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REVIEW

PRENATAL DIAGNOSIS WILEY

What should we tell parents? Congenital diaphragmatic hernia

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Abstract

Congenital diaphragmatic hernia (CDH) is characterized by a defect in the muscle dividing the thoracic and abdominal cavities. This leads to herniation of the abdominal organs into the thorax and a disturbance of lung development. Two-thirds of cases are identified by prenatal ultrasound in the second trimester, which should prompt referral to a tertiary center for prognosis assessment and counseling by a multidisciplinary team familiar with this condition. In this review, we summarize evidence on prenatal diagnosis and postnatal management of CDH. There is a focus on information that should be provided to expecting parents during prenatal counseling.

Key Points

What's already known about this topic?

- CDH is associated with 30% mortality and with significant morbidity
- Prenatal diagnosis is made in 70% of cases
- Based on prenatal assessment, personalized counseling on prenatal management options, as well as postnatal management and outcomes should be provided

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On behalf of the Workstream Prenatal Management, ERNICA European reference network.

What does this review add?

- We present a summary of the information that we feel should be provided to expecting parents
- We provide visual supporting material to improve parents' understanding

1 | INTRODUCTION

My baby has congenital diaphragmatic hernia. What does it mean?

Congenital diaphragmatic hernia (CDH) is a rare condition (1–4/10.000 pregnancies),[1] typically with unknown cause. The name refers to a defect in the muscle (the diaphragm) dividing the thoracic and abdominal cavities. The defect most commonly occurs on the left side, although it may more rarely be on the right side, or even bilateral. As early as the first trimester, abdominal organs herniate through this defect (Figure 1) and interfere with lung development predominantly on the side of the defect, although both lungs are eventually smaller than those of healthy newborns. Two-thirds of CDH cases are diagnosed before birth. Diagnosis should prompt referral to a tertiary center with experience in prenatal diagnosis and postnatal management of CDH. There, a multidisciplinary team will discuss prognosis with the parents, as well as antenatal options, perinatal management and any postnatal pathways that may be required.

Although parents perceive the prenatal diagnosis of CDH as an emergency, CDH is rarely lethal before birth (1%–2%). This provides time for proper assessment, severity stratification and personal reflection. After birth, the defect will need repair; however, this is not the most urgent nor the most difficult problem. The most significant challenge is managing the newborn's lung function. Evidence of pulmonary dysfunction only becomes apparent after birth, when the baby is separated from the placenta. Lungs of CDH-newborns are smaller, and contain fewer and abnormal airways and vessels.[2] This is termed pulmonary hypoplasia. Clinically, pulmonary hypoplasia is evidenced by abnormal gas exchange and higher blood pressure in the newborn's lungs. This respiratory compromise is fatal in up to one third of cases.[3] When the newborn is stabilized, the diaphragmatic defect is repaired. Before as well as after the operation, the newborn may stay several days to weeks in neonatal intensive care. After discharge, CDH babies will also require specialized multidisciplinary follow up to ensure any future complications are identified early and properly managed.[4]

This paper describes how today fetuses with CDH should be assessed and how their prognosis can be personalized. It describes the typical neonatal course of the disease, neonatal surgery, as well as the follow up that is best done during childhood. Additionally, we address genetic predispositions for CDH and the possibility of recurrence in later pregnancies. This information should be shared with parents to help them make an informed choice between expectant management and prenatal referral for elective delivery, termination of pregnancy, or, in selected patients, fetal intervention.

2 | PRENATAL DIAGNOSIS

Can one pick up CDH before birth? How?

Two-hirds of CDH cases are identified by prenatal ultrasound in the second trimester of pregnancy[5] typically because the heart and the abdominal organs are not in their normal position.[6] Left-sided CDH typically presents with a shift of the heart to the right, caused by herniation of the stomach, intestines, and in some cases part of the liver (Figure 1). The stomach bubble is seen at the level of the heart plane in about 80% of left-sided CDH cases.[7] This makes the diagnosis relatively easy. Prenatal diagnosis is more difficult in cases when only the bowel and/or liver are herniated, as these organs may be confused on ultrasound with lung parenchyma or with intrathoracic masses that cause mediastinal shift (such as congenital pulmonary airway malformations). Direct visualization of the -interrupted- diaphragm on a sagittal view may help discriminate between these conditions.

