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European Respiratory Society Task Force on Congenital Diaphragmatic Hernia

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Abstract

Infants with congenital diaphragmatic hernia (CDH) have significant mortality and long-term morbidity. Only 60 to 70% survive and usually in high volume centres. The current Task Force, therefore, has convened experts to evaluate the current literature and make recommendations on both the antenatal and postnatal management of CDH. The incidence of CDH varies from 1.7 to 5.7 per 10,000 live-born infants depending on the study population. Antenatal ultrasound scanning is routine and increasingly complemented by the use of magnetic resonance imaging. For isolated CDH, antenatal interventions should be considered, but the techniques need vigorous evaluation. After birth, management protocols are often used and have improved outcome in non-randomised studies, but of importance are immediate intubation at birth and gentle ventilation. Pulmonary hypertension is common and its optimal management is crucial as its severity predicts the outcome. Usually surgery is delayed to allow optimal medical stabilisation. The role of minimal invasive postnatal surgery remains to be further defined. There are differences in opinion about whether ECMO improves outcome. Survivors of CDH can have a high incidence of co-morbidities thus multidisciplinary follow up is recommended. Multicentre international trials are necessary to optimise the antenatal and postnatal management of CDH patients.

Introduction

Congenital diaphragmatic hernia (CDH) is an uncommon congenital malformation of the lung but one with important implications for diagnosis, management and prognosis. It is associated with high mortality and although improvements in medical and surgical management have improved the outlook, survival remains at 60-70% [1-6]. Newer modalities including antenatal screening and intervention are available but are often introduced without formal evaluation. The current Task Force has convened experts in neonatal and paediatric respiratory medicine, paediatric pathology, fetal medicine, and paediatric surgery to evaluate the current literature and to make recommendations for the management of CDH.

Epidemiology of CDH

To provide population-based incidence of congenital anomalies, the European Community's European Surveillance of Congenital Anomalies (EUROCAT) collects data from 43 European registries in 20 European countries capturing approximately 29% of Europe's birth population [7]. The reported incidence for CDH in 2008 for all pregnancies from 20 weeks onwards from EUROCAT was 2.62/10,000 [7] and 1.76/10,000 for live-borns compared to 1.7 – 5.7/ 10,000 reported by other studies [3, 8-10].

Pathology of CDH

The diaphragm is complete by eight weeks of gestation from its components including the septum transversum and the pleuroperitoneal membranes. In CDH, the defect forms during the embryonic phase of lung development usually on the left side (85-90%) but can occur on the right or bilaterally and may be associated with other anomalies. The commonest (70%) defect involves the posterolateral (Bochdalek) region of the diaphragm (Figure 1) but the anterior (Morgagni 25-30%) or central regions (2-5%) can also be affected [11]. Airway generations and

terminal bronchioles are markedly decreased; alveolar septa are thickened; and there is decreased complexity of the respiratory acinus and alveolar volume [12-15]. Arterial medial wall thickness is increased and peripheral muscularization of smaller pre-acinar arteries occurs [12, 16, 17]. Overall, the lungs are hypoplastic, with lower than normal DNA and protein content, more so in the ipsilateral than contralateral lung [18].

Imaging modalities for CDH

Antenatal ultrasound (US) scanning for anomalies is routine in most industrialised countries and increasingly identifies congenital anomalies such as CDHs. Magnetic resonance imaging (MRI) is also increasingly used and should be seen to complement ultrasound scanning. Both these imaging modalities are discussed in detail in the on-line supplement. Our recommendations for antenatal management for delivery are summarized in Table 1.

Antenatal presentation and imaging characteristics of CDH

Antenatal ultrasound screening identifies over 70% cases of CDH [19, 20]. Intrathoracic abdominal organs are the hallmark of CDH (Figure 2). Left sided CDH typically presents with mediastinal shift to the right, caused by herniation of the stomach and intestines. Viscera may show peristalsis and contrast with the more echogenic fetal lung. In right-sided CDH, part of the liver is visible in the chest. Because the liver is echogenic, it may be difficult to differentiate from the lung. Doppler studies of the umbilical vein and hepatic vessels, or location of the gall bladder may be used as additional landmarks. MRI is useful to confirm the diagnosis of CDH in cases of equivocal sonographic findings, to characterise the content of the herniated tissues [21]. Diaphragmatic eventration, characterised by defective diaphragmatic muscularization, can be challenging to differentiate antenatally from CDH. The former shows a cephalic displacement of the diaphragm and is often associated with pleural and/or pericardial effusion [22]. Pathologies

associated with CDH include cardiac, renal, central nervous system and gastrointestinal anomalies [23]. Amniocentesis and genetic consultation to screen for chromosomal anomalies are advised [24].

