ALMA MATER STUDIORUM UNIVARSITA DI BOLOGNA

2° LEVEL INTERNATIONAL MASTER DEGREE

MINIMALLY INVASIVE AND ROBOTIC PEDIATRIC SURGERY

Congenital Diaphragmatic Hernia:

From the "–otomy" to "–oscopy". A new reality?

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I hereby confirm that the thesis was written independently by myself without the use of any sources beyond those cited, and all passages and ideas from other sources are cited accordingly.

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ABSTRACT:

Anatomically the congenital diaphragmatic hernia (CDH) is an anomaly which is characterized by a defect in the diaphragm resulting in protrusion of abdominal intestines and organs into the thorax. The size of the defect ranges from a small opening to complete agenesis. Pathophysologically the most important problem that interferes with the mortality of the disease is lung hypoplasia and pneumonic hypertension. CDH is a surgical condition that the surgical treatment does not change directly the course of the disease. The progress in the field of prenatal diagnosis has contributed to better overall management of the disease, both conservatively and surgically. Until the first half of the last century CDH it was considered an emergency and was operated soon after birth by open approach (-otomy) mainly through abdominal or less through the thoracic access. In today's era when minimal invasive surgery (MIS) is gaining more and more acceptance, under some conditions- but not necessary- the thoracoscopic repair, mainly, and the laparocopic aprroach (-oscopy) are carried out. Regardless of which surgical method is chosen, CDH is no longer being regarded as an urgent and is operated on within 48-72 hours after stabilization in the neonatal intensive care unit.

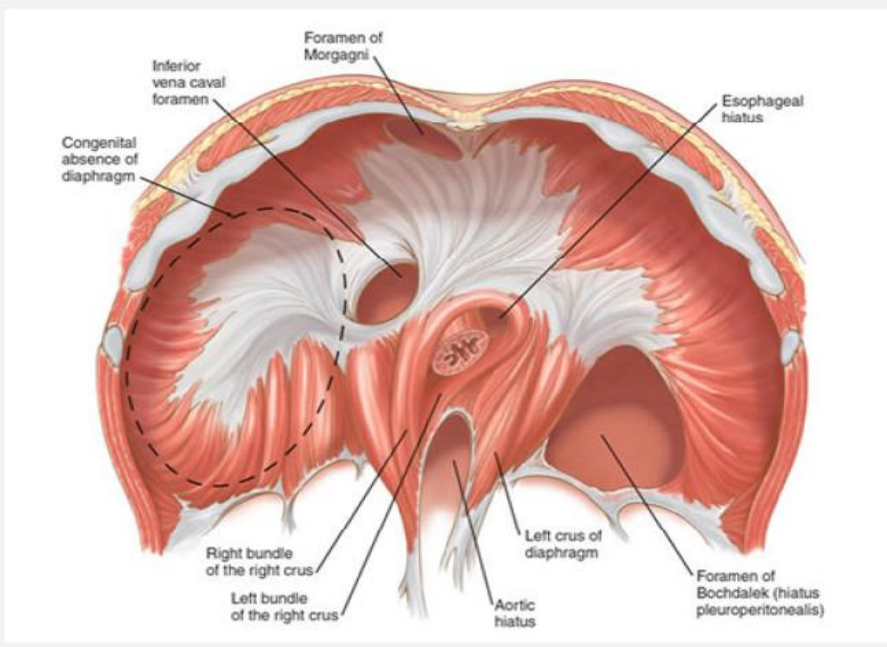
ASTRATTA:

Anatomicamente hernia diaframmatica congenita (CDH) è un'anomalia caratterizzata da un difetto nel diaframma con conseguente protrusione dell'intestino e degli organi addominali nel torace. La dimensione del difetto varia da una piccola apertura alla completa agenesia. Fisiopatologicamente il problema più importante che interferisce con la mortalità della malattia è l'ipoplasia polmonare e l'ipertensione polmonare. CDH è una condizione chirurgica che il trattamento chirurgico non modifica direttamente il decorso della malattia. I progressi nel campo della diagnosi prenatale hanno contribuito a una migliore gestione complessiva della malattia, sia in chiave conservativa che chirurgica. Fino alla prima metà del secolo scorso la CDH era considerata un'emergenza e veniva operata subito dopo la nascita per via aperta (-otomia) principalmente attraverso l'accesso addominale o meno attraverso l'accesso toracico. Nell'era odierna in cui la chirurgia minimamente invasiva (MIS) sta guadagnando sempre più accettazione, in alcune condizioni ma non necessarie, vengono eseguite principalmente la riparazione toracoscopica e l'approccio laparocopico (-oscopia). Indipendentemente dal metodo chirurgico scelto, il CDH non è più considerato urgente e viene operato entro 48-72 ore dalla stabilizzazione nell'unità di terapia intensiva neonatale.

CHAPTER 1: GENERAL ASPECTS IN CDH

1.1 INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a variable size anatomic defect of the diaphragm delimited by the anterior rim of diaphragm, medially by the crus of the diaphragm, and laterally and posteriorly by the costal margin with or without some remains of muscle; which allows abdominal viscera to herniate into the thorax. CDH is estimated to be 1 per 2,000 to 5,000 births[1] [2] but some assume that this number is even higher because of the hidden mortality (30% of fetuses who have CDH will die before birth).[3] [4] [5]



Picture 1. Foramens and congenital defects of diaphragm.

CDH can be either as an isolated congenital anomaly, or with a combination of other congenital anomalies. Under the term “isolated CDH”, the pulmonary hypoplasia, patent ductus arteriosus, patent foramen ovale, and malrotation[1] [6] [7] [8] are considered as consequences of CDH instead of different anomalies. In almost 40% of affected infants one or more associated anomalies

are present[9]. Approximately 60% of these anomalies are cardiac, 23% are genitourinary, 17% are gastrointestinal, 14% involve the central nervous system (CNS), and 10% are chromosomal.[3] Karyotypic abnormalities are usually trisomies 18, 13 and 21. [10] The most common syndromes that CDH is present are: Fryns syndrome, Pentalogy of Cantrell, Apert, Brachmann-Cornelia De Lange, Beckwith-Wiedemann, CHARGE, Coffin-Siris, Goldenhar sequence, Simpson Golabi-Behmel, Stickler, Pierre Robin sequence and VACTERL.[2 9 11] Associated extralobar pulmonary sequestrations also have been described, as has esophageal atresia and omphalocele. [11 12]

