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Congenital Diaphragmatic Hernia: A Major Challenge for Neonatologists

Rameshwar Prasad

Abstract

Congenital diaphragmatic hernia (CDH) is a major congenital anomaly of the neonates, characterized by the herniation of abdominal contents into the thoracic cavity during fetal life. This results in significant pulmonary hypertension and hypoxemia after birth, which responds poorly to therapeutic interventions. CDH is associated with high morbidity and mortality. The exact pathogenesis is not well understood, and genetic factors have been proposed. The management starts in utero, with antenatal diagnosis and identification of prenatal predictors for the outcomes, which help in the selection of cases suitable for fetal therapy. The postnatal management is complicated by the need for variable cardio-respiratory support and even extra corporeal membrane oxygenation (ECMO), before corrective surgery is undertaken. Improvement in the understanding of the pathophysiology of the underdeveloped lungs and pulmonary vessels has contributed to substantial progress in the management of CDH, which has translated into improved outcomes and survival. Still, many questions regarding CDH remain unanswered and the management is largely based on weak evidence.

Keywords: congenital diaphragmatic hernia, fetoscopic endoluminal tracheal occlusion, hypoxemia, pulmonary hypertension, diaphragmatic eventration, pulmonary hypoplasia

1. Introduction

CDH is a rare and major congenital anomaly. It is characterized by the partial or complete absence of diaphragm on one or both sides with herniation of abdominal content into the thorax. The dual-hit hypothesis, proposed by Keijzer et al, has suggested that the early insult in lungs' development is bilateral, occurring before and independent of the diaphragmatic defect; and a later second hit to the ipsilateral lung via compression from the herniated abdominal content leads to the characteristic pulmonary hypertension and hypoxemia in the neonate [1].

Advanced prenatal evaluation and a multidisciplinary perinatal management approach have contributed significantly to the improvement in the outcome of CDH. Several prognostic indicators have been forwarded in an attempt to identify candidates with better outcome potential who could benefit maximally from the antenatal and postnatal interventions. CDH is considered to be a medical emergency and the initial intensive management is determined by the severity of the cardiorespiratory failure, which is a consequence of lungs hypoplasia, pulmonary

vascular maldevelopment, and the ventricular dysfunction, the three outstanding pathological features of the anomaly. The surgical repair is generally deferred by consensus among the neonatologists and the surgeons. The management is more complicated if CDH is associated with other organ anomalies, which might make the outcome worse. CDH is one of the most challenging morbidities in the neonates. In this article, an evidence based overview of the current status of the disease entity is provided.

2. Epidemiology

The reported prevalence of CDH varies among studies [2–5]. The European Surveillance of Congenital Anomalies (EUROCAT) registry data analysis (1980–2009) has described the prevalence to be 2.3 per 10,000 births for all-inclusive and 1.6 per 10,000 for isolated cases [6]. Balayla *et al.* reported an incidence of 1.93 per 10,000 births in the United States [7]. The variability in the reported prevalence is due to differences in the studied geographical population, data collection methodologies, inclusion and exclusion criteria, case ascertainment and hidden mortality [8]. A decreasing trend in the live births with CDH has been reported, most likely due to an increasing number of termination of pregnancies with antenatal diagnosis of fetuses with CDH [5, 6]. Overall, the survival rate in CDH, although variable among centers, is >70% and has consistently improved over time [9, 10]. A non-significant improvement in the survival of CDH cases which are complicated with major cardiovascular or chromosomal anomalies has been recently reported [10]. The implementation of the standardized management protocols has improved the survival rate from 67% to 88% [11]. Overall, the evaluation of epidemiology and risk factors for CDH is arduous due to the heterogeneity among the studies.

CDH is more common in males [7]. The reports regarding the association of high maternal age with increased risk of CDH are conflicting [5–7, 12]. Pre gestational hypertension [5, 13] and alcohol abuse are other proposed maternal risk factors [7, 13, 14]. The impacts of ethnicity, race, maternal tobacco use and pre gestational diabetes on the risk for CDH are unclear and need further research, although a slightly lower occurrence in blacks has been documented. The identification of modifiable antenatal risk factors help in deciding the direction of prenatal screening and thus the prevention of CDH.

3. Classification of CDH

Congenital diaphragmatic defects (CDD) are classified as posterolateral (Bochdalek, 70–75%) and non-posterolateral according to the location. Non-posterolateral hernias can be retrosternal (Morgagni-Larrey, 23–28%) or central (2–7%), that involves the non-muscular or central tendinous portion of the diaphragm [15]. This anatomical classification has drawbacks as the actual site of lesion may not be easy to discern. Around 85% of the posterolateral CDH are on the left, while 10% are right sided and 5% bilateral. The diaphragmatic eventration is a rare anomaly in which a part or whole of the hemi diaphragm is abnormally elevated into the thoracic cavity, as the normal diaphragmatic musculature is partly or fully replaced by a thin fibro membranous membrane [15], allowing the abdominal viscera to protrude upwards. In order to elucidate the developmental pathways of diaphragmatic defects more accurately, Ackerman et al developed a phenotype worksheet to capture the precise morphological data on CDD by retrospectively analyzing autopsies of 181 cases [16]. They proposed a new classification system

based on the location and other specifications. According to the fetal imaging CDH can also be classified as intrapleural and mediastinal; this might help in prenatal counselling [17]. Although inadequately studied, the patho-anatomy of the diaphragmatic defects is relevant for understanding the genetics of CDH, as well as for comparing the outcomes.

Sixty percent of the CDH cases are isolated and not associated with any other major malformations. Pulmonary hypoplasia, gut malrotation, cardiac dextro position and left sided heart hypoplasia are considered to be parts of the sequence of CDH and are not regarded as separate entities. The remaining 40% of complex CDH cases are associated with major congenital anomalies in either syndromic or non-syndromic form.

4. Etiopathogenesis of CDH

4.1 Environmental factors

Environmental factors contributing to CDH are not well investigated. Maternal vitamin A deficiency, nitrofen treatment and retinoid receptor knock-out in animal model are reported to result in CDH in their offsprings, suggesting a role of retinoid signaling pathway in the pathogenesis [18]. Similar effects are seen in WT1 and COUP-TFII mutant mouse models. Beurskens et al found a significantly higher risk of CDH in the infants born to mothers who had low vitamin A intake during pregnancy (Odds ratio, 7.2; 95% confidence interval, 1.5-34.4; $p = 0.01$) [19]. The cord blood in neonates with CDH is reported to have low retinol and retinol-binding protein levels. Thalidomide and quinine have also been implicated as possible causes of CDH [20].

