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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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References

- [1] Keijzer R, Liu J, Deimling J, Tibboel D, Post M. Dual-hit hypothesis explains pulmonary hypoplasia in the nitrofen model of congenital diaphragmatic hernia. *Am J Pathol* 2000;156:1299-1306. [https://doi.org/10.1016/S0002-9440\(10\)65000-6](https://doi.org/10.1016/S0002-9440(10)65000-6).
- [2] Dott MM, Wong L-YC, Rasmussen SA. Population-based study of congenital diaphragmatic hernia: Risk factors and survival in metropolitan Atlanta, 1968-1999. *Birth Defects Res Part A Clin Mol Teratol* 2003;67:261-267. <https://doi.org/10.1002/bdra.10039>.
- [3] Wright JCE, Budd JLS, Field DJ, Draper ES. Epidemiology and outcome of congenital diaphragmatic hernia: a 9-year experience. *Paediatr Perinat Epidemiol* 2011;25:144-149. <https://doi.org/10.1111/j.1365-3016.2010.01172.x>.
- [4] Levison J, Halliday R, Holland AJA, Walker K, Williams G, Shi E, et al. A population-based study of congenital diaphragmatic hernia outcome in New South Wales and the Australian Capital Territory, Australia, 1992-2001. *J Pediatr Surg* 2006;41:1049-1053. <https://doi.org/10.1016/j.jpedsurg.2006.01.073>.
- [5] Burgos CM, Ehrén H, Conner P, Frenckner B. Maternal Risk Factors and Perinatal Characteristics in Congenital Diaphragmatic Hernia: A Nationwide Population-Based Study. *Fetal Diagn Ther* 2019;46:385-391. <https://doi.org/10.1159/000497619>.
- [6] McGivern MR, Best KE, Rankin J, Wellesley D, Greenlees R, Addor MC, et al. Epidemiology of congenital diaphragmatic hernia in Europe: A register-based study. *Arch Dis Child Fetal Neonatal Ed* 2015;100:F137-F144. <https://doi.org/10.1136/archdischild-2014-306174>.
- [7] Balayla J, Abenhaim HA. Incidence, predictors and outcomes of congenital diaphragmatic hernia: a population-based study of 32 million births in the United States. *J Matern Neonatal Med* 2014;27:1438-1444. <https://doi.org/10.3109/14767058.2013.858691>.
- [8] Harrison MR, Bjordal RI, Langmark F, Knutrud O. Congenital diaphragmatic hernia: the hidden mortality. *J Pediatr Surg* 1978;13:227-230. [https://doi.org/10.1016/s0022-3468\(78\)80391-1](https://doi.org/10.1016/s0022-3468(78)80391-1).
- [9] Snoek KG, Greenough A, van Rosmalen J, Capolupo I, Schaible T, Ali K, et al. Congenital Diaphragmatic Hernia: 10-Year Evaluation of Survival, Extracorporeal Membrane Oxygenation, and Foetoscopic Endotracheal Occlusion in Four High-Volume Centres. *Neonatology* 2018;113:63-68. <https://doi.org/10.1159/000480451>.
- [10] Morini F, Lally KP, Lally PA, Crisafulli RM, Capolupo I, Bagolan P. Treatment Strategies for Congenital Diaphragmatic Hernia: Change Sometimes Comes Bearing Gifts. *Front Pediatr* 2017;5:195. <https://doi.org/10.3389/fped.2017.00195>.
- [11] Antonoff MB, Hustead VA, Groth SS, Schmeling DJ. Protocolized management of infants with congenital diaphragmatic hernia: Effect on survival. *J Pediatr Surg* 2011;46:39-46. <https://doi.org/10.1016/j.jpedsurg.2010.09.060>.
- [12] Yang W, Carmichael SL, Harris JA, Shaw GM. Epidemiologic characteristics of congenital diaphragmatic hernia among 2.5 million California births, 1989-1997. *Birth Defects Res Part A Clin Mol Teratol* 2006;76:170-174. <https://doi.org/10.1002/bdra.20230>.
- [13] Mcateer JP, Hecht A, De Roos AJ, Goldin AB. Maternal medical and behavioral risk factors for congenital diaphragmatic hernia. *J Pediatr Surg*

2014;49:34-38. <https://doi.org/10.1016/j.jpedsurg.2013.09.025>.

[14] Felix JF, van Dooren MF, Klaassens M, Hop WCJ, Torfs CP, Tibboel D. Environmental factors in the etiology of esophageal atresia and congenital diaphragmatic hernia: Results of a case-control study. *Birth Defects Res Part A Clin Mol Teratol* 2008;82:98-105. <https://doi.org/10.1002/bdra.20423>.

[15] Pober BR. Overview of epidemiology, genetics, birth defects, and chromosome abnormalities associated with CDH. *Am. J. Med. Genet. Part C Semin. Med. Genet.*, vol. 145, NIH Public Access; 2007, p. 158-71. <https://doi.org/10.1002/ajmg.c.30126>.

[16] Ackerman KG, Vargas SO, Wilson JA, Jennings RW, Kozakewich HPW, Pober BR. Congenital Diaphragmatic Defects: Proposal for a New Classification Based on Observations in 234 Patients. *Pediatr Dev Pathol* 2012;15:265-274. <https://doi.org/10.2350/11-05-1041-OA.1>.

[17] Mehollin-Ray AR, Cassady CI, Cass DL, Olutoye OO. Fetal MR imaging of congenital diaphragmatic hernia. *Radiographics* 2012;32:1067-1084. <https://doi.org/10.1148/rg.324115155>.

[18] Greer JJ, Babiuk RP, Thebaud B. Etiology of congenital diaphragmatic hernia: The retinoid hypothesis. *Pediatr Res* 2003;53:726-730. <https://doi.org/10.1203/01.PDR.0000062660.12769.E6>.

[19] Beurskens LWJE, Schrijver LH, Tibboel D, Wildhagen MF, Knapen MFCM, Lindemans J, et al. Dietary vitamin A intake below the recommended daily intake during pregnancy and the risk of congenital diaphragmatic hernia in the offspring. *Birth Defects Res Part A - Clin Mol Teratol* 2013;97:60-66. <https://doi.org/10.1002/bdra.23093>.

[20] David TJ, Illingworth CA. Diaphragmatic hernia in the south-west of England. *J. Med. Genet.* 1976 Aug 1;13(4):253-262.

[21] Kardon G, Ackerman KG, McCulley DJ, Shen Y, Wynn J, Shang L, et al. Congenital diaphragmatic hernias: From genes to mechanisms to therapies. *DMM Dis Model Mech* 2017;10:955-970. <https://doi.org/10.1242/dmm.028365>.

[22] Doray B, Girard-Lemaire F, Gasser B, Baldauf J-J, de Geeter B, Spizzo M, et al. Pallister-Killian syndrome: difficulties of prenatal diagnosis. *Prenat Diagn* 2002;22:470-477. <https://doi.org/10.1002/pd.342>.

[23] Frisova V, Svobodova IT, Tozzi M, Raskova D. Prenatal diagnosis of Pallister-Killian syndrome in pregnancy with normal CVS result and abnormal ultrasound findings in the second trimester. *Taiwan J Obstet Gynecol* 2018;57:726-729. <https://doi.org/10.1016/j.tjog.2018.08.021>.

[24] Kucińska-Chahwan A, Bijok J, Dąbkowska S, Jóźwiak A, Ilnicka A, Nowakowska B, et al. Targeted prenatal diagnosis of Pallister-Killian syndrome. *Prenat Diagn* 2017;37:446-452. <https://doi.org/10.1002/pd.5030>.

