Congenital diaphragmatic hernia

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Summary
Congenital diaphragmatic hernia (CDH) is a lethal human birth defect. Hypoplastic lung development is the leading contributor to its 30–50% mortality rate. Efforts to improve survival have focused on fetal surgery, advances in intensive care and elective delivery at specialist centres following in utero diagnosis.

The impact of abnormal lung development on affected infants has stimulated research into the developmental biology of CDH. Traditionally lung hypoplasia has been viewed as a secondary consequence of in utero compression of the fetal lung. Experimental evidence is emerging for a primary defect in lung development in CDH. Culture systems are providing research tools for the study of lung hypoplasia and the investigation of the role of growth factors and signalling pathways.

Similarities between the lungs of premature newborns and infants with CDH may indicate a role for antenatal corticosteroids. Further advances in postnatal therapy including permissive hypercapnia and liquid ventilation hold promise.

Improvements in our basic scientific understanding of lung development may hold the key to future developments in CDH care.

INTRODUCTION
Congenital diaphragmatic hernia (CDH) is an idiopathic birth malformation comprising the Bochdalek diaphragmatic defect, herniation of abdominal viscera into the thoracic cavity and pulmonary hypoplasia. An incidence of approximately 1:2,500 births1,2 results in a new case every 24–36 h in the UK. Despite current advances in neonatal care around 30–50% of affected infants die, largely due to respiratory insufficiency secondary to pulmonary hypoplasia3–5. This review discusses contemporary clinical management and highlights recent research developments in CDH.

The aetiology of CDH remains largely unclear. The majority are sporadic – only 2% occurring with a familial association.6 Although in most instances CDH is idiopathic, rare association with teratogens such as phenemetrine and thalidomide have been reported.7,8 Approximately 80% are left-sided defects and the majority occur as an isolated anomaly. CDH may, however, also occur as part of a syndromic genopathy. Genetic associations include trisomies 13 and 18 as well as syndromes including Fryns’s (MIM229850), Coffin-Siris (MIM135900) and Denys-Drash (MIM*194070). Survival is poor among infants with associated abnormalities. Mortality may be as high as 93%, many succumbing in the antenatal period.9

ANTENATAL DIAGNOSIS
Diagnosis of CDH is increasingly reported on antenatal ultrasound scans – either by routine anomaly scans at around 20 weeks gestation, or following clinical suspicion of maternal polyhydramnios. CDH is confirmed by visualising the stomach or loops of bowel within the thoracic cavity – ideally level with the “four-chamber” view of the fetal heart, along with mediastinal shift away from the side of the lesion. Antenatal diagnosis should prompt a careful search for cardiac and neural tube defects. Despite the increasing use of ultrasound, reports have

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suggested isolated CDH is antenatally diagnosed in only approximately 50% of cases. Early diagnosis provides an opportunity for parental counselling by a team of clinicians ideally including an obstetrician, neonatologist and paediatric surgeon.

**PROGNOSTIC INDICATORS**

One important aspect of counselling is the issue of prognosis. Should associated anomalies be found on the antenatal scan this will alter the projected outcome and each fetus should be considered individually. For isolated CDH defining accurate antenatal prognostic indicators has proved challenging. Features including early diagnosis (<25 weeks), polyhydramnios and the presence of an intrathoracic stomach bubble have all been suggested to equate with poor prognosis. None has been found to be consistently reliable. Given that the major determinant of outcome is the degree of pulmonary hypoplasia, an estimation of fetal lung growth would seem a logical indicator. Estimation of volume by ultrasound using a ratio of right lung diameter to head circumference (to normalise for overall fetal growth) known as the lunghead ratio (LHR), has been shown to be of use in predicting those at extreme ends of the scale with a value of <0.6 being correlated with 100% mortality. For the CDH fetus with an LHR in the mid-range it has proved less helpful. Fetal magnetic resonance imaging (MRI) has been suggested as a tool to give a three-dimensional estimation of lung growth. Initial reports are encouraging and results from larger studies are needed. Currently, a combination of LHR along with the presence of liver in the thoracic cavity (so-called “liver-up” cases) is used by fetal surgical centres considering antenatal intervention.

