

Congenital Diaphragmatic Hernia (CDH)

What is congenital diaphragmatic hernia (CDH)?

CDH is a defect in the diaphragm of the fetus. Most often (88 percent) CDH is a posterolateral defect in the left hemidiaphragm on one side. This leads to herniation of the viscera into the thorax, resulting in pulmonary hypoplasia and respiratory embarrassment. Associated anomalies are seen in 25 to 57 percent of all cases of CDH and 95 percent of stillborns with CDH. These anomalies include congenital heart defects, hydronephrosis, renal agenesis, intestinal atresia, extralobar sequestrations and neurologic defects, including hydrocephalus, anencephaly, and spina bifida. Chromosomal anomalies, including trisomy 21, 18, and 13, occur in association with CDH in 10 to 20 percent of cases that are diagnosed prenatally.



Above is an illustration of CDH with bowel and liver herniated into the chest.

What causes congenital diaphragmatic hernia (CDH)?

The cause of CDH is thought to be failure of the diaphragm to develop at nine to 10 weeks of gestation. When closure does not occur, the intestinal organs may herniate into the chest cavity through the defect in the diaphragm. What causes the failure of the diaphragm to close is unknown.

There is a slightly increased risk of CDH associated with mothers taking thalidomide, Benedectin, quinine or antiepileptic medications during early gestation.

What is the incidence of congenital diaphragmatic hernia (CDH)?

The incidence of CDH is estimated at approximately one in 2,500 to 5,000 live births and as frequently as one in 2,200 prenatal ultrasound studies. The discrepancy between neonates who survive birth and transport to a tertiary newborn treatment center and fetuses diagnosed by prenatal ultrasound supports the notion of a “hidden” mortality. With inclusion of cases that never reach the treatment stage of disease, the mortality approaches 75 percent. Survival rate depends on, in large part, the delivery at or the immediate transfer to a tertiary-care hospital where the newborn can be treated promptly by a staff skilled in CDH care.

Although familial cases with an autosomal-dominant inheritance have been reported, most cases of CDH are sporadic.

How is congenital diaphragmatic hernia (CDH) diagnosed?

The diagnosis of CDH is often an unexpected finding on routine prenatal ultrasound examination or on a scan prompted by polyhydramnios. Critical ultrasound findings include the presence of viscera in the right or the left hemithorax above the level of the inferior margin of the scapula or at the level of the four-chamber view of the heart. The hypoechoic signal of the fluid-filled stomach, gallbladder, or bowel can be distinguished from the hyperechoic signal of the fetal lung. A small ipsilateral lung, a defect in the ipsilateral diaphragm, and a shift of the mediastinum away from the affected side are other common findings. In the case of a right-sided CDH, the liver may be the only herniated organ, and it is difficult to distinguish it from the fetal lung because of their similar echo densities. Identification of the diaphragm does not exclude the possibility of CDH because at least a small portion of the diaphragm is usually present in CDH.



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The differential diagnosis includes Type I CCAM, bronchogenic cysts, neurenteric cysts, and cystic mediastinal teratoma, which may mimic the appearance of a herniated bowel. Identification of abnormal upper abdominal anatomy and presence of peristalsis in herniated bowel loops help distinguish CDH from other diagnoses. The location of the gallbladder in fetuses with CDH is helpful because it may be displaced to the midline or in the left upper quadrant or herniated into the right chest.

In most severe cases, the liver and the stomach are present in the thorax. Bowing of the portal vein or sinus venosus to the left of the midline or coursing of the portal branches to the lateral segment of the left lobe of the liver above the diaphragm can be seen with color flow Doppler imaging and is the best ultrasound predictor of liver herniation. In addition, the position of the stomach (easily seen in contrast to the more echogenic fetal lung) in a posterior or midthoracic location is also associated with liver herniation. Several ultrasound features have been suggested as prognostic indications in CDH, including polyhydramnios, early gestation diagnosis (less than 24 weeks), stomach herniation, herniation of the left lobe of the liver, evidence of fetal cardiac ventricular disproportion before 24 weeks of gestation and lung-to-head circumference ratios. However, no single ultrasound feature of CDH has been uniformly helpful in predicting outcome. A more direct estimate of pulmonary hypoplasia that correlates with neonatal outcome is needed.