[25] Karaman B, Kayserili H, Ghanbari A, Uyguner ZO, Toksoy G, Altunoglu U, et al. Pallister-Killian syndrome: Clinical, cytogenetic and molecular findings in 15 cases. *Mol Cytogenet* 2018;11. <https://doi.org/10.1186/s13039-018-0395-z>.

[26] Salzano E, Raible S, Kaur M, Wilkens A, Sperti G, Tilton R, et al. Prenatal profile of Pallister-Killian syndrome: Retrospective analysis of 114 pregnancies, literature review and approach to prenatal diagnosis. *Am J Med Genet Part A* 2018;176:2575-2586. <https://doi.org/10.1002/ajmg.a.40499>.

- [27] Wang T, Ren C, Chen D, Lu J, Guo L, Zheng L, et al. Prenatal diagnosis of Pallister-Killian syndrome using cord blood samples. *Mol Cytogenet* 2019;12:39. <https://doi.org/10.1186/s13039-019-0449-x>.
- [28] Clarkson KB, Coming K, Toburen A. Lethal Pallister-Killian syndrome and Fryns syndrome: diagnostic considerations. *Genet Med* 2000;2:77-77. <https://doi.org/10.1097/00125817-200001000-00091>.
- [29] Longoni M, Pober BR, High FA. Congenital Diaphragmatic Hernia Overview. In *GeneReviews®* [Internet] 2019 Mar 28. University of Washington, Seattle.
- [30] Garne E, Haeusler M, Barisic I, Gjergja R, Stoll C, Clementi M. Congenital diaphragmatic hernia: evaluation of prenatal diagnosis in 20 European regions. *Ultrasound Obstet Gynecol* 2002;19:329-333. <https://doi.org/10.1046/j.1469-0705.2002.00635.x>
- [31] Gallot D, Coste K, Francannet C, Laurichesse H, Boda C, Ughetto S, et al. Antenatal detection and impact on outcome of congenital diaphragmatic hernia: A 12-year experience in Auvergne (France). *Eur J Obstet Gynecol Reprod Biol* 2006;125:202-205. <https://doi.org/10.1016/j.ejogrb.2005.06.030>.
- [32] Russo FM, Cordier A-G, De Catte L, Saada J, Benachi A, Deprest J. Proposal for standardized prenatal ultrasound assessment of the fetus with congenital diaphragmatic hernia by the European reference network on rare inherited and congenital anomalies (ERNICA). *Prenat Diagn* 2018;38:629-637. <https://doi.org/10.1002/pd.5297>.
- [33] Metkus AP, Filly RA, Stringer MD, Harrison MR, Adzick NS. Sonographic predictors of survival in fetal diaphragmatic hernia. *J. Pediatr.* Surg., vol. 31, W.B. Saunders; 1996, p. 148-152. [https://doi.org/10.1016/S0022-3468\(96\)90338-3](https://doi.org/10.1016/S0022-3468(96)90338-3).
- [34] Peralta CFA, Cavoretto P, Csapo B, Vandecruys H, Nicolaides KH. Assessment of lung area in normal fetuses at 12-32 weeks. *Ultrasound Obstet Gynecol* 2005;26:718-724. <https://doi.org/10.1002/uog.2651>.
- [35] Knox E, Lissauer D, Khan K, Kilby M. Prenatal detection of pulmonary hypoplasia in fetuses with congenital diaphragmatic hernia: A systematic review and meta-analysis of diagnostic studies. *J Matern Neonatal Med* 2010;23:579-588. <https://doi.org/10.3109/14767050903551400>.
- [36] Odibo AO, Biron-Shental T, Tomlinson TM, Shim TL, Wanat K. Discussion: "Predictive value of lung-head ratio in congenital diaphragmatic hernia" by Yang et al. *Am J Obstet Gynecol* 2007;197:e1-e5. <https://doi.org/10.1016/j.ajog.2007.05.050>.
- [37] Russo FM, Eastwood MP, Keijzer R, Al-Maary J, Toelen J, Van Mieghem T, et al. Lung size and liver herniation predict need for extracorporeal membrane oxygenation but not pulmonary hypertension in isolated congenital diaphragmatic hernia: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2017;49:704-713. <https://doi.org/10.1002/uog.16000>.
- [38] Jani J, Keller RL, Benachi A, Nicolaides KH, Favre R, Gratacos E, et al. Prenatal prediction of survival in isolated left-sided diaphragmatic hernia. *Ultrasound Obstet Gynecol* 2006;27:18-22. <https://doi.org/10.1002/uog.2688>.
- [39] Lipshutz GS, Albanese CT, Feldstein VA, Jennings RW, Housley HT, Beech R, et al. Prospective analysis of lung-to-head ratio predicts survival for patients with prenatally diagnosed congenital diaphragmatic hernia.

J. Pediatr. Surg., vol. 32, W.B. Saunders; 1997, p. 1634-1636. [https://doi.org/10.1016/S0022-3468\(97\)90471-1](https://doi.org/10.1016/S0022-3468(97)90471-1).

[40] Ruano R, Takashi E, Da Silva MM, Campos JADB, Tannuri U, Zugaib M. Prediction and probability of neonatal outcome in isolated congenital diaphragmatic hernia using multiple ultrasound parameters. *Ultrasound Obstet Gynecol* 2012;39:42-49. <https://doi.org/10.1002/uog.10095>.

[41] Jani J, Nicolaides KH, Keller RL, Benachi A, Peralta CFA, Favre R, et al. Observed to expected lung area to head circumference ratio in the prediction of survival in fetuses with isolated diaphragmatic hernia. *Ultrasound Obstet Gynecol* 2007;30:67-71. <https://doi.org/10.1002/uog.4052>.

[42] Deprest JA, Flemmer AW, Gratacos E, Nicolaides K. Antenatal prediction of lung volume and in-utero treatment by fetal endoscopic tracheal occlusion in severe isolated congenital diaphragmatic hernia. *Semin Fetal Neonatal Med* 2009;14:8-13. <https://doi.org/10.1016/j.siny.2008.08.010>.

[43] Snoek KG, Peters NCJ, van Rosmalen J, van Heijst AFJ, Eggink AJ, Sikkink E, et al. The validity of the observed-to-expected lung-to-head ratio in congenital diaphragmatic hernia in an era of standardized neonatal treatment; a multicenter study. *Prenat Diagn.* 2017;37(7):658-665.

[44] Russo FM, Cordier A-G, Salazar L, Basurto D, Gomez O, Gratacos E, et al. 203: Prediction of survival in right sided congenital diaphragmatic hernia in the FETO era. *Am J Obstet Gynecol.* 2019;220(1):S147. Available from: <http://www.ajog.org/article/S0002937818312468/fulltext>

[45] Alfaraj MA, Shah PS, Bohn D, Pantazi S, O'Brien K, Chiu PP, et al. Congenital diaphragmatic hernia: Lung-to-head ratio and lung volume

for prediction of outcome. *Am J Obstet Gynecol.* 2011;205(1):43.e1-43.e8.

[46] Quintero RA, Kontopoulos E V, Quintero LF, Landy DC, Gonzalez R, Chmait RH. The observed vs. expected lung-to-head ratio does not correct for the effect of gestational age on the lung-to-head ratio. *J. Matern. Neonatal Med.* 2013;26(6):552-557.

[47] Ruano R, Aubry MC, Barthe B, Dumez Y, Benachi A. Three-dimensional ultrasonographic measurements of the fetal lungs for prediction of perinatal outcome in isolated congenital diaphragmatic hernia. *J Obstet Gynaecol Res.* 2009;35(6):1031-1041.