**PLAN FOR DELIVERY**

Antenatal counselling also provides an opportunity to formulate a plan for delivery. Ideally elective delivery should occur at an obstetric centre with easy access to paediatric surgical expertise to avoid long distances in the postnatal transfer of the infant. Caesarean section is usually reserved for obstetric indications.

**POSTNATAL DIAGNOSIS**

Should an antenatal diagnosis not be made, postnatal diagnosis most commonly occurs in the first few minutes of life. Signs of respiratory distress, a scaphoid abdomen and mediastinal shift away from the side of the lesion all suggest the diagnosis. X-ray appearances including an absent diaphragmatic outline, along with loops of bowel in the chest should confirm the diagnosis (Fig. 1). If necessary, the position of the tip of a nasogastric (NG) tube within the thorax, along with an upper gastrointestinal (GI) contrast study or postnatal ultrasound scan (in experienced hands) will help differentiate CDH from lesions such as cystadenomatoid malformations.

**MANAGEMENT**

At birth, or following diagnosis, the infant should be intubated and a large bore NG tube passed. Both interventions are designed to prevent any dilatation of the intrathoracic bowel, which would cause further respiratory embarrassment. Early postnatal management is aimed at providing adequate tissue oxygenation whilst avoiding high ventilatory pressures, that cause damage to the neonatal lungs through barotrauma. Traditionally this is achieved through routine use of sedation, with or without paralysis to prevent the infant “fighting” the ventilator. Peak inspiratory pressure and positive end expiratory pressures (PEEPs) are adjusted to maximise oxygenation and prevent the development of acidosis. Minimal handling and maintenance of normal pH are applied to minimise aggravating pulmonary hypertension, which inevitably accompanies pulmonary hypoplasia. Failure of conventional ventilation to provide adequate oxygenation may require the addition

![Figure 1](image-url)
of inhaled nitric oxide, high frequency oscillatory ventilation or extracorporeal membrane oxygenation (ECMO).

**INHALED NITRIC OXIDE**

Initial attempts to treat pulmonary hypertension in the newborn involved the use of systemic vasodilators such as tolazoline or prostaglandins. However, significant side-effects, in particular systemic hypotension, made their use unacceptable.\(^{25-27}\) Inhaled nitric oxide presented an attractive alternative. Inhalational delivery and rapid metabolism mean that systemic side effects are minimised. Initial trials in infants with persistent pulmonary hypertension of the newborn were very encouraging, some demonstrating a universal increase in $\text{SaO}_2.\(^{28-30}\) Studies in infants with CDH have shown a more variable response with many infants manifesting no benefit. A recent meta-analysis and Cochrane review showed an improvement in perinatal outcome only in infants with persistent pulmonary hypertension who do not have CDH.\(^{31,32}\)

**HIGH FREQUENCY OSCILLATORY VENTILATION**

The use of high frequency oscillatory ventilation (HFOV) has been widely adopted. This follows the concept that altering the mode of ventilation by increasing the ventilator rate to 100–150 breaths/min with gas exchange occurring through bulk diffusion rather than mass flow may improve gas exchange whilst decreasing barotrauma. Despite the outcome of an early multicentre randomised trial in North America suggesting no benefits in preterm neonates with respiratory failure,\(^{33}\) several anecdotal reports continue to report improvements in CDH.\(^{34,35}\) A recent Italian study reported on the outcome of 44 infants treated over a 10 year period showing an increase in survival from 67% to 94% by employing HFOV in the preoperative management of CDH.\(^{36}\) Surgical repair has also been undertaken whilst maintaining the infant on high frequency ventilation.\(^{36}\)

**EXTRACORPOREAL MEMBRANE OXYGENATION**

ECMO, introduced in the late 1970s, involves placing the infant on cardiopulmonary support to allow a period of “lung rest” and reduction in pulmonary vascular resistance whilst providing the infant with oxygenated blood via an artificial circuit. ECMO is an accepted treatment modality for the management of respiratory failure in newborns. In the UK its use is restricted to designated paediatric ECMO centres.

