Chapter from the book *Congenital Diaphragmatic Hernia - Prenatal to Childhood Management and Outcomes*


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Congenital Diaphragmatic Hernia and Congenital Heart Disease

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1. Introduction

Congenital Diaphragmatic Hernia (CDH) is a severe and life threatening condition which can occur in isolation or with associated malformations. Congenital Heart Disease may be associated in up to 40\% of cases with these infants often having a poor prognosis. This chapter aims to explore the association between CDH and congenital heart disease exploring the frequency of association, echocardiographic findings, prenatal diagnosis, use of cardiovascular biomarkers, surgical management and finally long term outcomes.

2. Methodology

Medline, PubMed, and Cochrane databases were searched for bibliography from Jan 1966 to December 2010. Key words used in the search were [Congenital Diaphragmatic Hernia], [Congenital heart disease], [Antenatal/Prenatal Diagnosis][Cardiovascular dysfunction], [Cardiac Biomarkers], [Surgical management and complications of CDH associated congenital heart disease], [Outcome in CDH associated congenital heart disease].

3. Frequency and type of congenital heart disease (CHD) associated with congenital diaphragmatic Hernia (CDH)

Congenital diaphragmatic Hernia (CDH) is a severe and life threatening malformation in infants. (Greenwood, Rosenthal et al. 1976) The reported incidence varies however the most recent series report a similar incidence of 1.4-4.5/10000 births (Dott, Wong et al. 2003) Infants with CDH may have an isolated diaphragmatic lesion, however complex CDH occurs with additional abnormalities either as part of a recognized syndrome, chromosomal abnormality or part of another major malformation accounts in 30 – 40\% of cases. (Pober 2007) Associated malformations increase the mortality rate in infants with CDH. (Betremieux, Lionnais et al. 2002)

CDH may clinically mimic congenital heart disease, at birth with an infant who has low arterial oxygen saturations whom is difficult to oxygenate. In the largest multicentre cohort
to date, Lin et al estimate the frequency of infants with non-syndromic CDH with associated congenital heart disease to vary from 10-15% (Lin, Pober et al. 2007) The frequency of CDH and congenital heart disease rises to between 25-40% if infants with underlying syndromes and chromosomal abnormalities are included. (Lin, Pober et al. 2007) Harmath et al also found CDH was associated with cardiovascular anomalies in up to 43% of cases. (n=71)(Harmath, Hajdu et al. 2006)

Congenital heart Disease has prevalence in Europe of 7 per 1000 births. (Dolk, Loane et al.) The coexistence of CHD and congenital heart disease is often predictive of a poor prognosis (Sharland, Lockhart et al. 1992) Cohen et al reviewed 31 infants with CDH and congenital heart disease concluding that heart disease remains a significant risk factor for death in infants with CDH (Cohen, Rychik et al. 2002) The most frequent congenital heart defect associated with CDH was a Ventricular Septal Defect (VSD) (29%) which is also the most frequent congenital heart disease lesion in the paediatric population. This was followed by arch obstruction, hypoplastic left heart syndrome and Tetralogy of Fallot (13%). Their findings suggested that it was not the congenital heart lesion but severity of pulmonary hypoplasia that was the strongest predictor of poor outcome in this group. None of the infants with Tetralogy of Fallot or Transposition of the Great Arteries survived.(Cohen, Rychik et al. 2002) Similarly Dott et al found VSD to be the most commonly associated CHD lesion followed by atrial septal defect, coarctation of the aorta and hypoplastic left heart syndrome. (Dott, Wong et al. 2003)

Many congenital heart disease lesions for example, coarctation of the aorta, transposition of the great arteries, and truncus arteriosus are associated with an increased risk of pulmonary hypertension. This coupled with the existing risk of pulmonary hypertension in infants with CDH may account for the poor prognosis in this group. (Clarkson, Neutze et al. 1976; Levin, Mills et al. 1979; Kumar, Taylor et al. 1993; Sreeram, Petros et al. 1994)