Antenatal management and prognosis of CDH

Ultrasonographic lung size assessment is best undertaken by the use of the observed/expected lung to head ratio (LHR – discussed in the online supplement) [25]. The LHR predicts survival, with a trend for better prediction at 32-33 rather than 22-23 weeks, and short term morbidity [26]. Right sided lesions have worse outcome [27]. 3D-ultrasound and MRI both permit absolute volumetry, but MRI is superior mostly because of better visualization of the ipsilateral lung [28]. MRI can quantify the extent of liver occupying the thorax [29, 30]. Herniation of the liver is also related to survival, but it remains a matter of debate whether this is an independent predictor [26, 30, 31]. Efforts have been made to document antenatal lung vascular development, but the predictive value is still being validated. Measurements of number of branches, vessel diameters, flow velocity or volume, and reactivity to maternal oxygen inhalation have been reported [32].

In all cases, delivery should be planned at a tertiary perinatal centre; in those with a poor prognosis e.g. having other congenital abnormalities, termination of pregnancy may be considered. For isolated CDH, antenatal therapy is an option. In utero anatomical repair improves lung development, but requires open fetal surgery and is not currently offered if there is liver herniation [33]. Alternatively, tracheal occlusion (TO) has been used to promote lung growth [34, 35]. Antenatal TO prevents egress of lung fluid, which increases airway pressure, causing cell proliferation, increased alveolar airspace and maturation of pulmonary vasculature. Sustained TO is deleterious as it reduces type II cells and surfactant expression. This can be alleviated by in utero release, a concept that was captured under the name “plug-unplug

sequence" [36]. Tracheal occlusion is possible by percutaneous fetoscopic endoluminal tracheal occlusion (FETO) via a 3.3 mm cannula without general anaesthesia [37]. The FETO consortium has the greatest experience (n=210) [27]. When compared to the predicted survival rate after expectant management, temporary FETO in fetuses with left CDH increased survival from 24% to 49% (left-sided), and from 0% to 35% (both $p<0.001$) for right-sided CDH [27]. The procedure may cause premature rupture of membranes (17% within 3 weeks). Changes in lung volume within 2 and 7 days after FETO may be predictive of subsequent survival but the technique is currently being evaluated in a randomized trial.

Clinical presentation of CDH

Clinical presentation of CDH is discussed in detail elsewhere [10, 38]. Although increasing numbers of affected infants have planned deliveries after diagnosis by antenatal scanning, undiagnosed infants usually present with acute respiratory distress in the neonatal period. Milder forms may present with later mild respiratory or gastrointestinal symptoms. Sudden onset of respiratory distress may occur later in life due to small defects.

Investigations for CDH

A chest radiograph should be performed. In infants with CDH this will demonstrate an opacified hemi-thorax with contralateral shift of the mediastinum. Bowel gas may be seen in the chest. The oesophageal portion of the naso-gastric tube is deviated to the right in infants with left-sided CDH and to the left if the lesion is on the right [39]. Introduction of a radio-opaque contrast medium into the stomach and proximal gastrointestinal tract can help to distinguish between a CDH and a congenital thoracic malformation such as congenital cystic adenomatoid malformation.

Echocardiography should be undertaken to exclude congenital cardiac lesions in infants with CDH and in any infant in whom pulmonary hypertension is suspected. It is important to determine right ventricular function, as the ability of the right ventricle to function under increased afterload is an important determinant of illness severity [40].

Postnatal management of CDH

Venue and timing of delivery

Infants with CDH should be delivered in the hospital at which they will undergo surgical intervention. Analysis of the outcomes of 2,140 infants demonstrated infants transported for repair had a higher mortality and need for ECMO [41]. Analysis of data of 628 term infants from the CDH Study Group registry demonstrated early term delivery by elective caesarean section (37 to 38 weeks versus 39 to 41 weeks) was associated with less use of ECMO and a trend towards greater survival later [42]. The CDH Study Group, however, found that the mode of delivery for 548 infants with CDH did not affect survival although vaginal delivery was associated with higher use of ECMO [43] suggesting that obstetric decisions should guide mode of delivery.