4.2 Genetics of CDH

CDH is genetically heterogeneous although can be monogenic. A genetic cause is found in 30% of the cases, even though most cases are sporadic and about 1-2% familial [21]. The application of the next generation sequencing technologies, e.g. DNA array and whole genome sequencing has contributed to the identification of cases with genetic etiology.

Chromosomal anomalies account for about 10% of the CDH cases. The common chromosomal aneuploidies associated with CDH are trisomy 18, 13 and 21. Morgagni hernia is more frequently found in trisomy 21 than Bochdalek hernia. Pallister Killian syndrome (PKS), characterized by mosaic tetrasomy 12p is a common chromosomal anomaly associated with CDH and occurs sporadically. The karyotype in PKS is often found to be normal due to a tissue specific distribution of chromosome 12p and reduced yield with culture aging [22, 23]. Establishing diagnosis in such cases depends on the tissue examined and genetic test used [24]. Isochromosome 12p is rarely isolated from cord blood lymphocytes, whereas its yield from the skin fibroblast is close to 100% [25]. Also, the chorionic villus sampling may miss mosaicism, while detection rate of amniocentesis is nearly 90% [23, 26]. Chromosome 12p targeted-FISH, array comparative genomic hybridization (aCGH) or other newer genetic technologies should be used to prevent misdiagnosis in the condition [24, 27]. The availability of information regarding genetic etiology equips the clinicians with better understanding of the prognosis for discussion with the parents.

Some of the common monogenic syndromes associated with CDH are Cornelia de Lange, Donnai Barrow and Simpson-Golabi-Behmel, while, others, like Fryn

syndrome, Pentalogy of Cantrell and thoracoabdominal syndrome are of unknown etiopathogenesis. Fryn syndrome, a close differential of PKS, is a clinical diagnosis and is associated with CDH in 80% of the cases. Other features of this syndrome are nail hypoplasia, high arched or cleft palate and a characteristic facies that is similar to PKS. Excellent reviews on genetics in CDH are available elsewhere [21, 28, 29].

4.3 Pathology and clinical presentation

The diaphragm, made primarily of muscle, connective tissue and central tendon, develops from the septum transversum, pleuroperitoneal folds, and the somites. The development is complete by 8 weeks of gestation. The defect in CDH is due to an abnormal development of diaphragm during the embryonic phase. Human post mortem reports and animal studies have demonstrated that in CDH, both lungs are hypoplastic, the ipsilateral one being more than the contralateral lung. Characteristically the lungs have decreased DNA and protein contents; diminished airway generations, terminal bronchioles and alveolar volume; thickened alveolar septum, and decreased complexity of the respiratory acinus. There is thickening of the pulmonary arterial medial wall and muscularisation of the smaller pre-acinar arteries.

CDH is mostly diagnosed in utero with ultrasonography (USG), magnetic resonance imaging (MRI), or both. However, some cases may present at birth without prenatal diagnosis. Clinically, the neonate develops respiratory distress, at times severe, at birth or within the first 24 hours of life. If the defect is small there may not be significant respiratory compromise. On physical examination, typically,

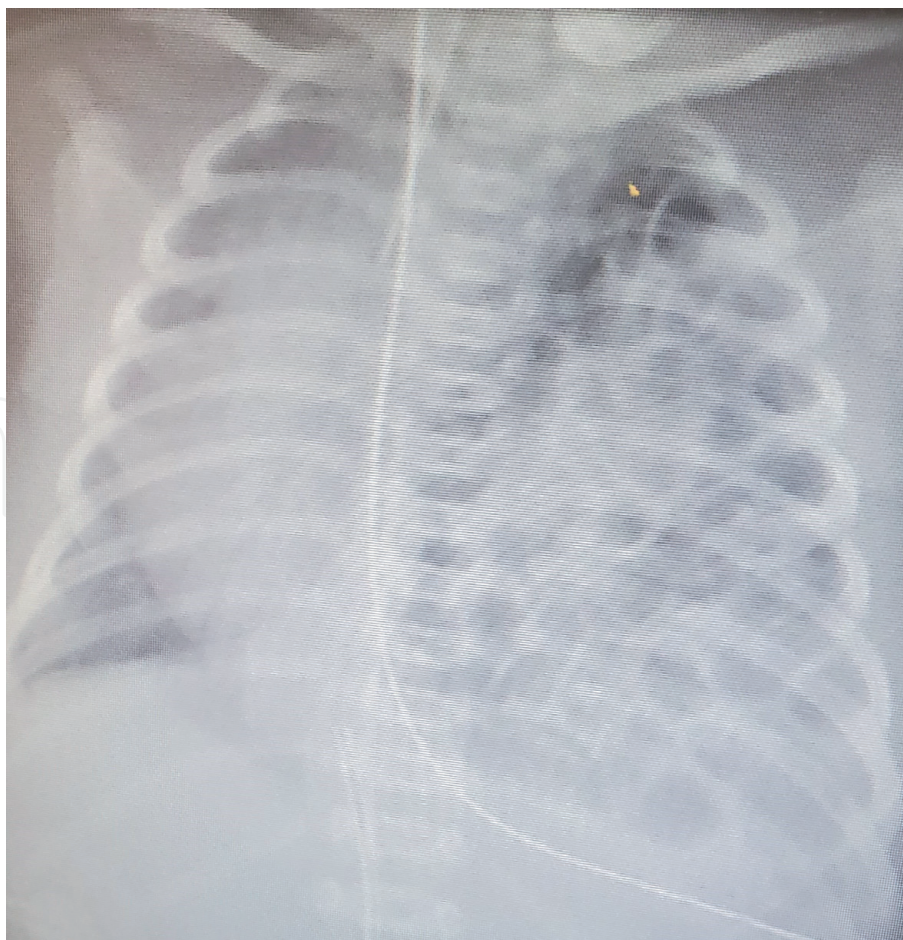


Figure 1.
Chest x-ray showing left sided diaphragmatic hernia in a newborn infant.

breath sounds are decreased on the affected side; abdomen is scaphoid; bowel sounds are heard in the thorax and heart may be displaced towards the contralateral side. Chest radiography is diagnostic (**Figure 1**).