[48] Ruano R, Benachi A, Joubin L, Aubry M-C, Thalabard J-C, Dumez Y, et al. Three-dimensional ultrasonographic assessment of fetal lung volume as prognostic factor in isolated congenital diaphragmatic hernia. *BJOG An Int J Obstet Gynaecol.* 2004;111(5):423-429. <http://doi.wiley.com/10.1111/j.1471-0528.2004.00100.x>

[49] Ruano R, Aubry MC, Dumez Y, Zugaib M, Benachi A. Predicting neonatal deaths and pulmonary hypoplasia in isolated congenital diaphragmatic hernia using the sonographic fetal lung volume-body weight ratio. *Am J Roentgenol.* 2008;190(5):1216-1219.

[50] Mahieu-Caputo D, Sonigo P, Dommergues M, Fournet JC, Thalabard JC, Abarca C, et al. Fetal lung volume measurement by magnetic resonance imaging in congenital diaphragmatic hernia. *BJOG An Int J Obstet Gynaecol.* 2001;108(8):863-868. <http://doi.wiley.com/10.1111/j.1471-0528.2001.00184.x>

[51] Barnewolt CE, Kunisaki SM, Fauza DO, Nemes LP, Estroff JA, Jennings RW. Percent predicted lung volumes as measured on fetal magnetic

resonance imaging: a useful biometric parameter for risk stratification in congenital diaphragmatic hernia. *J Pediatr Surg.* 2007;42(1):193-197.

[52] Weidner M, Hagelstein C, Debus A, Walleyo A, Weiss C, Schoenberg SO, et al. MRI-Based Ratio of Fetal Lung Volume to Fetal Body Volume as a New Prognostic Marker in Congenital Diaphragmatic Hernia. *Am J Roentgenol.* 2014;202(6):1330-1336. <http://www.ajronline.org/doi/abs/10.2214/AJR.13.11023>

[53] Balassy C, Kasprian G, Brugger PC, Weber M, Csapo B, Herold C, et al. Assessment of lung development in isolated congenital diaphragmatic hernia using signal intensity ratios on fetal MR imaging. *Eur Radiol.* 2010;20(4):829-837. <https://link.springer.com/article/10.1007/s00330-009-1633-x>

[54] Nishie A, Tajima T, Asayama Y, Ishigami K, Hirakawa M, Nakayama T, et al. MR prediction of postnatal outcomes in left-sided congenital diaphragmatic hernia using right lung signal intensity: Comparison with that using right lung volume. *J Magn Reson Imaging.* 2009;30(1):112-120. <http://doi.wiley.com/10.1002/jmri.21829>

[55] Kilian AK, Schaible T, Hofmann V, Brade J, Neff KW, Büsing KA. Congenital diaphragmatic hernia: Predictive value of MRI relative lung-to-head ratio compared with MRI fetal lung volume and sonographic lung-to-head ratio. *Am J Roentgenol.* 2009;192(1):153-158.

[56] Vuletin JF, Lim FY, Cnota J, Kline-Fath B, Salisbury S, Haberman B, et al. Prenatal pulmonary hypertension index: novel prenatal predictor of severe postnatal pulmonary artery hypertension in antenatally diagnosed congenital diaphragmatic hernia. *J Pediatr Surg.* 2010;45(4):703-708.

[57] Cruz-Martinez R, Moreno-Alvarez O, Hernandez-Andrade E, Castañon M, Done E, Martinez JM, et al. Contribution of intrapulmonary artery Doppler to improve prediction of survival in fetuses with congenital diaphragmatic hernia treated with fetal endoscopic tracheal occlusion. *Ultrasound Obstet Gynecol.* 2010;35(5):572-577. Available from: <http://doi.wiley.com/10.1002/uog.7593>

[58] Cruz-Martinez R, Castañon M, Moreno-Alvarez O, Acosta-Rojas R, Martinez JM, Gratacos E. Usefulness of lung-to-head ratio and intrapulmonary arterial Doppler in predicting neonatal morbidity in fetuses with congenital diaphragmatic hernia treated with fetoscopic tracheal occlusion. *Ultrasound Obstet Gynecol.* 2013;41(1):59-65.

[59] Moreno-Alvarez O, Hernandez-Andrade E, Oros D, Jani J, Deprest J, Gratacos E. Association between intrapulmonary arterial Doppler parameters and degree of lung growth as measured by lung-to-head ratio in fetuses with congenital diaphragmatic hernia. *Ultrasound Obstet Gynecol.* 2008;31(2):164-170. Available from: <http://doi.wiley.com/10.1002/uog.5201>

[60] Sokol J, Shimizu N, Bohn D, Doherty D, Ryan G, Hornberger LK. Fetal pulmonary artery diameter measurements as a predictor of morbidity in antenatally diagnosed congenital diaphragmatic hernia: A prospective study. *Am J Obstet Gynecol.* 2006;195(2):470-477.

[61] Moreno-Alvarez O, Cruz-Martinez R, Hernandez-Andrade E, Done E, Gómez O, Deprest J, et al. Lung tissue perfusion in congenital diaphragmatic hernia and association with the lung-to-head ratio and intrapulmonary artery pulsed Doppler. *Ultrasound Obstet Gynecol.* 2010;35(5):578-582. <http://doi.wiley.com/10.1002/uog.7592>

- [62] Done E, Allegaert K, Lewi P, Jani J, Gucciardo L, Van Mieghem T, et al. Maternal hyperoxygenation test in fetuses undergoing FETO for severe isolated congenital diaphragmatic hernia. *Ultrasound Obstet Gynecol.* 2011;37(3):264-271. Available from: <http://doi.wiley.com/10.1002/uog.7753>
- [63] Ruano R, Aubry MC, Barthe B, Mitanchez D, Dumez Y, Benachi A. Predicting perinatal outcome in isolated congenital diaphragmatic hernia using fetal pulmonary artery diameters. *J Pediatr Surg.* 2008;43(4):606-611.
- [64] Takahashi S, Oishi Y, Ito N, Nanba Y, Tsukamoto K, Nakamura T, et al. Evaluating mortality and disease severity in congenital diaphragmatic hernia using the McGoon and pulmonary artery indices. *J Pediatr Surg.* 2009;44(11):2101-2106.
- [65] Kitano Y, Nakagawa S, Kuroda T, Honna T, Itoh Y, Nakamura T, et al. Liver position in fetal congenital diaphragmatic hernia retains a prognostic value in the era of lung-protective strategy. *J Pediatr Surg.* 2005;40(12):1827-1832.
- [66] Werneck Britto IS, Olutoye OO, Cass DL, Zamora IJ, Lee TC, Cassady CI, et al. Quantification of liver herniation in fetuses with isolated congenital diaphragmatic hernia using two-dimensional ultrasonography. *Ultrasound Obstet Gynecol.* 2015;46(2):150-154. <http://doi.wiley.com/10.1002/uog.14718>
- [67] Lazar DA, Ruano R, Cass DL, Moise KJ, Johnson A, Lee TC, et al. Defining “liver-up”: Does the volume of liver herniation predict outcome for fetuses with isolated left-sided congenital diaphragmatic hernia? *J Pediatr Surg.* 2012;47(6):1058-1062. doi:10.1016/j.jpedsurg.2012.03.003.
- [68] Cannie M, Jani J, Chaffiotte C, Vaast P, Deruelle P, Houfflin-Debarge V, et al. Quantification of intrathoracic liver herniation by magnetic resonance imaging and prediction of postnatal survival in fetuses with congenital diaphragmatic hernia. *Ultrasound Obstet Gynecol.* 2008;32(5):627-632.
- [69] Kitano Y, Okuyama H, Saito M, Usui N, Morikawa N, Masumoto K, et al. Re-evaluation of stomach position as a simple prognostic factor in fetal left congenital diaphragmatic hernia: a multicenter survey in Japan. *Ultrasound Obstet Gynecol.* 2011;37(3):277-282. Available from: <http://doi.wiley.com/10.1002/uog.8892>
- [70] Cordier AG, Cannie MM, Guilbaud L, De Laveaucoupet J, Martinovic J, Nowakowska D, et al. Stomach position versus liver-to-thoracic volume ratio in left-sided congenital diaphragmatic hernia. *J Matern Neonatal Med.* 2015;28(2):190-195.
- [71] Basta AM, Lusk LA, Keller RL, Filly RA. Fetal Stomach Position Predicts Neonatal Outcomes in Isolated Left-Sided Congenital Diaphragmatic Hernia. *Fetal Diagn Ther.* 2016;39(4):248-255.
- [72] Spaggiari E, Stirnemann J, Bernard J-P, De Saint Blanquat L, Beaudoin S, Ville Y. Prognostic value of a hernia sac in congenital diaphragmatic hernia. *Ultrasound Obstet Gynecol.* 2013;41(3):286-290. Available from: <http://doi.wiley.com/10.1002/uog.11189>
- [73] Bouchghoul H, Marty O, Fouquet V, Cordier A-G, Senat M-V, Saada J, et al. Congenital diaphragmatic hernia has a better prognosis when associated with a hernia sac. *Prenat Diagn.* 2018;38(9):638-644. Available from: <http://doi.wiley.com/10.1002/pd.5326>
- [74] Ruano R, Takashi E, Silva MM da, Haeri S, Tannuri U, Zugaib M. Quantitative Lung Index, Contralateral Lung Area, or Lung-to-Head

