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REVIEW ARTICLE

Congenital diaphragmatic hernia: an overview of the etiology and current management

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Abstract

Aim: To review provide an overview of the etiology and current strategies in the management of congenital diaphragmatic hernia (CDH).

Methods: We did a comprehensive review of research trends, evidence based studies and epidemiologic studies.

Results: CDH is a life-threatening pathology in infants, and a major cause of death due to the pulmonary hypoplasia and pulmonary hypertension. There is much research related to elucidating the etiology of CDH and developing management strategies to improve the outcomes in these infants.

Conclusion: An early diagnosis with increased understanding of this disease is a crucial factor for a timely approach to managing the critically ill infant, and to offer the potential for improved outcomes and substantial reductions in morbidity.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is an anatomical defect in the diaphragm that permits abdominal contents to herniate inside the thoracic cavity. This anomaly is associated with a high morbidity and mortality, occurs in 2.5–3.8 cases per 10 000 births (live and stillbirths) and affects as many as 1 in 3000–4000 children each year (1,2). These patients develop severe respiratory complications that include pulmonary hypoplasia and pulmonary hypertension. CDHs may be considered 'isolated cases' (i.e. the only malformation is the diaphragmatic hernia) or 'nonisolated cases' (i.e. associated with other anomalies).

Colvin et al. (3) in a retrospective population based study of 116 cases in Western Australia from 1991 to 2002, found an incidence of associated major congenital anomalies in 46.6% of cases and of minor congenital anomalies in 38.8% of nonisolated CDH cases. The anomalies described more frequently are dysmorphic features, genitourinary, musculoskeletal, cardiovascular, neurologic, gastrointestinal and chromosomal malformations.

CDH is found to have a poor survival rate when it occurs in association with another major anomaly. In a retrospective study with 51 cases of CDH in Auvergne, France, Gallot and colleagues evaluated the rate of prenatal diagnosis and its impact on outcome in CDH. The author's found a significantly higher incidence of prenatal detection of non-isolated CDH (73%) with an associated anomaly (either detecting the CDH or the associated anomaly) compared to a prenatal detection rate in isolated CDH of only 45% of cases ($p = 0.03$). The overall survival rate of 41% depended much

Abbreviations

CDH, congenital diaphragmatic hernia; RALDH2, retinaldehyde dehydrogenase 2; RA, retinoic acid; L/T ratio, lung to thorax transverse area ratio; LHR, lung area to head circumference ratio; MRI, magnetic resonance imaging; ECMO, extracorporeal membrane oxygenation; RFLV, relative right-sided lung volume; FETO, fetoscopic tracheal occlusion; LW/BW ratio, lung weight to body weight ratio; TO, tracheal occlusion; HFPPV, high-frequency positive pressure ventilation; HFOV, high-frequency oscillatory ventilation; PDA, patent ductus arteriosus.

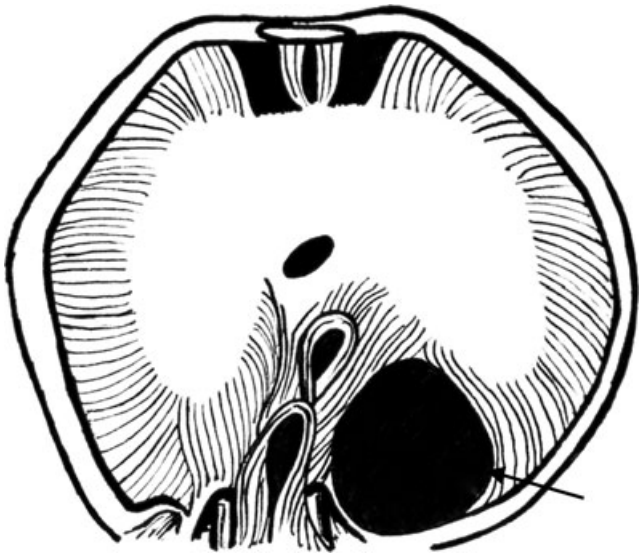

Figure 1 Bochdalek hernia. Inadequate closure of posterior pleuroperitoneal membrane (arrow) causing the left posteriorlateral defect.

on the associated anomalies and in the prenatal diagnosis; having significantly better survival rates in the non-prenatal diagnosed and isolated groups compared to survival in the prenatal detected cases (81% and 23%, respectively; $p = 0.0001$) (4).

Yang et al. (5) in a population based study found that the black population had a 37% less risk of developing isolated CDH compared with non-Hispanic whites; and also that the relative risk for developing a nonisolated CDH in maternal age >35-year olds was 50% elevated compared to that of the 20–24-year olds age group.