5. Prenatal assessment of CDH

5.1 Prenatal counselling to parents

Prenatal counseling is provided after a comprehensive assessment is made with the information obtained via advanced genetic testing, radio imaging and individualized prognosis based risk stratification. It is performed by a team that is experienced in the pre and postnatal management of CDH. A multidisciplinary approach in counseling the parents by specialists from obstetrics, neonatology, pediatric surgery, genetics and radiology is of paramount value and should be undertaken. It is imperative that an accurate prediction of the outcome is made. The goal is to help the parents in making crucial decision on the options such as, termination of pregnancy (TOP), fetal intervention and expectant management. It also provides guidance for the postnatal management of CDH. Once prenatally diagnosed, mothers should be referred to a tertiary care center that provides expertise in the pre and postnatal management of the neonatal disease.

5.2 Prenatal diagnosis and evaluation of outcomes

Antenatal ultrasound screening may identify >70% of the cases of CDH. The antenatal diagnosis is particularly difficult before 24 weeks of gestation [30, 31] when small, or right-sided hernia may be often missed. A standardized assessment of CDH via prenatal ultrasound has been proposed by the European Reference Network on Rare Inherited and Congenital Anomalies (ERNICA) [32]. The most important information sought from the imaging procedures are the assessment of pulmonary hypoplasia, severity of pulmonary hypertension and the presence of associated major congenital anomalies. Absolute volumetry is superior for confirming the diagnosis of CDH in cases with equivocal sonographic findings and can be done by both 3D ultrasound and MRI.

Several imaging parameters are used for the antenatal risk stratification of CDH (**Table 1**). The lung to head ratio (LHR) of the contralateral side, first described by Metkus et al, is dependent on the gestational age [33–37] and its predictive utility on the postnatal outcome in isolated CDH, or the one associated with liver herniation, is controversial. [35, 38–40]. Still, the observed to expected LHR (o/e LHR) is a widely utilized prediction parameter for counseling the parents and selecting patients for fetal therapy. O/e LHR demonstrates little change with gestational age and provides the ability to predict survival in both left and right sided CDH [41]. Based on o/e LHR, the severity of left sided CDH is classified as follows: < 15%-extreme; < 25%-severe; 25–34.9%, or 35–44.9% with intrathoracic liver herniation-moderate; 35–45% without liver herniation or $\geq 46\%$ -mild [42]. An o/e LHR value of < 25% predicts <25% survival after the first year of life in isolated left-sided CDH, compared to 86.7% in those who have an o/e LHR of 36–45% without liver herniation, or if the value is >45% [43]. In the right-sided CDH, an o/e LHR <45% predicts poor outcome [44]. Ultrasound measurement of o/e LHR is recommended to be performed between the 22nd and 32 weeks of gestational age, although it is reported to be accurate in predicting survival even between the 18 and 38 weeks of gestation in CDH [45]. Considering that o/e LHR varies with fetal

Assessment of Lung size Indirect methods: <ul style="list-style-type: none">• Contralateral LHR^a [33]• O/E LHR [41]• Quantitative lung index [46] Lung volumes <ul style="list-style-type: none">• Observed/expected contralateral fetal lung volume ratio [40, 47]• Observed/expected total fetal lung volume ratio [40, 48]• Fetal lung volume/fetal weight ratio [49]• Absolute TFLV^b [82]• o/e TFLV [50]• PPLV^c [51]• Fetal lung volume to fetal body volume [52]• Lung/liver signal intensity ratio [53, 54]• MRI Relative Lung-to-Head Ratio [55]	Evaluation of Pulmonary circulation <ul style="list-style-type: none">• Modified McGoon index [56]• Prenatal pulmonary hypertension index [56]• Pulsatility index [57, 58]• peak early diastolic reversed flow [57–59]• Fetal Pulmonary arterial diameter [60]• Fractional moving blood volume [61]• Hyperoxygenation tests (pulmonary artery Doppler response to maternal hyperoxia) [62]• Observed/expected diameters of pulmonary arteries [63]• Contralateral vascularization index [40]• Pulmonary artery index [64]
Liver herniation <ul style="list-style-type: none">• Binary –up/Down [65]• Liver-to-thoracic area ratio (%) [66]• %LH^d [67]• Liver-to-thoracic volume ratio (%) [68]	Stomach position (indirect marker of liver herniation) Grading: Kitnao [69] , Cordier [70], Basta [71] Presence of Hernial sac [72, 73]

^aLung-head ratio.
^bTotal fetal lung volume.
^cPercent predictive lung volume.
^dLiver herniation.

Table 1.
Antenatal imaging parameters to predict outcome.

maturation, Quintero et al proposed Quantitative Lung Index (QLI), which is independent of gestational age [46] This parameter however, , failed to show superior accuracy over other predictive criteria in subsequent studies [74].

In the left sided CDH, liver herniation (LH), present in almost 50% of the cases, is an independent prognostic predictor [65]. The predictive value of LH is lost in the right sided CDH as liver is almost always herniated [75]. LH has been described variably by ultrasonography (USG) as either binary (up or down) or liver-to-thorax ratio, whereas, it is evaluated as liver to thoracic volumes ratio (LiTR) and %LH by the magnetic resonance imaging. The presence of LH suggests a larger defect, a greater severity of the lung hypoplasia and a need for prosthetics to repair the defect [76]. Even though the sensitivity and specificity of the binary parameter are reported to be only 73% and 54% respectively [77], a meta-analysis has concluded that survival is significantly better if the liver is down than up (73.7% vs. 45.4%, $p < 0.005$).

Fetal MRI is a more useful procedure for defining the types of hernia. It predicts the outcome more accurately and allows the detection of other associated congenital anomalies [74, 78, 79]. Both lungs can be assessed by MRI. MRI is more reliable than three-dimensional USG in the characterization of the ipsilateral lung and the estimation of fetal lung volumes [80]. Fetal MRI is recommended in the moderate or severe cases, or if the sonographic evaluation is inconclusive [81]. The procedure can measure total fetal lung volume (TFLV), Observed/expected TFLV (o/e-TFLV),

percent predicted lung volume (PPLV), fetal lung volume to fetal body volume ratio, lung to liver signal intensity ratio and liver herniation (%LH) [80]. The TFLV estimated during late gestation can estimate the degree of compromise in the fetal lung growth and a value of <20 ml at 34 weeks of gestation is significantly associated with mortality, as well as the need for ECMO [82]. O/e TFLV < 0.25–0.35% [83, 84] and PPLV <15% have been associated with poor prognosis [85, 86]. A combination of MRI o/e-TFLV and %LH has the best reported accuracy (AUC 0.83, range 0.70–0.91) in predicting mortality and the need for ECMO [87]. The cut off values of o/e-TFLV <35% and that of %LH >20% are associated with increased risks for both death and pulmonary morbidities [88, 89]. Three-dimensional reconstruction of the defects in CDH by MRI is a promising radiological procedure to be utilized in the evaluation and management [90].