Ratio to Predict the Neonatal Outcome in Isolated Congenital Diaphragmatic Hernia? *J Ultrasound Med.* 2013;32(3):413-417. Available from: <http://doi.wiley.com/10.7863/jum.2013.32.3.413>

[75] DeKoninck P, Gomez O, Sandaite I, Richter J, Nawapun K, Eerdekens A, et al. Right-sided congenital diaphragmatic hernia in a decade of fetal surgery. *BJOG An Int J Obstet Gynaecol.* 2015;122(7):940-946. Available from: <http://doi.wiley.com/10.1111/1471-0528.13065>

[76] Kunisaki SM, Barnewolt CE, Estroff JA, Nemes LP, Jennings RW, Wilson JM, et al. Liver position is a prenatal predictive factor of prosthetic repair in congenital diaphragmatic hernia. *Fetal Diagn Ther.* 2008;23(4):258-262.

[77] Mullassery D, Ba'Ath ME, Jesudason EC, Losty PD. Value of liver herniation in prediction of outcome in fetal congenital diaphragmatic hernia: A systematic review and meta-analysis. *Ultrasound Obstet Gynecol.* 2010 May;35(5):609-614.

[78] Jani J, Cannie M, Sonigo P, Robert Y, Moreno O, Benachi A, et al. Value of prenatal magnetic resonance imaging in the prediction of postnatal outcome in fetuses with diaphragmatic hernia. *Ultrasound Obstet Gynecol.* 2008 Nov 1;32(6):793-799. Available from: <http://doi.wiley.com/10.1002/uog.6234>

[79] Bebbington M, Victoria T, Danzer E, Moldenhauer J, Khalek N, Johnson M, et al. Comparison of ultrasound and magnetic resonance imaging parameters in predicting survival in isolated left-sided congenital diaphragmatic hernia. *Ultrasound Obstet Gynecol.* 2014;43(6):670-674. Available from: <http://doi.wiley.com/10.1002/uog.13271>

[80] Jani JC, Cannie M, Peralta CFA, Deprest JA, Nicolaides KH,

Dymarkowski S. Lung volumes in fetuses with congenital diaphragmatic hernia: Comparison of 3D US and MR imaging assessments. *Radiology.* 2007;244(2):575-582.

[81] Puligandla PS, Skarsgard ED, Offringa M, Adatia I, Baird R, Bailey JAM, et al. Diagnosis and management of congenital diaphragmatic hernia: a clinical practice guideline. *CMAJ.* 2018;190(4):E103-E112.

[82] Lee TC, Lim FY, Keswani SG, Frischer JS, Haberman B, Kingma PS, et al. Late gestation fetal magnetic resonance imaging-derived total lung volume predicts postnatal survival and need for extracorporeal membrane oxygenation support in isolated congenital diaphragmatic hernia. *J Pediatr Surg.* 2011;46(6):1165-1171.

[83] Cannie M, Jani J, Meersschaert J, Allegaert K, Done' E, Marchal G, et al. Prenatal prediction of survival in isolated diaphragmatic hernia using observed to expected total fetal lung volume determined by magnetic resonance imaging based on either gestational age or fetal body volume. *Ultrasound Obstet Gynecol.* 2008 Oct 1;32(5):633-639. Available from: <http://doi.wiley.com/10.1002/uog.6139>

[84] Oluyomi-Obi T, Kuret V, Puligandla P, Lodha A, Lee-Robertson H, Lee K, Somerset D, Johnson J, Ryan G. Antenatal predictors of outcome in prenatally diagnosed congenital diaphragmatic hernia (CDH). *J. Pediatr. Surg.* 2017;52(5):881-888.

[85] Barnewolt CE, Kunisaki SM, Fauza DO, Nemes LP, Estroff JA, Jennings RW. Percent predicted lung volumes as measured on fetal magnetic resonance imaging: a useful biometric parameter for risk stratification in congenital diaphragmatic hernia. *J. Pediatr. Surg.* 2007;42(1):193-197.

- [86] Shieh HF, Barnewolt CE, Wilson JM, Zurakowski D, Connolly SA, Estroff JA, et al. Percent predicted lung volume changes on fetal magnetic resonance imaging throughout gestation in congenital diaphragmatic hernia. *J Pediatr Surg.* 2017;52(6):933-937.
- [87] Ruano R, Lazar DA, Cass DL, Zamora IJ, Lee TC, Cassady CI, Mehollin-Ray A, Welty S, Fernandes CJ, Haeri S, Belfort MA. Fetal lung volume and quantification of liver herniation by magnetic resonance imaging in isolated congenital diaphragmatic hernia. *Ultrasound Obstet. Gynecol.* 2014;43(6):662-669.
- [88] Zamora IJ, Olutoye OO, Cass DL, Fallon SC, Lazar DA, Cassady CI, Mehollin-Ray AR, Welty SE, Ruano R, Belfort MA, Lee TC. Prenatal MRI fetal lung volumes and percent liver herniation predict pulmonary morbidity in congenital diaphragmatic hernia (CDH). *J Pediatr Surg.* 2014;49(5):688-693.
- [89] Akinkuotu AC, Cruz SM, Abbas PI, Lee TC, Welty SE, Olutoye OO, Cassady CI, Mehollin-Ray AR, Ruano R, Belfort MA, Cass DL. Risk-stratification of severity for infants with CDH: prenatal versus postnatal predictors of outcome. *J Pediatr Surg.* 2016;51(1):44-48.
- [90] Prayer F, Metzelder M, Krois W, Brugger PC, Gruber GM, Weber M, Scharrer A, Rokitansky A, Langs G, Prayer D, Unger E. Three-dimensional reconstruction of defects in congenital diaphragmatic hernia: a fetal MRI study. *Ultrasound Obstet. Gynecol.* 2019;53(6):816-826.
- [91] Spaggiari E, Stirnemann JJ, Sonigo P, Khen-Dunlop N, De Saint Blanquat L, Ville Y. Prenatal prediction of pulmonary arterial hypertension in congenital diaphragmatic hernia. *Ultrasound Obstet Gynecol.* 2015;45(5):572-577.
- [92] Done E, Debeer A, Gucciardo L, Van Mieghem T, Lewi P, Devlieger R, et al. Prediction of Neonatal Respiratory Function and Pulmonary Hypertension in Fetuses with Isolated Congenital Diaphragmatic Hernia in the Fetal Endoscopic Tracheal Occlusion Era: A Single-Center Study. *Fetal Diagn Ther.* 2015;37(1):24-32.
- [93] Van Mieghem T, Cruz-Martinez R, Allegaert K, Dekoninck P, Castanon M, Sandaite I, et al. Outcome of fetuses with congenital diaphragmatic hernia and associated intrafetal fluid effusions managed in the era of fetal surgery. *Ultrasound Obstet Gynecol.* 2012;39(1):50-55. Available from: <http://doi.wiley.com/10.1002/uog.10097>
- [94] Le LD, Keswani SG, Biesiada J, Lim FY, Kingma PS, Haberman BE, et al. The congenital diaphragmatic hernia composite prognostic index correlates with survival in left-sided congenital diaphragmatic hernia. *J Pediatr Surg.* 2012;47(1):57-62.
- [95] Lally KP, Lally PA, Lasky RE, Tibboel D, Jaksic T, Wilson JM, et al. Defect size determines survival in infants with congenital diaphragmatic hernia. *Pediatrics.* 2007;120(3):e651-e657.
- [96] Congenital diaphragmatic hernia: Defect size correlates with developmental defect. *J Pediatr Surg.* 2013;48:1177-82.
- [97] Harting MT, Lally KP. The congenital diaphragmatic hernia study group registry update. *Semin. Fetal Neonatal Med.* 2014; 19(6):370-375.
- [98] Lally KP, Lasky RE, Lally PA, Bagolan P, Davis CF, Frenckner BP, et al. Standardized reporting for congenital diaphragmatic hernia - An