There are several types of hernias depending on the localization, the most common is the posterolateral hernia, also called Bochdalek hernia (Fig. 1). This hernia occurs more frequently on the left side of the diaphragm (78–84%) than on the right side of the diaphragm (14–20%) (3,5,6). The other types of hernias are non-posterolateral and include the retrosternal hernia (also called Morgagni hernia), parasternal hernias, anterior hernias, central hernias that involve the non-muscular portion of the diaphragm and eventration which is a thinning of the diaphragmatic leaflet that allows contents to herniate to the chest (7).

CDH has been simplistically described as a diaphragmatic hole and in the past was thought to be curable with surgery after birth (8). Currently, the etiology of CDH is unknown. Over the last 150 years there has been much research into the etiology and management of this malformation to determine the most efficacious treatment strategies (9,10).

Migliazza et al. (6) in a retrospective study of 111 cases found several causes for death in newborns with CDH. Persistent pulmonary hypertension was the major cause of death occurring in 76.5%, severe cardiac malformations in 14.7%, multiorgan failure, pulmonary haemorrhage and sepsis each in 2.9% respectively.

RESEARCH TRENDS LOOKING FOR AN ETIOLOGY

Research to determine the etiology of, and optimal management strategies for, CDH can be classified as teratogenically, genetically and surgically induced models (9).

Teratogenically induced models

In the teratogenically induced model, the major substance used to induce CDH is nitrofen (2,4-dichlorophenyl-p-nitrophenyl ether), a herbicide prohibited in the United States and European Union since 1980s. It has been used in pregnant rats since 1970s because it causes diaphragmatic defects similar to CDH in infants, and may represent a common underlying etiology (11). This herbicide has been studied in detail, searching for the exact mechanism of teratogenicity and several studies have concluded its effects are in the retinoic pathway (11–13).

Mey et al. (11) demonstrated the inhibition of retinaldehyde dehydrogenase 2 (RALDH2) with nitrofen that induced a defect in the posterolateral corner of the diaphragm, and also cardiac defects. A study by Noble and colleagues (13) using *in vitro* cells under the influence of nitrofen demonstrated a diminished efficacy of each isoform of the RADLH2 enzymes required to create retinoic acid (RA). When the study team administrated RA the nitrofen-induced inhibition was reversed, demonstrating that the defect affects the retinoid-signalling pathway. Similar to nitrofen, there are other compounds that induce a diaphragmatic defect similar to that of CDH (11).

In 1953 Wilson et al. (12) published evidence associating the retinoid pathway, using vitamin A derivatives in the pathophysiology of CDH. They noted that a deficient vitamin A diet in pregnant rats induced the development of a diaphragmatic hernia, and with the administration of vitamin A, the incidence of the defect was reduced from 31% in non-treated to 0% in the treated cohort if treatment was administered very early in pregnancy (10 to 11th day of gestation).

Babiuk RP et al. (14) demonstrated with rats that the administration of nitrofen at day 8 of gestation induced diaphragmatic hernia in 54% of study animals, and with early (i.e. day 10 or before) administration of vitamin A, the incidence of CDH was reduced from approximately 54% (nitrofen alone) to approximately 32%.

Moreover it is still not clear if the pathologic features in the lung development (pulmonary hypoplasia) related to CDH surge from a primary defect in pulmonary development or from the diaphragm defect. There is a 'dual-hit' hypothesis proposed by Keijzer et al. (15) where the authors prove that nitrofen independently affects the lung morphogenesis in rats before the diaphragmatic defect appears, and then the diaphragmatic defect becomes a second insult to the ipsilateral lung favouring more hypoplasia because of the mass effect. Thus, according to Keijzer and colleagues, two independent events contribute to the formation of pulmonary hypoplasia. Likewise, there have been similar studies with nitrofen demonstrating the dual hit hypothesis (16,17).

Mey et al. (11) support this theory with their study by finding the expression of RALDH2 in both, the diaphragm (pleuroperitoneal fold) and the lung (cervical mesenchyme) by immunolabelling RALDH2 in the developing stages (E13).

The results of these studies indicate that transient deficiencies caused by inadequate placental passage, dietary insufficiency, spontaneous non-regulation of a component in the retinoid pathway or a teratogenic insult, may disturb the formation of the primordial diaphragm at 4 to 5 weeks of gestation (8). Nonetheless, this does not rule out the possibility that other pathways may contribute to the pathology of this condition.