The wide implementation of first trimester anomaly screening has increased the possibility of detecting CDH earlier in pregnancy. In up to a quarter of cases, CDH is associated with an increased nuchal translucency in the first trimester,[8] which should lead to a detailed ultrasound in the early second trimester. That being said, the diagnosis of CDH in the first trimester remains challenging. This is particularly true in those cases in which the defect is small or the migration of the abdominal viscera occurs late. Even in the most recent studies, the diagnostic rates for CDH in the first trimester are lower than 30%.[8]

3 | ANTENATAL PREDICTION OF OUTCOME

What further prenatal tests are recommended? And what are my baby's chances to survive?

Although two-thirds of infants with CDH survive the neonatal period, mortality is variable and depends on a number of risk factors. Some of these factors may be identified prenatally. For that reason, the diagnosis or suspicion of CDH should lead to referral to a tertiary care center for further assessment and counseling (Figure 1). Over there:

(1) Additional structural anomalies will be ruled out with ultrasound and possibly magnetic resonance imaging (MRI)
(2) Amniocentesis or, in case of an early diagnosis, chorionic villous sampling will be performed to screen for genetic anomalies
(3) Lung size will be measured and the herniation of abdominal organs assessed
(4) Based on the former, a personalized prognosis can be made.

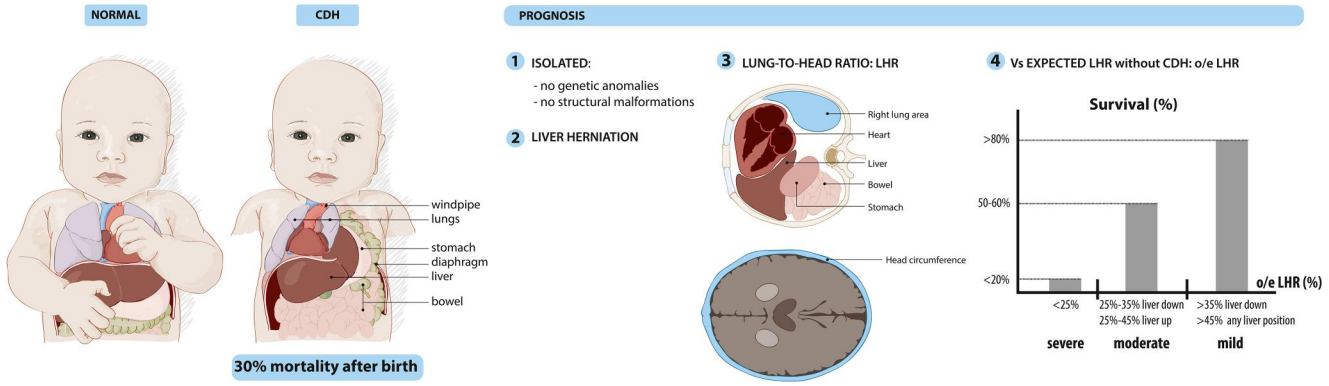

FIGURE 1 Visual aid 1. Antenatal prediction of prognosis in left-CDH. The left panel depicts the normal anatomy of the thorax and abdomen as compared to that in an infant with CDH. The central panel is a schematic representation of the ultrasound measurement of the LHR. In the right panel, survival rates in isolated cases are stratified based on the o/eLHR and liver herniation; CDH, congenital diaphragmatic hernia; LHR, lung-to-head ratio [Colour figure can be viewed at wileyonlinelibrary.com]

3.1 | Screening for associated structural anomalies

In almost half of CDH cases, nonpulmonary structural anomalies are found alongside the diaphragmatic defect.[9] This differentiates *complex* CDH from *isolated* CDH. To identify abnormalities, advanced ultrasound imaging is warranted. Particular attention should be paid to the fetal heart: cardiac defects are the most common anomalies associated with CDH and are found in roughly one third of fetuses.[10] Anomalies of the kidneys, brain, bones and spine may also be found in up to 10% of patients.[6] Of note, intrafetal fluid effusions are a relatively common ultrasound finding in CDH fetuses, present in up to 5% and 29% of left- and right-sided CDH cases, respectively.[11] However, in a small series the presence of these effusions did not affect fetal or neonatal outcome.[11] To increase the detection rate of associated structural defects, most centers include fetal MRI in the diagnostic flowchart.