Lung area-to-head circumference ratio (LHR) (two-dimensional area of right lung measured at the level of the four-chamber view of the heart) was assessed prospectively to determine its value in predicting the postnatal outcome with conventional therapy. The LHR, although still useful, has proven less reliable in predicting survival than was previously thought, especially in the most severe category. LHRs greater than 1.4 are still associated with an excellent survival rate in the 80 to 85 percent range with only 25 percent of patients requiring ECMO. An LHR between 1.0 and 1.4 is associated with survival of about 75 percent, with 69 percent requiring ECMO. The largest change has been the survival observed with patients with LHR less than 0.9 in which survival of up to 44 to 62 percent of patients can be expected, but almost all survivors require ECMO. It is not known if the improved survival with LHR less than 1.0 reflects improved neonatal care, such as the use of “gentilation” strategies, or if greater experience with larger numbers of patients in this category of LHR is now giving a more accurate reflection of survival.

The position of the fetal liver in left sided CDH remains an important prognostic factor. In recent experience, survival in left sided CDH with liver in the abdomen was 91 percent with only 24 percent requiring ECMO. Conversely, survival in left sided CDH with significant herniation of the left lobe of the liver was only 51 percent, with 79 percent of patients requiring ECMO. Note that these statistics apply only to cases of left sided CDH. The LHR does not apply to right-sided CDH in which the liver is almost always herniated and it is not necessarily associated with a worse prognosis. In fact, in a review of previous experience with 22 cases of prenatally and six cases of postnatally diagnosed right sided CDH, Hedrick et al, found an overall survival rate of 70 percent. Among those diagnosed prenatally, four cases chose to terminate the pregnancy and of the remaining 18, 16 survived (89 percent, or 73 percent if terminations are included). Half of the patients (12 of 23, or 53 percent) required ECMO, and of those, the survival rate was 75 percent. Unfortunately, none of the prognostic features that assist in counseling patients with a left sided CDH apply to



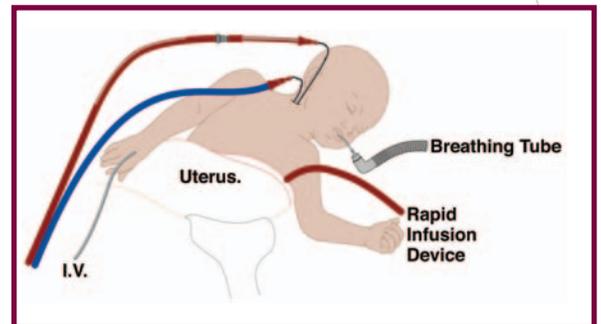
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right sided CDH. It is noteworthy however, that obstetrical complications including polyhydramnios, pre-term labor, and premature rupture of membranes occurred in 50 percent of the right sided CDH pregnancies.

Ultrafast fetal MRI is used to better define the severity of CDH, exclude associated anomalies and estimate fetal lung volume as a prognostic indicator. We recommend fetal MRI two times during gestation. The first MRI is obtained during the initial evaluation in order to demonstrate the anatomic defect and determine whether or not the liver is herniated, which may be difficult to determine with ultrasound alone. Fetal MRI is useful in excluding other associated abnormalities in the chest, abdomen and brain. We recommend a follow up fetal MRI at 34 to 36 weeks. The lung volumes obtained at this gestational age accurately predict the severity of CDH, survival and the need for ECMO. If you have questions about these prognostic findings on fetal MRI or would like to be evaluated, please contact the Fetal Care Center of Cincinnati.

How is pregnancy managed when congenital diaphragmatic hernia (CDH)? are detected?