Genetically induced models

It has been theorized that there is also a genetic role in this disease, as suggested by studies that have developed genetically altered mice to express phenotypes like that of CDH, occurrences of the disease through family generations and also the association of CDH in approximately 10% with chromosomal anomalies (18). Likewise, there has been much investigation into finding the genes thought to be involved in the development of CDH, as some of the genes regulated by RA (i.e. Hoxa4, TGF, N-myc, Shh and BMP4) have been associated with the development of the diaphragm and lungs (9).

It has been proposed that the non-muscular components of the pleuroperitoneal fold are involved in CDH, suggesting that mesenchymal cells are the affected tissue (19). The gene COUP-TFII was determined to be involved in this malformation, and has been found to be expressed in the foregut mesenchyme, posthepatic mesenchymal plate more in the left side, mesenchymal tissue contiguous to the esophagus, the septum transversum and in the developing lung (19). Supporting this, a study in mice that induced ablation of this gene in specific tissues revealed that mice developed diaphragmatic hernia (19).

When a chromosomal anomaly is associated with CDH, these patients typically have a very poor prognosis compared with isolated CDH (20). Deletion of 15q26 is the most frequently found of the chromosomal aberrations (20–22). These patients have similar phenotypes to Fryns syndrome, presenting with growth retardation, left sided CDH, heart anomalies and specific facial features (20).

It has also been noted that when certain regions in chromosomes such as 15q26.2, 8p23.1, 4p16.3 and 1q41-42 are either deleted or mutated there is a high association with the formation of CDH (22). In the chromosome 15q26 a region has been identified as 'the CDH region', suggested to be the smallest common deleted region in patients with CDH (21). This region contains four genes: the NR2F2 (COUP-TFII) involved in the retinoic metabolism, the chromodomain helicase 2 gene (CHD2), the repulsive guidance molecule gene (RGMA) and the sialyltransferase 8B gene (SIAT8B) (21). Missing a copy of any of these genes could cause a diaphragm defect. It is believed that gene mutations related to this pathology are '*de novo*' mutations, because there is no adequate familial correlation in patients having this anomaly through generations.

Surgically induced models

The surgically induced model is when the diaphragmatic defect is surgically created. This model has been utilized for the study of therapeutic interventions, and is often considered less informative as the procedure is typically performed on previously normal animals with normal lungs and diaphragm.

PROGNOSTIC INDICATORS

There have been several parameters proposed to be predictors of outcome in fetus or live born infants with CDH. One parameter is the position of the liver. Intrathoracic liver at birth has been correlated with worse outcomes than intra-abdominal liver at birth. Beck et al. (23) in a single centre analysis reported a survival of 43% in patients with intrathoracic liver compared with a 90% survival rate in total live born infants with intra-abdominal liver.

Lung to thorax transverse area ratio (L/T ratio) and the lung area to head circumference ratio (LHR) have been used as a parameters to asses pulmonary hypoplasia. Usui and colleagues, (24) in a retrospective study analysed and correlated the L/T ratio and LHR with survival of fetuses. They measured the LHR as the ratio of the contralateral lung area to the head circumference. The authors calculated the L/T ratio, by measuring the area of the contralateral lung and dividing by the thorax area and developed a system of classification of mortality rates correlated with the L/T ratio. The mild group, in which the L/T ratio was >0.13, had a mortality rate of 0%. The severe group with an L/T ratio of >0.08 and <0.13 had a mortality rate of 30%. And the lethal group having an L/T ratio of <0.08 with association of liver herniation had a mortality of 100% ($p < 0.05$). Using the LHR ratio they established a value for prediction of mortality that was <1.2 and for survival >2.0.

Other study concluded that when the observed and expected LHR (O/E LHR) was $<25\%$ of normal there was a very high probability for postnatal death, and these fetuses could be considered for an antenatal intervention (25).

The first 6 h of life of newborns are critical for predicting the outcome of the patient. It is theorized that if in the first 6 h of birth the patient does not have any symptoms then there is a reasonable lung function and therefore is likely to have higher survival rates. Conversely, if the patient has respiratory distress within the first 6 h of birth then the patient has a higher propensity for having pulmonary hypoplasia and thus higher mortality rates (26).

Hayakawa et al. (27) in a prospective study correlated the relationship between magnetic resonance imaging (MRI) findings with postnatal mortality and the need for extracorporeal membrane oxygenation (ECMO). They calculated a relative right-sided lung volume (RFLV) and noted that non-survivors had a lower percentage of RFLV ($<45\%$) compared with survivors ($>45\%$). The authors concluded that the percent RFLV calculated with MRI is a predictor of mortality and proposed a threshold for the need of ECMO therapy if the percentage RFLV was $<50\%$ at birth.

Prenatal detection of the aforementioned predictors of outcome may permit the recognition of high-risk fetuses and give the clinician an insight into developing the best management options for the patient.