Evidence to support the use of ECMO in CDH is conflicting. Early favourable reports were flawed by the use of historical controls.\(^{37-39}\) A North American study addressed the relative outcomes from two centres, one offering ECMO, the other offering conventional respiratory care.\(^{40,41}\) This report failed to show any consistent improvement in outcome with the use of ECMO. The results of a multicentre trial in the UK, whilst demonstrating benefits in infants with respiratory failure, failed to support the use of ECMO in CDH.\(^{42}\) This study has been criticised however for excessively stringent entry criteria necessitating near unsalvageable respiratory failure before inclusion of infants with CDH. A 2002 Cochrane Review on ECMO showed a significant survival advantage for all infants with respiratory failure. The advantage was least significant for CDH patients.\(^{43,44}\) Despite a lack of clear evidence for its use, ECMO is likely to remain a treatment modality for the infant with CDH.

**PERMISSIVE HYPERCAPNIA**

An alternative approach, first suggested by Wong et al. in 1985 from New York is permissive hypercapnia.\(^{45}\) This avoids the use of sedation, allowing the infant to breathe spontaneously on the ventilator. Peak inspiratory pressures are strictly limited, to avoid the effects of barotrauma on the hypoplastic lung, whilst PEEP is used to maximise alveolar recruitment. This technique permits arterial carbon dioxide levels to rise as necessary, whilst reserving sodium bicarbonate infusions to treat severe metabolic acidosis. The aim is to keep preductal pH > 7.2 with an arterial oxygen pressure of ≥65 kPa and an oxygen saturation of >90% whilst not allowing peak inspiratory pressure to exceed 30 cmH$_2$O. Impressive results (84% survival) have been reported using this technique,\(^{46-48}\) making this an important advance in postnatal therapy for infants with CDH.\(^{36}\)

**EXOGONOUS SURFACTANT THERAPY**

It is now widely accepted that the use of exogenous surfactant therapy to improve ventilation in premature infants is effective.\(^{49,50}\) The benefits in CDH are less clear. Researchers have used a variety of methods to evaluate the surfactant status (measurements of phospholipid, phosphatidylcholine and surfactant proteins) in experimental CDH models. Lungs from the CDH lamb model have been shown to be deficient in phospholipid and phosphatidylcholine.\(^{51,54}\) Similarly, lungs from the nitrofen rat CDH model are deficient in phospholipid and surfactant proteins.\(^{52,53,55}\) Work in human infants has been inconclusive. Studies addressing the levels of phospholipid and surfactant-related proteins in amniotic fluid and bronchoalveolar lavage fluid have failed to demonstrate any difference between CDH patients and age-matched controls.\(^{56,57}\)

The effects of exogenous surfactant therapy are not universally successful. Although in rats an early increase in pulmonary compliance was seen, this benefit was short-lived and no ongoing improvement was demonstrated.\(^{55}\) In humans, early work involving the administration of surfactant prior to the first breath (prophylactic administration)
was encouraging by showing improvements in ventilatory parameters. This experience was also mirrored in the lamb CDH model, where maximal benefit from exogenous surfactant was seen with prophylactic delivery. However, a small randomised trial of surfactant therapy in human infants with CDH has failed to demonstrate any sustained benefits. Larger multicentre randomised trials are needed.

ANTENATAL STEROID THERAPY

Antenatal steroids improve lung maturation of pre-term infants. In CDH animal models, antenatal glucocorticoids have been shown to improve morphological maturity and reduce hypermuscularisation of the pulmonary vasculature. Anecdotally, benefits have been reported in a small number of cases (D. Tibboel, pers. comm.)..