The status of fetal pulmonary circulation has been utilized to assist in the prediction of neonatal outcomes in CDH. In fetuses undergoing FETO, the fetal pulmonary vascular reactivity to maternal oxygen supplementation (Δ pulsatility index, Δ PI) and the observed/expected lung-to-head ratio (o/e LHR) are independent predictors of pulmonary hypertension and neonatal survival [57, 62]. These parameters, along with peak early diastolic reversed flow (PEDRF) help in identifying the subgroups that may have very poor outcome with fetoscopic endoluminal tracheal occlusion (FETO) [57]. O/e-LHR (>26%, Odds ratio 14.2, survival rate 90%), intrapulmonary artery PI (<1 Z score, Odds ratio 8.4) and PEDRF (<3.5 Z score, Odds ratio 5.7) are associated with survival. O/e LHR of < 26% predicts a survival rate of only 45%. If fetal o/e LHR is < 26%, Doppler parameters can identify cases who would have chances of survival between 0% to 66-71%. Other fetal MRI parameters, such as, McGoon index and pulmonary artery index, have also been used to predict the mortality [64].

The prenatal evaluation tests, however, poorly predict the severity, duration, and response to therapy of the postnatally appearing persistent pulmonary hypertension (PPH) in CDH. Spaggiari et al documented the association between the presence and degree of pulmonary hypoplasia and post natal PPH in CDH [91]. Modified McGoon index (MMI) and prenatal pulmonary hypertension index (PPHI) are reported to accurately predict the severity of PPH [56]. Done et al have demonstrated that the fetal pulmonary reactivity to maternal O₂ administration (Δ PI) and liver-to-thorax ratio (LiTR) are the best predictors of PPH that would last for \geq 28 postnatal days [92]. Notwithstanding, a recent meta-analysis failed to establish the predictive utility of any of these prenatal parameters for PPH in CDH cases [37].

The presence of a hernia sac predicts better survival [72, 73]. The location of fetal stomach, such as intraabdominal, anterior left chest, posterior-mid left chest or retro cardiac, has been shown to strongly predict neonatal outcomes in isolated left CDH [69–71]. An abnormal stomach position is associated with mortality (OR 4.8, 95% CI 2.1-10.9), ECMO requirement (OR 5.6, 95% CI 1.9-16.7), non-primary diaphragmatic repair (OR 2.7, 95% CI 1.4-5.5), and extended mechanical ventilation (OR 5.9, 95% CI 2.3-15.6), whereas, the presence of an intra-abdominal stomach predicts survival without significant respiratory morbidity or without the need for ECMO. Prenatal intra fetal fluid effusions, commonly observed in the antenatal USG in fetuses presenting with left and right-sided CDH, with the occurrence rates of 5% and 29% respectively, do not have any association with poor outcomes [93]. In an attempt to improve the predictive value of individual parameters, 10 prenatal tests were combined into a single congenital diaphragmatic hernia composite prognostic index (CDH-CPI) by Le et al, which is reported to be strongly associated with both, the survival and the need of ECMO in infants with CDH [94]. Estimation and Risk stratification at the time of diagnosis of CDH via scans at 18-20 weeks

of gestation that could provide an accurate assessment of the postnatal outcomes, would be the ideal tool to determine whether or not a timely termination of pregnancy should be undertaken.

5.3 Postnatal evaluation of outcomes

The neonatal survival in CDH, to a large extent depends on the postnatal management provided to the infant after birth. CDH may not be always diagnosed prenatally and may be detected unexpectedly at birth. Furthermore, in a prematurely born fetus, the antenatal predictions of the prognosis become non-applicable as a significant new risk factor for the outcome and survival is added. This necessitates a new evaluation at birth [94]. Most postnatal prediction tools have been derived from and validated by the large registries. The intraoperative defect size staging, and the presence of associated anomalies, together are probably the most reliable predictor of the severity of the morbidity as well as of the survival [95, 96]. Congenital Diaphragmatic Hernia Study Group (CDHSG) developed a staging system based on the size of the diaphragmatic defect, as detected intraoperatively during the diaphragmatic repair, and the presence or absence of major cardiac anomalies [97]. In their study, the stage I patients with isolated small defects had 99% survival rate, compared to only 39% for stage V patients who had large diaphragmatic defects associated with major cardiac anomalies; and 0% in the group that was not reparable [98]. A major limitation of this staging system is the fact that being an intraoperative classification method it cannot be applied to infants before operation or to those who do not survive for the surgery. Other postnatal prediction tools for the outcomes are the Wilford Hall/Santa Rosa clinical prediction formula (WHSRPF) [99], CDH study group predictive survival [100], arterial blood gas parameters [101–103], the Score for Neonatal Acute Physiology, Version II (SNAP-II) [104], the Score for Neonatal Acute Physiology Perinatal Extension (SNAPPE-II) [105] and Brindle score [106, 107].

Cardiovascular defects are the most common anomalies associated with CDH [6, 108]. A meta-analysis involving 28,974 CDH cases reported the occurrence rate of cardiovascular defects to be 15%, out of which 42% were of critical nature [109]. All infants with CDH must undergo a high-quality diagnostic echocardiogram during pregnancy, and a postnatal imaging should be performed at birth regardless of their antenatal imaging findings. About 61% of the cases of the commonest types of CDH present with other malformation, which include chromosomal defects, non-chromosomal syndromes, malformation sequences, malformation complexes and non-syndromic multiple congenital anomalies [108]. Malformations of the cardiovascular system (27.5%), urogenital system (17.7%), musculoskeletal system (15.7%), and central nervous system (9.8%) are the commonest congenital anomalies noted in CDH. A recognizable malformation syndrome may be identified in 57.1% of the cases of CDH.

