**Congenital Diaphragmatic Hernia**

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**Abstract**

Congenital diaphragmatic hernia (CDH) retains high mortality and morbidity due to lung hypoplasia, pulmonary hypertension and severe co-existent anomalies. This article offers a state-of-the-art review highlighting clinical advances in health care to develop new and better therapies for CDH.

**Key words :** congenital diaphragmatic hernia ; CDH ; fetal therapy ; ECMO : iNO ;

sildenafil ; surgery ; long term outcomes

# **Introduction**

Congenital diaphragmatic hernia (CDH) is a developmental human birth malformation characterised by a defect in the fetal diaphragm through which abdominal viscera migrate and herniate into the thoracic cavity. CDH occurs in some 1.76-2.3 per 10,000 live births [1-4], thus by definition it is considered a rare disease.[5] The resulting abnormal lung development leads to pulmonary hypoplasia and pulmonary hypertension, which are the primary determinants of morbidity and mortality for many patients. In some 30% of CDH patients, genomic analyses have identified a range of genetic defects, including chromosomal anomalies, copy number variants and sequence variants. Mutations in these genes affect diaphragm development and can have pleiotropic effects on pulmonary and cardiac development.[6] In 2021 CDH is still considered a highly lethal birth defect with overall mortality ranging from 30-50% resultant from the consequences of aberrant lung physiology and pulmonary vascular biology (PHTN).[2, 7, 8]

Advances leading to improvement(s) in survival have evolved from in utero diagnosis, delivery of index cases at ‘high-volume’ specialist centres , deployment of permissive hypercapnia, inhaled nitric oxide ( iNO ) and / or extracorporeal membrane oxygenation (ECMO) [1, 3, 9] With new treatments emerging including fetal endoscopic tracheal occlusion (FETO) and prenatal medical therapy(s) targeted to rescue lung hypoplasia and pulmonary vascular development it is anticipated better survival outcomes will emerge with a greater burden of increased health care costs linked with morbidity in ‘high risk’ survivors herein emphasizing the crucial need for multidisciplinary long term clinic follow up .[6, 7]

# **Embryogenesis**

The diaphragm is an essential mammalian respiratory muscle partitioning the thorax and abdominal cavities. The fully formed human diaphragm is composed of the dorsomedial crural muscle(s), the ventrolateral costal muscle(s), and centrally the amuscular tendon, which connects to the muscular components of the diaphragm [2]. Development of the diaphragm requires the coordinated activity of muscle, muscle connective tissue, tendon, nerves, and vasculature that derive from different embryonic sources. It is still unknown how the diaphragm is formed despite the identification of many CDH-associated genes, thus, the aetiology of CDH is incompletely understood [10] In mouse genetics, there is evidence that the pleuroperitoneal folds (PPFs), transient embryonic pyramidal-shaped structures that form between the thoracic and abdominal cavities, are the prime source of diaphragm muscle and connective tissue(s) regulating its development.

The earliest developmental events are the migration of muscle progenitors from the cervical somites followed by the projection of phrenic nerve axons from the cervical neural tube. Muscle progenitors and the phrenic nerve target then the PPFs and expand across the diaphragm surface of the liver to give rise to the muscle connective tissues central tendon, and the leading edge of their expansion precedes muscle morphogenesis, formation of the vascular network and outgrowth with branching of the phrenic nerve across the PPFs. The muscles lying at the periphery of the diaphragm derive from migrating cells delaminating from the somitic dermatomyotome(s), which also contribute to the skeletal muscle of the limbs and body wall [2]. Development and morphogenesis of the PPFs is critical for diaphragm formation and the striking migration of PPF cells essentially controls diaphragm morphogenesis. Abnormalities in the PPF connective tissue(s) result in failure of migration and differentiation of muscle precursor cells, leading to subsequent hernia formation [2, 10, 11].