LIQUID VENTILATION

Liquid ventilation using hyperbarically oxygenated fluid was briefly investigated for use in astronauts and divers during the 1950s. Theoretical advantages of liquid ventilation include the fact that, unlike gases, liquids spread uniformly in lung tissue, whilst decreasing the air–fluid interfaces and surface tension in alveoli. Initial efforts to use electrolyte solutions were unsuccessful due to poor gas solubility. However, the discovery of fluorocarbons has regenerated liquid ventilation as a potential therapy in CDH. Advantages of perfluorocarbon include a greater solubility for respiratory gases than blood, elimination by vapourisation (minimising metabolic derangements) and a terminal bromide molecule, which makes it radio-opaque. Initial studies in animal and human subjects showed encouraging results, with an increase in PaO₂ and pulmonary compliance. Added benefits of liquid ventilation may include stimulation of lung growth. A significant increase in lung volume and improvement in ventilatory mechanics in CDH neonates deemed to have a dismal prognosis at entry to the trial has been reported. Liquid ventilation may offer promise for improving survival in infants with CDH. Phase three clinical trials are underway to further evaluate this therapy.

LUNG TRANSPLANTATION

Lung transplantation is an established clinical treatment for paediatric patients with end-stage chronic respiratory insufficiency. Despite cumulative experience in the very young patient under the age of 1 year, lung transplantation has only been performed in a single infant with CDH. The concept of a temporary lung allograft, remaining in situ until the contralateral native lung has developed sufficiently to support postnatal life is an attractive proposition. The requirement for immunosuppression and its potential sequelae in neonates together with problems of donor availability and size match essentially limit the widespread clinical application of this technique.

SURGERY FOR CDH

Surgical repair of CDH has varied little in operative technique from the original reports. Operation is usually via a subcostal incision, although a thoracotomy may rarely be considered for right-sided lesions. Gentle reduction of abdominal viscera from the thorax is followed by identification and excision of any hernia sac (found in 10%). Diaphragmatic closure is achieved by approximating freed native tissue with non-absorbable sutures. The anterior rim is frequently well formed, whilst the posterior rim is often more sparse or even absent. Where insufficient natural tissue exists, prosthetic material e.g. Goretex® (W.L. Gore and Associates, Flagstaff, AZ) may be utilised to complete closure. Other innovative techniques include the creation of a muscle flap from either the latissimus dorsi or rectus abdominus to close the diaphragmatic defect. Similarly if primary abdominal closure is difficult or complicated by unacceptably high ventilatory pressures, a prosthetic patch may be incorporated into the abdominal wall.

Patients on ECMO present a technical challenge. The use of anticoagulation to maintain the ECMO circuit precludes aggressive dissection of native diaphragmatic tissue. In such cases prosthetic patch closure is common.

An interesting recent development has been the deployment of laparoscopy to repair diaphragmatic defects. Although the technique has been described with some success in adults and older children, its application in the high-risk CDH infant must be interpreted with caution.

LONG-TERM OUTCOME

Long-term follow up of survivors is required. Apart from neurological sequelae resulting from chronic neonatal hypoxia, a high proportion of patients have chronic respiratory insufficiency secondary to pulmonary hypoplasia and the consequences of iatrogenic lung injury. Gastrooesophageal reflux and its attendant complications are perhaps related to diaphragmatic malfunction and may entail anti-reflux surgery. Deformity of the spine and/or chest wall following CDH repair may similarly require surgical treatment. In particular, results of long-term follow-up studies following CDH patch repair indicate the need for close scrutiny, since nearly half will suffer from patch failure and recurrent herniation. The continuing evolution of treatments for CDH means that true long-term follow-up is destined only to identify the inadequacies of previous therapies. The first substantial series reporting survival after CDH repair date from the 1940s. Whilst significant impairments of lung function are not observed in school age survivors, it is highly plausible that with
continued improvements in neonatal respiratory care, morbidity from this birth defect will substantially increase.\textsuperscript{98,99}

**FETAL SURGERY FOR CDH**

Failure of conventional postnatal therapies to significantly alter the prognosis of infants with CDH prompted pediatric surgeons to consider repair of the hernia antenatally. It was postulated that fetal diaphragmatic hernia repair would remove the compressive forces on the developing lung and permit lung growth to improve on the dismal survival of CDH. To address this hypothesis, surgeons created a surgical model of diaphragmatic hernia in fetal lambs and simulated antenatal closure of the defect with improved survival at birth.\textsuperscript{100} This led to the development of experimental fetal surgery for humans with CDH. Initial findings from the San Francisco group, operating on fetuses without liver herniation, demonstrated no survival benefit over standard postnatal therapy – suggesting the risks of antenatal surgery were not justified in this group.\textsuperscript{101,102}