If CDH is suspected, the mother should undergo a detailed ultrasound to confirm the diagnosis and detect possible associated abnormalities. Prenatal karyotyping (the study of the chromosomes of cells) is recommended because of the high incidence of associated chromosomal abnormalities. Fetal echocardiography is recommended in all cases of CDH because of the increased incidence of congenital heart disease.



Above is an illustration of EXIT-to-ECMO

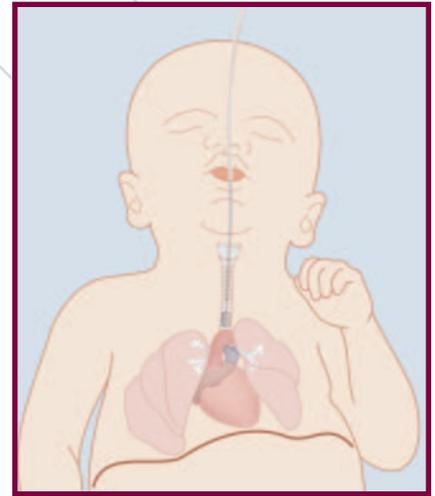
What are the fetal interventions for congenital diaphragmatic hernia (CDH)?

Despite the advances in neonatal care, such as “gentilation,” high-frequency oscillatory ventilation, inhaled nitric oxide, and ECMO, the mortality rate of isolated CDH remains substantial. Out of frustration with these grim statistics, Harrison and colleagues pioneered fetal surgery for CDH. Unfortunately, survival following complete in utero repair was poor. These failures were due to herniation of the left lobe of the liver. Reduction of the liver during repair inevitably resulted in kinking of the umbilical vein, leading to fetal bradycardia and cardiac arrest. Herniation of the left lobe of the liver became an exclusion criterion for complete in utero repair of CDH. However, even if cases with left lobe herniation are excluded, the survival rate in the series by Harrison and colleagues was only 41 percent, which was no better than with conventional postnatal therapy at the time. A prospective trial sponsored by the National Institutes of Health confirmed these findings; thus, there is currently no indication for complete repair of CDH in utero. The shortcomings of in utero repair led to the development of a new approach.

Known for decades, fetal tracheal occlusion results in accelerated fetal lung growth in animal models. It was not until 1994, however, that tracheal occlusion was applied to the problem of CDH. In the animal models of CDH, tracheal occlusion induces lung growth, increases alveolar surface area and alveolar number, as well as visceral reduction from the chest. The results of these experiments were so compelling that fetal tracheal occlusion was applied in human fetuses with severe CDH. The

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results of open fetal surgery for tracheal clip procedure in high-risk CDH were disappointing in both the University of California, San Francisco (UCSF) and the Children's Hospital of Philadelphia (CHOP) experience. As a result of the poor outcomes with the procedure, a procedure was developed using transuterine endoscopy or FETENDO. The results from the FETENDO approach in high-risk CDH were promising, and the NIH sponsored a trial of fetoscopic tracheal clip application compared to conventional postnatal therapy. Shortly after initiation of the FETENDO trial for CDH, the UCSF group developed a less invasive endolumenal balloon tracheal occlusion technique requiring only a single port as opposed to the five for the FETENDO approach. This approach, using a detachable balloon was incorporated into the NIH sponsored trial. The trial was halted after enrollment and randomization of 24 patients because of an unexpectedly high survival rate with standard postnatal care. The Data and Safety Monitoring Board concluded that further recruitment would not result in significant differences between the groups. Eight of 11 (73 percent) in the tracheal occlusion group and 10 of 13 (77 percent) in the group that received standard postnatal care survived. There are several important lessons to be learned from this trial. First, these results primarily apply to fetuses with LHR > 0.9 and < 1.4 . It remains unknown if the most severely affected fetuses with LHR < 0.9 and liver herniation would do better with fetal tracheal occlusion. Second, the outstanding survival achieved with "standard" therapy was obtained at a tertiary center that cares for a large volume of diaphragmatic hernia patients. These results may not be generalizable to centers that do not have extensive experience caring for critically ill newborns with severe pulmonary hypoplasia due to CDH.



Above is an illustration of a balloon tracheal occlusion.