Hypoplastic left heart syndrome (HLHS) is rarely associated with CDH (Nishimura, Taniguchi et al. 1992) despite many infants with CDH noted to have left heart hypoplasia. This is thought to result from compression by an enlarged right ventricle, but with structurally normal aortic and mitral valves and aortic arch with normal volume. (Lin, Pober et al. 2007) These infants are at increased risk of a low left ventricular mass which has been confirmed at post mortem.(Schwartz, Vermilion et al. 1994) Left ventricle mass measured on two-dimensional echocardiogram may predict outcome in infants with CDH, Schwartz et al concluded that left ventricular mass, indexed to patient weight was significantly diminished in patients with left sided CDH, (n=31) and this tool may be useful in determining suitability for Extracorporeal membrane oxygenation (ECMO) prior to surgical repair and possibly to help predict survival. (Schwartz, Vermilion et al. 1994) Case reports of infants with CDH and congenital heart disease exist with individual good outcomes. Noimark et al report a case of transposition of the great arteries VSD and CDH. The infant in their case survived, likely because the underlying cardiac defect could be repaired surgically.

### 4. Echocardiography in congenital diaphragmatic Hernia

Many studies have tried to correlate outcomes with the size of the main pulmonary artery (PA) measured by angiography or echocardiography. In infants with congenital heart disease indices of pulmonary artery size may be used to predict outcome before surgical
correction of obstructive right heart lesions. (Suda, Bigras et al. 2000) These measures relate pulmonary artery size to the size of the aorta (McGoon Index) or body surface area (Nakta Index). Suda et al attempted to correlate the combined size of the proximal pulmonary arteries (as an indicator of pulmonary hypoplasia) with clinical outcome. They concluded that non survivors had significantly smaller hilar pulmonary arteries than survivors. (Suda, Bigras et al. 2000)

Similarly Okazaki et al reviewed the size of the left and right pulmonary arteries (LPA/RPA) on echocardiography to determine if pulmonary artery size and blood flow have prognostic value in CDH. (n=28) All patients who required treatment with Nitric Oxide (NO) had significantly smaller LPA and RPA and significantly smaller LPA/RPA ratio. All those died required treatment with NO (12%) and they concluded that a small LPA/RPA ratio appeared to be a simple highly reliable indicator of the necessity for NO therapy, and PA size may be a prognostic indicator in CDH. (Okazaki, Okawada et al. 2008)

Fetal echocardiographic measures of pulmonary hypoplasia and size in infants with CDH may be prognostic factors. (Thebaud, Azancot et al. 1997) Thebaud et al retrospectively measure the size of the cardiac ventricles, aorta and pulmonary arteries and calculated a measure of cardiac index comparing left and right ventricles and Aorta and pulmonary arteries. (n=32) Cardiac ventricular disproportion, expressed by the LV/RV ratio, appeared to correlate well with a poor outcome, concluding that Doppler flow studies may be helpful to improve understanding of left ventricular hypoplasia. (Thebaud, Azancot et al. 1997)

In the future methods such as tissue Doppler Imaging (TDI) may be useful as a prognostic indicator in CDH both pre and post surgery. In three cases TDI demonstrated improvement in both left and right sided myocardial performance index (MPI) following surgery, with both left and right MPI correlating well with clinical course. (Cua, Cooper et al. 2009)

5. Prenatal diagnosis of congenital heart disease associated with CDH - Planning for delivery

In the last twenty years prenatal diagnosis of CDH has improved significantly from 15% in the mid 1980s to almost 60% in the late 1990s. (Done, Gucciardo et al. 2008) Previously the outcome of fetuses with prenatally diagnosed CDH was thought to be poor, (Adzick, Vacanti et al. 1989) however as many cases are now diagnosed antenatally, prenatal diagnosis can no longer be considered a useful predictor of poor outcome.

CDH is suspected on antenatal ultrasound, in the presence of an absent or intrathoracic stomach bubble, cystic features noted in the chest, failure to identify the diaphragm, polyhydraminos, mediastinal and cardiac shift away from the side of the herniation and in extreme cases fatal hydrops. (Geary 1998) Polyhydraminos is found in more than 75% of pregnancies complicated by fetal CDH, and is thought to be a predictor of adverse outcome (Adzick, Harrison et al. 1985)

When CDH is suspected, associated anomalies must be looked for carefully on detailed fetal anomaly scans. As the association between chromosomal abnormalities and CDH is thought to range from 5% - 18% with many genetic disorders also being linked discussion should commence regarding fetal karyotyping (Cunniff, Jones et al. 1990; Bollmann, Kalache et al. 1995) The added incidence of chromosomal abnormalities, CDH and congenital heart
disease, being as high as 25-40%, (Lin, Pober et al. 2007) favours karyotyping as a useful investigation.