MANAGEMENT

Initially it was thought that the primary management of a newborn with CDH should be surgical repair. It is now known that the mortality of these infants is due to pulmonary complications related to pulmonary hypoplasia and pulmonary hypertension, and that infants initially managed with surgical repair have increased mortality rates due to these complications (28). Some tertiary centres have reported improved survival rates as high as 60–80% with newer therapies and strategies over the past two decades (29,30). Currently the initial approach to the management of CDH is focused on the restoration of optimal respiratory function prior to surgical repair. Nakayama et al. (31) demonstrated significantly increased respiratory compliance in patients who underwent preoperative respiratory function stabilization ($p < 0.02$); however, it is very important for the newborn to be delivered in a neonatal intensive care unit where a paediatric surgical facility is available.

Several treatment strategies have been proposed that focus on restoring pulmonary function, either by ventilation modalities, medically with surfactant, steroids, growth factors, (32) vitamin A or with new intrauterine strategies like the fetoscopic tracheal occlusion (FETO). Nonetheless, many of these treatment strategies remain controversial and evidence that supports their use in humans remains inadequate (32–35). In addition to restoration of an optimal pulmonary function, the treatment strategies have been focused on improving pulmonary hypertension, aiming to a decrease in morbidity and mortality.

Prenatal interventions

An important factor in the development of the lungs is the negative pressure inside the intrathoracic cavity, which is lost with a diaphragmatic defect. Therefore, intrauterine strategies are aimed to improve the development of the lung before delivery. A growing strategy is the FETO, which consists of stimulation of the lungs to grow after the trachea is occluded. As it is known that fetuses with upper airway obstruction are born with increased lung volumes (36). Some studies have demonstrated increased fetal lung volumes after this therapy (25,37–40).

Deprest et al. (37) in a small population study found that after the use of FETO with human fetuses, ultrasound imaging revealed augmentation in the LHR to a range of 1.1 to 2.9 from previous LHR of 0.4 to 0.9 after 2 weeks from the surgical FETO, and intensification of the lung echogenicity after 48 h.

Baird et al. demonstrated in a study with rat dams, that fetuses with CDH initially had a decreased lung weight to body weight ratio (LW/BW ratio), less airspace percentage and decreased branching of the lung compared to controls. And after treatment of these fetuses with tracheal occlusion (TO) at gestational day 19 they were found to have an increased LW/BW ratio ($p = 0.42$), greater airspace percentage but no changes in the branching of the lungs. Concluding that the TO stimulates distal airway proliferation but does not change the poor development of the bronchial branching (41).

Recently Saura et al. (42) after classifying fetuses in high risk for severe pulmonary hypoplasia by anatomical evaluation considering the liver position and lung size, and also utilizing the LHR ratio. They utilized the inutero FETO technique in these patients with poor prognosis. They found that these patients initially with poor prognosis after FETO required similar ventilatory support and better discharge times compared to patients with better prognostic factors (i.e. LHR >1.4) not treated with FETO. Concluding with a reduction in mortality rates in the patients treated with FETO. Although since this technique is intrauterine manipulation and increases the risk for premature rupture of membranes and preterm delivery, in this study none of the fetuses was born before 34 weeks gestation.

Postnatal management

Aggressive hyperventilation to avoid shunting in infants with pulmonary hypertension was initially thought to be an appropriate course of treatment; however, aggressive hyperventilation has been shown to be associated with increased mortality related to barotrauma (43). Currently the strategy, introduced by Wung et al. (44) in 1995, is 'gentle ventilation' by ventilating at minimal airway pressures (i.e. peak inspiratory pressure below 25 cm H_2O). This gives the advantage of minimizing barotrauma and diminishing the interference with venous return from the systemic circulation resulting in increased survival rates (44). The positive results of Wung et al. have been echoed in other studies that demonstrate increased survival rates with the use of the 'gentle ventilation' technique compared with conventional ventilation (45–47).

Boloker et al. (45), using the approach of preoperative stabilization, demonstrated a decreased need for ECMO and increased survival rates (75.8%). Their approach was to decrease the exposure to high ventilator settings, giving pressure limited constant flow, allowing the infants to breathe spontaneously, allowing controlled hypercapnia (<60–65 mmHg) and avoiding the use of a chest tube postoperatively. Whenever this ventilation strategy failed (defined as pH <7.25, PCO_2 >60 mmHg, O_2 saturation <80%, severe paradoxical chest movement, severe retractions or tachypnea) they used high-frequency positive pressure ventilation (HFPPV) or high-frequency oscillatory ventilation (HFOV) as alternate stabilization methods before using ECMO.