In 30% of CDH patients, detailed genomic analyses have identified a range of genetic defects, including chromosomal anomalies, copy number variants and sequence variants. The affected genes identified include transcription factors, such as *GATA4*, *ZFPM2*, *NR2F2* and *WT1*, and signaling pathway components, including members of the retinoic acid pathway. Mutations in genes affecting diaphragm development have pleiotropic effects also on pulmonary and cardiac development.[6, 11]

Human lung development is a complex, multistep process, and perturbation of any of these steps can lead to pulmonary defects – Figure 1 . The lung starts to develop around 4 weeks of gestation, the ***‘*** *embryonic stage ‘* ***,*** with ventral budding from the foregut endoderm which separates the anterior foregut into the trachea and two primary lung buds and the dorsal esophagus. [2, 3]. At 5-16 weeks of gestation the ‘ *pseudoglandular stage* ‘ of lung development begins where the two lung buds undergo repeated branching to generate a tree-like structure of airways. Critical for airway branching morphogenesis is the expression of two transcription factors notably Sox 2 in the non-branching proximal airways and Sox9 in branching distal airway. Sox2-positive cells differentiate into the cells of the conducting airways, which are also capable of partially reprograming AECs-2 into those with a ciliated pattern or non-ciliated airway characteristics [12, 13]. Meanwhile Sox9 is expressed at the distal tips of the branching airway epithelium and regulates the balance between proliferation and differentiation as well as the establishment of the extracellular pulmonary matrix. [14, 15]

The conducting airways of the lungs have formed after 16 weeks of development, and then followed by the ‘ *canalicular stage* ‘ of lung development. The formation of the respiratory zone(s) begins at 16-26 week of gestation where the terminal bronchioles divide into respiratory bronchioles, which branch into alveolar ducts. The blood vessels form de novo through vasculogenesis with the airways acting as a template for the formation of the pulmonary vessels. At this stage, where the blood air interface is established, AECs-1 and AECs-2 differentiate from a bipotent progenitor gas exchange unit to sustain life ie. ‘ air breathing ‘ becoming possible for humans at birth [16, 17]. The *‘ saccular stage ‘* of lung development ( 26–38 weeks of gestation ) is denoted by the formation of epithelial sacs, which become more closely connected with the maturing pulmonary capillary bed. There are also the formation of terminal saccules, differentiation of alveolar epithelial cells and surfactant production from type II pneumocytes. The final

‘ *alveolar stage ‘*of lung development occurs near birth onwards to 7-8 years of age. Epithelial sacs will continue to form further alveoli through secondary septation, at which point the capillary bed will be exposed to the surfaces of two alveoli simultaneously.[2, 3] The process of secondary septation greatly increases the respiratory surface area for gas exchange within the lung, and because it occurs immediately ‘ prenatally ‘ and continues

‘ postnatally’ , it provides an attractive ‘ target window’ for designing therapeutic interventions in patients with CDH and other neonatal lung diseases[2].

# **Abnormal pulmonary development in CDH**

Structural lung pathology is invariably seen in all patients with CDH and the severity of hypoplasia and pulmonary hypertension most directly determines the outcome for infants born with CDH. [3, 4, 9, 18] Much of our mechanistic understanding of pulmonary defects in CDH have come from the study of animal models, particularly genetic models showing both diaphragm and lung defects. Even though major bronchial anatomy may be normal in human lung autopsy specimens the number of intermediate bronchial branches are often severely reduced in the ipsilateral lung on the side of the CDH defect and to a lesser extent in the contralateral lung. The alveoli that do exist have thicker walls and septae, impairing the close association of the airspaces to the nourishing capillaries and the abnormal matrix composition of the pulmonary interstitium contributes to reduced lung compliance. Moreover CDH patients have impaired lung perfusion with imaging showing VQ mismatch throughout life.

Vascular growth, which is considered necessary for alveolization, is even more compromised than alveolar growth. Evidence from a recent extensive review by Montalva et al. [19] found that there is impairment of epithelial cell homeostasis present in lung hypoplasia resulting in increased smooth muscle cell proliferation, resistance to apoptosis and aberrant vasoconstriction properties. The increased muscularization of the smaller pulmonary arterioles contributes to hypoxia related pulmonary hypertension. [3, 20, 21]

# **Prenatal Imaging**

Accurate prenatal diagnosis of CDH is now possible with obstetric screening ultrasound with detection rates steadily approaching 80-90% in many Western countries [1, 5, 22]. Mean gestational age (GA) at index diagnosis is generally around 23-25 weeks [23, 24]. Expectant mothers should be referred to specialist expert centers where perinatal management and full risk assessment are offered by the multidisciplinary care team (MDT). Prenatal diagnosis affords the opportunity for informed counselling by an experienced MDT team, which should include a paediatric surgeon, neonatologist, midwife and obstetrician. A study from the Canadian Neonatal Network and a further multi-centre study from France strongly supports the concept of health care management at high-volume centres ie defined here as those institutions treating more than 12-14 CDH cases / annum with survival at such units reportedly better ( 90%vs 77% *p*<.01) [25]