Associated structural malformations may be components of syndromes or chromosomal disorders.[12] It should be noted that even in centers with optimal prenatal diagnostic skills, in 2%–5% of cases genetic syndromes and/or structural defects are not diagnosed until after birth.[13]

3.2 | Screening for associated genetic anomalies

The London Dysmorphology Database lists >100 genetic syndromes where CDH can be part of. Syndromic cases are more common in bilateral CDH patients, or in those with a family history of CDH. Besides these cases, several associations with CDH have been identified which do not fit into a well-known syndrome. Diagnosis of a syndrome caused by a single gene mutation or chromosomal imbalance has an independent impact on survival and long-term prognosis. For example, since intellectual disability is commonly observed in these patients. Genetic conditions may not be associated with additional structural anomalies. We recommend genetic testing in all cases. In our hands, micro array's analysis has led to reclassification in 8% of cases that were originally diagnosed as isolated based on prenatal imaging.[14]

Major trisomies (13, 18, 21) only account for a minority of syndromic CDH cases.[12] For this reason, there is limited added value from noninvasive prenatal testing in the diagnosis of CDH. Invasive testing with DNA microarray analysis is recommended. This enables the identification of genome-wide copy number variations (CNVs). CNVs are present in approximately 10% of apparently isolated CDH,[14] compared to 6%–19% in nonisolated postnatal cases.[15,16] Alternatively, targeting testing can be performed if specific syndromes are suspected because of patterns of associated abnormalities or a strong family history. Detection of single nucleotide variants may be achieved by Mendeliome or whole exome sequencing (WES). This identifies all known disease-associated genes or all known genes, respectively. At present, WES is available but in many countries limited by cost and long processing times. Pathogenic or likely pathogenic variants have been identified in approximately 10% of prenatally CDH-cases initially diagnosed as isolated.[17] Yet, the interpretation of advanced genetic testing remains complex and a comparison with parental sequences may be helpful.

When associated organ malformations are present but no exact diagnosis can be made, counseling remains challenging. Many (ultra-) rare or even unique conditions exist, with limited medical knowledge regarding their natural history. Moreover, a wide variety of genetic syndromes means outcome predictions often come with a relatively broad range and uncertainty (e.g., with regard to the severity of the developmental delay/intellectual disability). Recent experience indicates that known syndromes which present prenatally are typically more extreme in nature than those which become apparent after birth.[18] It is also possible that a genetic or syndromic cause may be missed during genetic testing. One example is mosaic tetrasomy 12p, which causes Pallister–Killian syndrome. This syndrome is typically missed on routine chorionic villus sampling unless a direct examination of the trophoblastic cells is performed.[19] Finally, not all genes causing CDH have been identified. For all these pitfalls of prenatal genetic testing, a clinical re-assessment after birth is indicated.

3.3 | Severity determination

In *complex* CDH the outcome is co-determined by the severity of such associated abnormalities.[1] In *isolated* cases, mortality correlates with the severity of pulmonary hypoplasia. This can be predicted prenatally based on fetal lung size and liver herniation (other factors, e.g., stomach position, have also been used).[20–22] Using ultrasound, lung size is commonly estimated by measuring the ratio between the area of the lung contralateral to the defect and the head circumference (lung-to-head ratio, LHR). Because lung size and head circumference change at different paces during pregnancy, the LHR is best expressed as a proportion of the *observed* (measured) over the *expected* (in a normal fetus of the same gestational age) ratio (o/eLHR). The o/eLHR allows for a prediction of prognosis independent of gestational age.[22] In left-CDH fetuses, liver herniation through the diaphragm is also positively correlated with mortality.[23] Based on the combination of liver herniation and o/eLHR, fetuses can be classified as having severe, moderate, or mild pulmonary hypoplasia, with progressively increased survival rates [14]. In left-sided CDH, an o/eLHR under 25% is defined as severe and is associated with survival rates below 20%. An o/eLHR of 25%–34.9% (irrespective of the liver position) or 35%–44.9% with a herniated liver is defined as moderate and has a survival rate of around 50%. Above these ranges, CDH is considered mild (Figure 1).