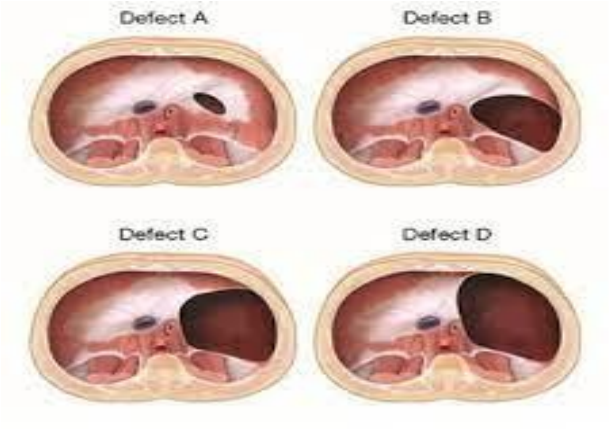
The main cause of morbirity and mortality in CDH patients comes from irreversible pulmonary hypoplasia or severe persistent pulmonary hypertension, despite surgical repair of the hernia. Prenatally diagnosed survival rates are 71% and 83% when diagnosed postnatally.[13] Over the last decades, since the adoption of delayed surgical repair with permissive hypercapnea and gentle ventilation, survival has improved and has been reported to be 70-90% in non-ECMO infants and up to 50% in infants who undergo ECMO.[2 14]

The_etiology of CDH remains unclear but is considered multifactorial. Some patients have associated chromosomal abnormalities and single-gene disorders. Individually or in combination; genetic, environmental and nutritional factors have been proposed to be causes for CDH. Nitrofen and vitamin A disturbance have been associated with CDH in animal studies. Additionally in neonates with CDH, low retinol and retinol-binding protein levels from cord blood samples have been detected.[1 2 15 16]

Four types of CDH according to the anatomy of the defect are recognized. The Bochdalek (postero-lateral) hernia is the most common type of CDH (70-75%) and from those 85% are located on the left side, 13% on the right side, and 2% of them are bilateral. This probably happen because of earlier closure of the right pleuroperitoneal canal than the left. The Morgagni (anterior) hernia counts 23-28% of CDH and central hernias is the remaining 2-7%.[2] Eventration is not consider as different type of CDH but may be mistaken as one. The diaphragm is

intact but thinner, is more commonly located on the right side and is not associated with severe lung hypoplasia.

A different type of classification is according to the size of the defect, as defined by surgical findings (picture 1). The size of the diaphragmatic defect may vary from a small one to total diaphragmatic agenesis; and according to this, the surgical treatment is determined. The size of this diaphragmatic hole not only determines the surgical technique itself but also the severity of the disease. The greater the defect is, the greater the content of hernia and, by extension, the worse the pulmonary hypoplasia. The operative finding in type D defect, is an absent of posterior rim beyond the spine, an absent of posterior–lateral rim, and an anterior/anterior–medial rim, which is minuscule.



Picture 2. Defect A: smallest defect, usually "intramuscular" defect with >90% of the hemi-diaphragm present. This defect involves <10% of the circumference of the chest wall. Defect B: 50-75% hemidiaphragm present. This defect involves <50% of the chest wall. Defect C: <50% hemidiaphragm present. This defect involves >50% of chest wall. "Defect D": largest defect (previously known as "agenesis") with complete or near complete absence of the diaphragm with <10% hemidiaphragm present; this defect involves >90% of the chest wall.[17]

1.2 PRENATAL DIAGNOSIS

Prenatal ultrasound is a cornerstone for the course of the disease as it provides anticipatory counseling. CDH is diagnosed 68% prenatally[13] with more than 50% of CDH cases being detected at a mean gestational age of 24 weeks.[2] Findings that indirectly support the diagnosis of CDH are polyhydramnios (80%),[3] presence of stomach or intestine or liver at the level of the four-chamber view of the heart, in a combination with no detection of the stomach in the abdomen. Differential diagnosis must include any space-occupying lesion in the chest that causes mass effect with mediastinal shift and displacement of the heart, such as congenital cystic adenomatoid malformation, brochogenic cysts, pulmonary sequestration, enteric, neuroenteric and thymic cysts as foregut duplications.[17] By 18th gestational week, the diaphragm can be recognized as an uninterrupted hypoechoic line, separating thorax and abdomen. The combination of heterogeneous echoes in the thoracic cavity and the inability to visualize the entire diaphragm on the ipsilateral side is suggestive of a diaphragmatic hernia. Isolated right-sided CDH is extremely difficult to diagnose by ultrasound if the liver is the only organ that has herniated because of the similar echodensity with lungs. Color flow Doppler may aide the diagnosis by identifying the gall bladder and vasculature in the liver[18].

LHR (lung-to-head ratio) is a simple ultrasonographic parameter introduced by Metkus et al in 1996, calculated by obtaining a transverse axial image through the chest at the level of the four-chamber view of the heart divided by the head circumference and could be evaluated as a prognostic value of postnatal survival. LHR values less than <0.6 is associated with a postnatal mortality approaching 100%; while mortality in infants whose LHR is greater than 1.35 approaches 0.[2 3 9 11 19] Since these measurements vary by gestational age, as lung and head grow in different rates during fetal life, Jani et al introduced O/E (observed to expect) LHR which is a modified index that explains the expected LHR according the given gestational age. O/E LHR values < 15% predict extreme pulmonary hypoplasia and associated with 0% survival,

15 to 25% severe pulmonary hypoplasia and 20% survival, 26 to 45% moderate pulmonary hypoplasia and 30 to 60% survival, and > 45% mild pulmonary hypoplasia and over 75% survival.[10]

Another U/S finding used as a prognostic indicator of CDH mortality is the liver position. Accordingly, liver can be found "up" into the thorax, or "down" into the abdomen which can be reconfirmed by color flow Doppler. Liver herniation is associated with worse prognosis. It also indicates of whether the patient will need ECMO (80% - liver-up vs. 25% - liver-down) and survival (45% - liver-up vs. 93% liver-down).[2 20]

Fetal magnetic resonance imaging (MRI) contributes to the diagnosis and differential diagnosis of diaphragmatic occupational lesions such as CDH, pulmonary sequestration or cystic adenomatoid dysplasia. It clarifies the liver position compared with U/S, measures fetal lung volumes and calculates observed-to-expected total fetal lung volume (o/e TFLV) or percent predicted lung volume (PPLV).[21 22 23 24]

1.3 PRENATAL INTERVENTIONS

Fetal endoscopic tracheal obstruction (FETO) is the latest intrauterine step of trying to minimize the morbidity of CDH due to pulmonary hypoplasia and hypertension. The concept is that by occlusion of the trachea, the liquid that is produced in the lungs has no way out to the amniotic cavity and remains into the lungs to expand them and force them to grow. Despite this, there is not enough evidence that vascular growth and remodeling develop in parallel. The balloon placement is generally suggested to be done between 27–32 weeks of gestation depending on severity of the case. The goal is that the balloon remains in place until 34th week. It is generally accepted that FETO under certain conditions increases neonatal survival but at the same time leads to a higher rate of premature rupture of membranes and decreased gestational age at delivery by nearly 2 weeks.[13] Because of possible complications that may arise, a close follow up of any signs of preterm labor is mandatory.