ECMO has been used either preoperatively or postoperatively for high-risk patients in which conventional management failed (26). Also it has been utilized to avoid further barotrauma, instead of escalating the ventilator strategies or in association with severe congenital heart disease (48). After the lung function is stabilized with preoperative ECMO therapy these newborns then could undergo surgical treatment. Although Bernbaum et al. (49) demonstrated that patients who underwent ECMO therapy with

CDH had multiple respiratory, feeding and neurodevelopmental complications on a long-term basis.

Pulmonary hypertension is a severe complication of this disease secondary to pulmonary hypoplasia. A patent ductus arteriosus (PDA) is very helpful in these patients to create a right to left shunt and decrease the right ventricular pressure and prevent right ventricular dysfunction. Prostaglandin infusion could be used in this manner and also to stabilize the patient preoperatively (48), although currently it has not proven to increase survival compared with the use of nitric oxide alone (50). In patients with severe pulmonary hypertension ECMO is another alternative to use, but weaning these patients may be very difficult and require the use of other alternatives like nitric oxide. The use of vasodilators (nitric oxide or sildenafil) with pulmonary hypertension in these patients has not been proven to improve mortality (51).

Surgical repair

Several studies and different techniques have developed to repair CDH, such as prosthetic patches, tissue grafts, muscle flaps and several new laparoscopic approaches (52–54). Dutta et al. (54) utilized a laparoscopic approach using prosthetic patches to repair Morgagni hernias and were successful repairing tension free and proposed a possible less predisposition for recurrence. Brant-Zawadzki et al. (52) reported in a study using abdominal wall muscle flaps to be a safe technique to use in anticoagulated patients as the technique proved to have good outcomes without bleeding. They also concluded a recurrence rate of 19% using abdominal wall muscle flaps because they are good for large defect repairs, compared with the high recurrence rates in large defect repairs with prosthetic patches.

Long-term morbidity

The patient with CDH continues to be one of the most challenging to the paediatric surgeon, neonatologist and paediatric pulmonologist due to its high variability and complexity. Approximately half of the live-born infants with CDH will survive beyond one year of age with currently available management (3). Unfortunately, only few survivors will be able to cope free of associated medical problems. It is well documented in the literature that the rest of survivors have a high incidence of pulmonary, neurological, gastrointestinal, musculoskeletal and nutritional co-morbidities (3,55–58).

It is important to point out that the significant improvement in mortality of these patients over the past few decades may be related to an increase in long-term morbidities (46). For this reason and because of the high complexity of cases, we favour that all survivors be followed by a multidisciplinary team at intervals specified for each individual case.

CONCLUSION

CDH has a variable prognosis for the infant because of its association with pulmonary developmental defects. An early diagnosis is a crucial factor for a timely approach to managing the critically ill infant, which also has an impact in the morbidity and mortality. Prenatal detection can give the infant an opportunity for fetal interventions and an early maternal transfer to a competitive facility. The initial approach to repair the defect immediately via surgical intervention has been found to not significantly improve patient outcome, and focus is now on the restoration of the pulmonary function prior to surgical intervention.

Likewise there has also been much investigation focused on understanding the etiology and underlying pathology associated with the formation of CDH. Although the etiology remains unclear, we have a better understanding of CDH and its relationship with several genes and the involvement of the retinoic pathway in the pathogenesis of the defect.

Many advances have been made in determining more efficacious treatment strategies and the need for immediate treatment as a result of early identification. Increased understanding and early intervention to reduce or avoid pulmonary hypoplasia offers the potential for improved outcomes and substantial reductions in morbidity. New treatments alternatives such as FETO therapy and early vitamin A treatment show particular promise as new treatment options become available.