Some studies have suggested that disease severity may also be predictive of neonatal morbidity. Severity may predict the duration of assisted ventilation, neonatal oxygen requirements, the need for patch repair, the time taken until full enteral feeding, and the occurrence of pulmonary hypertension.[24,25] Yet, it should be noted that the accuracy of morbidity prediction remains controversial. In the future, these estimates may include additional parameters such as stomach position, the proportion of liver herniated, and the state of the pulmonary vasculature. Unfortunately, many postnatal factors or events are not easily modeled. For example, at present it has not been possible to reliably predict prenatally the occurrence, severity and persistence of pulmonary hypertension.[26]

MRI may also be employed to predict disease severity.[27] MRI can estimate the volume of both lungs by calculating the proportion of the bilateral lung volume/body weight over what is expected in a normal fetus (observed-to-expected total lung volume, o/eTLV). MRI also enables quantification of the degree of liver (liver-to-thorax ratio) and stomach herniation.[28,29] That being said, the superiority of MRI over ultrasound imaging for prognosis determination in CDH is still under debate.[30,31]

Antenatal prediction of prognosis should be performed by experienced operators. Several studies have shown significant discrepancies between the initial assessment in a referring center and that in an experienced fetal therapy unit. Both qualitative (the nature and extent of the fetal anomaly) and quantitative (measurement of lung size) inconsistencies have been found.[13,32] In more than 10% of patients, assessment in an experienced center results in a detection of additional fetal anomalies.[13] This is likely to influence the parents' decisions about treatment options. It has also been shown that an accurate measurement of lung size requires time and experience, implying that increased clinical exposure may improve competency in CDH diagnosis and characterization.[33] A multicenter nation-wide study has shown that the predictive value of the o/eLHR is significantly higher in larger centers (>14 cases/year).[32] This evidence indicates that referring physicians should be cautious when making severity estimates without expert opinion.

Finally, it is important to appreciate the temporal aspect to prediction accuracy. The accuracy of prediction of outcome increases with increased gestational age. Thus, although the o/eLHR provides useful prognostic information at 22–23 weeks, it is more accurate at 26 weeks,[34] and very likely even more reliable at a later stage. For this reason, in countries where management options remain unrestricted, a formal assessment later in pregnancy may be preferable.

3.4 | Uncommon CDH variants

Particular reference should be made to right-sided CDH. This is a rare diagnosis. Infants have lower overall survival (53%) and/or higher morbidity than those with left-CDH. For this reason, many consider right-CDH as a separate entity.[35,36] Like in left-CDH, the o/eLHR correlates with survival. Average survival rate is 20% when the o/eLHR is below 50% (severe hypoplasia).[37] As liver herniation is almost always present, it has no discriminatory value for the assessment of severity. Because of the rarity of right-CDH, the prediction of prenatal outcome remains less validated.

A particular anatomical form of CDH is represented by the hernia sac, a peritoneal layer covering the digestive organs herniated in the thorax in 15%–20% of cases. These cases are in the majority not diagnosed prenatally, and are usually associated with a better prognosis.[38]

4 | ANTENATAL MANAGEMENT

What are my options now?

Once a personalized prognosis has been shared, parents can choose between:

(1) Expectant management with prenatal referral for elective delivery
(2) Termination of pregnancy where allowed
(3) In selected patients, fetal intervention.

When expectant management is chosen, maternal follow up is comparable to those of uncomplicated pregnancies. Given the increased occurrence of polyhydramnios (more than 30% by the third trimester[39]), ultrasound scans are usually performed on a monthly basis. In cases with polyhydramnios and shortening of the cervix ultrasound-guided drainage of the excessive amniotic fluid may be

performed. Given the increased risk of stillbirth, especially close to term,[40] weekly assessment of fetal wellbeing by cardiotocography from 36 weeks of gestation onwards is performed in many centers.

