterior leaf of diaphragm and a variably developed posterior leaf, which often becomes attenuated along the ribs of the lateral chest wall. The posterior leaf typically is rolled up into a muscular ridge in the retroperitoneum, which requires that the overlying peritoneum be incised and the muscle “unrolled” to assess its adequacy fully. If there is enough muscle, the defect can be closed primarily with interrupted, nonabsorbable suture.

If there is inadequate diaphragm to accomplish a primary repair, a number of reconstructive techniques make use of nearby musculature, such as the latissimus dorsi or the internal oblique and transversus abdominus muscles. If there is any chance that the infant might require ECMO, procedures that require extensive dissection are contraindicated because of the risk of postoperative bleeding. Most surgeons favor diaphragm reconstruction with prosthetic material, most commonly Gortex®. Besides infection, the major drawback to prosthetic patch closure is the risk of detachment and reherniation.

Abdominal wall closure after diaphragmatic hernia repair may result in unacceptably high intraabdominal pressures, even after extensive stretching of the abdominal wall. In these instances, simple skin closure (without closure of abdominal wall musculature) may be possible. Alternatively, a prosthetic
silo can be attached to the margins of the abdominal incision and the extra-abdominal viscera reduced gradually over several days, with autologous tissue closure undertaken as soon as is safely possible in the postoperative period.

Chest tubes are not used routinely, except for active bleeding or uncontrolled air leak from barotrauma.

**POSTOPERATIVE MANAGEMENT**

Postoperatively, meticulous attention must be given to ventilator management, fluids, and cardiovascular performance. Ventilator support should ensure adequate tissue oxygenation and the avoidance of hypercarbia and acidosis. Postoperative fluid requirements may be significant, and hypotension must be avoided at all costs. The infant must receive adequate narcotic analgesia and sedation and should begin nutrition by the parenteral route shortly after surgery because the time to resolution of intestinal ileus permitting enteral nutrition often is prolonged.

Systemic antibiotics are administered perioperatively, with the duration of the postoperative course (usually 1 to 5 d) determined by whether a prosthetic patch was used. Weaning from the ventilator is gradual and determined by the degree of pulmonary hypoplasia present. Regular chest radiographs are helpful in monitoring the size and growth of the lungs and the return to midline of the mediastinum.

**SURGERY AND ECMO**

The best strategy for timing of repair in infants who have CDH and require ECMO remains unclear. Currently, the options range from “early” repair (usually within 2 days of institution of bypass) to repair after decannulation. The principle advantage to early repair is that it allows postoperative stabilization of pulmonary hypertension at the expense of postoperative hemorrhagic risks associated with anticoagulation. Postweaning and decannulation repair, on the other hand, are associated with lower bleeding risks, although removing the ECMO “safety net” increases the risks associated with postoperative pulmonary hypertension. No comparative study has been performed, but most centers have adopted a policy of delayed repair on ECMO after successful weaning, but prior to decannulation.

The incidence of significant bleeding in affected patients undergoing repair on ECMO has been reported to be 57%. Among patients who require reoperation for bleeding after CDH repair on ECMO, the usual site of hemorrhage is the posterior muscle flap or the intercostal vessels. A number of technical modifications can be adopted to reduce this risk, including minimal dissection of the posterior flap, careful placement of sutures around the posterior ribs and away from the neurovascular bundle, and application of topical thrombin to all suture lines. Intraoperatively, the heparin infusion should be titrated to yield an activated clotting time in the range of 180 to 200 seconds, and this should be maintained until decannulation. Finally, antifibrinolytic agents such as e-amino caproic acid can be administered intraoperatively and continued for a period of time postoperatively or until decannulation.

**Outcome**

The overall survival rate for infants who have CDH is difficult to ascertain because of the heterogeneity of geographic and institutional practices in terms of referral patterns; ventilator management; ancillary therapies such as surfactant, iNO, and ECMO; and timing of surgical repair. Recent data from the CDH Study Group reported a mean survival rate of 63%, which is reflective of the survival rate reported by most large referral centers that offer ECMO support.

**Fetal Therapy For CDH**

Although antenatal diagnosis of CDH is relatively easy, the real challenge for those interested in fetal therapy has been to establish “prenatal prognosis” and in doing so, to identify those fetuses to whom an intervention should be offered. A number of potential prognostic indicators, including detection of CDH prior to 25 weeks’ gestation, polyhydramnios, presence of intrathoracic stomach, small lung-to-thorax transverse area ratio, and heart hypoplasia, all have been reported, but none is accepted or applied universally. More recently, it has become clear that the two best prognostic indicators are the presence or absence of liver herniation into the chest (“liver “up” or “down”) and ultrasonographic measurement of the lung-to-head ratio (LHR) (Table).