international consensus. *J Pediatr Surg.* 2013;48(12):2408-2415. doi:10.1016/j.jpedsurg.2013.08.014.

[99] Schultz CM, DiGeronimo RJ, Yoder BA. Congenital diaphragmatic hernia: a simplified postnatal predictor of outcome. *J Pediatr Surg.* 2007;42(3):510-516.

[100] Lally KP, Jaksic T, Wilson JM, Clark RH, Hardin WD, Hirsch RB, et al. Estimating disease severity of congenital diaphragmatic hernia in the first 5 minutes of life. *J Pediatr Surg.* 2001;36(1):141-145.

[101] Kays DW, Talbert JL, Islam S, Larson SD, Taylor JA, Perkins J. Improved survival in left liver-up congenital diaphragmatic hernia by early repair before extracorporeal membrane oxygenation: optimization of patient selection by multivariate risk modeling. *Journal of the American College of Surgeons.* 2016;222(4):459-470.

[102] Gentili A, Pasini L, Iannella E, Landuzzi V, Lima M, Bacchi Reggiani ML, et al. Predictive outcome indexes in neonatal Congenital Diaphragmatic Hernia. *J Matern Neonatal Med.* 2015 ;28(13): 1602-1607.

[103] Jancelewicz T, Brindle ME, Harting MT, Tolley EA, Langham MR, Lally PA, et al. Extracorporeal Membrane Oxygenation (ECMO) Risk Stratification in Newborns with Congenital Diaphragmatic Hernia (CDH). *J Pediatr Surg.* 2018;53(10):1890-1895.

[104] Skarsgard ED, Macnab YC, Qiu Z, Little R, Lee SK. SNAP-II Predicts Mortality among Infants with Congenital Diaphragmatic Hernia. *J Perinatol.* 2005;25:315-319.

[105] Chiu LW, Desai J, Shanti C, Rane S, Agarwal P, Thomas RL, et al.

SNAPPE II Score As a Predictor of Survival in Neonates with Congenital Diaphragmatic Hernia: A Single Center Experience. *Eur J Pediatr Surg.* 2016;26(4):316-321. Available from: <http://www.thieme-connect.de/DOI/DOI?10.1055/s-0035-1554103>

[106] Brindle ME, Cook EF, Tibboel D, Lally PA, Lally KP. A clinical prediction rule for the severity of congenital diaphragmatic hernias in newborns. *Pediatrics.* 2014;134(2):e413-e419.

[107] Bent DP, Nelson J, Kent DM, Jen HC. Population-based Validation of a Clinical Prediction Model for Congenital Diaphragmatic Hernias HHS Public Access. *J Pediatr.* 2018;201:160-165.

[108] Stoll C, Alembik Y, Dott B, Roth MP. Associated non diaphragmatic anomalies among cases with congenital diaphragmatic hernia. *Genet Couns [Internet].* 2015;26(3):281-298.

[109] Montalva L, Lauriti G, Zani A. Congenital heart disease associated with congenital diaphragmatic hernia: A systematic review on incidence, prenatal diagnosis, management, and outcome. *J Pediatr Surg.* 2019;54(5):909-919.

[110] Schnitzer JJ, Hedrick HL, Pacheco BA, Losty PD, Ryan DP, Doody DP, Donahoe PK. Prenatal glucocorticoid therapy reverses pulmonary immaturity in congenital diaphragmatic hernia in fetal sheep. *Annals of surgery.* 1996;224(4):430.

[111] Schmidt AF, Gonçalves FLL, Nassr ACC, Pereira LAVD, Farmer D, Sbragia L. Antenatal steroid and tracheal occlusion restore vascular endothelial growth factor receptors in congenital diaphragmatic hernia rat model. *Am J Obstet Gynecol.* 2010;203(2):184.e13-184.e20.

- [112] Suen HC, Bloch KD, Donahoe PK. Antenatal glucocorticoid corrects pulmonary immaturity in experimentally induced congenital diaphragmatic hernia in rats. *Pediatr Res.* 1994;35(5):523-529.
- [113] Davey MG, Danzer E, Schwarz U, Adzick NS, Flake AW, Hedrick HL. Prenatal glucocorticoids and exogenous surfactant therapy improve respiratory function in lambs with severe diaphragmatic hernia following fetal tracheal occlusion. *Pediatr Res.* 2006;60(2):131-135.
- [114] Mayer S, Klaritsch P, Sbragia L, Toelen J, Till H, Deprest JA. Maternal administration of betamethasone inhibits proliferation induced by fetal tracheal occlusion in the nitrofen rat model for congenital diaphragmatic hernia: a placebo-controlled study. *Pediatric surgery international.* 2008;24(12):1287-1295.
- [115] Kay S, Flageole JM, Laberge H, Richardson S, Belanger S, Piedboeuf B. Use of antenatal steroids to counteract the negative effects of tracheal occlusion in the fetal lamb model. *Pediatr Res.* 2001;50(4):495-501.
- [116] Davey MG, Danzer E, Schwarz U, Robinson L, Shegu S, Adzick NS, et al. Prenatal glucocorticoids improve lung morphology and partially restores surfactant mRNA expression in lambs with diaphragmatic hernia undergoing fetal tracheal occlusion. *Pediatr Pulmonol.* 2006;41(12):1188-1196. Available from: <http://doi.wiley.com/10.1002/ppul.20516>
- [117] Roubliova XI, Lewi PJ, Verbeken EK, Vaast P, Jani JC, Lu H, et al. The effect of maternal betamethasone and fetal tracheal occlusion on pulmonary vascular morphometry in fetal rabbits with surgically induced diaphragmatic hernia: A placebo controlled morphologic study. *Prenat Diagn.* 2009;29(7):674-681.
- [118] Lally KP, Bagolan P, Hosie S, Lally PA, Stewart M, Cotten CM, et al. Corticosteroids for fetuses with congenital diaphragmatic hernia: Can we show benefit? *J Pediatr Surg.* 2006;41(4):668-674.
- [119] Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita ATN, Reddy UM, Saade GR, et al. Antenatal beta-methasone for women at risk for late preterm delivery. *N Engl J Med.* 2016;374(14):1311-1320.
- [120] Luong C, Rey-Perra J, Vadivel A, Gilmour G, Sauve Y, Koonen D, et al. Antenatal sildenafil treatment attenuates pulmonary hypertension in experimental congenital diaphragmatic hernia. *Circulation.* 2011;123(19):2120-2131.
- [121] Kashyap AJ, Dekoninck PLJ, Rodgers KA, Thio M, McGillick EV, Amberg BJ, et al. Antenatal sildenafil treatment improves neonatal pulmonary hemodynamics and gas exchange in lambs with diaphragmatic hernia. *Ultrasound Obstet Gynecol.* 2019;54(4):506-516.
- [122] Russo FM, Toelen J, Eastwood MP, Jimenez J, Miyague AH, Velde G Vande, et al. Transplacental sildenafil rescues lung abnormalities in the rabbit model of diaphragmatic hernia. *Thorax.* 2016 Jun 1;71(6):517-525.
- [123] da Silva Ferreira RD, Negrini R, Bernardo WM, Simões R, Piato S. The effects of sildenafil in maternal and fetal outcomes in pregnancy: A systematic review and meta-analysis. *PLoS One.* 2019;14(7): e0219732.
- [124] Sharp A, Cornforth C, Jackson R, Harrold J, Turner MA, Kenny LC, et al. Maternal sildenafil for severe fetal growth restriction (STRIDER): a multicentre, randomised,