Fetal surgery continues to provoke significant interest for the high-risk CDH fetus with liver herniation. The seminal observation that infants with laryngeal atresia develop enlarged hyperplastic lungs\textsuperscript{103,104} led to the deployment of the “PLUG” (Plug the Lung Until it Grows) technique – surgical occlusion of the fetal trachea in an attempt to stimulate hypoplastic lung growth.\textsuperscript{105,106} Early studies of fetal tracheal occlusion performed by open fetal surgery have been superseded by a fetoscopic approach – the “FETENDO” (FETal ENDOscopy) procedure – to overcome the problems of preterm labor.\textsuperscript{107,108} The fetal trachea is clipped at 24–26 weeks gestation\textsuperscript{109} and the occlusion is left in place until an EXIT (EX-uterine Intrapartum Treatment) procedure is performed by Caesarean section at elective delivery.\textsuperscript{110} FETENDO surgery is currently being investigated in a National Institutes of Health trial for the high-risk “liver-up” CDH fetus (M. Harrison, pers. comm.).

**BASIC SCIENCE – LUNG DEVELOPMENT IN CDH**

In recent years there has been an increased appreciation that CDH is more than just a “hole in the diaphragm”. The recognition of associated anomalies in 30–50% of CDH newborns implies that the key features of CDH may represent a global embryopathy.\textsuperscript{1,111–113} This proposal suggests that lung hypoplasia arises during the embryonic period and before the fetal diaphragmatic hernia develops. Closure of the human diaphragm at 8 weeks gestation precludes any detailed investigation of lung development prior to the effect of herniated viscera. The use of teratogenic models has allowed detailed embryological investigation to occur.

A number of chemicals have been shown to induce CDH in rodents.\textsuperscript{114,115} One of these, nitrofen (2,4-dichloro-4‘-nitro diphenyl ether), is administered to pregnant rodents as a single oral dose at a specific point in gestation to produce CDH with severe lung hypoplasia in a proportion of the litter.\textsuperscript{116–119} Associated malformations in the nitrofen Sprague-Dawley rat model closely mimic the incidence and spectrum of those seen in human CDH.\textsuperscript{120–126} Since nitrofen is administered during early organogenesis it provides (unlike the surgically created lamb CDH model) the opportunity to examine the embryology of CDH and associated lung hypoplasia.

Development of an organotypic culture system along with detailed morphometric measurements of lungs in organ culture has facilitated comparison of pulmonary growth between nitrofen-treated rat embryos and untreated controls (Fig. 2).\textsuperscript{127} Such observations have revealed that disruption of stereotyped airway branching correlates with and precedes CDH, indicating an intrinsic defect of lung development in CDH.\textsuperscript{127} These observations were further confirmed by D. Tibboel’s group, who postulated the “dual-hit” hypothesis.\textsuperscript{128} Lung culture systems are now providing invaluable research tools for manipulating lung hypoplasia and investigating the role of growth factor and cell signalling pathways.

**GROWTH FACTORS**

Mammalian lung development requires the interaction of the fibroblast growth factor (FGF) family, cognate receptors (FGFRs) and heparan sulphate (HS) proteoglycans. This has been elucidated from studies in mice and the fruitfly, Drosophila melanogaster.\textsuperscript{129} Branchless and breathless are Drosophila mutants lacking FGF and its receptor.
display CDH together with left lung agenesis and significant right lung hypoplasia.\textsuperscript{125}

Experimental studies into the possible restorative role of vitamin A in hypoplastic CDH lungs have had interesting results. Strikingly Thebaud and colleagues have shown that prenatal treatment with vitamin A in the nitrofen model of CDH reduces the incidence of CDH at term, as well as demonstrating improvements in lung growth and maturation in perinates.\textsuperscript{36,137}