A recent report from California , USA further supported these findings by showing a significantly lower mortality in high volume centre(s) ie. defined ≧ 6 CDH / annum ,14.4% vs 25.1% (*p*=0.002) Adjusted odds ratios of mortality were all significantly lower at treatment centers with higher volume rates of CDH operative repair (OR, 0.41; 95% CI, 0.23-0.75; P = .003[26]

Associated anomalies are found up to 40% of CDH cases, and outcome(s) here may be co-determined by the severity of allied disorders. These should be detected in the prenatal period by advanced genetic testing and where applicable with additional imaging eg fetal MRI , cardiac assessment. [22] Expectant mothers should all be offered amniocentesis and fetal karyotyping.[1, 22] Structural anomalies most frequently associated with congenital diaphragmatic hernia are listed here in Table 1( 22)

|  |  |
| --- | --- |
| Cardiovascular malformations (25-30%) | Ventricular septal defects and atrial septal defects; |
|  | Tetralogy of Fallot |
|  | Hypoplastic left heart syndrome |
|  | Transpostion of great vessels (TGA) |
|  | Double outlet right ventricle |
|  | Aortic coarctation |
| Genitourinary abnormalities (5-10%) | Undescended / ectopic testis |
|  | Ectopic kidney |
|  | Horse-shoe kidney(s) |
|  | Gonadal aplasia and hypoplasia, sex ambiguity |
| Central nervous system abnormalities (1-10%) | Neural tube defects |
|  | Hydrocephalus |
|  | Corpus callosum agenesis (rare) |
| Musculoskeletal anomalies (1-15%) | Polydactyly |
|  | Syndactyly |
|  | Limb reduction defects |
| Gastro-intestinal malformations (2-10%) | Foregut Malrotation / Atresia EA-TEF , ARM |
|  | Omphalocele |
|  | Situs inversus / Heterotaxy syndromes |
| Chest anomalies (2-5% | Bronchopulmonary sequestration |
|  | Congenital pulmonary airway malformation |

**Table 1 – Associated Spectrum Of Anomalies Recorded With Congenital Diaphragmatic Hernia**

Prenatal detection raises the debate of fetal risk assessment, survival and outcome(s). Detailed sonography and echocardiography with or without fetal MRI aims to exclude associate abnormalities most notably congenital heart disease and chromosomal anomalies.

Various parameters linked to worse prognosis in CDH include ( i ) right-sided defect RCDH , ( ii ) intrathoracic liver herniation designated ‘ liver up ‘ , ( iii ) associated congenital / chromosomal anomalies and ( iv ) observed-to-expected LHR (O/E LHR)

[27-29]. Thus, in specialist fetal medicine centres, imaging should record the laterality of the CDH defect, presence or absence of liver herniation ‘ liver up ‘ , stomach in the chest and a true accurate estimate of the observed : expected lung head ratio (O/E LHR). [30].

# **Side Of CDH Defect**

Right‐sided CDH (RCDH) is considered a poor prognostic factor because many studies have reported lower survival rates in right side defects compared to left CDH [31-34] However , a recent national cohort study revealed that after risk adjustment(s) ( liver position and o/e LHR ) hernia laterality did not appear to be an independent predictor of survival. With ‘ hidden mortality’ and only some 13.3% of right-sided CDH cases included in this study results here may lack adequate statistical power for true outcome comparison and reporting. [35, 36].

# **Liver herniation**

The utility of the liver position to accurately predict outcome in isolated left congenital diaphragmatic hernia was reported by a study published in 2007. It was noted that ECMO was required here in some 39 of 49 fetuses (80%) with ‘liver up’ compared with 10 of 40 fetuses (25%) designated ‘liver down’ ( *p* < .0001). Overall survival rates were significantly lower in the fetus with ‘ liver up ‘ ( 45%, vs 93% ) *p* < .00005) [37]. In a systematic review and meta-analysis study published in 2010 by the CDH research group in Liverpool, UK it was convincingly showed that liver herniation strongly correlated with poor prognosis

( ‘ liver up ‘ 45% survival vs ‘ liver down ' 74% survival *P* < 0.005 ). [28] Grading the severity of liver herniation may provided further ‘ high risk group ‘ categorization To this end additional studies have tried to scale quantifiy liver herniation using MRI - %liver herniation or with 2D Ultrasonography US-LiTR [28, 38, 39, 40, 41]