1.4 POSTNATAL DIAGNOSIS

The clinical signs that indicate CDH are those of cyanosis and respiratory distress, soon after birth. Clinical examination reveals mediastinal shift, absent or decreased breath sounds on the ipsilateral side and rarely, intrathoracic bowel sounds. Scaphoid abdomen in combination with limited or absent bowel sounds may change to a distended one, as the swallowed air from respiratory distress cause intestinal distension. When distended viscera herniate in the thorax may be clinically visible as a barrel chest. In case of severe mediastinal shift, venous return is compromised causing poor perfusion and hypotension. 10% to 20% patients with CDH present in older age usually with chronic cough, recurrent respiratory infections or more rarely with gastrointestinal symptoms due to gastric volvulus or intestinal obstruction.[3 25 26]

Diagnosis is confirmed by chest and abdominal radiographs where gas filled loops are depicted into the thoracic cavity. There is absence of a diaphragmatic shadow to the ipsilateral side, the nasogastric tube confirms the abnormal position of the stomach in the chest, and a contralateral mediastinal shift is shown.

1.5 POSTNATAL CARE

Hemodynamic and respiratory stability are necessary to a newborn with diagnosis of CDH. Immediate endotracheal intubation and avoiding the use of bag-mask ventilation is a routine for all these infants, in order to avoid distension of intestine. Ventilation using a T-piece resuscitation is preferred to avoid high airway pressures. At the same time nasogastric tube must be placed to empty the stomach. Pre-ductal pulse oximeter is placed on the right upper extremity. Umbilical vessels are the first option for catheterization ensuring access to administer fluids and inotropes. Alternatively, it may be preferable to obtain a preductal arterial line in the right radial or ulnar artery. In order to ablate the stress response, as it is considered a stimulus of pulmonary

vasoconstriction, infants with CDH should be deeply sedated with combinations of narcotics and hypnotics agents.

The goals of ventilation, are to achieve acceptable post-ductal oxygen saturation according to metabolic needs, avoid respiratory acidosis and prevent extended lung injury. The conventional ventilation with low pressure is actually the best first option using a combination of high rate and modest mean airway pressure. Target of pre-ductal saturations are maintained between 85– 95% while post-ductal >70%, with parameters PIP <25-28 cmH2O, PEEP 3-5cm H2O, and rate 40-60/min. When an infant is not responding (PIP >28 cmH2O in order to maintain PaCo2 <60 mmHg) or barotrauma, high frequency ventilation (HFVO) is applied.[2] The settings on HFOV are not well defined by the existing literature. Mean airway pressure (MAP) is usually adjusted to maintain adequate inflation of the contralateral lung to 8 ribs in a range of 13–17 cm H2O. If both conventional and high frequency ventilation fails and there are no other contraindications the infant starts extracorporeal mechanical oxygenation (ECMO).

For circulation management, fluid boluses and vasopressor agents are used according to the stability goals that indicate adequate tissue blood perfusion. Those are: pH >7.2, lactate <5mM/L, and urine output >1ml/kg/h. Dopamine, dobutamine, epinephrine or norepinephrine are the first line agents given for maintenance blood pressure under their vacoconstrictor activity. Low-dose hydrocortisone is beneficial in vasopressor-resistant hypotension in the immediate postnatal period. [2]

After stabilization, ultrasonography and echocardiography as also fetal karyotyping are performed.

Inhaled nitric oxide (iNO) is the most widely accepted used pharmaceutical agent for the treatment of CDH pulmonary hypertension. It is a selective smooth muscle cells pulmonary vasodilator which quickly degrades once it reaches the systemic circulation. It is generally acceptable to start iNO after assessment of the oxygenation index (OI) of ≥20 and evidence of right-to-

left shunting by clinical exam (a pre- postductal saturation difference of ≥10%) and/or echocardiographic evidence of extrapulmonary right to left shunting. (Note: oxygenation index (OI), = Mean airway pressure x FiO2 x 100 ÷ PaO2)[2]. Although it has confirmed benefits, continuing iNO therapy in the absence of response could be detrimental. Summarizing the action of nitric oxide may play an important role in treating exacerbations of pulmonary hypertension but has no effect in the need of ECMO in CDH patients. Other pharmaceutical treatment consists of Prostaglandin (PGE1) especially in the setting of right heart failure, Sildenafil, Milrinone and Bosentan. But because their application in newborns CDH patients is not demonstrably safe, their use is concerned.[2]

Extra Corporeal Mechanical Oxygenation is the last life saving measure in many cases of pulmonary hypoplasia and hypertension after conventional and high frequency ventilation has failed. Respiratory failure in CDH patients refractory to conventional or high frequency ventilation means: (a) Inability to maintain preductal saturations >85% or postductal saturations >70% along with (b) increased PaCO2 and respiratory acidosis with pH: <7.15 despite optimal ventilator management, (c) PIP > 28cmH20 or MAP >17 cmH2O to achieve saturations >85%, (d) inadequate oxygen delivery with metabolic acidosis, (e) systemic hypotension resistant to fluid and vasopressor therapy resulting in urine output <0.5ml/kg/h for a 12-24h period and (f) consistently elevated OI> 40.[2 3] Venoarterial (VA) or venovenous (VV) ECMO can be applied. The only unanimously accepted restrictions in the use of ECMO, are infants who have CDH and other major lethal anomalies, gestational age less than 32 weeks, weight <2kg or a pre-existing hemorrhagic CNS injury.[2 3] Prolonged duration of ECMO is a predictor of increased mortality.