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References

1. Torfs CP, Curry CJ, Bateson TF, Honore LH. A population-based study of congenital diaphragmatic hernia. *Teratology* 1992; 46: 555–65.
2. Skari H, Bjornland K, Haugen G, Egeland T, Emblem R. Congenital diaphragmatic hernia: a meta-analysis of mortality factors. *J Pediatr Surg* 2000; 35: 1187–97.
3. Colvin J, Bower C, Dickinson JE, Sokol J. Outcomes of congenital diaphragmatic hernia: a population-based study in Western Australia. *Pediatrics* 2005; 116: e356–63.
4. Gallot D, Coste K, Francannet C, Laurichesse H, Boda C, Ughetto S, et al. Antenatal detection and impact on outcome of congenital diaphragmatic hernia: a 12-year experience in Auvergne, France. *Eur J Obstet Gynecol Reprod Biol* 2006; 125: 202–5.
5. Yang W, Carmichael SL, Harris JA, Shaw GM. Epidemiologic characteristics of congenital diaphragmatic hernia among 2.5 million California births, 1989–1997. *Birth Defects Res A Clin Mol Teratol* 2006; 76: 170–4.
6. Migliazza L, Bellan C, Alberti D, Auriemma A, Burgio G, Locatelli G, et al. Retrospective study of 111 cases of congenital diaphragmatic hernia treated with early high-frequency oscillatory ventilation and presurgical stabilization. *J Pediatr Surg* 2007; 42: 1526–32.
7. Pober BR. Overview of epidemiology, genetics, birth defects, and chromosome abnormalities associated with CDH. *Am J Med Genet C Semin Med Genet* 2007; 145: 158–71.
8. Greer JJ, Babiuk RP, Thebaud B. Etiology of congenital diaphragmatic hernia: the retinoid hypothesis. *Pediatr Res* 2003; 53: 726–30.
9. Beurskens N, Klaassens M, Rottier R, de Klein A, Tibboel D. Linking animal models to human congenital diaphragmatic hernia. *Birth Defects Res A Clin Mol Teratol* 2007; 79: 565–72.