# **Stomach position**

It is easy to determine intrathoracic stomach position rather than quantify liver herniation, as the stomach is anechoic and liver echogenicity is close to or identical to that of lung. [41] A study on 90 fetuses found that fetal stomach position was strongly associated with neonatal outcomes in isolated left CDH. Increasingly abnormal stomach position was linearly associated with an increased odds risk of death (OR 4.8, 95%CI 2.1–10.9), requirement for ECMO (OR 5.6, 95%CI 1.9–16.7), non-primary diaphragm repair (OR 2.7, 95%CI 1.4–5.5), prolonged mechanical ventilation (OR 5.9, 95%CI 2.3–15.6), and intensified respiratory support (OR 4.0, 95%CI 1.6–9.9) [42]. Cordier et al. [43] found that postnatal survival may be also correlated with stomach position and grade ( *P* < 0.00 ) with severity linked to 4 category variables according to ‘ stomach relation to the heart ‘. Multivariable analysis by the study authors also showed postnatal survival was independently correlated with stomach position grade (*P* = 0.010) and O/E‐LHR (*P* = 0.049).

**LHR and O / E LHR**

Metkus *et al* working *at UCSF, USA* first described the predictive value of the lung‐to‐head ratio (LHR) in fetuses with CDH in 1996 [44] This has now been superseded by the O/E LHR as a more accurate determinant of fetal outcome(s). [45 ]A recent meta-analysis study found that lung-to-head ratio (LHR) odds of survival with LHR <1.0 and liver herniation on ultrasound imaging were 0.14 (CI 0.10-0.27) and 0.21 (CI 0.13-0.35) respectively. [46 ] Mean LHR, o/e LHR, absolute total fetal lung volume - TFLV, o/e TFLV, PPLV and liver herniation all predict survival, but o/e LHR and o/e TFLV performed best in a prediction model tool. [ 47, 48 ] The most discriminatory threshold for O/E LHR and O/E TFLV was considered set at 25% vs normal gestational matched healthy fetus. An LHR <1 was predictive of likelihood for ECMO. Liver position as well as o/e LHR, o/e TFLV (thresholds of 25%) and liver herniation are all therefore considered good predictors of mortality in CDH [49, 50] In left-sided CDH O/E-LHR < 25% is therefore defined as ‘severe high risk ‘and an O/E-LHR 25-34.9% (irrespective of liver position) or 35-44.9% with liver up ‘moderate risk’. Conversely without liver herniation, or when O/E-LHR >45%, CDH is considered ‘mild risk ‘ [35]. High risk isolated CDH cases where O/E-LHR < 25% are considered ‘ fetal candidate ‘ eligibility groups for the FETO RCT trial.

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# Fetal MRI

Fetal MRI can provide detailed information on pulmonary hypoplasia and liver herniation yielding valuable data on observed‐to‐expected fetal lung volume(s). Moreover MRI can be invaluable in the detection of RCDH where uncertainity may exist over accurate ultrasound diagnosis ie. CDH vs diaphragm eventration. Imaging to assess associated structural anomalies is also invaluable [51] MRI can quantifiy liver herniation which combined with observed-to-expected total fetal lung volume, improves prediction characteristics [52, 9 ] Prayer et al. [53] has reported that MRI 3D reconstruction of the fetal diaphragm in CDH has been validated to visualize, locate, classify and quantify the defect. These images can therefore be fully utilised as part of prenatal assessement to accurately predict the need for patch diaphragm repair in the fetus and can function to aid customize patch design based on 3D‐printable templates.

# **Management of the unborn patient**

The overall goal(s) of prenatal management are to best define fetal prognosis and provide parents with true factual information. This should lead to a pathway of health care that includes ( i ) expectant management of the fetus with prenatal referral to a high volume center for carefully timed elective delivery, ( ii ) optional termination of pregnancy ( if parents wish or desire this option ) or ( iii ) fetal intervention in those with a normal karyotype who are considered ‘high risk ‘ cases as identified by measurement of O / E LHR ( < 25% ), and liver herniation. [ 41, 54 ]

# **Amniocentesis and the search of associated structural anomalies**

Genetic testing is a voluntary option for parents in the UK though this can permit more accurate prenatal counseling and dictates eligibility for fetal therapy [35] A genetic etiology may be found in some 35% cases by conventional karyotypin. An additional 9% of CDH cases have clinically relevant copy number variants identifiable by comparative array genomic hybridization whilst a further 10% may require targeted re-sequencing [35]. In cases of associated fetal structural defects, the search for recognized disorders is strongly recommended eg Pallister Killian syndrome. The established varied syndromic and non-syndromic genetic causes of CDH are listed elsewhere for the reader [6]