6. Antenatal interventions to improve outcome

Antenatal steroids (ANS, betamethasone and dexamethasone) are reported to improve the morphological, physiological and biochemical indicators of pulmonary immaturity, and effectuate the vascular remodeling in animal models of CDH [110, 111]. ANS variably affects the surfactant production in CDH [112, 113]. Researchers have demonstrated contrasting effects of ANS on the tracheal occlusion procedure (TO). The fetal lung growth acceleration by TO is noted to be countered by steroids [114]. On the other hand, TO adversely affects the type II pneumocytes, whereas,

ANS increases type II pneumocytes cell density and SPmRNA expression [115], thus partially correcting the surfactant deficiency caused by the procedure [116]. Combined TO and betamethasone treatment might have additive effects on reducing the muscularization of pulmonary arteries in hypoplastic lungs of CDH [117]. However, although the expression of vascular endothelial growth factor receptors is found to be restored by both TO and dexamethasone individually, the results are not noted to be additive. The antenatal betamethasone therapy was studied in a randomized controlled human trial by administering two doses of 12.5 mg, given 24 hours apart, followed by 12.5 mg given weekly for 2 weeks to pregnant women carrying CDH fetuses of 34 weeks of gestation. An interim analysis of the 32 enrolled cases showed no differences in the perinatal mortality, the duration of mechanical ventilation or the length of hospitalization between the treated and placebo groups. The study ended prematurely, as it was calculated that >1700 prenatally diagnosed CDH pregnancies would be needed to be enrolled in order to show a 10% improvement in the survival. CDH registry also failed to show any beneficial effects of the late gestation steroids therapy in CDH fetuses [118]. In the light of beneficial effects of ANS in reducing the respiratory morbidities in late preterm babies [119], Canadian CDH guideline recommends a single dose of antenatal steroids until the gestational age of 36 weeks is achieved [81]. A large multicenter trial is needed to be conducted in order to resolve the issues related to the role of ANS in CDH.

Persistent pulmonary hypertension (PPH) is one of the main causes of mortality and morbidity in CDH. Prenatal sildenafil administration in the expectant mothers has been shown to prevent fetal and neonatal vascular changes that lead to pulmonary hypertension in animal models [120]. The beneficial effects of antenatal sildenafil on neonatal pulmonary hemodynamics in lambs with diaphragmatic hernia (DH) were demonstrated in another study [121]. Conversely, sildenafil is found to decrease the lung-vessel density and vascular branching in normal lungs without CDH in animal models, raising concerns about its safety in human fetuses [120, 122]. Antenatal sildenafil has been investigated for fetal benefits in several randomized controlled trials for the prevention of preeclampsia, fetal growth restriction (FGR) and idiopathic oligohydramnios [123]. The multicenter STRIDER trial (Sildenafil Therapy in Dismal Prognosis Early Onset Fetal Growth Restriction) didn't show any benefit of antenatal sildenafil in FGR, although no adverse effects were attributed to the drug [124]. The recent meta-analyses suggest the use of sildenafil during pregnancy to be safe and to be associated with improved fetal weight at birth [123, 125]. However, the safety data for the use of antenatal sildenafil on human fetuses with CDH are scant. In view of the lack of safety data, a phase I/IIb placental transfer and safety study in human fetuses afflicted with CDH is currently underway (Antenatal Sildenafil Administration to Prevent Pulmonary Hypertension in Congenital Diaphragmatic Hernia, SToP-PH) [126].

The drug, retinoic acid crosses placenta and improves lung maturation in the nitrofen rat model of CDH [127]. However, more information is needed about its teratogenic effects before human trials can be undertaken. Other potential drugs, such as, Imatinib, [128], Vitamin E [129], bombesin [130] and stem cell based therapies [130, 131] are still limited to preclinical trials.

7. Postnatal management

The decision about the location of delivery in centers with high versus low volumes of CHD cases is controversial. Grushka et al. observed that the survival was higher in infants who were born in centers that had > 6 cases per year [132]. However, the evidence in the study was weak. There is no evidence supporting any

positive relationship between the numbers of available specialized surgeons and the morbidity related outcomes [133]. It has been documented that the out born neonates have higher odds of mortality (Odd's ratio 2.8, $P=0.04$) than those who are inborn [134]. The transfer of pregnant mothers with fetus in-utero is strongly recommended and must be done as often as possible. Current data support the decision that the prenatal care and delivery should be conducted at an optimally equipped hospital, which would be capable of providing the best care for best outcomes in newborns suffering from CDH [135]. However, the VICI-trial (High Frequency Oscillation Versus Conventional Mechanical Ventilation in Newborns with Congenital Diaphragmatic Hernia) observed similar survival rate between patients born at ECMO or at non-ECMO centers [136].

The timing of delivery is controversial and decided by the caretaking team as per the case. The gestational age at birth is a strong predictor of outcome [137]. Scheduled delivery at ≥ 39 weeks, or otherwise as per the maternal indications is considered to be the best approach in the wake of current knowledge. An analysis of 928 CDH neonates born vaginally after spontaneous onset of labor, showed a reduction in the mortality if the delivery occurred at 40 weeks of gestation (16.7%) compared to 37 weeks (25%) [138]. The Canadian Pediatric Surgery Network (CAPSNet) studied prenatally diagnosed cases of CDH under three gestational age groups (<37 weeks, 37-38 weeks, >39 weeks) and observed no differences in the mortality, ECMO requirement, duration of mechanical ventilation, the length of stay, or dependence on supplemental oxygen at discharge [139]. The outcome of CDH is worse in the prematurely born infants. It is demonstrated that the FETO procedure puts preterm neonates at a higher risk for mortality and morbidity [140]. Poor neurodevelopmental outcome has been reported in CDH survivors who are born prematurely [141]. The CAPSNet data [139] and CDH Study Group (CDHSG) reports [137] do not support any preferred delivery mode, i.e. vaginal or Cesarean section.

The resuscitation of the antenatally diagnosed cases of CDH should be performed according to the neonatal resuscitation guidelines from the American Heart Association [142] and the American Board of Pediatrics. These are endorsed by both the CDH EURO Consortium [143] and Canadian CDH collaboration [81]. The Neonatal Resuscitation Program (NRP) recommends immediate endotracheal intubation and avoidance of bag-mask ventilation in neonates with CDH. An orogastric tube should be inserted with continuous or intermittent suctioning to prevent bowel distension. A T-piece resuscitator should be used and peak inspiratory pressure (PIP) > 25 cm H₂O should be avoided in order to prevent lung injury. The European guidelines also suggest a trial of spontaneous breathing in cases where good lung volume was predicted in the prenatal assessment [143]. In a series of five CDH patients with good lung development (LHR >2.5 or o/e LHR $>50\%$, liver down), it was found feasible to avoid the routine intubation after birth [144].