10. Golombek SG. The history of congenital diaphragmatic hernia from 1850s to the present. *J Perinatol* 2002; 22: 242–6.
11. Mey J, Babiuk RP, Clugston R, Zhang W, Greer JJ. Retinal dehydrogenase-2 is inhibited by compounds that induce congenital diaphragmatic hernias in rodents. *Am J Pathol* 2003; 162: 673–9.
12. Wilson JG, Roth CB, Warkany J. An analysis of the syndrome of malformations induced by maternal vitamin A deficiency. Effects of restoration of vitamin A at various times during gestation. *Am J Anat* 1953; 92: 189–217.
13. Noble BR, Babiuk RP, Clugston RD, Underhill TM, Sun H, Kawaguchi R, et al. Mechanisms of action of the congenital diaphragmatic hernia-inducing teratogen nitrofen. *Am J Physiol Lung Cell Mol Physiol* 2007; 293: L1079–87.
14. Babiuk RP, Thebaud B, Greer JJ. Reductions in the incidence of nitrofen-induced diaphragmatic hernia by vitamin A and retinoic acid. *Am J Physiol Lung Cell Mol Physiol* 2004; 286: L970–3.
15. Keijzer R, Liu J, Deimling J, Tibboel D, Post M. Dual-hit hypothesis explains pulmonary hypoplasia in the nitrofen model of congenital diaphragmatic hernia. *Am J Pathol* 2000; 156: 1299–306.
16. Jesudason EC, Connell MG, Fernig DG, Lloyd DA, Losty PD. In vitro effects of growth factors on lung hypoplasia in a model of congenital diaphragmatic hernia. *J Pediatr Surg* 2000; 35: 914–22.
17. Guilbert TW, Gebb SA, Shannon JM. Lung hypoplasia in the nitrofen model of congenital diaphragmatic hernia occurs early in development. *Am J Physiol Lung Cell Mol Physiol* 2000; 279: L1159–71.
18. Kantarci S, Donahoe PK. Congenital diaphragmatic hernia (CDH) etiology as revealed by pathway genetics. *Am J Med Genet C Semin Med Genet* 2007; 145: 217–26.
19. You LR, Takamoto N, Yu CT, Tanaka T, Kodama T, Demayo FJ, et al. Mouse lacking COUP-TFII as an animal model of Bochdalek-type congenital diaphragmatic hernia. *Proc Natl Acad Sci U S A* 2005; 102: 16351–6.
20. Klaassens M, Galjaard RJ, Scott DA, Bruggenwirth HT, van Opstal D, Fox MV, et al. Prenatal detection and outcome of congenital diaphragmatic hernia (CDH) associated with deletion of chromosome 15q26: two patients and review of the literature. *Am J Med Genet A*. 2007; 143: 2204–12.
21. Klaassens M, van Dooren M, Eussen HJ, Douben H, den Dekker AT, Lee C, et al. Congenital diaphragmatic hernia and chromosome 15q26: determination of a candidate region by use of fluorescent in situ hybridization and array-based comparative genomic hybridization. *Am J Hum Genet* 2005; 76: 877–82.
22. Slavotinek AM, Moshrefi A, Davis R, Leeth E, Schaeffer GB, Burchard GE, et al. Array comparative genomic hybridization in patients with congenital diaphragmatic hernia: mapping of four CDH-critical regions and sequencing of candidate genes at 15q26.1–15q26.2. *Eur J Hum Genet* 2006; 14: 999–1008.
23. Beck C, Alkasi O, Nikischin W, Engler S, Caliebe A, Leuschner I, et al. Congenital diaphragmatic hernia, etiology and management, a 10-year analysis of a single center. *Arch Gynecol Obstet* 2008; 277: 55–63.
24. Usui N, Okuyama H, Sawai T, Kamiyama M, Kamata S, Fukuzawa M. Relationship between L/T ratio and LHR in the prenatal assessment of pulmonary hypoplasia in congenital diaphragmatic hernia. *Pediatr Surg Int* 2007; 23: 971–6.
25. Gucciardo L, Deprest J, Done E, Van Mieghem T, Van de Velde M, Gratacos E, et al. Prediction of outcome in isolated congenital diaphragmatic hernia and its consequences for fetal therapy. *Best Pract Res Clin Obstet Gynaecol* 2008; 22: 123–38.
26. Frenckner B, Ehren H, Granholm T, Linden V, Palmer K. Improved results in patients who have congenital diaphragmatic hernia using preoperative stabilization, extracorporeal membrane oxygenation, and delayed surgery. *J Pediatr Surg* 1997; 32: 1185–9.
27. Hayakawa M, Seo T, Itakua A, Hayashi S, Miyauchi M, Sato Y, et al. The MRI findings of the right-sided fetal lung can be used to predict postnatal mortality and the requirement for extracorporeal membrane oxygenation in isolated left-sided congenital diaphragmatic hernia. *Pediatr Res* 2007; 62: 93–7.
28. Sakai H, Tamura M, Hosokawa Y, Bryan AC, Barker GA, Bohn DJ. Effect of surgical repair on respiratory mechanics in congenital diaphragmatic hernia. *J Pediatr* 1987; 111: 432–8.
29. Rocha GM, Bianchi RF, Severo M, Rodrigues MM, Baptista MJ, Correia-Pinto J, et al. Congenital diaphragmatic hernia. The post-neonatal period. *Part II. Eur J Pediatr Surg* 2008; 18: 307–12.
30. Doyle NM, Lally KP. The CDH Study Group and advances in the clinical care of the patient with congenital diaphragmatic hernia. *Semin Perinatol* 2004; 28: 174–84.
31. Nakayama DK, Motoyama EK, Tagge EM. Effect of preoperative stabilization on respiratory system compliance and outcome in newborn infants with congenital diaphragmatic hernia. *J Pediatr* 1991; 118: 793–9.
32. Nagata K, Masumoto K, Uesugi T, Yamamoto S, Yoshizaki K, Fukumoto S, et al. Effect of insulin-like-growth factor and its receptors regarding lung development in fetal mice. *Pediatr Surg Int* 2007; 23: 953–9.
33. Van Meurs K. Is surfactant therapy beneficial in the treatment of the term newborn infant with congenital diaphragmatic hernia? *J Pediatr* 2004; 145: 312–6.
34. Baptista MJ, Melo-Rocha G, Pedrosa C, Gonzaga S, Teles A, Estevao-Costa J, et al. Antenatal vitamin A administration attenuates lung hypoplasia by interfering with early instead of late determinants of lung underdevelopment in congenital diaphragmatic hernia. *J Pediatr Surg* 2005; 40: 658–65.
35. Oshiro T, Asato Y, Sakanashi M, Ohta T, Sugahara K. Differential effects of vitamin A on fetal lung growth and diaphragmatic formation in nitrofen-induced rat model. *Pulm Pharmacol Ther* 2005; 18: 155–64.
36. Wigglesworth JS, Desai R, Hislop AA. Fetal lung growth in congenital laryngeal atresia. *Pediatr Pathol* 1987; 7: 515–25.
37. Deprest J, Gratacos E, Nicolaides KH. Fetoscopic tracheal occlusion (FETO) for severe congenital diaphragmatic hernia: evolution of a technique and preliminary results. *Ultrasound Obstet Gynecol* 2004; 24: 121–6.
38. Flake AW, Crombleholme TM, Johnson MP, Howell LJ, Adzick NS. Treatment of severe congenital diaphragmatic hernia by fetal tracheal occlusion: clinical experience with fifteen cases. *Am J Obstet Gynecol* 2000; 183: 1059–66.
39. Harrison MR, Sydorak RM, Farrell JA, Kitterman JA, Filly RA, Albanese CT. Fetoscopic temporary tracheal occlusion for congenital diaphragmatic hernia: prelude to a randomized, controlled trial. *J Pediatr Surg* 2003; 38: 1012–20.
40. Peralta CF, Jani JC, Van Schoubroeck D, Nicolaides KH, Deprest JA. Fetal lung volume after endoscopic tracheal occlusion in the prediction of postnatal outcome. *Am J Obstet Gynecol* 2008; 198: 60 e1–5.
41. Baird R, Khan N, Flageole H, Anselmo M, Puligandla P, Laberge JM. The effect of tracheal occlusion on lung branching in the rat nitrofen CDH model. *J Surg Res* 2008; 148: 224–9.
42. Saura L, Castanon M, Prat J, Albert A, Caceres F, Moreno J, et al. Impact of fetal intervention on postnatal management of congenital diaphragmatic hernia. *Eur J Pediatr Surg* 2007; 17: 404–7.