placebo-controlled, double-blind trial. *Lancet Child Adolesc Heal.* 2018;2:93.

[125] Dunn L, Greer R, Flenady V, Kumar S. Sildenafil in pregnancy: a systematic review of maternal tolerance and obstetric and perinatal outcomes. *Fetal Diagn. Ther.* 2017;41:81-88. <https://doi.org/10.1159/000453062>

[126] Russo FM, Benachi A, Van Mieghem T, De Hoon J, Van Calsteren K, Annaert P, et al. Antenatal sildenafil administration to prevent pulmonary hypertension in congenital diaphragmatic hernia (SToP-PH): study protocol for a phase I/IIb placenta transfer and safety study. *Trials.* 2018;19:524. <https://doi.org/10.1186/s13063-018-2897-8>.

[127] Schmidt AF, Gonçalves FLL, Regis AC, Gallindo RM, Sbragia L. Prenatal retinoic acid improves lung vascularization and VEGF expression in CDH rat. *Am J Obstet Gynecol.* 2012;207(1):76.e25-76.e32.

[128] Burgos CM, Davey MG, Riley JS, Jia H, Flake AW, Peranteau WH. Lung function and pulmonary artery blood flow following prenatal maternal retinoic acid and imatinib in the nitrofen model of congenital diaphragmatic hernia. *J Pediatr Surg.* 2018;53(9):1681-1687.

[129] Islam S, Narra V, Côté GM, Manganaro TF, Donahoe PK, Schnitzer JJ. Prenatal vitamin E treatment improves lung growth in fetal rats with congenital diaphragmatic hernia. *J Pediatr Surg.* 1999;34(1):172-177.

[130] Sakai K, Kimura O, Furukawa T, Fumino S, Higuchi K, Wakao J, et al. Prenatal administration of neuropeptide bombesin promotes lung development in a rat model of nitrofen-induced congenital diaphragmatic hernia. *J Pediatr Surg.* 2014;49(12):1749-1752.

[131] Takayama S, Sakai K, Fumino S, Furukawa T, Kishida T, Mazda O, et al. An intra-amniotic injection of mesenchymal stem cells promotes lung maturity in a rat congenital diaphragmatic hernia model. *Pediatr Surg Int.* 2019;35(12):1353-1361.

[132] Grushka JR, Laberge JM, Puligandla P, Skarsgard ED. Effect of hospital case volume on outcome in congenital diaphragmatic hernia: the experience of the Canadian Pediatric Surgery Network. *J Pediatr Surg.* 2009;44(5):873-876.

[133] Morche J, Mathes T, Jacobs A, Pietsch B, Wessel L, Gruber S, Neugebauer EA, Pieper D. Relationship between volume and outcome for surgery on congenital diaphragmatic hernia: a systematic review. *J Pediatr Surg.* <https://doi.org/10.1016/j.jpedsurg.2020.03.025>

[134] Nasr A, Langer JC. Influence of location of delivery on outcome in neonates with congenital diaphragmatic hernia. *J Pediatr Surg.* 2011;46(5):814-816.

[135] Carmichael SL, Ma C, Lee HC, Shaw GM, Sylvester KG, Hintz SR. Survival of infants with congenital diaphragmatic hernia in California: impact of hospital, clinical, and sociodemographic factors. *J Perinatol.* 2020;40(6):943-951. <https://doi.org/10.1038/s41372-020-0612-6>

[136] Snoek KG, Capolupo I, Van Rosmalen J, De Jongste-Van Den Hout L, Vijfhuizen S, Greenough A, et al. Conventional mechanical ventilation versus high-frequency oscillatory ventilation for congenital diaphragmatic hernia. A randomized clinical trial (The VICI-trial). *Ann Surg.* 2016;263(5):867-874.

[137] Burgos CM, Frenckner B, Luco M, Harting MT, Lally PA, Lally KP. Prenatally diagnosed

congenital diaphragmatic hernia:
Optimal mode of delivery? *J Perinatol.*
2017;37(2):134-138.

[138] Hutcheon J, Butler B, Lisonkova S, Marquette G, Mayer C, Skoll A, et al. Timing of delivery for pregnancies with congenital diaphragmatic hernia. *BJOG An Int J Obstet Gynaecol.* 2010;117(13):1658-1662. Available from: <http://doi.wiley.com/10.1111/j.1471-0528.2010.02738.x>

[139] Safavi A, Lin Y, Skarsgard ED. Perinatal management of congenital diaphragmatic hernia: When and how should babies be delivered? Results from the Canadian Pediatric Surgery Network. *J Pediatr Surg.* 2010;45(12):2334-2339.

[140] Ali K, Grigoratos D, Cornelius V, Nicolaides K, Davenport M, Greenough A. Gestation at delivery and outcome in CDH infants following fetoscopic tracheal occlusion. *Eur Respir J.* 2012;40(Suppl 56).

[141] Danzer E, Hoffman C, D'Agostino JA, Gerdes M, Bernbaum J, Antiel RM, et al. Neurodevelopmental outcomes at 5 years of age in congenital diaphragmatic hernia. *J Pediatr Surg.* 2017;52(3):437-443.

[142] Wyckoff MH, Aziz K, Escobedo MB, Kapadia VS, Kattwinkel J, Perlman JM, et al. Part 13: Neonatal resuscitation: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* 2015;132(18):S543-S560.

[143] Snoek KG, Reiss IKM, Greenough A, Capolupo I, Urlesberger B, Wessel L, et al. Standardized Postnatal Management of Infants with Congenital Diaphragmatic Hernia in Europe: The CDH EURO Consortium Consensus - 2015 Update. *Neonatology.* 2016;110(1):66-74.

[144] Snoek KG. A Dive into the Wondrous World of Congenital Diaphragmatic Hernia: An international multicenter clinical approach [Thesis]. Erasmus MC: University Medical Center Rotterdam; 2016.