CHAPTER 2: EMBRYOLOGY-PATHOPHYSIOLOGY

Diaphragmatic embryologic development begins at the 4th week of gestation and is completed by 12th week. Four elements compose the embryonic diaphragm and fuse in different stages; the septum transversum which forms the central tendon, the pleuroperitoneal membranes, the mesentery of the esophagus that forms crural and dorsal structures, and muscle fibers from the thoracic intercostal muscle groups.

The septum transversum migrates dorsally and interacts with the dorsal mesentery of the esophagus. At the same time, the pleuroperitoneal membranes invaginate from lateral body wall mesenchyme, and fuse with the mesentery of the esophagus and the septum transversum ventrally thereby defining the pleuroperitoneal canals. Until 6th to 7th gestational week pleuroperitoneal folds fuse with the septum transversum and complete the structure of diaphragm. The right side closes before the left side. Then myoblasts migrate from the thoracic intercostals muscle groups and forming a peripheral muscular rim during the 9th to 12th week.

One theory supports that in case this procedure disrupts then a defect is formed at the pleuroperitoneal fields and Bochdaleck hernia is resulted. During the 10th week intestines return into the abdominal cavity from the extraembryonic phase and infiltrate through the defect in the thoracic cavity.[3] This compression of developing fetal lungs by herniated abdominal viscera impairs pulmonary growth and maturation.

A different speculation is that lung hypoplasia may be the leading causal factor in the pathophysiology of diaphragmatic hernia and not the result. A distribution in lung bud development subsequently causes problem in the development of post hepatic mesechymal plate, resulting in a defective diaphragm.

A combination of these two theories composes the “dual-hit” hypothesis, based on rat model, for the embryological origin of CDH and explains why both

lungs are hypoplastic, but the ipsilateral lung is more affected than the contralateral side.

The pulmonary vasculature has decreased number of vessels per unit of lung. In addition, pulmonary vascular remodeling with medial hyperplasia and peripheral extension of the muscle layer in the small preacinar and intra-acinar arterioles is evident.[2] Consequently there is an increase in pulmonary vascular resistance and finally persistent pulmonary hypertension develops. This leads to right ventricle (RV) dysfunction. Secondary to pulmonary hypertension, there is shunting of blood from right to left across the patent foramen ovale and the patent ductus arteriosus. Left ventricular dysfunction along with left atrial dysfunction results in pulmonary venous hypertension and worsening of pulmonary arterial hypertension.[2 3]

CHAPTER 3: HISTORICAL REVIEW

3.1 MILESTONES IN THE HISTORY OF CDH

In 1848, Bochdalek described congenital diaphragmatic hernia.[27] At the begging of the 19th century, surgery was almost not an option for CDH treatment and even more that the condition was not amenable of treatment.[28] It was thought that if a CDH patient survived more than a few days, the opening was wide enough to prevent obstruction and subsequently no intervention was needed. This is proved by reports about some CDH patients, to whom when they had to be operated on; a herniotomy was performed for the opening widening and no attempt was made to transfer the intestine to the abdominal cavity.[29]

Over five decades later, following the conviction that CDH was not a surgical condition, CDH became a great challenge for the pediatric surgeon compared to now. Reported by Gross and Ladd in 1934, only the fittest to survive arrived for surgical consideration.[11] The first neonate operated within 24 hours of life was reported in 1946[27]. Due to lack of knowledge about pulmonary hypoplasia and pneumonic hypertension, it was considered as an acute neonatal surgical emergency on the first day of life. The sicker the child was the sooner was surgery undertaken.[30]

Only in 1971 pulmonary hypertension was first demonstrated in CDH patients by Rowe and Uribe.[11] Until the late 1980s the overall survival rate was approximately 50 per cent with no improvement in compare to the previous 20 years. [14 30 31 32]. In more detail it is stated that the 1 year survival increased later to 1980 from 19% (1968–71) to about 54% (1996–99).[1]

The classification of the disease divided CDH in four types; combing the criteria according to the location and size of the defect: (i) Hernia through the pleuroperitoneal folds (ii) Central hernia through the dome of the diaphragm. (iii) Hernia through the oesophageal orifice (iv) Absence of the left half of the diaphragm.[29] Left sided (Bochdaleck) was considered the most frequent location of the CDH, whereas the right one (Morgagni) was extremely rare. By 1920s from the whole literature contained but 8 recorded cases of hernia through the

foramen of Morgagni.[29] Also Hume, classified CDH into the following groups[8]: i) Hernia through the dome of the diaphragma which included also eventration as the mildest form ii) Hernia through or in relation to the oesophageal opening as the commonest type at that time iii) Agenesia of both halves of the diaphragm. iv) Hernia through a peritoneal fold (posterolateral more frequently at the left side) v) Hernia through one of the vascular or nervous foramina.

Since prenatal ultrasound was widely used in hospitals after 1970s and the first prenatally diagnosed cases occurred in 1988[1], the diagnosis was based mainly on clinical examination. Respiratory distress and/or cyanosis from birth was mentioned to be the only symptoms[30 28]. Auscultation of the thorax used to point, as it does now, diverted cardiac ossification as an indication of heart and mediastinum displacement. Also the hearing of bowel sounds into the chest and not in the abdominal cavity in combination with the scaphoid outline of the abdominal wall[8] was raising the suspicion of CDH diagnosis.

Chest x-ray was the diagnostic examination, and sometimes combined with barium swallow,[8 32] when there was differential diagnosis between air-containing bowel, lung cyst, or pneumothorax. Reference to the relative position of the esophagus and the stomach shadow used to show the position of the opening in the diaphragm.

In the first half of the previous century the open approach of CDH repair was done either through the abdomen or thoracic cavity or even through thoraco-abdominal incision. Following the observation that the presence of associated gastro-intestinal rotational anomalies was very common, many surgeons used to choose the abdominal approach so they could concurrently repair malrotation. Reduction of herniated viscera was thought to be easier by this approach comparatively to the thoracic[8 27 28 33]. Less often and especially in cases that correction of associated cardiovascular and gastro-intestinal anomalies was attempted, the thoraco-abdominal approach was an alternative option, but had the disadvantage of being more complicated procedure. [30 32] In 1922 Bettman and Hess[27 28 34] reported the successful surgery on the youngest patient up to

then with CDH. First extensive thoracotomies, were performed by removal of a large portion of the 7th rib and wide retraction of the parts, so they could give an excellent exposure of the upper surface of the dome and a view of the thoracic contents. In the begging of 19th century, instead of the defect closure, especially if the stomach was content of hernia, this was reduced as far as possible from the thoracic aspect, and its margins sutured to the opening in the diaphragm (Beckman, Downes).[29] Only in 1940, when Ladd and Gross reported 16 cases treated by operation with 9 survivors, the surgical repair of CDH became an accepted treatment.[27] At large size defects the use of muscle patch described in 1962 when Meeker and Snyder first used the anterior abdominal wall for repair of a CDH and later in 1971, Simpson and Gossage used a split abdominal wall muscle flap.[14] In 1995 the first CDH laparoscopic repair is puplished[35 36] while in 2001 thoracoscopic repair is starting to take hold.[35] In 2002, Philippe et al. described MIS procedures performed by the GECI members.[35]