Congenital heart disease is present in up to 15% of infants with CDH. (Pober 2007) These lesions may coexist because formation of the fetal diaphragm and the development of the fetal heart occur at similar times embryologically. (Noimark, Sellwood et al. 2000) Although the available data estimates antenatal diagnosis of congenital heart disease to be approximately 23%, this data is ten years old and when CDH is suspected, fetal echocardiography should be carried out by an experienced paediatric cardiologist. (Allan)

In the past it was suggested that left heart hypoplasia as detected on fatal echocardiogram may predict poor outcome. (Crawford, Drake et al. 1986; Sharland, Lockhart et al. 1992) In order to see if fetal echocardiographic variables could be used to predict outcome in fetuses with CDH, VanderWall et al all reviewed echocardiographic evaluations in fetuses with CDH and compared them to normal fetuses. Left and right ventricular width were significantly less than controls of the same gestational age, as were the left ventricular volume and mass, however they concluded that no echocardiographic parameters could predict survival. (n=12) (VanderWall, Kohl et al. 1997) Fetal echocardiographic measures of pulmonary hypoplasia and size in infants with CDH may be prognostic factors. (Thebaud, Azancot et al. 1997) Thebaud et al retrospectively measured the size of the cardiac ventricles, aorta and pulmonary arteries and calculated these as a measure of cardiac index. (n=32) Cardiac ventricular disproportion, expressed by the LV/RV ratio, appeared to correlate well with a poor outcome, concluding that Doppler flow studies may be helpful to improve understanding of left ventricular hypoplasia. (Thebaud, Azancot et al. 1997) The pathophysiological process for the underdevelopment of the left side of the heart remains unclear, with mechanical compression from the herniated abdominal viscera still being the most likely cause, which is supported by the VanderWall findings. (Siebert, Haas et al. 1984; VanderWall, Kohl et al. 1997)

Detecting CDH and congenital heart disease prenatally allows careful planning of both maternal and fetal care with multi speciality involvement. Delivery can be planned and should ideally take place in a tertiary referral centre with neonatal expertise available for elective intubation at birth and with easy access to paediatric surgery and paediatric cardiology if not available on site. In France in utero referral to a tertiary centre increased survival from 41–66%. (Gallot, Coste et al. 2006) The Canadian Neonatal Network demonstrated that centres receiving more than 12 infants per year with CDH had 13% higher survival rates. (Javid, Jaksic et al. 2004)

Prenatal diagnosis also allows early therapeutic decisions to be made. Recent evidence may favour the role of extra corporeal membrane oxygenation (ECMO). Infants who have antenatal measures of an abnormal lung to head ratio for gestational age or herniation of the liver are more likely to require ECMO, therefore delivery should be planned in a tertiary centre who can provide ECMO. (Jani, Nicolaides et al. 2007). Other novel therapeutic measures include the use of Prostaglandin to maintain patency of the ductus arteriosus and to improve left ventricular diastolic dysfunction. (Inamura, Kubota et al. 2005)

Counselling should also be undertaken at this stage, as a number of children who survive CDH have higher indices of gastro oesophageal reflux, feeding dysfunction and bronchopulmonary dysplasia at one year of age. In the longer term those who survive CDH surgery have a
significant risk of developmental delay and seizures. Prenatal diagnosis of CDH and congenital heart disease allows time for parental counselling, potential assessment of prognosis, planning for delivery in a Tertiary Referral centre and in the future may allow for antenatal intervention.