[145] Foglia EE, Ades A, Hedrick HL, Rintoul N, Munson DA, Moldenhauer J, et al. Initiating resuscitation before umbilical cord clamping in infants with congenital diaphragmatic hernia: A pilot feasibility trial. *Arch Dis Child Fetal Neonatal Ed.* 2020 May 1;105(3):F322-F326.

[146] Boucherat O, Benachi A, Chailley-Heu B, Franco-Montoya ML, Elie C, Martinovic J, et al. Surfactant maturation is not delayed in human fetuses with diaphragmatic hernia. *PLoS Med.* 2007;4(7):1205-1215.

[147] Cogo PE, Simonato M, Danhaive O, Verlato G, Cobellis G, Savignoni F, et al. Impaired surfactant protein B synthesis in infants with congenital diaphragmatic hernia. *Eur Respir J.* 2013;41(3):677-682.

[148] Van Meurs K. Is surfactant therapy beneficial in the treatment of the term newborn infant with congenital diaphragmatic hernia? *J Pediatr.* 2004;145(3):312-316.

[149] Lally KP, Lally PA, Langham MR, Hirschl R, Moya FR, Tibboel D, et al. Surfactant does not improve survival rate in preterm infants with congenital diaphragmatic hernia. *J Pediatr Surg.* 2004;39(6):829-833.

[150] Colby CE. Surfactant replacement therapy on ECMO does not improve outcome in neonates with congenital diaphragmatic hernia. *J Pediatr Surg.* 2004;39(11):1632-1637.

[151] Logan JW, Rice HE, Goldberg RN, Cotten CM. Congenital diaphragmatic

hernia: a systematic review and summary of best-evidence practice strategies. *J Perinatol.* 2007;27(9):535-549.

[152] Hagadorn JI, Brownell EA, Herbst KW, Trzaski JM, Neff S, Campbell BT. Trends in treatment and in-hospital mortality for neonates with congenital diaphragmatic hernia. *J Perinatol.* 2015;35:748-754.

[153] Guidry CA, Hranjec T, Rodgers BM, Kane B, McGahren ED. Permissive hypercapnia in the management of congenital diaphragmatic hernia: our institutional experience. *J Am Coll Surg.* 2012; 214:640-47. doi: 10.1016/j.jamcollsurg.2011.12.036.

[154] Puligandla PS, Grabowski J, Austin M, Hedrick H, Renaud E, Arnold M, et al. Management of congenital diaphragmatic hernia: A systematic review from the APSA outcomes and evidence based practice committee. Vol. 50, *J Pediatr Surg.* 2015;50:1958-1970.

[155] Wung JT, Sahni R, Moffitt ST, Lipsitz E, Stolar CJH. Congenital diaphragmatic hernia: Survival treated with very delayed surgery, spontaneous respiration, and no chest tube. *J Pediatr Surg.* 1995;30(3):406-409.

[156] Boloker J, Bateman DA, Wung JT, Stolar CJH. Congenital diaphragmatic hernia in 120 infants treated consecutively with permissive hypercapnea/spontaneous respiration/ elective repair. *J Pediatr Surg.* 2002;37(3):357-366.

[157] Finer NN, Tierney A, Etches PC, Peliowski A, Ainsworth W. Congenital diaphragmatic hernia: Developing a protocolized approach. *J Pediatr Surg.* 1998;33(9):1331-1337.

[158] Bagolan P, Casaccia G, Crescenzi F, Nahom A, Trucchi A, Giorlandino C,

et al. Impact of a Current Treatment Protocol on Outcome of High-Risk Congenital Diaphragmatic Hernia. *J Pediatr Surg;* 2004;39(3):313-318.

[159] Murthy V, D'Costa W, Nicolaides K, Davenport M, Fox G, Milner AD, et al. Neuromuscular Blockade and Lung Function during Resuscitation of Infants with Congenital Diaphragmatic Hernia. *Neonatology.* 2013;103(2):112-117.

[160] Harris J, Ramelet AS, van Dijk M, Pokorna P, Wielenga J, Tume L, et al. Clinical recommendations for pain, sedation, withdrawal and delirium assessment in critically ill infants and children: an ESPNIC position statement for healthcare professionals. *Intensive care medicine.* 2016;42(6):972-986.

[161] Giordano V, Edobor J, Deindl P, Wildner B, Goeral K, Steinbauer P, et al. Pain and Sedation Scales for Neonatal and Pediatric Patients in a Preverbal Stage of Development: A Systematic Review. *JAMA Pediatrics.* 2019;173(12):1186-1197.

[162] Watterberg KL, Cummings JJ, Benitz WE, Eichenwald EC, Poindexter BB, Stewart DL et al. Prevention and management of procedural pain in the neonate: An update. *Pediatrics.* 2016;137(2). e20154271. <https://doi.org/10.1542/peds.2015-4271>

[163] Patel N, Lally PA, Kipfmueller F, Massolo AC, Luco M, Van Meurs KP, et al. Ventricular dysfunction is a critical determinant of mortality in congenital diaphragmatic hernia. *Am J Respir Crit Care Med.* 2019 Dec 15;200(12):1522-1530.

[164] Byrne FA, Keller RL, Meadows J, Miniati D, Brook MM, Silverman NH, et al. Severe left diaphragmatic hernia limits size of fetal left heart more than does right diaphragmatic

hernia. *Ultrasound Obstet Gynecol.* 2015;46(6):688-694.

[165] Buijs EAB, Reiss IKM, Kraemer U, Andrinopoulou ER, Zwiers AJM, Ince C, et al. Increasing mean arterial blood pressure and heart rate with catecholaminergic drugs does not improve the microcirculation in children with congenital diaphragmatic hernia: A prospective Cohort study. *Pediatr Crit Care Med.* 2014;15(4):343-354.

[166] Patel N. Use of milrinone to treat cardiac dysfunction in infants with pulmonary hypertension secondary to congenital diaphragmatic hernia: a review of six patients. *Neonatology.* 2012;102(2):130-136.

[167] Sluiter I, van der Horst I, van der Voorn P, Boerema-de Munck A, Buscop-van Kempen M, de Krijger R, et al. Premature differentiation of vascular smooth muscle cells in human congenital diaphragmatic hernia. *Exp Mol Pathol.* 2013;94(1):195-202.

[168] Mous DS, Buscop-van Kempen MJ, Wijnen RMH, Tibboel D, Rottier RJ. Changes in vasoactive pathways in congenital diaphragmatic hernia associated pulmonary hypertension explain unresponsiveness to pharmacotherapy. *Respir Res.* 2017; 18(1):187.

[169] Solari V, Piaseczna Piotrowska A, Puri P. Expression of heme oxygenase-1 and endothelial nitric oxide synthase in the lung of newborns with Congenital diaphragmatic hernia and persistent pulmonary hypertension. *J. Pediatr. Surg.* 2003; 38(5):808-813.

[170] Sood BG, Wykes S, Landa M, De Jesus L, Rabah R. Expression of eNOS in the lungs of neonates with pulmonary hypertension. *Exp Mol Pathol.* 2011;90(1):9-12.

[171] Shinkai T, Shima H, Solari V, Puri P. Expression of vasoactive mediators

during mechanical ventilation in nitrofen-induced diaphragmatic hernia in rats. *Pediatr Surg Int;* 2005;21(3):143-147.

[172] Shehata SMK, Sharma HS, Mooi WJ, Tibboel D. Pulmonary hypertension in human newborns with congenital diaphragmatic hernia is associated with decreased vascular expression of nitric-oxide synthase. *Cell Biochem Biophys.* 2006;44(1):147-155.

[173] Montalva L, Antounians L, Zani A. Pulmonary hypertension secondary to congenital diaphragmatic hernia: factors and pathways involved in pulmonary vascular remodeling. *Pediatric research.* 2019 ;85(6):754-768.