# **Fetal Therapy**

Fetal therapy in high risk fetuses is currently subject to an international randomized controlled trial - TOTAL Trial - deploying percutaneous fetoscopic endoluminal tracheal occlusion (FETO) findings which will be shortly reported in 2021 ( PI - Jan Deprest University Of Leuven , Belgium personal communication ) – Figure 2 . [35, 40, 41, 55, 56] In brief FETO seeks to exploit mechanical forces notably ‘ lung stretch ‘ with lung liquid physics based on the hypothesis that tracheal occlusion prevents egress of lung liquid, which in turn causes increased pulmonary stretch, hence accelerated lung growth as evidenced by several compelling animal experiments. [ 57 ] Selective entry criteria for the CDH fetus with isolated CDH requires an O/E LHR < 27–28% with liver herniation ( termed “liver up” ) being incorporated with trial entry [1] In the most severe cases ( o/e LHR/ TFLV less than 25% ), the FETO task force initially proposed insertion of the balloon device at 26-28 gestation under epidural anaesthesia and for moderate cases at 30-32 weeks under local anaesthesia. Early occlusion was prone to more complications. Reversal of occlusion is proposed at 34 weeks [41, 58 ] with 90% of cases undertaken in utero by fetoscopy guided balloon retrieval (67.1%) or by ultrasound-guided puncture (21.2%)[58, 59]. Many novel techniques are currently being explored experimentally to facilitate safer balloon removal from the fetus such as the ‘long tail balloon’ device [60] and the ‘smart-TO’ balloon which can be deflated in the magnetic field of an MRI scanner [ 61] Compared to historical controls from the antenatal CDH registry, FETO increased survival in severe LCDH from 24.1% to 49.1% (P < 0.001)[70]. These results were further supported in another study by DeKoninck et al. in 2015 [34] with RCDH fetuses having FETO. The survival rate here was notably better in the RCDH fetus receiving FETO (17% vs 42%; *P* =0.09).

# **Delivery and postnatal management**

Delivery (if parents opt for continuation of pregnancy) is scheduled with induction of elective labour and normal vaginal delivery as near term as possible ideally at 38 weeks to allow adequate pulmonary maturation. Spontaneous onset of labour should be avoided if at all possible which may prove hazardous if birth of a CDH newborn occurs at a remote community hospital. Ideally, the delivery should take place in a specialist tertiary centre, fully equipped for neonatal resuscitation. [1, 62] Hutcheon et al. [63] showed that CDH mortality significantly decreased with advancing gestation age from 25% at 37 weeks to 17% at 40 weeks. The neonatal resuscitation guidelines from the American Heart Association, American Academy of Pediatrics [64] and CDH Euro Consortium consensus [65] support immediate endotracheal intubation for neonates with a known diagnosis of CDH and the strict avoidance of aggressive bag-valve-mask ventilation for these patients. Measurements of heart rate, pre- and post ductal saturations and intra-arterial blood pressure are recommended [9] Based on expert consensus opinion, in those infants who are predicted to have good lung development based on prenatal assessment ( e.g. left-sided defect, O/E LHR >50%, and liver down ), spontaneous breathing should be first considered to prevent aggressive ventilator-induced lung injury.[ 65] An orogastric or nasogastric tube should be immediately inserted with regular continuous suction to prevent gastric / bowel distension which may cause respiratory embarrassment. Following stabilization a full clinical examination is undertaken to exclude associated anomalies. Chest radiography confirming the diagnosis and an echocardiogram is performed promptly to screen for cardiac anomalies – Figure 3 [1,65 ]