The liver position can be determined accurately by high-resolution ultrasonography and color flow Doppler interrogation of the umbilical vein and hepatic vessels. LHR is determined by obtaining a transverse axial image through the chest at the level of the four-chamber view of the heart at 24 to 26 weeks’ gestation. Two measurements of the right lung are made at this location: the greatest length and its perpendicular length (in mm). The product of these measurements is divided by the head circumference in mm. LHR less than 1.0 is associated with a postnatal mortality approaching 100%; mortality in infants whose LHR is greater than 1.4 approaches 0. For LHR between 1.0 and 1.4, the mortality is approximately 60%. Both retrospective and prospective studies have confirmed the usefulness of LHR in predicting postnatal survival.

Fetal surgery for diaphragmatic hernia repair began as a technically difficult, open procedure that failed to offer any survival advantage over postnatal repair for the highest risk (“liver-up”) fetuses in a prospective randomized trial. However, work in animal models of CDH and subsequently in humans suggested that obstructing the fetal trachea could correct the pulmonary hypoplasia associated with CDH. Normally, fetal lungs produce a continuous flow of fluid that exits the trachea into the amniotic space. In the presence of tracheal obstruction, the lungs grow, and there is gradual reduction of herniated viscera back into the abdomen. Following a period of intrauterine tracheal occlusion sufficient to invoke “catch-up” lung growth and reversal of pulmonary hypoplasia, the fetus is delivered and maintained on placental...
support until the tracheal obstruction is relieved and an adequate neonatal airway is established. This therapeutic strategy has been used successfully to treat human fetuses who had CDH. Initially an “open” technique (requiring hysterotomy) of tracheal occlusion was used; more recently, a “fetoscopic” technique has been employed in which an occlusive clip is applied to the trachea after it has been exposed by dissection performed by miniturized instruments through three small (5 mm) uterine incisions or “ports.” This approach is the subject of a prospective clinical trial that will randomize the highest risk patients (“liver-up,” unfavorable LHR) to either fetoscopic tracheal occlusion or postnatal repair.

### Other Future Therapies

Despite the many advances made in therapy for CDH, no single treatment has had a significant impact on survival or cost of care, which is significant for survivors, particularly those who have the greatest pulmonary disability.

Liquid ventilation, of which there are two types, partial (PLV) and total (TLV), is a form of ventilation in which an inert liquid (perfluorocarbon) rather than air is used as a medium for gas exchange. In addition to their excellent gas exchange properties, perfluorocarbons contribute to reduced alveolar surface tension, cause favorable pulmonary blood flow redistribution, and lavage away small airway debris. PLV has been used in infants who had CDH and could not be weaned from ECMO with anecdotal success. It awaits evaluation in the form of a clinical trial.

Other forms of antenatal therapy under continued investigation are pharmacologic and hormonal strategies that target pulmonary growth and development. Corticosteroids appear to have a favorable effect on alveolar development and compliance and medial thickness of the pulmonary vasculature in animal models of CDH. A number of growth factors have been implicated in lung development and maturation; these factors and their potential application to pulmonary hypoplasia associated with CDH await elucidation.

### SUGGESTED READING


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**TABLE. Clinical Characteristics and Outcome of Patients Who Have Left-Sided CDH According to Liver Position**

<table>
<thead>
<tr>
<th>LIVER POSITION</th>
<th>NUMBER OF PATIENTS</th>
<th>GENDER (M:F)</th>
<th>GESTATIONAL AGE (WKS) AT DELIVERY</th>
<th>ASSOCIATED ANOMALIES</th>
<th>ECMO SUPPORT (%)</th>
<th>POSTNATAL SURVIVAL (%)</th>
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<td>Up</td>
<td>32</td>
<td>12:15</td>
<td>37.5 (34 to 40)</td>
<td>4</td>
<td>17 (53)†</td>
<td>13/30 (43)‡</td>
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<tr>
<td>Down</td>
<td>16</td>
<td>10:11</td>
<td>38.3 (34 to 40)</td>
<td>1</td>
<td>3 (19)</td>
<td>14/15 (93)</td>
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ECMO: extracorporeal membrane oxygenation.

*Two patients in the “liver-up” group and one in the “liver-down” group died in utero.

†P<0.05 compared with “liver-down” patients.

‡P<0.05 compared with “liver-down” patients.

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