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CHAPTER 42

Congenital diaphragmatic hernia: New evidence and current and future therapeutic options

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Alisson Juliani[1], Giovanna Costa Moura Velho[2], Fernanda Rabelo Vieira[3] and Larissa da Silva[4]

ABSTRACT

Objectives: To compile the information available in the medical literature and to present the new forms of intervention possible for fetuses and neonates affected by congenital diaphragmatic hernia (CDH). Methodology: a non-systematic literature review of the medical literature was carried out, using the LILACS, SciELO and PubMed databases, with no established period, prioritizing higher levels of scientific evidence. Results: CDH consists of a defect in the embryological closure of the diaphragm, resulting in protrusion of abdominal contents into the thorax. Although rare, CDH imposes significant restrictions on fetal lung development, causing high mortality rates of up to 83%. Its pathogenesis has not yet been fully elucidated, especially at the molecular level, which hinders specific therapeutic approaches. It can occur alone or in association with other congenital malformations. Most cases are diagnosed in the prenatal period by ultrasound, which would make it possible to use early therapeutic techniques to reduce the morbidity caused by the hernia. This type of intervention arouses growing interest among scholars on the subject, seeking methods that can attenuate the severity of pulmonary hypoplasia and pulmonary hypertension, in addition to reducing mortality. Currently, promising results have been observed with endoscopic fetal tracheal occlusion (FETO), a minimally invasive procedure capable of stimulating lung development in fetuses with CDH. However, the most evident change in the approach to the condition was the replacement of emergency surgery in the newborn by clinical stabilization followed by correction of the defect, changing the paradigm of CDH from surgical urgency to "physiological emergency". New therapeutic methods are under development, including attempts to use already known drugs, such as sildenafil and rosiglitazone, with no conclusive results yet. The prognosis varies according to the severity of the diaphragmatic defect and the therapeutic approaches available. Conclusion: numerous studies seek new resources capable of modifying the natural history of CDH. Several techniques have been established, but none has a universal indication. Not even the ideal method of mechanical ventilation of the neonate affected by CDH has been defined in the literature. Therefore, large clinical trials are still needed to determine the best therapeutic options for CDH.

Keywords: Diaphragmatic Hernia, Congenital, New Therapeutic Options, Treatment, Prenatal Intervention.

LIST OF ABBREVIATIONS AND ACRONYMS

AP/FC: ratio of lung area to head circumference
ECMO: extracorporeal membrane oxygenation
HR: heart rate
FETUS: endoscopic fetal tracheal occlusion
FiO2: fraction of inspired oxygen
RR: respiratory rate
PAH: pulmonary arterial hypertension
CDH: congenital diaphragmatic hernia

[1] Physician specializing in general surgery
North Wing Regional Hospital
[2] Undergraduate student in Medicine
University Center of Brasilia
[3] Undergraduate student in Medicine
University Center of Brasilia
[4] Undergraduate student in Medicine
University Center of Brasilia

iNO: inhaled nitric oxide
MCP-1: monocyte chemoattractant protein 1
O/E: ratio of observed to expected value
BP: blood pressure
PaCO2: partial pressure of carbon dioxide
PEEP: positive end-expiratory pressure
PIP: peak inspiratory pressure
PRC: lung-to-head ratio
RPMO: premature rupture of ovular membranes
SatO2: pre- and post-ductal oxygen saturation
VOAF: high-frequency oscillatory ventilation

INTRODUCTION

The diaphragm, a dome-shaped structure that separates the thoracic cavity from the abdominal cavity, is the main muscle involved in breathing, as it performs the function of maintaining the pressure difference between the cavities (SCHWARTZ, 2014). Congenital diaphragmatic hernias (CDH) consist of a defect in the embryological closure of the diaphragm, with consequent protrusion of abdominal contents into the thoracic cavity, causing damage to lung development (SKARI *et al.*, 2000; Smith, N. P., et al., 2005; JESUDASON; LOSTY, 2002; CHINOY, 2002).

Although 75% of cases are diagnosed with ultrasound examination during prenatal care, the therapeutic approach to patients with CDH remains challenging (LEEUWEN and FITZGERALD, 2014; STEINHORN, 2014). Efforts in recent years have focused on the prevention of lung injury through the use of extracorporeal membrane oxygenation (ECMO), high-frequency oscillatory ventilation (HFOV), and permissive hypercapnia, with variable results regarding overall survival (CHANDRASEKARAN *et al.*, 2017).

Until the 1980s, the standard treatment was immediate neonatal surgery followed by postoperative clinical stabilization. However, the understanding of CDH as "physiological emergencies", as opposed to surgical emergencies, has changed the way these cases are conducted (AIHOLE *et al.*, 2018). Currently, urgent surgical correction of diaphragmatic defect in neonates is no longer indicated (JANI *et al.*, 2006; GORINCOUR *et al.*, 2005; MATHIEU-CAPUTO, 2001). Thus, it is recommended to stabilize respiratory and hemodynamic parameters before the surgical approach (REISS *et al.*, 2010).