6. Use of cardiovascular biomarkers in children with CDH

Biochemical markers such as cardiac Troponin T and I and B-Type Natriuretic peptide (BNP), are well established markers of myocardial ischaemia and cardiac failure in adults and children (Koch and Singer 2003; Fromm 2007) (Spies, Haude et al. 1998). BNP is a 32 amino acid ring structure which has its sequence present on chromosome 1. It is found in high concentration in the ventricles of the heart and is released in response to volume and pressure loading and ventricular stress. Pro BNP is the inactive precursor and is cleaved into BNP, the active component and N-terminal pro-BNP (NTpBNP), an inactive by-product. (El-Khuffash, Davis et al. 2008) BNP and NTpBNP levels are high at birth and fall slowly over the first two weeks of life. Normal ranges of BNP and NTpBNP have been established in neonates but vary depending on age of neonate and the testing kit used. (Ellis 1991) (Koch and Singer 2003) (El-Khuffash and Molloy 2009) (El-Khuffash and Molloy 2007)

BNP and NTpBNP are used to aid diagnosis, assess prognosis and to monitor ventricular dysfunction in various types of congenital heart disease. BNP is significantly increased in patients with ventricular dysfunction. (Koch, Zink et al. 2006) El Khuffash et al have also demonstrated the use of pro BNP and Troponin as an adjunct to echocardiography to predict poor neonatal outcome (grade III/IV intraventricular haemorrhage or death) in preterm infants with a PDA. (El-Khuffash, Slevin et al.)

Infants with persistent pulmonary hypertension of the newborn also have elevated levels of BNP (El-Khuffash and Molloy 2009) In the clinical setting, in the absence of paediatric cardiology onsite to confirm tricuspid regurgitation PPHN can be difficult to diagnose. This process may be aided using BNP, as BNP levels correlate well with pressure gradient across the tricuspid valve, and rising BNP levels indicate a worsening clinical condition (n=47). (Reynolds, Ellington et al. 2004) Pulmonary hypertension is a recognised complication of CDH. A small series (n=28) of infants with CDH showed that NTpBNP levels correlated well with estimated pulmonary artery pressure, Right Ventricle (RV) Tei index (a measure of global myocardial performance) and RV diastolic impairment. Infants with an elevated NTpBNP also had a worse prognosis. (Baptista, Rocha et al. 2008)

Troponins are the calcium binding site of the myofibrillary thin filament of the cardiac sacromere. There are three distinct proteins, Troponin T, Troponin C and Troponin I. The majority of cardiac troponins are bound in the contractile apparatus and Troponin C and I are released in response to myocardial ischaemia. Troponin T is a marker of cardiac injury in adults with ischaemic or haemorrhagic stroke in the absence of myocardial cell injury. (Fromm 2007)

Normal Troponin I levels in children are less than 2.0 ng/ml (n=120). (Hirsch, Landt et al. 1997) Fenton et al found increased Troponin I on admission in 57% of patients and at 12 hrs in 46% of pediatric intensive care patients admitted with septic shock and cardiovascular failure. (Fenton, Sable et al. 2004) Admission Troponin I levels inversely correlate with
ejection fraction and fractional shortening and is directly proportional to wall stress. Children who had increased admission Troponin I had lower heart rate corrected mean velocity of circumferential fibre shortening (preload and heart rate independent measure of left ventricular systolic function) and higher wall stress (measure of afterload) compared with those with normal Troponin I. Admission Troponin I correlated with mortality. (Fenton, Sable et al. 2004) Troponin T is a good predictor of myocardial injury in asphyxiated neonates. (Hirsch, Landt et al. 1997) but has not yet been assessed in children with CDH.

7. Surgical management of CDH and congenital heart disease

Survival for infants with CDH has improved dramatically as new approaches to treatment arise. Gross first reported surgical repair of CDH in 1946. (Gross 1946) Since then the primary focus has shifted away from immediate surgery to stabilisation and optimising the physiological derangements in infants prior to surgery. (Chiu and Hedrick 2008). A better understanding of the underlying physiological processes that result from pulmonary hypoplasia has improved initial management and increased survival rates to as high as 90% in some tertiary paediatric centres over the last five years. (Boloker, Bateman et al. 2002; Downard and Wilson 2003; Chiu, Sauer et al. 2006)