# **Postnatal diagnosis ‘ Late presenting CDH ‘**

According to a French registry report the overall prenatal detection rate of CDH was 54% [66] In some 20-30% of patients, diagnosis of CDH may therefore not be possible ‘in utero’ eg. small defect or RCDH lesion may be missed. In such cases, herniation of abdominal viscera into the thorax is considered to take place after delivery through a small diaphragmatic defect [1, 67]. Herniation may also occur through a diaphragmatic defect that had been previously ‘ plugged ‘ by the spleen or liver. [68] It should be noted that these infants are at a potential risk for gut infarction from incarcerating thoracic viscera through a small diaphragm defect. Late presenting CDH can sometimes be difficult to diagnose due to non-specific clinical symptoms. Such cases may present in the immediate newborn period or first few days of life whilst others may remain asymptomatic until adulthood even in later life. Al Ghafri et al. [69] reported a patient with left-CDH who presented with a tension gastrothorax at 9 weeks old. According to a review by the International CDH study group registry , late-presenting symptoms may include respiratory (43%), gastrointestinal (33%), ‘ mixed ‘ (13%), and / or asymptomatic incidental detection (11%) [1] Clinical findings may reveal bowel sounds on chest auscultation. There may be signs of decreased air entry on the affected side of the defect and rarely mediastinal shift. Diagnosis is often made on a chest x-ray but may require an upper gastrointestinal contrast study for better confirmation.[1] The morbidity and mortality of late presenting congenital diaphragmatic hernia is considered low once appropriately managed in an specialist centre [68]. In late-presenting CDH, primary repair is usually achieved with almost 100% survival expected. [1]

# **Stabilisation and ventilation strategy**

Perhaps the most important factor(s) that have improved survival of CDH in the last few decades has been the introduction of ‘ gentle ventilation’ and avoidance of ventilator-induced lung injury to the immature hypoplastic CDH lung [1]. The concept(s) of permissive hypercapnia and 'gentle ventilation’ were first pioneered by Wung, Stolar et al at Columbia Babies Hospital New York City, USA in 1985 [71, 72 ]. Currently, more than 90% of International CDH Registry centers cite the use of permissive hypercapnia strategies [1, 73]. Low peak inspiratory pressures, preferably <25 cm H2O, are strictly recommended to avoid lung injury [71, 72] Key principles are therefore avoidance of high airway pressures and the establishment of adequate tissue perfusion and oxygenation ( based on preductal arterial saturation, SpO2 measurements ). Both pre-and post-ductal blood gas monitoring and oxygenation are important. Preductal PaO2 reflects cerebral oxygenation whereas umbilical artery PaO2 monitoring records post-ductal tissue oxygen. Thus, the arterial line should be inserted into the right radial artery. Measures to increase systemic blood pressure with inotropes may minimize right-to-left shunting. However, there is no need to increase blood pressure levels to supranormal values if preductal saturation(s) remain above 80%.[71,72] There is no evidence to support the routine administration of exogenous surfactant with delivery. A CDH study group report firmly concluded that surfactant does not improve survival in infants born with congenital diaphragmatic hernia. [74] The physiologic rationale for use of HFOV derived from its ability to preserve end-expiratory tidal lung volume(s) and therefore restrict pulmonary injury. The international VICI-trial recently concluded there were no statistically significant differences observed comparing mortality (%) or BPD incidence between two modes of ventilation ie. HFOV vs CMV though a significantly shorter number of days on ventilation and a reduced need for ECMO support favours use of conventional ventilation (CMV). [75]

# **Other therapies— ECMO, nitric oxide (iNO) and sildenafil**

ECMO has been used to manage and rescue babies with CDH failing conventional ventilation strategies since the late 1970’s. A UK ECMO trial ( 1996 ) led by David Field , - a neonatologist working in Leicester, UK however later failed to convincingly show significant survival benefits here for CDH babies vs other ECMO cohort group(s) eg meconium aspiration syndrome. [76] A Cochrane review updated some years later made similar conclusions. [ 77 ] A meta-analysis study ( 2006 ) by contrast reported significant survival benefits from ECMO use in CDH [78] In 2020 - a seminal report from Jancelwicz, Langham , Harting et al USA have clearly redefined the benefits of ECMO in the ‘ high risk CDH infant group only ‘ citing high volume care at expert centres as compelling evidence. [79] The Extracorporeal Life Support Organisation (ECLS ) have updated their CDH management care guidelines in 2021. [80]

Despite reports failing to extol the benefits of Inhaled Nitric Oxide (iNO) therapy in CDH, its use is widespread in clinical practice with practice variation evident with its indication(s) and care protocol(s) l[81]. Transient response to iNO in CDH is not uncommon [81, 82]. Studies in neonates receiving iNO have found that it can improve oxygenation index (OI) and reduce need for ECMO in some 30-40% of cases . However not uncommonly iNO has failed to show sustained benefits for many CDH babies. A recent report regarding use of iNO has documented possibly worse outcomes in CDH with fatalities. [82]

Sildenafil, a phosphodiesterase 5 inhibitor (PDE5) acts as a potent vasodilator and has been reported to improve oxygenation in some 42% of CDH infants. [84] IV sildenafil use has been also associated with improved oxygenation and a reduced degree of right of left shunting in CDH [85,86]. The CoDiNOS multicentre international randomized controlled trial launched in 2019 by Erasmus Netherlands and the CDH Euroconsortium seeks to explore the utility of intravenous sildenafil vs inhaled nitric oxide (iNO) for treatment of pulmonary hypertension in CDH [87]. At time of writing trial outcome data are awaited.