Labour ward management

Infants with CDH should be immediately intubated and ventilated and peak inspiratory pressures below 25 cmH_2O employed. Face-mask and T-piece or bag and mask resuscitation should not be used, as this can cause distension of the herniated bowel, increasing respiratory embarrassment. A large bore naso-gastric tube (e.g. French gauge 8) should be sited to decompress the stomach and small bowel. Some advocate use of neuromuscular blocking agents to prevent swallowing and further gas distending the bowel.

Management in the neonatal unit

Standardised protocols have recently been published [44, 45] for the postnatal management of CDH with most recommending gentle ventilation and aggressive treatment of pulmonary hypertension. Both Tracy *et al* [45] and van den Houten and colleagues [1] have claimed improvements after introduction of standardised protocols, but the comparison is with historical controls thus it is unclear if the improvements are due to the introduction of the protocols or advances in medical care. Nevertheless, standardised protocols do ensure focus on essential aspects of management of CDH thus we have based our recommendations on a consensus statement (Table 2) [44]. It is important to emphasise that there have been few randomised trials evaluating the management of infants with CDH and multicentre international trials are urgently required to optimise the postnatal management of CDH infants.

Respiratory support

The best outcomes for CDH infants are achieved by early medical stabilisation and delay of surgical repair until optimisation has occurred [46]. Gentle ventilation, i.e. avoidance of high pressures (peak pressure <25cmH_2O and PEEP <5cmH_2O [47]) and accepting higher levels of $PaCO_2$ (permissive hypercapnia up to a PCO_2 of 60-65mmHg [48]) is preferred [49]. More than 90% of the International CDH Registry centres aimed to minimise lung injury by limiting the peak airway pressure and allowing permissive hypercapnia, rather than aiming for a low $PaCO_2$ to reduce pulmonary vascular resistance [50]. Some centres routinely use neuromuscular blocking agents, whereas others avoid them [51], as muscle paralysis may have an adverse effect on ventilation [49]). Indications for alternative forms of support (high frequency oscillation (HFO), inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation (ECMO)) are a pH of less than 7.25, PCO_2 greater than 60mmHg and the preductal SpO_2 less than 80-85% with an

inspired oxygen concentration of 60% [52]. There is an on-going multi-centre randomised study (CDH-EURO Consortium) assessing whether elective high frequency oscillatory ventilation (HFOV) improves survival and/or has other benefits (http://www.vicitrial.com/), the results will be very welcome to inform the choice of respiratory support.

Analysis of data from 6147 neonates from the Extracorporeal Life Support Organisation database (1991-2010) demonstrated an overall mortality rate of 49% for CDH infants supported by ECMO [53]. The short-term outcomes of veno-arterial and veno-venous ECMO were similar [53]. In the UK collaborative ECMO trial, there were no significant differences in survival, but only a small number of patients were recruited [54]. Meta-analysis of three RCTs (only 39 infants in total) indicated a reduction in early mortality with ECMO, but no long term benefits [55]. Prediction scores may be useful to identify those at very high risk of mortality amongst infants managed with ECMO [56]. Survival appears higher if surgical repair is after ECMO, rather than when the infant is on ECMO [57]. Opinions differ whether ECMO has superior outcomes than established optimal medical management.

There is debate whether CDH infants have evidence of surfactant insufficiency [58]. Analysis of data from the CDH Study Group failed to highlight any significant benefits of surfactant administration in over 500 neonates [59].

Blood pressure support

Arterial blood pressure levels should be maintained at levels normal for gestational age, but if there is evidence of pulmonary hypertension, the arterial blood pressure in term born infants should be maintained at higher levels (i.e. $\geq$50 mmHg). Echocardiography should be undertaken to determine if volume expansion is appropriate. There are no RCTs to determine which

inotropes are the most effective in infants with CDH.

Treatment of pulmonary hypertension

Pulmonary hypertension is common in infants with CDH [60]). The severity of pulmonary hypertension predicts the outcome; non-survivors in one series [60]) having persistent systemic or supra-systemic pressures unresponsive to therapy for more than three weeks after birth. Inhaled nitric oxide improves oxygenation in up to 50% of cases [52], but the effect may be transitory and use of iNO does not influence overall outcome. No effect on mortality was seen with iNO administration in two randomised studies [61, 62], (RR 1.20, 95% CI 0.74, 1.96) and there was a slight increase in the requirement of ECMO (RR 1.27, 95% CI 1.00, 1.92) [63]**.** Sildenafil, a phosphodiesterase type 5 inhibitor, has been used to improve oxygenation and cardiac output by reducing pulmonary hypertension refractory to iNO [64, 65]**.** It may also prevent rebound pulmonary hypertension during weaning of iNO [66]. There are only case reports of other therapies such endothelin antagonists and tyrosine kinase inhibitors for pulmonary hypertension [49] and clearly need further evaluation.