[174] Nair J, Lakshminrusimha S. Update on PPHN: Mechanisms and treatment. *Semin. Perinatol.* 2014;38(2):78-91.

[175] Keller RL, Tacy TA, Hendricks-MunozK, XuJ, Moon-GradyAJ, NeuhausJ, et al. Congenital diaphragmatic hernia: Endothelin-1, pulmonary hypertension, and disease severity. *Am J Respir Crit Care Med.* 2010;182(4):555-561.

[176] Mohseni-Bod H, Bohn D. Pulmonary hypertension in congenital diaphragmatic hernia. *Semin Pediatr Surg.* 2007 ;16(2):126-133.

[177] Hofmann SR, Stadler K, Heilmann A, Häusler HJ, Fitze G, Kamin G, et al. Stabilisation of cardiopulmonary function in newborns with congenital diaphragmatic hernia using lung function parameters and hemodynamic management. *Klin Padiatr.* 2012;224(4).

[178] Gien J, Kinsella JP. Management of pulmonary hypertension in infants with congenital diaphragmatic hernia. *J. Perinatol.* 2016;36(2):S28-S31.

[179] Kumar VH., Dadiz R, Koumoundouros J, Lakshminrusimha S.

Response to Pulmonary Vasodilators in Infants with Congenital Diaphragmatic Hernia. *Pediatrics*. 2018;142:184-184.

[180] McNamara PJ, Laique F, Muang-In S, Whyte HE. Milrinone improves oxygenation in neonates with severe persistent pulmonary hypertension of the newborn. *J Crit Care*. 2006;21(2):217-222.

[181] Bassler D, Choong K, McNamara P, Kirpalani H. Neonatal persistent pulmonary hypertension treated with milrinone: Four case reports. *Biol Neonate*. 2006;89(1):1-5.

[182] Lakshminrusimha S, Keszler M, Kirpalani H, Van Meurs K, Chess P, Ambalavanan N, et al. Milrinone in congenital diaphragmatic hernia – a randomized pilot trial: study protocol, review of literature and survey of current practices. *Matern Heal Neonatol Perinatol*. 2017;3(1):1-5.

[183] Finer NM. Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. *Pediatrics*. 1997;99(6):838-845.

[184] Putnam LR, Tsao K, Morini F, Lally PA, Miller CC, Lally KP, et al. Evaluation of variability in inhaled nitric oxide use and pulmonary hypertension in patients with congenital diaphragmatic hernia. *JAMA Pediatr*. 2016;170(12):1188-1194.

[185] Kelly LE, Ohlsson A, Shah PS. Sildenafil for pulmonary hypertension in neonates. *Cochrane Database of Systematic Reviews*. 2017(8). <https://doi.org/10.1002/14651858.CD005494.pub4>

[186] Noori S, Friedlich P, Wong P, Garingo A, Seri I. Cardiovascular effects of sildenafil in neonates and infants with congenital diaphragmatic hernia and pulmonary hypertension. *Neonatology*. 2007;91(2):92-100. <https://doi.org/10.1159/000097125>

[187] Bialkowski A, Moenkemeyer F, Patel N. Intravenous sildenafil in the management of pulmonary hypertension associated with congenital diaphragmatic hernia. *Eur J Pediatr Surg*. 2015; 25(2):171-176. <https://doi.org/10.1055/s-0033-1357757>.

[188] Kipfmüller F, Schroeder L, Berg C, Heindel K, Bartmann P, Mueller A. Continuous intravenous sildenafil as an early treatment in neonates with congenital diaphragmatic hernia. *Pediatr Pulmonol* 2018;53:452-460. <https://doi.org/10.1002/ppul.23935>.

[189] Cochius-den Otter S, Schaible T, Greenough A, van Heijst A, Patel N, Allegaert K, et al. The CoDiNOS trial protocol: an international randomised controlled trial of intravenous sildenafil versus inhaled nitric oxide for the treatment of pulmonary hypertension in neonates with congenital diaphragmatic hernia. *BMJ open*. 2019;9:e032122. <https://doi.org/10.1136/bmjopen-2019-032122>.

[190] More K, Athalye-Jape GK, Rao SC, Patole SK. Endothelin receptor antagonists for persistent pulmonary hypertension in term and late preterm infants. *Cochrane Database of Systematic Reviews*. 2016(8). <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010531.pub2>.

[191] Steinhorn RH, Fineman J, Kusic-Pajic A, Cornelisse P, Gehin M, Nowbakht P, et al. Bosentan as Adjunctive Therapy for Persistent Pulmonary Hypertension of the Newborn: Results of the Randomized Multicenter Placebo-Controlled Exploratory Trial. *J Pediatr*. 2016;177:90-96.e3. <https://doi.org/10.1016/j.jpeds.2016.06.078>.

[192] Pedersen J, Hedegaard ER, Simonsen U, Krüger M, Infanger M, Grimm D. Current and Future Treatments for Persistent Pulmonary Hypertension in the

Newborn. Basic Clin Pharmacol Toxicol. 2018;123(4):392-406. <http://doi.wiley.com/10.1111/bcpt.13051>

[193] Turek JW, Nellis JR, Sherwood BG, Kotagal M, Mesher AL, Thiagarajan RR, et al. Shifting Risks and Conflicting Outcomes—ECMO for Neonates with Congenital Diaphragmatic Hernia in the Modern Era. *J Pediatr*. 2017;190:163-168.e4. <https://doi.org/10.1016/j.jpeds.2017.08.010>.

[194] Saugstad OD. When increased mortality indicates improved care: CDH ECMO registry data. *J Pediatr*. 2017;190:4-5. <https://doi.org/10.1016/j.jpeds.2017.09.037>.

[195] Kays DW. ECMO in CDH: Is there a role? *Semin Pediatr Surg*. 2017;26(3):166-170. <https://doi.org/10.1053/j.sempedsurg.2017.04.006>.

[196] Section on Surgery and the Committee on Fetus and Newborn. Postdischarge follow-up of infants with congenital diaphragmatic hernia. *Pediatrics*. 2008 ;121(3):627-632.

[197] IJsselstijn H, Breatnach C, Hoskote A, Greenough A, Patel N, Capolupo I, et al. Defining outcomes following congenital diaphragmatic hernia using standardised clinical assessment and management plan (SCAMP) methodology within the CDH EURO consortium. *Pediatr Res* 2018;84:181-189. <https://doi.org/10.1038/s41390-018-0063-3>.

[198] Poley MJ, Stolk EA, Tibboel D, Molenaar JC, Busschbach JJV. Short term and long term health related quality of life after congenital anorectal malformations and congenital diaphragmatic hernia. *Arch Dis Child* 2004;89:836-841. <https://doi.org/10.1136/ad.2002.016543>.

[199] Fritz KA, Khmour AY, Kitzerow K, Sato TT, Basir MA. Health-related quality of life, educational and family

outcomes in survivors of congenital diaphragmatic hernia. *Pediatr Surg Int*. 2019;35(3):315-20. <https://doi.org/10.1007/s00383-018-4414-2>.

[200] Michel F, Baumstarck K, Gosselin A, Le Coz P, Merrot T, Hassid S, et al. Health-related quality of life and its determinants in children with a congenital diaphragmatic hernia. *Orphanet J Rare Dis*. 2013;8(1). <https://doi.org/10.1186/1750-1172-8-89>.

[201] Bojanić K, Grizelj R, Vuković J, Omerza L, Grubić M, Čaleta T, et al. Health-related quality of life in children and adolescents with congenital diaphragmatic hernia: A cross-sectional study. *Health Qual Life Outcomes*. 2018;16(1). <https://doi.org/10.1186/s12955-018-0869-z>.