In fetuses with severe or moderate lung hypoplasia, surgical intervention in utero may be considered. Lung growth can be promoted by insertion of a balloon into the fetal windpipe. This is currently done without serious maternal morbidity through a minimally invasive, percutaneous procedure (referred to as FETO, fetoscopic endoluminal tracheal occlusion) under local maternal anesthesia. As the developing lungs produce fluid, prenatal airway occlusion traps these secretions; this precipitates stretch-induced lung growth. Later in gestation, the balloon is deflated to promote lung maturation. Yet, FETO carries an increased risk for preterm delivery, partly offsetting the benefits of fetal therapy. Preterm rupture of membranes occurs in one out of four patients, and delivery before 34 weeks in one third.[41] A recent multicenter cohort study has shown significant survival benefit of FETO in fetuses with right-sided CDH and severe lung hypoplasia.[37] Two randomized controlled trials investigating the potential survival benefit in left-sided CDH with severe or moderate hypoplasia have just been concluded, but the results remain to be awaited.[42]

5 | NEONATAL RESUSCITATION

What will happen at birth?

In most centers, delivery is carefully planned to allow optimal neonatal and surgical management. Several studies have shown that higher gestational age at birth is related to better survival rates; induction should therefore be planned at term, although early (37–38 weeks) or late (>39 weeks) term remains controversial.[43,44] The route of delivery does not appear to impact neonatal survival or short-term morbidity.[45] It has been demonstrated that birth and standardized management in a high-volume center increases neonatal survival.[46] Parents should be informed on the nature of the intensive management required at birth:

- Immediate intubation and ventilation
- Sedation
- Use of drugs to support the circulation and treat pulmonary hypertension.

Ventilation is performed using limited peak inspiratory pressures to avoid damage to the hypoplastic lungs. Newborns are sedated to facilitate intubation but do not routinely require paralysis.[47] Current neonatal management strategies consist of gentle ventilation, pulmonary vasodilatation and cardiac support[47] (Figure 2). Management continues to be optimized: trials are ongoing to investigate whether, in selected cases, spontaneous breathing can be tolerated at birth. Additionally, resuscitation with delayed cord clamping has been performed in small series[48,49] and is being evaluated in randomized trials.

Pulmonary hypertension occurs in 30%–50% of CDH newborns and should be screened for and managed by repeated cardiac ultrasound.[50] Persistent severe pulmonary hypertension at 3 months of age is correlated with a more than 50% discharge mortality.[51] Treatment of pulmonary hypertension is challenging. In the acute setting, most centers use inhaled nitric oxide (iNO), but this is currently under debate.[52] Also support of cardiac function and circulation by inotropic drugs and vasopressors is frequently used.[47] Alternative drugs are being investigated for management of infants' pulmonary hypertension. One such drug is sildenafil, which is currently being studied as first-line therapy in the CODINOS trial.[53] Extra corporeal membrane oxygenation (ECMO, also known as "artificial lung") has also been employed. ECMO allows for milder ventilation settings and may reduce the need for medical treatment of pulmonary hypertension, and may prevent the lung damage caused by a long term ventilation. However, ECMO also carries risks. The most common one is bleeding. If this occurs in the brain, there may be brain damage causing long term morbidity or death. The use of ECMO remains controversial[54]: some centers use it widely,[55] whilst others are reluctant because of its associated morbidity.[56]

6 | NEONATAL SURGERY

How is congenital diaphragmatic hernia treated after birth?

Surgical repair of the defect is one of many steps in the care of a CDH child. Important counseling elements are:

- CDH is not a surgical emergency: over the past few decades it has become evident that the best outcomes are obtained when newborns are stabilized before undergoing surgery. This may take days.[57] Most neonatal deaths (78% in a recent prospective national study performed in UK[58]) occur before the operation
- The outcome of CDH mainly depends on the lungs. Although prenatal estimation of lung size is possible, actual lung function can only be reliably assessed in the postnatal setting, when the neonate starts breathing and full lung circulation is established [59]
- The escalation of different modalities of respiratory support may delay the surgery and increase morbidity and mortality. It may also increase overall parental stress[60]
- CDH can be repaired through the abdomen (by laparotomy or laparoscopy) or the chest (by thoracotomy or thoracoscopy).[61] The most common approach is through a laparotomy, although thoracoscopy is emerging as a valid alternative approach still limited to high volume centers.[62]