Surgical management of CDH

Surgical closure of the diaphragmatic defect is generally an uncomplicated procedure. Nevertheless there are some issues which are controversial. These include timing of surgery, nature of the repair (prosthetic patch vs. primary repair), need for abdominal closure and merits of a minimally-invasive approach.

Timing and technique of surgery

The only two prospective randomized trials and one systematic review of early or delayed closure have failed to show a statistically significant difference in mortality and secondary

variables (such as length of hospital stay, need for ECMO and duration of respiratory support) [67-69].

There are no universal criteria to define pre-operative stabilization and this can occur with minimal delay in some, yet extend to many days in others [70]. While scientific evidence is lacking, it seems reasonable to delay surgery until medical stability has been achieved. Most surgeons now follow this protocol as shown by the survey of 461 infants from the CDH Study Group [71]. More recent data has confirmed this trend (Table 3)[72].

No consensus exists on when patients being stabilized on ECMO should be operated on. Some centres prefer to decannulate the patient before surgical repair, while others prefer to repair the diaphragm early or late in the ECMO course.

Surgical technique

The standard surgical approach to repair the diaphragmatic defect consists of a subcostal incision with removal of the herniated abdominal viscera from the thorax and complete exposure of the defect. A true hernia sac is sometimes observed (<20% of cases) and, if present, should be excised. Closure of the defect can be accomplished primarily, using non-absorbable sutures, or by means of a prosthetic patch (e.g. GORE-TEX®, Marlex®, Permacol®) if the defect is large [70, 73]. Because synthetic material lacks the capacity for growth, hernia recurrence may reach up to 50% in some series [71]. Alternatively, muscle flaps have been used or a tissue-engineered diaphragm substitute has been proposed to close very large defects or even complete agenesis of the diaphragm [74, 75]. Little attention has been paid to the size of the prosthetic patch when performing a patch repair. A large dome shaped patch bulging into the thorax compared to a small flat patch has the theoretical advantages of increasing the abdominal volume and

decreasing the risk of patch dehiscence when the child grows. However, this question has not been evaluated scientifically. Up to half of those operated on for CDH will need a patch repair (Table 4a).

Closure of the abdominal wall may compromise ventilation and hemodynamic stability due to the small size of the abdominal cavity. In such circumstances coverage of the abdominal viscera may be achieved by: skin closure leaving a fascial defect; interposition of a prosthetic patch between the fascial edges; or creation of a surgical silo (Table 4b). A chest tube is not usually used; the rationale being to encourage the lung to enlarge gradually, displacing fluid and air, rather than forcefully due to a negative suction pressure applied through a thoracostomy drain [73, 76].

Neonates repaired on ECMO almost invariably will need a patch repair as there is a strong correlation between the severity of the disease and the size of the defect [77]. These patients pose some specific problems related to bleeding. Careful inspection of the operative field and meticulous haemostasis should be performed at the end of the surgical procedure. Fibrin sealants or even the use ε-aminocaproic acid have been recommended in this setting [76]. However, in one of the author's (BF) experience, the use of ε-aminocaproic acid has led to serious clotting in the ECMO circuit in several instances. Successful repair without bleeding complications was instead achieved in 34 of the recent 36 infants repaired on ECMO by a meticulous surgical haemostasis in combination with fibrin glue in the operating field (unpublished data).

Surgical repair can be accomplished by minimally invasive techniques, although the latent cardio-pulmonary instability of such neonates have made some surgeons hesitate in using this approach. Certainly, hypercarbia and acidosis are almost invariable using CO_2 insufflation.

Nevertheless, recent reports have shown the feasibility and safety of this approach even in unselected groups of patients [78-80]. It also seems that in contrast to the open technique where the abdominal approach is standard, thoracoscopic repair is somewhat easier. The role of minimally invasive surgery remains to be further defined and formally evaluated.