Chiu et al found that the current focus of postnatal CDH management should be to firstly support oxygenation and ventilation while simultaneously trying to prevent ventilator induced lung damage, secondly to maintain cardiovascular stability though the use of ECMO, thirdly to treat pulmonary hypertension and finally to ultimately minimise overall morbidity. (Chiu and Hedrick 2008) In those with CDH surgical repair is no longer a surgical emergency, and mortality is not increased by waiting to improve ventilation. (Azarow, Messineo et al. 1997) (Langer, Filler et al. 1988) Those who undergo early versus late repair have similar survival rates (68% vs 62%) with the frequency of cardiac defects having the biggest influence on poor outcome, 26% in survivors vs 55% in non survivors. (n=111) (Rozmiarek, Qureshi et al. 2004) Infants are now managed with gentle ventilation strategies, which consist of permissive hypercapnea, that is accepting post ductal arterial pCO2 levels as high as 55 mmHg / 7.32 kPa with a compensated pH>7.35 provided cardiac performance and pulmonary pressures remain stable; preductal oxygen saturations >85% and restriction of airway pressure with early conversion to high-frequency oscillatory ventilation (HFOV) to minimise ventilator induced lung damage. (Chiu and Hedrick 2008)

ECMO is now used to stabilise the infant with CDH, when the pulmonary vasculature is still reactive, however pulmonary hypertension and pulmonary hypoplasia remain the commonest causes of death in CDH infants while on ECMO. Many centres have suggested that survival has improved since the introduction of ECMO therapy however numbers are small. Patient selection for various treatments have not been standardised nor has criteria for separating patients with severe pulmonary hypoplasia, who have a high mortality from those with adequate lung development who have ductal shunting but whom have a lower mortality. (Azarow, Messineo et al. 1997)

In infants with CDH and congenital heart disease, surgery should be delayed until the pulmonary vascular resistance has decreased to acceptable levels. (Lin, Pober et al. 2007) The anatomic defect appears to be of secondary importance to the physiological effects of
pulmonary hypoplasia. The spectrum of disorders associated with CDH such as pulmonary hypertension, left ventricular hypoplasia, ductal shunting still presents an overwhelming management challenge. A supra systemic elevation in the pulmonary vasculature resistance, that may coexist with both congenital heart disease and CDH produces a significant increase in the afterload on the right ventricle, having the potential to cause right ventricular failure, (Stayer and Liu) therefore medical management rather than surgical is important in the first instance. Providing the right ventricle with the means to ‘pop off’ through a shunt may prevent life threatening right heart failure. Maintaining the PDA serves this purpose as it remains patent through the presence of high flow in cases of suprasystemic RV pressure. If the PDA is restrictive, or closed intravenous prostaglandin may restore or maintain the patency of the PDA. (Bohn 2002; Berman Rosenzweig and Barst 2006) Pulmonary hypertension can be associated with both congenital heart malformations and CDH, with up to 34% of patients referred for evaluation of pulmonary hypertension in a tertiary centre having CDH. (Geggel 2004) It develops when the pulmonary vascular resistance (PVR) remains elevated after birth, resulting in left to right shunting through fetal circulatory pathways. (Stayer and Liu). Pulmonary hypertension in infants with congenital heart disease is most commonly seen in those who have a large left to right shunt. The size and location of the shunt as well as blood flow through the shunt are the most important risk factors for the development of pulmonary arterial hypertension. Infants with CDH have underdevelopment of the pulmonary vasculature, producing a fixed elevation of the PVR. Doppler echocardiography is necessary to measure the systolic tricuspid regurgitant jet in order to estimate pulmonary artery pressure. Treatment in infants with pulmonary hypertension depends on the underlying condition. Inhaled Nitric Oxide, a pulmonary vasodilator, has redefined the management of pulmonary hypertension, however to date no real benefit has been noted in those infants with congenital diaphragmatic hernia. (Shah, Jacob et al. 1994) (Stayer and Liu) (1997)

In the future intervention with fetal surgery may improve outcomes in children with CDH. Fetal surgery is justifiable if the natural history and pathophysiology of the disease are well understood, the prenatal diagnosis if accurate, if in utero correction is shown to be efficacious in animal models and if maternal risk is acceptably low. (Harrison and Adzick 1991) Percutaneous fetal valvuloplasty and atrial septostomy are exciting new advances in infants with critical aortic stenosis and hypoplastic left heart syndrome. (Allan) In infants with CDH there is a higher degree of pulmonary hypoplasia on the side of the lesion, fetal intervention may lead to sufficient parenchymal growth, by alleviating the space occupying lesion essentially formed by the abdominal viscera. (Deprest, Flake et al.; Gucciardo, Deprest et al. 2008) Measurements such as the lung-to-head ratio (LHR) and the position of the liver in utero (Jani, Keller et al. 2006) may help to predict the postnatal outcome for infants with isolated CDH, therefore helping to select those who may benefit from fetal intervention.