Milrinone a phosphodiesterase 3 inhibitor (PDE3) has shown improvement(s) in oxygenation as well as systolic and diastolic RV function in CDH [88]. A RCT launched in 2017 is being conducted to determine if milrinone infusion can improve oxygenation in CDH neonates born ≥36 weeks. [89]

# **Timing of Surgery**

CDH was once regarded as a surgical emergency with operative repair performed emergently after delivery to seek to improve ventilation by reducing the herniated viscera from the thoracic cavity. Currently, it is widely accepted that preoperative stabilisation of labile physiology is paramount with delayed surgery scheduled during regular ‘ normal working hours ‘ ( 0800- 18-00 hrs ) where possible after optimisation of respiratory and cardiac status[ 1, 90] The timing of CDH operation in those that require ECMO remains controversial with advantages and pitfalls cited for operation ‘ on ECMO’ or ‘ off ECMO’ etc (80) The classical operation is undertaken using a subcostal incision with the herniated contents returned to the abdominal cavity from the thorax and the diaphragm defect repaired with hernia sac excision if present – Figure 4 . In the majority of cases (60–70%), a primary closure of the native diaphragm is achieved [1, 90] A hernia sac seen in some 10-15% CDH cases is associated with significantly better survival outcomes ([91-92] In patients with a large size defect ( Grade C or D – International CDH registry grading ) a prosthetic patch must be deployed to partition the defect. There are a number of different materials available to the surgeon, e.g., GORE-TEX ( PTFE ) or biosynthetic substitute(s) ie. SURGISIS. Bioprosthetic materials show high rate(s) of hernia recurrence and should be avoided [1] Experience from high volume centres notably Children’s Hospital Philadelphia, USA and Alder Hey Liverpool, UK record low rates of hernia recurrence with prosthetic patch repair ( <10%) with GORE-TEX. [93-94] The routine use of a chest tube postoperatively to drain an effusion filling the pleural cavity has now been abandoned. This does not preclude its use however in individual cases to drain a refractory effusion that is symptomatic (eg chylothorax . There are few (if any) true indications for a Ladd's operation for the “non-rotated” gut seen in the CDH patient with open and / or MIS repair. Such additional (and unnecessary) procedures increase patient morbidity and the relative risk(s) for adhesive intestinal obstruction.[1, 90]

# **Minimally Access Surgery (MIS)**

Minimal access surgery (MIS) was first pioneered by Francois Becmeur, France in 2001 and has the advantage(s) of superior aesthetics and reduced post-operative pain – Figure 5 . [95 ]. A systematic review from Liverpool, UK in 2010 , however showed higher rates of hernia recurrence ( x 3 fold ) with MIS vs. classical open operation. [96] Reports from Japan and APSA further support and reaffirm these early observations. [ 97, 98 ] The diaphragm defect is visualised thoracoscopically and the hernia contents repositioned in the abdominal cavity , endoscopic repair then follows with or without patch insertion – Figure. Surgeon case selection incorporating ‘lower risk’ patients with smaller size diaphragmatic defects ( Grades A and B ) should see high recurrence rates here decline. To this end the ‘ high risk ‘ CDH newborn may not be the most ideal suitable cohort group for MIS best deferring endoscopic operation to ‘ late presenting CDH ‘ cases encountered in later childhood or adolesence. To allow for a better future comparison of outcome metrics in MIS studies it is strongly recommended that surgeons record the diaphragmatic defect size ( Grade A – D ) in all surgeries. [96, 99]

# **Morbidity**

Pleural effusion is a common occurrence after CDH repair with chylothorax reported in some 6%–27% of operated CDH patients [1,90] The majority of effusions are small and respond adequately to needle thoracocentesis. A recurrent troublesome chylothorax may require a pleural drain, octreotide, and a period of fasting and total parenteral nutrition with graded introduction of oral feeds with medium chain triglyceride (MCT) formula [100] Risk factors for chylothorax appear to be highest in those babies repaired on ECMO [1,90] and having patch repair for large defects [1,90] Fibrin glue sealants ie. TISSEEL can be very useful at reducing risk(s) of lymph fluid accumulation(s) [1]

A nationwide Japanese survey found that 13.5% of CDH patients develop pneumothorax at some point during initial hospital stay and this is more likely in newborns with large diaphragm defects [101] A pneumothorax will often suddenly present with a deterioration in cardiorespiratory physiology in the ventilated baby too often with fatal outcome ].