Long-term prognosis of CDH

Infancy

Lung and vascular developmental abnormalities associated with CDH are the primary causes of morbidity and mortality in infants which may be compounded by the secondary effects of postnatal management including hyperoxic, high pressure mechanical ventilation. Prematurity is associated with worse prognosis [81]. Lung hypoplasia, due to impairment of both airway branching and alveolarization, results in markedly decreased alveolar surface area [82].

Significant advances in the postnatal management of patients with CDH have resulted in improved survival rates over the past two decades [46]. Nevertheless, most series still reported overall postnatal survival in isolated CDH around 60-70%, although some survival rates higher than 90% have recently been reported [83, 84]. A significant survival advantage has been suggested for infants with CDH treated in high-volume centres [85]. However, survival estimates derived from institutional or unit-based data lend themselves to multiple biases. A recent careful evaluation of survival variables by comparing all institution and population data from the province of Ontario, Canada demonstrated a clear discrepancy in institution-based reporting [86, 87]. The number of deaths reported by the institutions was found to be 32% less than that of the population data.

Late-presenting CDHs represent less than 3% of cases [88]. Diagnosis may be in the school

years, with respiratory or gastrointestinal presenting symptoms. The prognosis is excellent.

The American Academy of Pediatrics has suggested follow up guidelines for survivors of CDH after discharge [89]. These patients have a high incidence of respiratory, nutritional, musculoskeletal, neurological and gastrointestinal morbidities [46, 90-92]. Furthermore, the recent improved survival of very sick babies is associated with increased particularly pulmonary morbidity among survivors [2, 46] persisting beyond the initial hospitalization, especially in those treated with ECMO [93, 94]. Speol and colleagues recently observed that mean maximal expiratory flows at functional residual capacity (V'max FRC) were significantly lower than predicted values at 6 and 12 months of age in CDH survivors [95]. Furthermore, FRCpleth was increased especially in those patients who had received ECMO. Oxygen dependency is also common with 50% being oxygen dependent at 28 days of age [1] and 16% requiring oxygen at the time of discharge for a mean duration of 14.5 months [93]. Up to 2% remained oxygen-dependent at 2 years of age [94]. Bronchodilators may be needed in 40% of patients in the first year of life [93]. Angiogenesis remains defective in hypoplastic lungs [96]. Pulmonary hypertension may persist in up to 30% of patients at 2 months of age [97] and is associated with increased risk for early death [94, 97]. Pulmonary artery hypoplasia or stenosis, and pulmonary vein stenosis or delayed venous return may contribute to persistent pulmonary hypertension [98].

Childhood

Several follow-up studies have explored long-term pulmonary morbidity (Table 5). These studies report catch-up of lung volumes [99-104]. In contrast, perfusion studies have demonstrated persistent perfusion defects in the ipsilateral lung [99-101]. Reduced airflows and poor response to bronchodilator inhalation [101, 104-106] suggest increases in lung volume occur by distension rather than by alveolar number. The few lung morphometric studies

following CDH repair [107, 108] all found persistent decreases in airway, alveolar, and arterial numbers in both lungs, the ipsilateral lung being most affected. Nevertheless, studies evaluating the diffusion capacity for carbon monoxide and exercise capacity have found normal values when compared with controls [102, 104-106] .

Because CDH is associated with long-term morbidities that affect quality of life, survival alone is no longer a sufficient parameter for successful treatment of children with CDH. Long-term follow-up by a multidisciplinary team is recommended for these children [89, 109], to detect and treat both pulmonary morbidities and other co-morbidities.

Conclusions

CDH remains a challenging condition for optimal management and for optimal outcomes. Despite recent improvements in survival, the management both ante- and post-natally remains to be optimised including the role of antenatal interventional management such as FETO. After birth, innovations have been made in treating both respiratory failure and pulmonary hypertension but robust assessment of newer therapies is necessary. As survival improves, further studies are required to ensure that the survivors have a high quality of life after discharge which can only occur with regular follow up by a multi-disciplinary team.

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Table 1: Recommendations for the antenatal management and delivery of CDH infants

- Routine antenatal ultrasound scanning for anomalies is essential in industrialised countries
- MRI is useful to confirm the diagnosis of CDH in cases of equivocal ultrasound findings
- Ultrasound lung size assessment is best determined by the use of the observed/expected lung to head ratio (LHR) which can be used to predict survival
- Herniation of the liver is related to survival although it is debatable if it is an independent predictor of survival and at this stage should not be used to inform counselling
- Antenatal counselling is essential and should be conducted by a multidisciplinary team
- Genetic consultation and amniocentesis to screen for chromosomal anomalies are advised
- In those with a poor prognosis, for example fetuses having other congenital abnormalities, termination of pregnancy should be sensitively considered
- Antenatal surgical intervention should be considered in selected cases after discussion with the parents, but going forward this should be done in the context of randomised trials
- Delivery should be planned wherever possible in a tertiary perinatal centre
- Obstetric decisions should guide the mode of delivery

Table 2: Postnatal Recommendations for the Management of CDH based on the consensus statement of the CDH-EURO consortium. (Ref 44).