43. Wilson JM, Lund DP, Lillehei CW, Vacanti JP. Congenital diaphragmatic hernia–a tale of two cities: the Boston experience. *J Pediatr Surg* 1997; 32: 401–5.
44. Wung JT, Sahni R, Moffitt ST, Lipsitz E, Stolar CJ. Congenital diaphragmatic hernia: survival treated with very delayed surgery, spontaneous respiration, and no chest tube. *J Pediatr Surg* 1995; 30: 406–9.
45. Boloker J, Bateman DA, Wung JT, Stolar CJ. Congenital diaphragmatic hernia in 120 infants treated consecutively with permissive hypercapnea/spontaneous respiration/elective repair. *J Pediatr Surg* 2002; 37: 357–66.
46. Chiu PP, Sauer C, Mihailovic A, Adatia I, Bohn D, Coates AL, et al. The price of success in the management of congenital diaphragmatic hernia: is improved survival accompanied by an increase in long-term morbidity? *J Pediatr Surg* 2006; 41: 888–92.
47. Bagolan P, Casaccia G, Crescenzi F, Nahom A, Trucchi A, Giorlandino C. Impact of a current treatment protocol on outcome of high-risk congenital diaphragmatic hernia. *J Pediatr Surg* 2004; 39: 313–8.
48. Chiu P, Hedrick HL. Postnatal management and long-term outcome for survivors with congenital diaphragmatic hernia. *Prenat Diagn* 2008; 28: 592–603.
49. Bernbaum J, Schwartz IP, Gerdes M, D'Agostino JA, Coburn CE, Polin RA. Survivors of extracorporeal membrane oxygenation at 1 year of age: the relationship of primary diagnosis with health and neurodevelopmental sequelae. *Pediatrics* 1995; 96: 907–13.
50. Shiyanagi S, Okazaki T, Shoji H, Shimizu T, Tanaka T, Takeda S, et al. Management of pulmonary hypertension in congenital diaphragmatic hernia: nitric oxide with prostaglandin-E1 versus nitric oxide alone. *Pediatr Surg Int* 2008; 24: 1101–4.
51. Shah N, Jacob T, Exler R, Morrow S, Ford H, Albanese C, et al. Inhaled nitric oxide in congenital diaphragmatic hernia. *J Pediatr Surg* 1994; 29: 1010–4.
52. Brant-Zawadzki PB, Fenton SJ, Nichol PF, Matlak ME, Scaife ER. The split abdominal wall muscle flap repair for large congenital diaphragmatic hernias on extracorporeal membrane oxygenation. *J Pediatr Surg* 2007; 42: 1047–50.
53. Nguyen TL, Le AD. Thoracoscopic repair for congenital diaphragmatic hernia: lessons from 45 cases. *J Pediatr Surg* 2006; 41: 1713–5.
54. Dutta S, Albanese CT. Use of a prosthetic patch for laparoscopic repair of Morgagni diaphragmatic hernia in children. *J Laparoendosc Adv Surg Tech A* 2007; 17: 391–4.
55. Chen C, Jeruss S, Chapman JS, Terrin N, Tighiouart H, Glassman E, et al. Long-term functional impact of congenital diaphragmatic hernia repair on children. *J Pediatr Surg* 2007; 42: 657–65.
56. Fauza DO, Wilson JM. Congenital diaphragmatic hernia and associated anomalies: their incidence, identification, and impact on prognosis. *J Pediatr Surg* 1994; 29: 1113–7.
57. Muratore CS, Kharasch V, Lund DP, Sheils C, Friedman S, Brown C, et al. Pulmonary morbidity in 100 survivors of congenital diaphragmatic hernia monitored in a multidisciplinary clinic. *J Pediatr Surg* 2001; 36: 133–40.
58. Nobuhara KK, Lund DP, Mitchell J, Kharasch V, Wilson JM. Long-term outlook for survivors of congenital diaphragmatic hernia. *Clin Perinatol* 1996; 23: 873–87.