8. Long term outcomes in children with CDH and congenital heart disease

Throughout France, Australia and the United Kingdom survival rates of infants with isolated CDH are currently estimated to be between 50-70% with emphasis made on long term follow up. (Done, Gucciardo et al. 2008) As the survival rates continue to improve survivors are noted to have a higher incidence of respiratory, nutritional, musculoskeletal, neurological and
gastrointestinal morbidities. (Chiu and Hedrick 2008) With newer treatments such as pre and post surgery ECMO survival rates of infants with CDH continue to improve. While ECMO may ultimately improve survival it is not without risk. Complications include perinatal asphyxia, hypoxaemia and intracranial bleeding secondary to the systemic heparinisation treatment used in conjunction with ECMO. (Frisk, Jakobson et al.) (Hedrick, Danzer et al. 2007)

Many studies to date focus on the short term neurodevelopmental outcomes of CDH survivors. Those infants who have not undergone ECMO as part of their treatment appear to have better outcomes than survivors who did receive ECMO. However these studies date back to the mid 1990s so further research is required. (Stolar, Crisafi et al. 1995) In the non ECMO therapy group, 8-9.5% are hearing impaired(Nobuhara, Lund et al. 1996), 8-13% have brain abnormalities(Lund, Mitchell et al. 1994) and up to 19% were developmentally delayed(Davenport, Rivlin et al. 1992). The long term survivors have lower intelligent quotient (IQ) with up to 50% experiencing emotional or behavioural problems. (Peetsold, Huisman et al. 2009)

There is a paucity of data on long term neurodevelopmental outcomes. Frisk et al followed a cohort of CDH survivors, (n=27) none of whom had undergone ECMO. Comparison to a peer control group revealed low rates of developmental issues reported in preschool infants, however as children progressed through school more educational difficulties became apparent. Between 23-46% of non-ECMO treated CDH survivors demonstrated clinically significant academic difficulties with parents reporting higher rates of attention difficulties and social problems. (Frisk, Jakobson et al.)

The Boston Circulatory Arrest trial provides the most comprehensive detail of neurodevelopmental outcomes in children following cardiac surgery. (Bellinger, Jonas et al. 1995; Bellinger, Wypij et al. 2003) Infants who had transposition of the great arteries who underwent the arterial switch operation were randomised to total circulatory arrest or low flow cardiopulmonary bypass during cardiac surgery and were followed up at eight years of age. Those who had longer postoperative stay in the cardiac intensive care unit had lower IQ scores at eight years of age. Use of circulatory arrest is associated with greater functional deficits than the use of low flow cardiopulmonary bypass, although both are associated with increased risk of neurodevelopmental problems. (Bellinger, Wypij et al. 2003) Children who undergo cardiac surgery for correction of congenital heart lesions also undergo circulatory arrest and this is associated with a higher risk of delayed motor development and neurological abnormalities at the age of one year than is surgery with low-flow bypass. Therefore infants who have CHD and an associated congenital heart defect will undergo a minimum of two surgeries and will have an increased risk of long term neurodevelopmental problems. Children who have congenital heart disease alone and who undergo surgery are at increased risk of growth and developmental problems as a result of cyanosis, heart failure, frequent hospitalisation, feeding difficulties and surgical intervention. This coupled with those surviving CDH surgery may contribute to the number of infants with short and long term neurodevelopmental problems.

9. Conclusion

CDH with associated congenital heart disease is a complex condition. With advances in both prenatal diagnosis and fetal surgical intervention these infants may have both better short
and long term outcomes. Novel techniques such as the use of cardiovascular biomarkers may aid in the diagnosis of cardiovascular dysfunction, guide therapy and ultimately improve the outcomes in these infants. The paucity of data on long term cardiac function in infants surviving CDH surgery highlights an important area of future research.

10. References


Congenital Diaphragmatic Hernia – Prenatal to Childhood Management and Outcomes


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