Appropriate timing of the umbilical cord clamping (UCC) in CDH has not been studied well. A feasibility trial (delayed vs immediate UCC) showed that intubation and ventilation before UCC in CDH are both safe and feasible and the neonates with delayed UCC have significantly higher hemoglobin and mean blood pressure at 1 hour of age than controls [145]. However, overall, the recommendations regarding the delivery room management of CDH cases are not evidence based and more research is needed on this issue. As for the recommendations on the preductal arterial saturations targets in CDH that would ensure adequate tissue perfusion and oxygenation, the CDH EURO consortium recommends preductal SpO₂ in the delivery room to be between 80–95%. If supplemental oxygen is used at resuscitation, it should be rapidly titrated according to the specific preductal oxygen saturation target.

The surfactant status of the lungs in human fetuses with CDH is controversial and needs more information. Studies in the animal models have demonstrated surfactant to be deficient in the lungs with CHD, which might further complicate the pathophysiology of the disease process. In one study, the surfactant amount or its maturation were not found to be deficient in CDH lungs [146], while in a separate study that measured surfactant components in the tracheal aspirates of CDH neonates, both the synthesis rate and amount of SP-B were detected to be lower [147]. A retrospective analysis of 522 term infants who suffered from CDH and were enrolled in the CDHSG registry, showed an increase in the mortality, the need for ECMO, and the occurrence of chronic lung disease in those 122 infants who were treated with exogenous surfactant [148]. Furthermore, retrospective analyses published by the CDH Study Groups found no significant advantage of surfactant when given in the preterm infants with <37 weeks of gestation, and in infants on ECMO who were of > 35 weeks of gestational age, raising questions over its routine use [149, 150]. A meta-analysis also did not show any benefit of postnatal surfactant therapy in CDH cases [151]. Regardless, surfactant is used in the preterm infants with CDH almost invariably, and the trends in this matter have been stable [152]. It is reasonable to think that some specific subsets of neonates with CDH could benefit from the postnatal surfactant administration. These issues need to be evaluated via prospective trials in the future.

The strategies of permissive hypercapnia and 'gentle ventilation' have been demonstrated to improve the outcomes of neonates with CDH [151, 153, 154]. Ventilator induced lung injury caused by high ventilator settings could further damage the hypoplastic lungs and worsen the pulmonary hypertension. A retrospective analysis by Wung, et al has reported improved survival in CDH patients who were managed with minimal sedation, low peak pressures, permissive hypercapnia, avoidance of paralytics and delayed surgery [155]. A prospective study of 120 CDH neonates treated with permissive hypercapnia, permissive hypoxemia, spontaneous respiration and elective surgery found the survival to discharge rate to be at 84.4% [156]. In these cases, the oxygenation targets were set at lower levels as long as other blood gas parameters remained in acceptable range and the markers for adequate tissue perfusion were maintained within the normal values [157]. In a retrospective analysis of 70 high risk CDH patients, the survival significantly improved from 47% to 90% with the routine use of permissive hypercapnia and gentle ventilation [158].

The controversy regarding the optimal preductal and postductal saturation targets is still unresolved and more prospective trials are needed to address the issues. In the first 2 hours after birth, a preductal SpO₂ of 70% is adjudged to be acceptable, if it is improving without ventilator changes, is associated with a pH >7.2 suggesting satisfactory organ perfusion, and the ventilation is adequate with PaCO₂ below 65 mm Hg. The pulmonary vessels responds to hypoxia by vasoconstriction but hyperoxia has not been shown to result in vasodilation; instead free oxygen radical injury may ensue in such conditions. For these reasons, the SpO₂ is preferred to be kept between 90-95% in pulmonary hypertension [81].

The VICI trial provided insight into the optimum initial ventilation management of CDH patients [136]. In this study 171 antenatally diagnosed CDH patients were randomized to be initiated at either conventional ventilation (CMV) or high frequency ventilation (HFO) within 2 hours after birth. Even though, the primary outcome (death/bronchopulmonary dysplasia at day of life 28) was similar in both groups, the conventional mechanical ventilation group had significantly shorter duration of ventilation; as well as, less need for inhaled iNO, sildenafil or ECMO; shorter duration of vasoactive medication and less occurrence of treatment failure. In this crossover study, the neonates were switched over to the other ventilation mode or put on ECMO if the signs of failure of initial ventilation mode occurred and persisted for 3 hours or more. Although the trial was terminated prematurely

and only a total of 171 patients were enrolled against the desired sample size of 200 per group, the result of this trial suggested an advantage of initiating CMV over HFOV in regards to several important secondary outcomes.

It is recommended that, along with minimal stimulation, a judicious use of routine sedation and analgesia should be exercised during mechanical ventilation in CDH. Morphine sulfate and fentanyl are the preferred drugs for such purposes. Deep sedation and muscle relaxation impair respiratory functions in newborns with CDH and should be avoided [159]. The validated tools for neonatal pain assessment e.g. Neonatal Pain, Agitation and Sedation Scale (N-PASS), COMFORTneo and COMFORT behavioral scales evaluate both analgesia and sedation [160–162] and help in guiding the therapy as well as in monitoring the effects of medications.