The operation enables repositioning of herniated organs back into the abdominal cavity, alongside surgical repair of the diaphragmatic defect. Simultaneously, correction of any abnormal bowel rotations may be performed (Figure 2). The disadvantages of

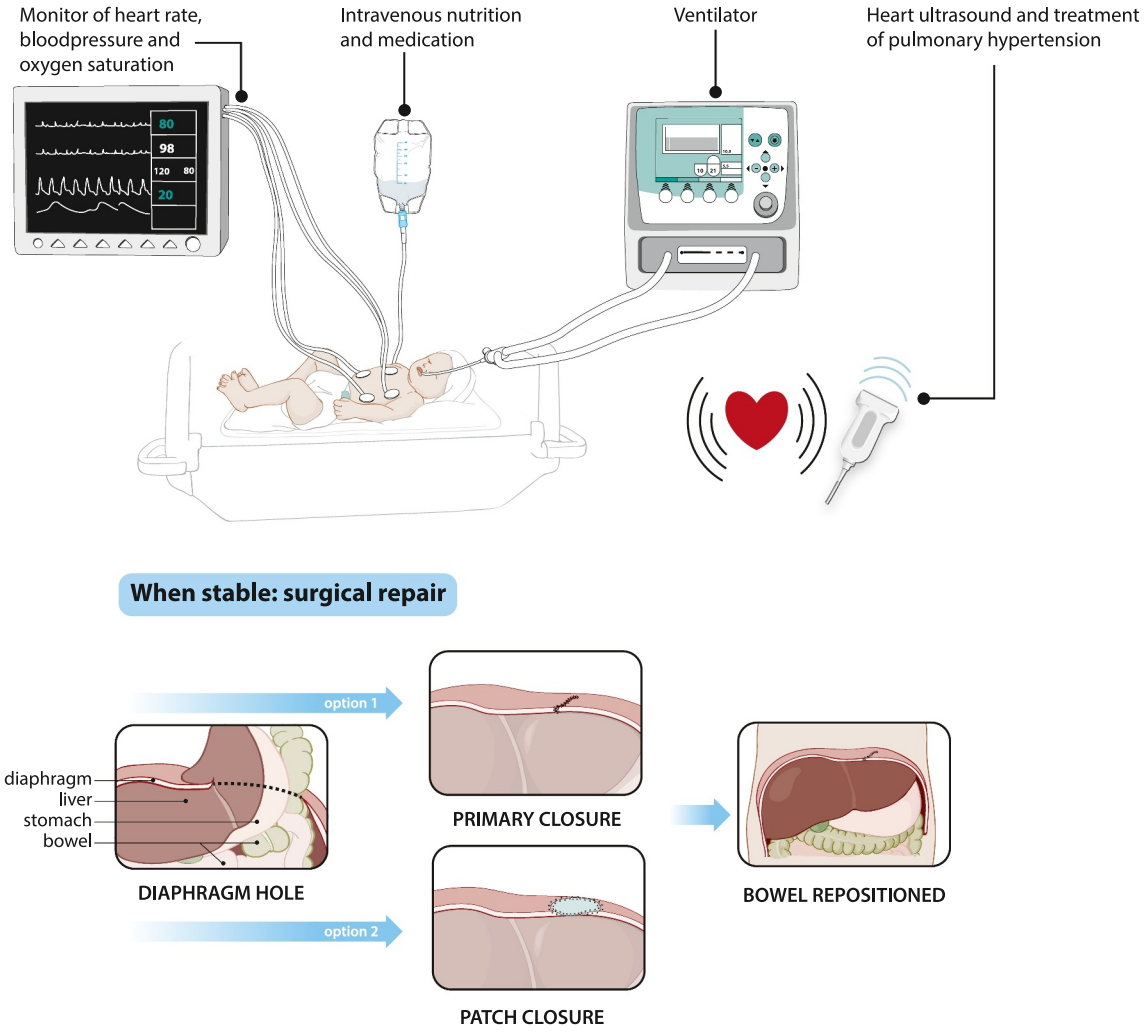

FIGURE 2 Visual aid 2. Neonatal care and surgery. The upper panel depicts the tools for neonatal resuscitation. The lower panel is a schematic representation of the postnatal diaphragmatic repair [Colour figure can be viewed at wileyonlinelibrary.com]

laparotomies include cosmetic challenges (children are left with relatively big scars) and increased risk of abdominal adhesions, which may cause future episodes of bowel obstruction (10% of cases).[63]