Treatment in the delivery room	• No resuscitation delivered by bag and mask • Immediate intubation • Peak pressure below 25cm H_20 • Nasogastric tube
Treatment in the NICU	• Adapt ventilation to obtain preductal saturation between 85%-95% • pH > 7.20, lactate 3-5 mmol/L • Conventional ventilation (CMV) or high frequency oscillation (HFOV) maximum peak-pressure 25-28cmH_20 in CMV and mean airway pressure 17cmH_20 in HFOV • Targeting blood pressure: normal value for gestational age • Consider inotropic support
Pulmonary hypertension	• Perform echocardiograhy • Inhaled nitric oxide (iNO) but stop if no response • In the chronic phase: phosphodiesterase - inhibitors, endothelin antagonist, tyrosine kinase inhibitors
Extracorporeal membrane oxygenation (ECMO) indications	• Inability to maintain preductal saturation above 85% • Respiratory acidosis • Inadequate oxygen delivery (lactate>5mmol/L)
Timing of Surgical repair	• Fraction of inspired oxygen (FiO_2) below 0.5 • Mean blood pressure normal for gestational age • Urine output > 2ml/kg/hour • No signs of pulmonary hypertension

Table 3. Data from the Congenital Diaphragmatic Hernia Study Group registry (http://utsurg.uth.tmc.edu/pedisurgery/cdhsg/CDHSG.pdf) between Jan 1st 2000 and Dec 31st 2009. During this period 3863 patients were entered into the registry. 685 of these were never repaired. Data obtained by courtesy of Kevin P. Lally, MD, Suite 5.258, 6431 Fannin Street, Houston , TX 77030, USA (Ref 72).

Number of patients whose diaphragmatic defect was repaired within different time intervals after birth.

	0 – 24 h	**24 – 48 h**	**>48 h**	**No repair**	**Incomplete data**	**Total**
No of patients	185	376	2607	685	10	3863

Table 4. Data from the Congenital Diaphragmatic Hernia Study Group registry (http://cdhsg.net/) between Jan 1st 2000 and Dec 31st 2009. During this period 3863 patients were entered into the registry. 685 of these were never repaired. Data obtained by courtesy of Kevin P. Lally, MD, Suite 5.258, 6431 Fannin Street, Houston , TX 77030, USA (Ref 72).

a) Number of patients with primary repair vs patch repair.

	Primary repair	**Patch repair**	**No repair**	**Incomplete data**	**Total**
No of patients	1562	1598	685	18	3863

b) Number of patients with primary closure of the abdominal wall vs some type of secondary closure.

	Primary closure	**Silo, patch etc.**	**No repair**	**Incomplete data**	**Total**
No of patients	2595	371	685	212	3863

Table 5: long-term outcomes of CDH

Features	% (unless otherwise specified)	References
Thoracic scoliosis	~8	[103]
Pectus excavatum	4-21	[102, 103]
Mean TLC	89-101% predicted	[102-104]
	0.16 Z-score	[105]
Mean FEV_1	79-90% predicted	[102-104]
	-1.45 Z-score	[105]
Mean perfusion ratio of the affected side	53-67	[99-101]
Mean volume ratio of the affected side	82-88	[99-101]
Wheezing ever	17-37	[102, 104]
VO_2max (% of control)	95-100	[102, 105]

Legends

Figure 1

(a) only 0.5cm (approx.) of residual diaphragm observed resulting in half of the liver, all small bowel, stomach, spleen and pancreas, large part of colon, left adrenal, approx. ¾ of the left kidney herniating inot left thoracic cavity. Spleen is the RIGHT chest behind the oesophagus but in front of the aorta. (b) Lung weighing 13.43g compared to an expected weight of 40.6 ± 17.1 g. Lung/body ratio was 0.0045 (expected >0.01).