Timing of delivery	Scheduled delivery at ≥ 39 weeks or at obstetric indication
Preferred delivery mode	No evidence of any preferred mode: vaginal or caesarean section.
Resuscitation	<ul style="list-style-type: none">• Immediate endotracheal intubation and avoidance of bag-mask ventilation• Use T-piece resuscitator and peak inspiratory pressure ≤ 25 cm H₂O
Timing of the UCC ^a	Insufficient data
Surfactant	Avoid routine use
Preductal SpO ₂	<ul style="list-style-type: none">• In delivery room SpO₂ 80-85%• First 2 hours after birth: SpO₂ 70% acceptable if pH>7.2, PaCO₂ <65 mm Hg.
Optimum initial ventilation	Conventional ventilation, rescue HFOV ^b
Sedation and Analgesia	<ul style="list-style-type: none">• Use Judiciously• Use pain and sedation assessment scales
Fluid management	Fluid boluses restricted to 10-20 ml/kg.
Inotropes	<ul style="list-style-type: none">• Improve blood pressure without improving microcirculation
Prenatal predictors of PPH ^c	Inconsistent results
Increasing SVR ^d	Not recommended to reverse right to left shunt by increasing SVR
Severe PPH + right to left atrial and ductal shunting	<ul style="list-style-type: none">• Maintain the patency of ductus arteriosus with prostaglandin E1• May respond to iNO^e
LV dysfunction + left-to-right atrial shunting + right to left ductal shunting	<ul style="list-style-type: none">• Impaired LV filling results in elevated left atrial pressure and right to left atrial shunting• Consider pulmonary venous hypertension• Poor response to iNO and potential to develop pulmonary hemorrhage• Milrinone preferred
Resource poor settings/iNO unavailable	Sildenafil – oral / Intravenous

^aUmbilical cord clamping.

^bHigh frequency oscillatory ventilation.

^cPersistent pulmonary hypertension.

^dSystemic vascular resistance.

^eInhaled nitric oxid.

Table 2.
Key points for postnatal management of congenital diaphragmatic hernia.

In order to meet the goal of ensuring adequate tissue perfusion the following clinical and biochemical markers should be maintained and monitored while managing a case of CDH: normal heart rates and blood pressure for the gestational age, urine output ≥ 1.0 ml/kg/h and serum lactate concentration <3 mmol/l. The monitoring of intra-arterial blood pressure should be done via an indwelling umbilical artery catheter. If a peripheral arterial line is used, it should preferably be inserted in the right radial artery in order to allow the measurement of pre-ductal PaO₂. An echocardiography should be done immediately after or within the first 24 hours of birth and repeated serially as indicated. The left ventricular hypoplasia and cardiac dysfunction are known to be important independent determinants of mortality in CDH and need particular attention [163]. The echocardiography helps in evaluating the myocardial dysfunction, pulmonary hypertension and right to left shunt, in addition to identifying associated structural cardiac anomalies. These information guide medical therapy. Echocardiography helps in differentiating the hypotension due to myocardial dysfunction from that of volume depletion and thus determines the appropriate management in the poor perfusion states. It also evaluates the right ventricular dysfunction and/or right ventricular overload. In CDH left ventricular dysfunction is common and should be monitored for its degree, and be treated appropriately and promptly. Other cardiac complications, such as reduced ventricular compliance and increased vascular resistance may be present and if so contribute to the reduced cardiac output. Poor left ventricles compliance in CDH generates a risk for pulmonary edema with excessive fluid administration [164]. Therefore, judicious fluid resuscitation with fluid boluses restricted to 10-20 ml/kg is advisable. If there is no response after 2 boluses, inotropic and/or vasopressor agents should be strongly considered and started. In cases who are refractory to inotropes, hydrocortisone can be added although its role in CDH is not well established and the subject requires further information. A cohort study involving 28 newborn infants has demonstrated that dopamine, epinephrine and norepinephrine improve blood pressure without improving microcirculation in CDH [165]. There is a dearth of randomized controlled trials comparing inotropes in CDH. The drug milrinone reduces afterload and improves right and left ventricular dysfunction and may be used in selected cases [166]. It is imperative to maintain continuous hemodynamic monitoring of the central venous and arterial pressures, as well as of arterial and mixed venous saturation via appropriately placed catheters. In addition, timely assessment of cardiac functions via serial echocardiographs is an essential and vital components of the management of CDH (**Table 2**).

8. Pulmonary hypertension

Pulmonary hypertension in CDH is persistent, recalcitrant and difficult to treat. The management is compromised by the scarcity of good quality research and evidence. The presence of PPH is the most significant predictor and cause of morbidity and mortality, as well as of the need for ECMO [83]. Pulmonary hypertension in CDH is characterized by the hypoplasia of pulmonary vascular bed, remodeling of pulmonary vasculature, and an altered vasoreactivity of the pulmonary vessels. The pulmonary vasculature remodeling is characterized by the medial and adventitial thickening of the mid-sized and large vessels' walls and by the neomuscularisation of small capillaries. The vascular remodeling is evidenced to begin as early as the 19th weeks of gestation in human lungs of CDH patients, and is associated with an earlier maturation of the pulmonary vasculature [167]. The pulmonary hypertension in CDH has both fixed and variable components. Reduced pulmonary vascular cross sectional area and the vascular remodeling contribute to the fixed component

of PPH. The reactive component of PPH is balanced by the circulating vasoconstrictor and vasodilator agents and defines the response to vasodilator treatment. Increased expression of the vasoconstrictive factors (endothelin A and B receptors, endothelin converting enzyme-1) and a decreased expression of the vasodilators (prostaglandin- I_2 receptor) have been reported in CDH [168]. The reports about the concentration of endothelial nitric oxide (eNOS) in CDH patients are conflicting [169–172]. An extensive review of the factors and pathways involved in the vascular remodeling in CDH has been published [173].

The utility and selection of pulmonary vasodilator agents for the treatment of PPH often change, as the underlying pathophysiology evolves during the days and weeks following the birth. The management strategies need to be adjusted as the pulmonary vascular abnormalities progress from acute to subacute and finally to the chronic stage. A poor response to the vasodilator therapies during acute phase is attributed to the left ventricular (LV) hypoplasia and dysfunction, in association with pulmonary venous hypertension [174]. In some CDH patients, there may be a “honeymoon” period displaying good oxygenation during the 1st few hours of life. Ratio of the pulmonary arterial to systemic arterial pressure (P/S ratio) is used to evaluate the degree of PPH. A P/S ratio $<2/3$ of systemic systolic pressures is considered as normal or mild; whereas, that of $\geq 2/3$ of systemic pressure denotes moderate; and if \geq systemic pressure, severe PPH [175]. Important parameters to check in the neonatal echocardiography are the direction and velocity of flow at ductal and foramen ovale shunts, flattening or left deviation of the interventricular septum, and tricuspid regurgitation jet velocity. Functional evaluation of the right and left ventricles is the key that guides the appropriate pulmonary vasodilator therapy. Lung recruitment with adequate positive end-expiratory (PEEP) or mean airway pressure and/or with surfactant to achieve an expansion up to 8- to 9-ribs during inspiration is the goal. Overriding right-to-left shunt by increasing systemic vascular resistance is not recommended. Severe PPH with right to left shunt at the atrial level necessitates the emptying of right ventricle, which is accomplished by maintaining the patency and reopening of ductus arteriosus with prostaglandin E1 if needed [176, 177]. Such cases may respond favorably to the inhaled nitric oxide therapy (iNO). LV dysfunction is associated with left-to-right atrial shunting and suggests the presence of pulmonary venous hypertension, which is associated with poor response to pulmonary vasodilator therapy [178]. Milrinone is recommended in patients with LV dysfunction due to its lusitropic, inotropic and pulmonary vasodilator properties [174]. A retrospective study reported improved cardiac function and reduced right ventricular pressure with milrinone in PPH associated with CDH [179]. As there is a potential risk of systemic hypotension, the avoidance of loading dose or priming the system with normal saline bolus were suggested by the researchers in some case series studies [180, 181]. Prospective RCTs of milrinone in CDH complicated by PPH are lacking and are warranted [182].