Recurrence of the defect occurs in 6% to 30% of cases (Figure 3). Various durable materials have been used to "patch" or repair the defect. Degradable patches are associated with a higher chance of recurrence. In the past, surgeons believed that the use of patch was associated with higher recurrence rates. However, it is now widely accepted that this association was confounded by the patches being more commonly used on large defects, which themselves have a higher recurrence rate. More recent studies indicate that patch use reduces tension across the diaphragmatic repair, hence lowers recurrence risk.[64]

After surgery, ventilation is weaned and, where possible, enteral feeding is started. The duration of invasive ventilation is variable and is dependent on the degree of pulmonary hypoplasia and pulmonary hypertension. The median duration of hospital stay is 6–8 weeks. In complicated cases, this may be prolonged to months or longer.

7 | CHILDHOOD MORBIDITY

What may happen after discharge?

The morbidity of CDH survivors frequently extends beyond discharge from the intensive care unit (Figure 3).

- Up to 75% of surviving CDH infants have feeding problems like gastro-esophageal reflux disease, need for tube feeding, oral aversion.[65] Approximately one in five CDH newborns are discharged on partial tube feeding[66] (Figure 3). Feeding problems may persist for several months to years and can rarely extend into adulthood. Growth in CDH children is poor in the first years of life, but often improves during childhood. There are multiple reasons for this initial low weight gain and poor growth, including feeding problems and increased energy expenditure.[67] Long-term follow up is necessary to prevent complications from untreated reflux disease

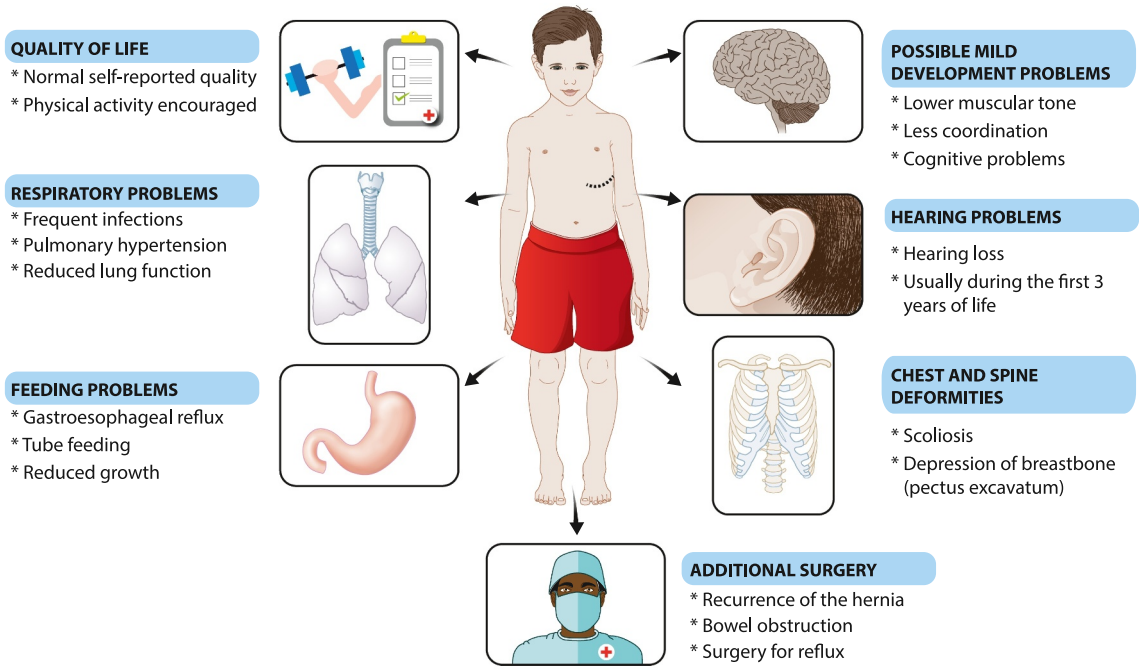

FIGURE 3 Visual aid 3. Long term outcomes. The most common long term complications are depicted on an organ-base [Colour figure can be viewed at wileyonlinelibrary.com]