Abdominal compartment syndrome (ACS) must be considered a risk factor in CDH patients where the volume of herniated abdominal contents returned to the abdomen is so large often requiring patch repair and / or primary diaphragm repair under tension. The risk of developing ACS can be minimised here by reducing intra-abdominal pressure(s) with the liberal use of an abdominal wall patch—“abdominoplasty”. [94]

Hernia recurrence(s) occur most often in patients with large defects requiring patch repair [1] and / or CDH repair by thoracotomy[1, 90, 102]. Technical factors with patch inlay technique by the surgeon may be relevant here. [94]

Other morbidity recorded in large contemporary series include adhesive bowel obstruction (10%) , volvulus (5%) and gut perforation (3%). [103] Rate(s) of bowel obstruction may also depend on the nature of prosthesis or type of mesh used for diaphragm repair. [1, 90, 103]

# **Reported outcome(s) and long-term follow up**

Reporting of outcome metrics in CDH shows survival rates widely ranging from 40 - 80% in different countries likely reflecting the variable quality of birth defect anomaly reporting registries. [1,90,104 ] Survival for CDH in specialist ‘ high volume ‘ centres now approaches 75% or higher with post-operative survival reaching 93%[1,90, 93, 94 ]. Improving survival has created a ' new cohort population ‘ with a corresponding increase in patient related morbidity with the most vulnerable being those having ECMO or FETO contributing to cohort studies. ALL CDH patients should therefore be enrolled in interdisciplinary specialist follow-up clinic programs [1, 90, 104]

Pulmonary morbidity is evidenced in almost 45% of CDH survivors [1,90,]. Primary lung pathology with ventilator-induced lung injury contributes greatly to long-term problems. [105] Toussaint-Duyster et al. [106] recommend that CDH patients should be followed into adulthood as they are at a cumulative risk for worsening airflow obstruction and decreased diffusion capacity ( VQ mismatch ) at school age, irrespective of ECMO therapy.

Gastroesophageal reflux (GER) is observed in some 22-81% of CDH newborns. [1,90,] Although symptoms may resolve on medical therapy with proton pump blockers without surgical intervention those infants with large diaphragm defects requiring a patch and / or ECMO life support often develop severe GER requiring fundoplication [ 90,107-108]

Pectus chest wall deformity is recorded in 10% of all patients after primary CDH repair[133] and up to 47% and 54% respectively following operations where muscle flap and / or prosthetic patch is needed. Scoliosis observed in 7-15% of CDH survivors may require orthopaedic bracing or spinal surgery. [109]

Fifty-one per cent of CDH survivors show evidence of neurocognitive deficit(s), learning difficulties , muscle tone problems and language skill disability. Hearing loss is also prevalent in survivors that may be ( i ) congenital , ( ii ) linked to medications

( aminoglycosides ) or ( iii ) ventilatory strategy mode / hypoxia. [1,90,110] In recent years greater recognition of the increased risk(s) of autism (10% ) vs healthy general population is evident requiring special support [111]

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**Figure Legends**

Figure 1 – Stages of mammalian lung development

Figure 2 – FETO CDH fetal therapy

Figure 3 – Chest X-ray of a newborn with left side CDH (LCDH. Note bowel content in left thoracic cavity, mediastinal shift and dextrocardia.

Figure 4 – Classical operative repair CDH - ( A ) Viscera are displaced in the thorax through a Bochdalek posterolateral diaphragm defect. ( B ) Hernia contents have been reduced into the abdomen. A row of interrupted non-absorbable sutures have been placed to secure primary diaphragm closure. ( C ) Primary repair completed , ( D ) Prosthetic patch material deployed to secure closure for large left side defect (Grade C).

Figure 5 – MIS CDH operation – A left side diaphragm defect (LCDH) is visualized from the thorax above with the endoscopic instruments.

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