ECMO, which has been used to treat neonatal respiratory failure since 1976 when Bartlett et al. reported the first survivors of PPH treated with extracorporeal membrane oxygenation.[19 27]

The history of FETO starts in 1990s when Harrison et al. reported the first successful repair of a CDH in a human fetus performed through maternal laparotomy and hysterotomy;[27 37] but because there was no remarkable difference in survival compared to mortality with postnatal repair, this technique was abandoned. Also, an increasing in premature births was observed because of the large uterine incision. The treatment of tracheal ligation in CDH was raised when they noticed they noticed that fetal lungs of fetuses with laryngeal or tracheal atresia were hyperplastic.[13] Later studies confirmed that tracheal occlusion could lead to improved lung volume as well as functional improvement in the lung of the fetal CDH lamb model. Initially, tracheal occlusion was performed via open hysterotomy but as a fetoscopy was evolved in animal trials, it was possible to adjust it in human fetuses.[38] This method was originally named as Fetendo Clip and was gradually turned into percutaneous

approach and today it is a good alternative treatment option under certain criteria.

MILESTONES IN THE HISTORY OF CDH[11 27 28]

1848	Bochdalek defines CDHs' posterolateral defect
1880's	First surgical attempts by Naumann
1900-1920's	Clinical symptoms & Surgical recommendations Classification & Embryological development
1922	Successful surgery on the youngest patient with CDH, by Bettmann and Hess
1931	Mortality 75% in neonates
1940	Successful (series) surgery "CDH is not longer a pathological curiosity" by Ladd and Gross
1945-1952 (1946)	Integrating pathophysiology as basis for timing surgery First survived neonate operated within 24h of life
1960s	First newborn mechanical ventilators
1962	Use of muscle patch by Meeker and Snyder
1970's	Intensive preoperative resuscitation
1971	Persistent Pulmonary Hypertension was first demonstrated in CDH patients by Rowe and Uribe Use of a split abdominal wall muscle flap by Simpson and Gossage
1976	Use of ECMO to support neonatal respiratory failure in CDH Report of an intrathoracic balloon mimicking

	CDH in fetal sheep by Hailer et al.
1980's	CDHs' Survival 50%
1983	Muscle flaps as an alternative to a prosthetic repair by Bianchi
1984	Emergent surgery questioned
1989	First prenatally diagnosed cases of CDH
1990's	First report of repairs during ECMO stabilization First report of successful in utero repair by Harrison Improvement in conservative antenatal care (iNO, HFVO)
1995	First CDH Laparoscopic Repair
1996	Introduction of LHR as a predictor factor
1998	First clinical experience with FETO
2001-2005	First series of Thoracoscopic Repair
1990's until present	"CDH is a physiologic emergency, not a surgical one"

3.2 IDEAS THAT EVOLVED THE HISTORY OF CDH

The high mortality rate led scientists to revise the views they had until then about CDH treatment. First they noticed that the mortality rate of children who underwent surgery early in life was higher than those of older children.[5] Then on autopsies, it was found out that pulmonary mass was severely hypoplastic by measuring lung weight at CDH patients dying of respiratory failure within 48 h.[39] They agreed that pulmonary hypoplasia is a major determinant of survival but until later they couldn't prove it without comparing the lung weight of children who die with those surviving.[30]

Another important observation concerned fetuses with congenital high airway obstruction syndrome (CHAOS) who had hyperplastic lungs. This gave birth to the idea where the intentional obstruction of upper airway leads to the hypoplastic lung to grow. [24] [40] [41] In 1976 Hailer et al. reported a model that mimics CDH by implanting and inflating an intrathoracic balloon in fetal sheep.[27]

CHAPTER 4: SURGICAL TREATMENT OF CDH

4.1 GENERAL

CDH no longer represents a surgical emergency, but physiologic one. Respiratory function and pulmonary hypertension will not immediately respond to the reduction of abdomen contents from the thoracic cavity. The most appropriate time to repair CDH still remains controversial especially in patients who require ECMO.

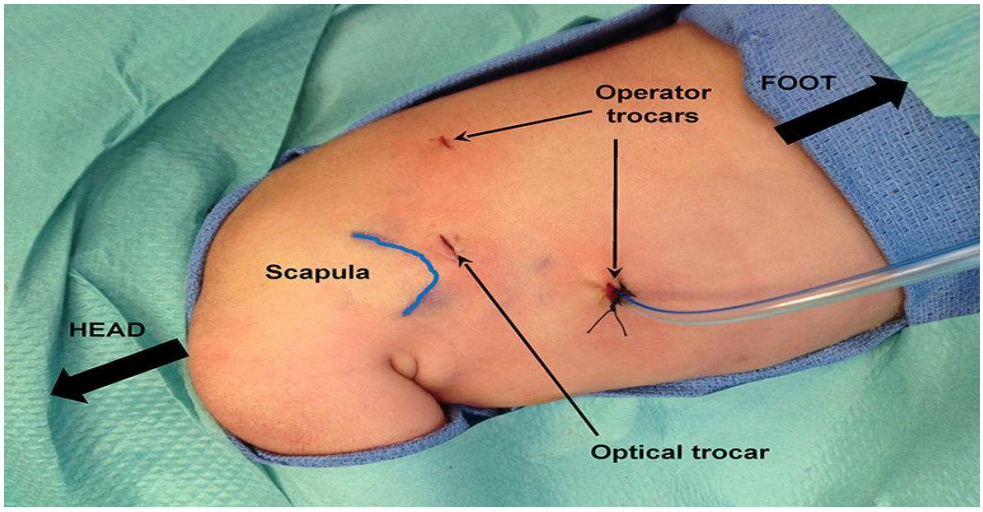
All various surgical approaches to CDH repair carry theoretical advantages and disadvantages. The objective of this chapter is to provide the reader with information on each surgical technique with advantages and disadvantages and to document which one tends to be preferred. While in the past we used to repair CDH through an open laparotomy approach, nowadays this can be performed in a minimally invasive approach (MIS), most preferable through thoracoscopy. According to data from the Congenital Diaphragmatic Hernia Registry, MIS techniques have been used in 20 of the 93 centers (21.5%).[14] [42] Specifically innovative approaches to endoscopic and even laparoscopic efforts at repair now are considered routine for 25% to 45% of newborns with CDH.[11] Zani et al.[10] presented an international survey mirroring the heterogeneity in CDH surgical treatment. According the type hernia the preferences varied. In case of left CDH, 70% of surgeons opt for laparotomy, 23% for thoracoscopy, 5% for an open thoracic approach, and only 2% for laparoscopic repair. Thoracoscopy, laparoscopy, and open laparotomy are analyzed below. Thoracotomy was chosen not to be detailed because it is rarely used anymore.