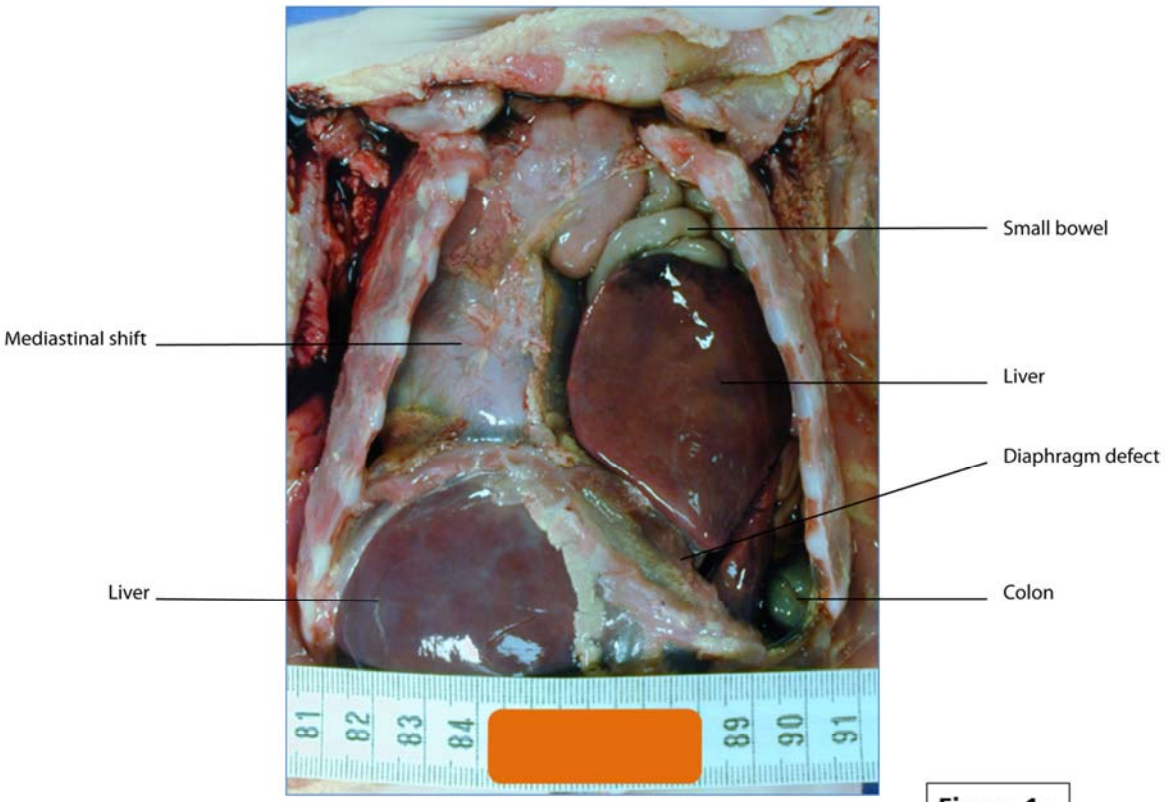

Figure 1a

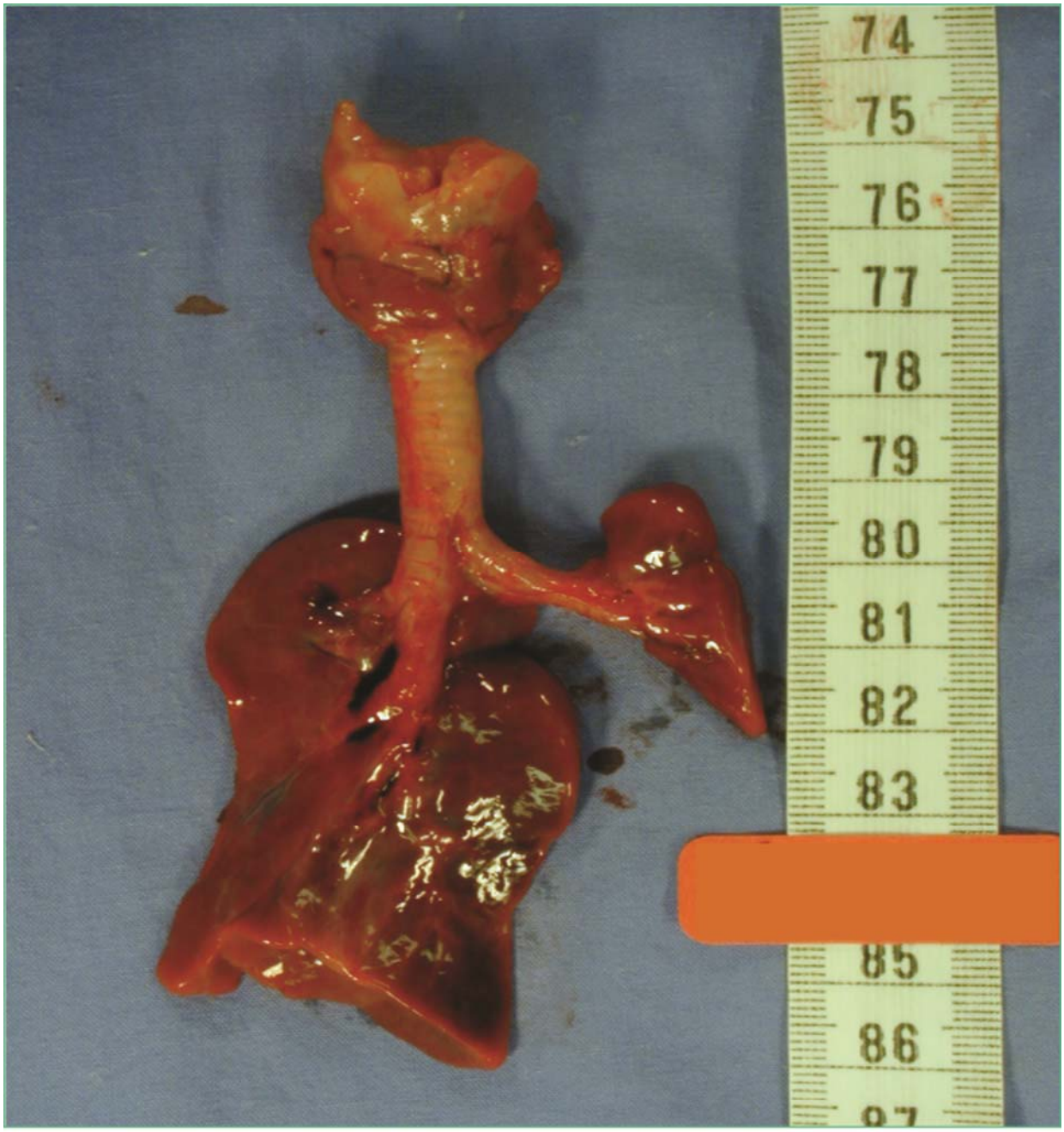

Figure 1b

Figure 2

Fetal magnetic resonance images (left: coronal view, upper right: axial view) and antenatal ultrasound (lower right: axial view) of a left-sided congenital diaphragmatic hernia at