**TRANSGENIC MODELS**

The ability to manipulate the expression of specific genes in transgenic mice has provided a powerful means of dissecting the genetic regulation of development and investigating the molecular events underpinning many malformations. Several mutant phenotypes have been described in which diaphragmatic hernia may feature. Whilst the inactivation of several genes may predispose to CDH, gene targeting typically does not ensure CDH in knockout offspring. This suggests a complex interaction of multifactorial events in the genesis of CDH. For example, homozygous inactivation of WT-1 (the gene found to be deleted in familial cases of Wilm’s tumour) yields CDH with overgrown, underdeveloped lungs and renal malformations in rodents,\textsuperscript{138} whilst deletion of both murine retinoic-acid receptors (RARs) yields a high incidence of cranial, vertebral, limb, cardiac, foregut and pulmonary malformations with a low incidence of CDH.\textsuperscript{133,139} Although transgenic studies are useful, information gathered needs to be translated to the human situation with caution. Scientists in Scandinavia assessed the incidence of WT-1 mutations in a population of human infants with CDH. They found no significant abnormalities, indicating that although WT-1 deletion may give rise to CDH in rodents, it is not an important factor in the genesis of the human phenotype.\textsuperscript{140}

**FUTURE DIRECTIONS**

What are the future therapeutic implications for clinicians treating CDH? Selection of patients for fetal surgery will require more accurate prognostic indicators of poor perinatal outcome. Fetal surgery at present may be “too little too late” to correct an established embryopathy in pulmonary development. Antenatal corticosteroid therapy is the subject of a multicentre trial. Fetoscopic delivery of targeted growth factors to enhance airway development in CDH will require careful appraisal. The concept of a pharmacological agent or medical “PLUG” to reverse pulmonary hypoplasia is a goal for the future. Postnatal therapies to reduce barotrauma will salvage those newborns with the less severe degrees of pulmonary hypoplasia. Finally the prevention of the birth defect by preconceptual prophylaxis (as in the case of neural tube defects) may represent the ultimate solution for this highly lethal human anomaly.

**VITAMIN A**

Vitamin A is important in lung development. In 1953, Wilson and colleagues noted a high incidence of CDH in the pups of vitamin A deficient rats.\textsuperscript{133} Interestingly it has been noted that human infants with CDH have significantly reduced levels of retinol and retinol-binding protein compared to age-matched controls.\textsuperscript{134} A strain of transgenic mice in which both copies of the retinoic acid receptor (vitamin A binding receptor) gene have been deleted

![Figure 3](image-url)  
**Figure 3** Photomicrographs of normal and nitrofen-treated (hypoplastic) lung primordia in culture. The nitrofen treated lungs are smaller and demonstrate an abnormal response to fibroblast growth factor 1 (FGF1) and FGF2. (a) No FGF. (b) FGF1 + 1 µg/ml heparin. (c) FGF2 alone.

(FGFR), respectively.\textsuperscript{129} Sugarless and sulphateless mutants lack HS. All these *Drosophila* mutants share abrogated airway branching.\textsuperscript{130}

Utilising this knowledge, we studied the effects of exogenous growth factors on embryonic lung development. Testing the effects of FGF1 ± heparin, we noted stimulated branching morphogenesis of normal lung primordia in *vitro*. In contrast, whilst nitrofen-exposed lung primordia were unexpectedly inhibited by FGF1, they also exhibited strikingly abnormal responses to FGF2 ± heparin (Fig. 3). Most notably, FGF2 produced massive dilatation of the epithelial lumen of nitrofen lungs, whilst having only minor transient effects on normal lungs.\textsuperscript{131,132}

Whilst confirming a role for the FGF pathway in embryonic lung development, this work suggested that FGF1 alone is unlikely to rescue hypoplastic lung growth in *vivo*. The abnormal responsiveness of nitrofen-exposed lungs to FGFs further indicate they are *intrinsically* abnormal prior to visceral herniation. It has been postulated that disturbance of the FGF/FGFR/H5 network (or its downstream intracellular targets) may comprise at least part of such a signalling defect.\textsuperscript{132} Clarifying the exact nature of such a lesion presents a formidable task.
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