The Neonatal Inhaled Nitric Oxide Study (NINOS), which included 53 infants with CDH showed no difference in the combined primary outcome of death or ECMO utilization between the iNO-treated patients and controls [183]. In fact, ECMO utilization was higher in the iNO-treated group (80% vs 54% control, $p = 0.043$), indicating an adverse effect of iNO if used early in the course of PPH associated with CDH [183]. The ventilation approach, choice of the ventilator and the OI at enrollment in this study were different from the current practices. Their result further supported the important role of left ventricular dysfunction in PPH in CDH cases [178]. The use of iNO was associated with significantly higher mortality in CDHSG registry cases as well [184]. However, despite a lack of evidence, inhaled nitric oxide is commonly used in the management of PPH in CDH [179, 184].

In the nonresponders to iNO, or in the resource poor settings where iNO is often unavailable, sildenafil is a feasible option. Trials to evaluate the effect of sildenafil in newborns with persistent pulmonary hypertension of the newborn (PPHN) have been conducted. A meta analysis showed that sildenafil reduces mortality and improves oxygenation in PPHN [185]. However, there are limited data on the use of sildenafil in CDH patients. In retrospective studies, both oral and IV formulations of sildenafil were shown to improve oxygenation in CDH patients [186, 187], although IV sildenafil resulted in an increased need for inotropic support [188]. The Congenital Diaphragmatic hernia Nitric Oxide versus Sildenafil (CoDiNOS) trial is the first prospective RCT that has been recently proposed [189]. Other drugs under consideration are epoprostenol, treprostinil, inhaled alprostadil and bosentan. At this time, there is insufficient evidence in regards to their efficacy or safety for use in PPHN [190–192]. It is reasonable to comment that an accurate prediction of the reversibility of PPHN is not possible with the current knowledge.

9. Extracorporeal membrane oxygenation

Congenital diaphragmatic hernia is the most common non-cardiac indication for extracorporeal membrane oxygenation in the neonates, even though the benefits of the intervention in terms of mortality in CDH are questionable. A retrospective study of the extracorporeal life support organization (ECLS) registry data revealed the overall survival of 48.1% in term neonates representing a 13.8% reduction in survival of neonates with CDH who were treated with ECMO [193]. This result probably represents the fact that more serious CDH cases were subjected to ECMO [194]. CDHSG registry data, on the other hand, have documented an improved survival in the most severely affected CDH patients with ECMO [195]. The recently published VICI trial [136] failed to demonstrate any difference in CDH outcomes between ECLS and non-ECLS centers, further questioning the role of ECMO in CDH. The indication and utility of ECMO in CDH is still evolving, as is the timing of surgery. It should be discussed during prenatal counselling and may be considered as a therapeutic option in those centers that offer it.

10. Surgery

The reduction of herniated abdominal contents does not improve PPH in CDH and thus the outcome remains largely unaffected. A systematic review on the subject has not favored either early or late surgery [154]. The recommended physiologic criteria for preparedness for surgery are not supported by evidence [81, 143]. However, it is possible that early repair on ECMO may improve outcome [154]. In stable patients, CDH repair is usually done between 48–72 h after birth. Recurrence rate is significantly lower in open repair [154]. Polytetrafluoroethylene (PTFE) is the most durable patch repair material. Even though the survival in patients requiring patch repair has significantly improved, it is still lower than those who do not require a patch (76.9% vs 96.5%) [10].

11. Follow-up and outcomes

A multidisciplinary approach is needed for the comprehensive long term follow up of the neonates with CDH. A myriad of significant morbidities may affect these neonates, which includes respiratory disorders (chronic lung disease, pulmonary

hypertension, obstructive pulmonary disease, reduced exercise capacity, recurrent pulmonary infection), gastroesophageal reflux, nutritional derangements, neuro-developmental delays, hernia recurrence, hearing deficits and orthopedic deformities [196, 197]. The Health-related Quality of Life (HRQoL) has been reported to improve as the survivors grow older, while it may be variably compromised during the childhood [198–201]. A single-center prospective study evaluated a cohort of 32 CDH survivors at the mean age of 8 ± 4 years and recorded that about 62% of them needed medical equipment, 18% home health services and 28% special education [199]. The HRQoL in the survivors did not differ from that of healthy children, although it was diminished among those who required special education. The study concluded that even though many CDH survivors continue to require home medical equipment and home health services at school age, most have normal parent-reported HRQoL, and that the need for special education and the higher family impact of neonatal CDH lead to decreased HRQoL.

The guidelines for the follow-up of CDH survivors have been outlined by the American Academy of Pediatrics and are available [196]. A review of current follow up practices in CDH EURO consortium centers revealed that even though 15 out of 19 centers had structured and standardized follow up program for the CDH patients, the annual follow up until 16 years of age was not done in any of the participating centers [197]. The study group proposed the implementation of standardized follow-up of CDH patients for extended evaluation of the survivors for their long term outcomes [197].

12. Conclusion

Despite advances in the ante- and postnatal management, CDH is still a major medical and surgical challenge. Major determinants of the outcome in isolated CDH cases are the severity of pulmonary hypertension and concomitant cardiac dysfunction. Postnatal management targeted towards the correction of the underlying right and left ventricular dysfunction may lead the way to improved outcomes in the neonates with CDH. It is anticipated that the translational research and stem cell therapy might revolutionize the management of CDH in the future.

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