gestational age 26 weeks. The level of both axial views is shown on the coronal image (white arrows). The herniated tissue is outlined on the images (white dots). Legend: ‘H’ heart, ‘L’ left lung, ‘R’ right lung, ‘St’ stomach, ‘Int’ intestines.

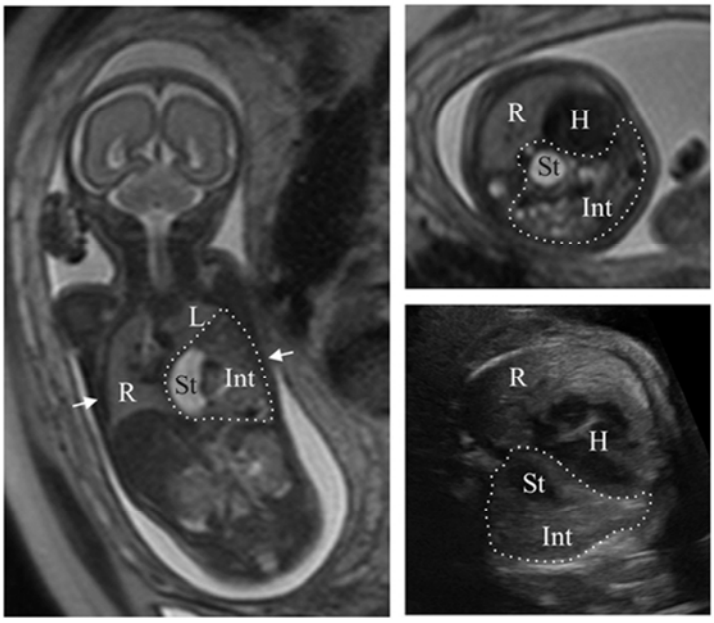

Figure 2