In the most severe cases of diaphragmatic hernia, fetal intervention is still being investigated. In Belgium, Jan Deprest was first to perform reversible fetoscopic balloon tracheal occlusion for CDH with LHRs < 0.9 and herniation of the liver. The results are preliminary, involving small numbers of patients, but survival of 90 percent has been reported. Reversible tracheal occlusion for severe CDH is now being offered at the Fetal Care Center of Cincinnati. This innovative therapy is available only for left sided CDH with herniation of the left lobe of the liver, normal karyotype analysis, normal fetal echocardiogram and no associated anomalies.

An alternative fetal treatment also offered at the Fetal Care Center of Cincinnati for high-risk CDH is the EXIT-to-ECMO strategy. The use of EXIT-to-ECMO was first described by Crombleholme for the management of severe CDH (liver herniation and LHR < 0.9) associated with congenital heart disease. This has now been applied to cases of isolated high-risk CDH. We use the same selection criteria for EXIT-to-ECMO that we do for reversible tracheal occlusion. It must be a case of left sided CDH, with herniation of the left lobe of the liver and LHR < 0.9 . The rationale for this approach is that by transitioning directly from placental support to ECMO support the infant is never hypoxic, acidotic, or hypotensive and is never exposed to barotrauma from vigorous neonatal resuscitation.

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In addition, during VV ECMO, oxygenated blood is delivered into the right heart and the pulmonary vascular bed, which may have direct therapeutic effects. From a maternal risk standpoint, this approach obligates the mother to a surgical delivery. From the fetal standpoint, because this approach is reserved for high risk CDH, as previously described, no additional fetal risk is incurred. Whether EXIT-to-ECMO improves survival or reduces morbidity associated with CDH is not known.

What are treatment options for the newborn?

All infants with CDH are managed at the Fetal Care Center of Cincinnati by the CDH Team consisting of two pediatric surgeons (Timothy M. Crombleholme, MD and Richard A. Falcone, MD) and two neonatologists (Jon H. Fridriksson, MD and Beth E. Haberman, MD). The CDH Team collectively has many years of experience with the care and management of hundreds of infants with severe CDH. The CDH Team is assisted by nurses, cardiologists, geneticists, developmental pediatrics, neurologists, nutritionists and social workers who are well versed in the problems that infants with CDH face. A consistent approach to management, including protocols for “gentilation,” as a ventilatory strategy, and aggressive management of pulmonary hypertension, is the hallmark of the CDH Team. The consistent care these infants receive ensures that outcomes are optimized. All aspects of the infants’ care, from prenatal diagnosis through long-term follow-up, are orchestrated and coordinated through the Center. The Fetal Care Center has experience coordinating care for patients from distant parts of the United States who choose to have their baby cared for here. If you have questions about evaluations, coordination with your doctor or how the Fetal Care Center of Cincinnati collaborates with your obstetrician and pediatrician, please contact us.

What is the long-term outcome with congenital diaphragmatic hernia (CDH)?

The long-term outcome of infants with CDH who survive the neonatal period depends on the severity of the underlying pulmonary hypoplasia, the severity of pulmonary hypertension and the degree of chronic lung disease resulting from long-term breathing support. Also affecting the long-term outcome are other health conditions seen in up to 20-30 percent of infants with CDH. Such conditions can include neurological problems, reactive airway disease, hearing loss, seizures and developmental delay.

Gastroesophageal reflux may affect as many as 50-62 percent of CDH survivors. Musculoskeletal problems affecting the stability of the trunk can also develop. Some infants who survive CDH fail to thrive, suffering feeding difficulties that can result in some 30 percent remaining below the fifth percentile in weight despite optimal caloric intake. Although not all infant survivors of CDH develop these problems, our follow-up programs are focused on early intervention when problems are recognized to optimize patient outcomes.

Contact the Fetal Care Center of Cincinnati

For more information, please call 1-888-FETAL59 or email us at info@fetalcarecenter.org.

References

For a detailed reference list, visit our web site at www.fetalcarecenter.org.