4.2 THORACOSCOPIC TECHNIQUE:

The first thoracoscopic repair of CDH in children was reported in 2001 by Becmeur et al[35] [43]. It was initially restricted to late-onset hernias but since then, many pediatric surgeons advocate this procedure as the routine practice for selected CDH patients. Since the first reports, the thoracoscopic approach for the

treatment of CDH has increased substantially. This approach is currently being performed by 89% of all participating members of the International Pediatric Endosurgery Group (IPEG).[44] Postoperative MIS complication rates ranged from 11 to 55%.[45]

The operation is performed under general endotracheal anesthesia, without needing single-lung ventilation.[45] The patient is placed in a lateral decubitus position and the upper arm is left free. The surgeon stands at the patient's head so that his eye, the diaphragm, and the monitor be on the same line.[35] The entire left side of the chest is prepared from spine to sternum, including the left axilla and the abdomen, in case of open conversion. Three or sometimes four trocars are required as seen below in picture 3.[46] The telescope (5-mm trocar, 30°) is placed under direct visualization just below the edge of the scapula. The anterior port is placed in the 5th intercostal space on the anterior axillary line, whereas the posterior port is placed in the 4th intercostal space, between the telescope and the spine.[9] [35] Otherwise, the 5-mm trocar can be positioned over the middle axillary line in the 5th intercostal space, and the other two 3mm- trocars are placed in the 6th intercostal space over the anterior and posterior axillary line, respectively.[12]



Picture 3 Trocars position in thoracoscopic repair of CDH

Insufflation pressure of 4-6 mmHg is applied at a flow rate of 0.5-1 L per minute and maintains with intermittent insufflation to reduce side effects of CO2 absorption. This low-pressure CO2 insufflation has the effect of a simple pneumothorax and provides a good exposure of the diaphragm. As soon as the pressure reaches the desire value lung will collapse and the herniated content will gently return into the abdomen. The insufflations can stop as soon as the viscera are reduced. If "automatic" reduction does not happen, herniated viscera are recognized and reduced, starting by pushing down the stomach, the colon, and the small intestine and at the end the reintegration of the spleen. Spleen needs special consideration, not to be drawn straight though but only pulled through the lesser omentum. After delineation of the edge of the diaphragm, if a hernia sac is present it may be resected or not. Some authors prefer to keep the hernia sac and invert it to the underside of the defect so it can be used as a natural underlay buttress.[12 44 47] By this method, the sac would be compressed by the abdominal organs flat against the underside of the diaphragm closure. On the contrary surgeons who recommend excising the hernial sac if present (83% according to Zani et al.) claim that in this way they avoid leaving a space-occupying lesion in the chest and ensure proper healing of the defect. The diaphragmatic defect is then closed from lateral to medial border.[48] Depending on the size of the defect a primary closure, a prosthetic patch repair or a combination of synthetic materials with additional biologic layers is possible.[2] Interrupted non-absorbable sutures (Ethibond 2/0 or 3/0)[9 10] are preferred for primary closure. Chest tube is at the discretion of the surgeon whether to place it or not.[14 44 45]

The advantages of all MIS are widely known. As well as for thoracoscopic CDH repair include; less postoperative analgesia, wound healing, improved cosmesis, shorter time to full feeds, shorter time of hospitalization, less incisional complications, lower percentage of adhesive bowel obstruction and better postoperative musculoskeletal function by avoiding a thoracotomy.[3 11 14 44 45]

A full visualization of the thoracic cavity can reveal any associated lung lesions which can be resected at the same time.[12]

Although the benefits of thoracoscopy in small children have been well documented, technical limitations of MIS such as; longer operative time, longer learning curve, less complete mobilization of the posterior muscular rim, difficulty to repair large defects or when a patch is needed, and limitation to identify malrotation or any other intraabdominal anomaly, are factors that lead many surgeons to be skeptical of applying thoracoscopic repair for CDH repair[47]. Especially, reports on higher recurrence rates and hemodynamic side effects of the capnothorax such as prolonged and severe intra-operative hypercapnia and acidosis prevent them from performing CDH repairs through thoracoscopic approach.[44] [49] For the endoscopic repair of a large defect which requires patch repair- although it is no longer a deterrent element and technically is possible- considerations still exist about the additional time required for this procedure and the increased risk to the patient. The mean operative time for this approach is 112-180 minutes.

Previously, thoracoscopic repair of CDH was reserved for stable infants with anticipated small defects. [35] Today, the use of this technique has expanded to those infants with more severe sequelae of CDH but still open to doubt. The majority of pediatric surgeons define preoperative selections criteria for thoracoscopic repair of CDH that would optimize the chances for a successful clinical outcome. In general, those criteria are; intraabdominal stomach position, which is interpreted as small defect that could be repair primarily and stable preoperative pulmonary function without clinical signs of pulmonary hypertension at the time of surgery[48]. Okazaki et al.[49] considered as selection criteria the stable cardiopulmonary status in the decubitus position in neonatal intensive care unit (NICU) under CMV or HFOV and tolerance of manual ventilation to allow transfer to the operating room. Yang et al. considered a candidate for thoracoscopic CDH repair should be the neonate who has no major associated anomalies, no need of ECMO preoperatively or during the surgery,

PIP ≤ 25 cmH20, peak end-expiratory pressure (PEEP) of 5 cmH20, respiratory rate (RR) less than 70 breaths per minute and Oxygenation Index (OI) 5 or less on the day of surgery.[14 48]

Nonetheless recent studies demonstrate that when a patient uses ECMO but is stable, or presents liver herniation has no longer absolute contraindication for thoracoscopic repair.[50] Similarly as stomach herniation usually led to conversion to an open repair, now does not necessarily exclude thoracoscopic repair. [45] On the other hand a favorable LHR correlated with successful repair by thoracoscopic approach. The majority of pediatric surgeons IPEG-members (78%), according Lacher's et al. study, consider as thoracoscopic repair's contraindication the patient on ECMO during operation time, but only 42% of them, the one who preoperatively needs for ECMO.[44] Other relevant contraindications according the aforementioned study include right-sided hernia, liver-up, patient's weight < 2.5kg, and persistent R-to-L shunt.