- Long-term respiratory problems are related to the degree of pulmonary hypoplasia at birth, the chronic complications of neonatal ventilation, the altered pulmonary growth, and chest wall or spinal deformities. Recurrent respiratory tract infections and asthma-like symptoms are the most frequently reported problems in childhood, occurring in 30%–50% of cases[68,69] (Figure 3). These problems are likely to lead to re-hospitalization during infancy. On pulmonary function testing, CDH patients tend to have signs of airway obstruction as well as small airway disease.[70] Exercise capacity is reduced and tends to deteriorate over time. This is irrespective of past ECMO treatment. Nevertheless, it is essential that physical activity is encouraged in children with a history of CDH [71]
- Long-term follow up studies indicate that impaired neurodevelopmental outcome is a common morbidity amongst CDH survivors. Most studies report on outcomes at 1–2 years of age; data at school age and beyond is scarce. In early life, motor and cognitive difficulties positively correlate with the duration of ventilation in the neonatal period.[72] At school age, 50% of CDH patients will have special educational needs.[73] Hearing problems are more frequent, particularly in ECMO-treated patients. For this reason, hearing screening before discharge is advised in all CDH patients. Additionally, whilst the majority of infants will pass the newborn hearing screen, 20%-50% can still develop sensorineural hearing loss later [74]
- Chest wall and spine deformities are present in 30%–50% of growing children with CDH, most frequently in those that underwent patch repair.[75]

The above problems may compromise quality of life and increase family burden. Nevertheless, the self-reported quality of life at school age is comparable to that of age matched controls. This is true even if medical problems secondary to the condition are more frequent.[76,77]

8 | RECURRENCE RISK

Are my future pregnancies at risk?

The exclusion of a genetic cause is important for prediction of the recurrence risk. In isolated nonfamilial cases, the recurrence risk is low (below 2%); in syndromic CDH patients, the recurrence risk may range from 1% to 50%, depending on specific etiology.[78] In the subsequent pregnancies, offering first and second trimester in expert hands is recommended, as the ruling out of CDH will mitigate parental stress.

9 | REFLECTION

Upon prenatal diagnosis of a fetal anomaly, most prospective parents want immediate and reliable information.[79] Specific research into the information needs of parents with a prenatal diagnosis of CDH is currently lacking; however, the needs of parents caring for a child with CDH may provide some guidance. For these parents, a lack of specialized knowledge and poor channels of communication amplify parental insecurity, inducing distress and decreasing satisfaction with care provision.[80] Although the prenatal circumstance is not entirely comparable, it is characterized by many of the same uncertainties. Thus, similar efforts in communication should be executed. Information on the

cause of CDH, a realistic and reliable description of the condition, information on the prenatal options available, and the expected range of postnatal outcomes should be provided.[81] Visual and written information for parents to reread and reconsider at a later date are recommended.[79,82,83] Additionally, care should be taken over the manner in which information is given. In this vulnerable situation, parents are sensitive to every word, gesture and sign of the healthcare professional. Every aspect will be remembered even years after the diagnosis.[79] Information should be simple, delivered in a lay language and repeated more than once during the conversation. Care providers should appreciate that it is difficult for parents to assimilate all the information during their initial visit. It has been demonstrated that less than 30% of information provided is absorbed by parents during their first consultation.[84] For this reason, more than one prenatal counseling meeting should be offered. Furthermore, information about support groups should be incorporated into prenatal counseling practice. Patients' organizations and charities provide an easily accessible platform for expecting parents to receive emotional support and advice from other parents and patients facing similar problems.[84]

Presence of a human element in medical communication increases parents' confidence in healthcare professionals and enhances their emotional resilience and preparedness. This ethos remains true in cases of nonviability or where parents have decided to terminate the pregnancy. Information is preferably given in person, and if possible, with both parents present.[81]

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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