The references from bibliography about conversion to an open access range from 3.4 to 14%. The reasons why some thoracoscopic surgeries need to be converted to an open approach include: insufficient operative view, inability to place the patch and the large size of the diaphragmatic defect, cardiopulmonary instability or intra-operative acidosis, and bleeding due to spleen trauma.[48 49] The presence of stomach herniation was initially an almost absolute contraindication for thoracoscopic repair but as MIS method is evolved, now is performed, despite the fact that may be associated with the need for conversion to an open procedure. Also, until recently, patch repair was an absolute indication for conversion to open repair, but up to now several reports of successful thoracoscopic patch repair are reported.[45] In conclusion those cases that were previously consider as contraindications now they are the main ones reasons for conversion. It is a fact that these decisions are inextricably linked to the surgeon's competency.

Recurrent rate for thoracoscopic repair of congenital diaphragmatic hernia ranges from 5% to 23.1%.[9 42 51 50] It mostly occurs within the first year of life.

This recurrence rate is justified by several factors. The main ones are; incomplete mobilization of the posterior muscular rim, large defect, patch repair, non tension - free repair, and lack of surgeon's experience. Weaver et al. negates most of them; such as, the size of the defect, the presence of a hernia sac, as well as the hernia contents of liver, colon/ small bowel, or stomach but suggests that infants who require vasopressor therapy or HFOV, may be at a higher risk of recurrence.[43] Tsai et al reported a recurrence rate of 5.4% after patch repair versus 4.3% after a primary repair. Similarly, Garriboli et al reported 8.8% after patch repair versus 5.6% after a primary repair. This correlates with the aforementioned relevant contraindications, such us, large defects and repair under tension, and indicate that patch repair indeed has a higher recurrence rate. Zani et al. state that in case of hernia recurrence, 66% surgeons would take the same operative approach of the first repair and 29% would perform a thoracoscopic repair.[9]

Immediate complications after thoracoscopic treatment of CDH are recurrence, adhesion-related bowel obstruction and chylothorax due to lesions to the thoracic duct. Long follow up of patients who undergone surgery for CDH reveals the late complications which are gastroesophageal reflux, exercise intolerance and wheezing, scoliosis, and chest wall asymmetry.

4.3 LAPAROSCOPIC TECHNIQUE

In 1995 the first case of laparoscopic CDH repair in an infant is reported.[35] Theoretically, the laparoscopic approach for CDH repair seems more logical, but in practice has some disadvantages comparing to thoracoscopic one.

The patient is placed supine with legs apart. Surgeon stands between the legs, the assistant on the left side and the scrub nurse on the right one. The telescope is placed through supraumbilical incision using a 5 mm trocar under direct visualization. Two additional 5 mm trocars are introduced in the right and left flank. Herniated viscera and defect are recognized. The viscera are reduced

by gentle traction. After evaluation of the size of the defect if possible primarily closure is performed or otherwise a patch is placed.[52]

Thoracoscopy was shown to be superior to the laparoscopic approach for several reasons.[35] When applying pneumoperitoneum, insufflation is required during the whole procedure, in contrast to thoracoscopy in which when the content has been reduced, the insufflation may stop and still there is enough surgical field for suturing the defect, due to pulmonary hypoplasia. The pneumoperitoneum continues to push bowel loops which have already been reduced back into the thorax and when all the content are place back to the abdominal cavity, the intraabdominal pressure raises and the defect is less visible. Thus, the sutures can sometimes be difficult to be placed. Special attention should be paid in organs, especially the bowel and the spleen which are difficult to bring back into the abdominal cavity. At the same time intrabdominal pressure increases more when content return back to the abdominal cavity and may affect ventilation. The laparoscopic approach is best first option between MIS approaches for CDH repair when incarcerated hernia is suspected because of better visibility to check possible ischemic damage to the bowel and the ability to check for any rotational anomalies of the gut. Also is preferred for Morgagni hernia repair when compared to thoracoscopy.[11]

4.4 OPEN TRANSABDOMINAL REPAIR

Until last two decades the vast majority of neonatal repairs for CDH were performed through a subcostal laparotomy (91%).[14] Thoracotomy tends to be eliminated as an open approach treatment modality of CDH repair, because during laparotomy there is easier reduction of intrathoracic viscera, better visibility and by extension better mobilization of posterior diaphragmatic rim, simultaneous treatment of any gut malrotation and avoidance of any subsequence chest deformities.

In transabdominal open CDH repair, the infant is placed on a supine position and small bump is placed under the left flank. During the operation

intraabdominal pressure must be monitored by the use of Foley catheter and naso- or orogastric tube are placed with a stopcock. Pressures greater than 8 to 10 mmH20 during the procedure indicates decreased compliance. Drapes should be accomplished to allow access to the abdomen and both sides of the chest. A subcostal incision on the side of the hernia approximately one – two finger breadths below the costal margin, is performed and the viscera are reduced from the chest and eviscerated from the abdomen so the defect is identified. Special attention must be directed to a gentle reduction of the stomach due to the fragile connection of the short gastric vessels to the herniated spleen, perfusion of the bowel and correct orientation of the mesentery. If a sac is present can also be or not removed for the reasons already mention in thoracoscopic approach. The rims of diaphragm are determinate and after lifting up the anterior rim, the posterior is revealed, which may appear rolled on itself in the retroperitoneum and covered by a thin peritoneal adhesion. This overlying peritoneum is divided and then the rim is unrolled. If the length of the muscle is adequate the defect can be closed primarily with simple or mattress, interrupted, non absorbable sutures. In case that there is not enough rim, sutures around the ribs can be placed to anchor the anterior rim directly to the chest wall. Alternatively a prosthetic replacement is required in all, or a part of the deficit with additional biologic layers.[2] The patch has to be greater than the defect, to have a conical shape and be fixed in position with interrupted nonabsorbable sutures. A different surgical option to patch replacement are reconstructive techniques make use of nearby musculature, such as the latissimus dorsi or the internal oblique and transversus abdominus muscles. When viscera return in the abdominal cavity, appendectomy is not necessary to be performed in the same procedure. If abdominal cavity is small to accommodate the viscera, abdominal stretching is performed in order to give some more space. Despite this maneuver, abdominal wall closure after diaphragmatic hernia repair may result in abdominal compartment syndrome due to elevated intrabdominal pressure. Under these circumstances, a Gortex prosthesis or preferably Vicryl mesh is

used under a skin closure or alternatively, a ventral hernia without closure of abdominal wall musculature, is a small price to improve survival and can be easily rectified later.

Apparently one of the main reasons that there is still a favor for laparotomy approach is the allowance to inspect all bowel and look for rotation anomalies. Okazaki et al. refers to the EUPSA Network Office report that two-thirds of surgeons check and correct intestinal malrotation in infants with CDH. In a retrospective study, Rescorla et al reported that 2.9% patients with CDH not treated for malrotation, presented with midgut volvulus.

4.5 DIAPHRAGMATIC REPLACEMENTS

CDH Registry records 48.3% of infants undergoing repair require a patch.[14] When primary closure of the defect is not feasible, diaphragmatic replacement with a prosthetic patch or autologous tissue is unavoidable. According to the patch material use, this is heterogenous. During the study among IPEG members;[44] 86% of the participants use nonabsorbable meshes (polytetrafluoro ethylene [Goretex]), polypropylene [Marlex], polyethylene terephthalate [Dacron], and silicone [Silastic]), 24% repair the defect with biosynthetic materials (e.g., Surgisis, SIS, Alloderm, LifeCell). Abdominal wall muscle flaps (e.g., internal oblique and transversalis) are fashioned by 8% of surgeons, and only 2% use thoracic wall musculature e.g., latissimus dorsi and serratus anterior muscle. This is also confirmed by Zani et al. in whom study the use of synthetic, nonabsorbable prosthetic patches, and Gore-Tex is by far the most popular of all.[10].

PTFE or Gore-Tex and Marlex are commonly preferred because of easily sized, less tissue dissection and mobilization, and are immediately available for use. The main problem with those meshes is recurrence because scarification and subsequently shrinkage of the diaphragm over time. In response to that problem, Loff and colleagues[53] constructed a cone-shaped, double-fixed PTFE patch to allow the patch to expand over time, while Riehle and colleagues[54]

described use of a double-sided composite patch consisting of PTFE on one side and type-1 monofilament, macroporous polypropylene (Marlex) on the other. Additional disadvantages are reported; increased incidence of bowel obstruction, need for splenectomy, patch infections, and abdominal wall deformities.[14]

On the other hand, the advantages of absorbable biosynthetic materials are; lower risk of infection and ability to grow with the patient. Some of them have been widely used for the repair of CDH. Surgisis and Permacol contribute to the neodiaphragm to be more pliable and, subsequently, less prone to recurrence. AlloDerm has greater durability, and PLGA promotes neovascularization and autologous tissue regeneration and as a result a thicker neodiaphragm. Despite the theoretical advantages, biological patches are associated with adhesive bowel obstruction and inflammatory response. Taking into account the aforementioned, biosynthetic patches have fallen out of favor with many surgeons.

Persistent complications with synthetic and biosynthetic patches have prompted some surgeons to advocate for primary repair with autologous muscle flaps, or staged reconstruction of large diaphragmatic defects with an initial synthetic patch followed by an autologous muscle flap. Several different abdominal muscle flaps have been described as a diaphragmatic replacement.

In 1962, Meeker and Snyder first described using anterior abdominal wall for repair of a CDH. In 1971, Simpson and Gossage described use of a split abdominal wall muscle flap to repair a large defect in a 1-day-old neonate. Scaife and colleagues described using a split abdominal muscle flap of the internal oblique and transversus abdominis muscles for primary repair of large diaphragmatic hernias. Chest wall muscles have also been used to repair diaphragmatic hernia. The reverse latissimus dorsi muscle flap was first described by Bianchi and colleagues in 1983. For very large defects, such as agenesis of the diaphragm, combined use of the latissimus dorsi and serratus anterior muscles has been described. In the course of time some surgeons have advocated using the reverse latissimus dorsi flap with a microneural anastomosis

of the phrenic nerve to the thoracodorsal nerve, to prevent muscle atrophy and to allow physiologic muscle movement. The main disadvantage with using local muscle flaps is the associated deformity of the body wall. A reasonable deed is to reserve muscle flaps primarily for reconstruction in the setting of recurrence.

FINAL REMARKS:

The scope of this thesis was an attempt; to quote the history of congenital diaphragmatic hernia (CDH) with a retrospective review of the published literature from the 19th century through the 20th century, to define the management of CDH and to provide information to the reader which surgical treatment is being attempted under specific conditions.

A distinctive characteristic of CDH is the fact that is a rare disease. Most of its outcomes data come from hospital databases, network registries, and single centers' experiences. A few remaining cases relate to prospective controlled clinical trials examining various interventions for infants with CDH. Therefore there is not much high-quality clinical evidence to support innovations in surgical treatment of CDH. According to the CDH Registry, the average number of CDH infants seen per center is less than 10 per year. Due to the broad spectrum of disease even large centers may not have much experience with novel treatment modalities.

Nevertheless, it is undeniable that the treatment concept for CDH patients changed dramatically over the last decades and now include; not urgent surgical repair, minimal invasive surgery (MIS) as an alternative surgical option, a variety of ventilatory techniques, inhaled nitric oxide, extracorporeal membrane oxygenation (ECMO), and fetal endoscopic tracheal occlusion (FETO).

Cases that were previously considered as contraindications over the years became causes for conversion and nowadays this tends to change as well. It is a fact that these decisions are inextricably linked to the surgeon's competency.

Worldwide, in selected centers, under certain criteria, traditional transabdominal approach trends to be equally or even replaced by thoracoscopic CDH repair. Surgeons keep try to understand which patients are the best candidates for MIS and to limit controversial issues.

As a "food for thought" is worth to mention that Lacher et al. in his survey on MIS for CDH patients, concludes and worries about the high percentage of surgeons who believe that CDH can be repaired equally by thoracoscopy and

open surgery. No one can dispute the benefits of MIS repair but is currently no evidence to support a standardized surgical approach to thoracoscopic repair.

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