New therapeutic modalities have also been developed. Despite the interest in surgical correction of CDH even during intrauterine life, a technique tested for the first time in 1986, the high mortality rate made it unfeasible and lowered expectations about an effective antenatal treatment (SANTOS; RIBEIRO, 2008). This changed rapidly with the development of endoscopic fetal tracheal occlusion (FETO), a percutaneous and minimally invasive technique initially introduced by Harrison *et al.* (1980) and with promising results on pulmonary hypoplasia (DEPREST; THANKFUL; NICHOLAIDES, 2004). New drugs and management techniques for the neonate with CDH have also been studied.

However, even with significant recent advances, important morbidity and mortality rates are still observed in newborns with CDH, especially due to complications such as pulmonary hypoplasia and pulmonary arterial hypertension (PAH) (BROWNLEE, 2009). Thus, the scientific community continues to search for new approaches capable of reducing the impact of CDH.

This chapter aims to compile the information available in the literature and present the new forms of intervention developed for fetuses and neonates affected by CDH, in addition to

highlighting new approaches under study, which may be implemented in the future. To this end, a non-systematic literature review of the medical literature was conducted, using the LILACS, SciELO and PubMed databases, with no established period, submitted to the author's scrutiny, prioritizing evidence of a better level.

EPIDEMIOLOGY

Congenital diaphragmatic hernia is a rare condition with high mortality and morbidity, accounting for 8% of all congenital malformations *Major* (ALY, 2012; POBER, 2007). Its prevalence varies according to the population analyzed in the studies, as there are studies that analyze prenatal diagnoses and studies that analyze only newborns who survive childbirth. Thus, its prevalence ranges from 1/1750 to 1/1588 at birth (POBER, 2007) – without being influenced by maternal age (KOSIŃSKI; MIROSŁAW, 2017). In addition, the findings regarding the predilection for males, ethnicities, or geographic areas are inconsistent (SHANMUGAN *et al.*, 2017).

In most cases, the pathology is evident after birth, being asymptomatic in only 5 to 10% of affected newborns (POBER; RUSSELL; ACKERMAN,). Mortality varies considerably and is directly related to the severity of cardiopulmonary pathology (ZANI, A., et al., 2022). In the centers studied, the data show rates from 21 to 83% (CHAN; HO; JOSEPH, 1997, BAGOLAN *et al*., 2004). In developing countries, survival of 50% to 65% is reported, on the other hand, in developed countries this number reaches 85 to 90%, due to the implementation of PAH treatment protocols, financial support and the availability of ECMO (ONTARIO CONGENITAL ANORMALIES STUDY GROUP, 2004; JAVID *et al*., 2004; JAIN, 2002).

ETIOLOGY

Physiologically, the development of the diaphragm should be completed by approximately the ninth week of gestation, with closure of the left side occurring one week after the right side (KOSIŃSKI; MIROSŁAW, 2017). It develops from four structures: the transverse septum, the pleuroperitoneal membranes, the dorsal mesentery of the esophagus, and the musculature of the lateral wall of the body (SANTOS; RIBEIRO, 2008).

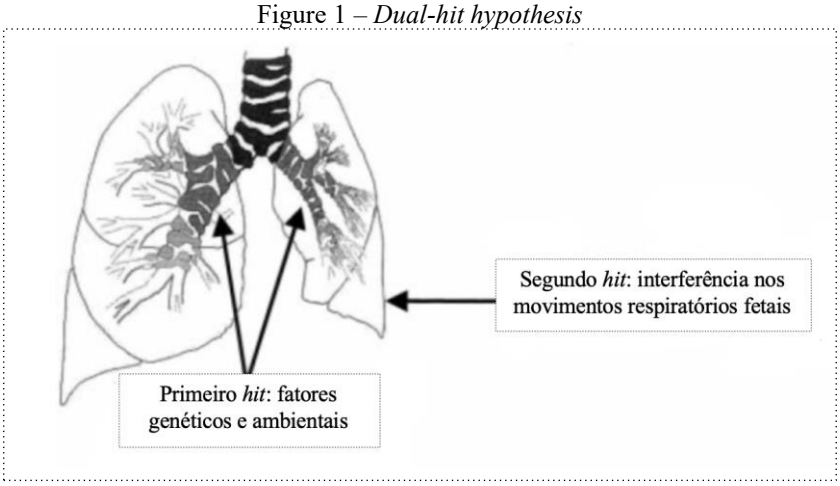
Incomplete fusion of any of the diaphragm components can lead to defects, ranging from small openings to complete absence of the diaphragm (KOSIŃSKI; MIROSŁAW, 2017; CHANDRASEKHARAN *et al*., 2017).

Although the etiology is still unknown, congenital diaphragmatic hernia has a polygenic origin in approximately one third of cases (ZANI, A., et al., 2022; CAETANO, 2016). In addition, several theories attempt to explain the pathology, the most likely of which suggests that visceral herniation into the thoracic cavity occurs due to failure of the normal closure of the pleuroperitoneal

membrane or due to environmental triggers that prevent the normal differentiation of mesenchymal cells during diaphragm formation (SLAVOTINEK, 2014).

Some authors suggest that pulmonary hypoplasia would be the primary causal factor of the defect, with herniation of abdominal viscera into the thorax due to the lack of lung parenchyma – which would later prevent the closure of the diaphragm (SHEHATA; LIN, 2012; IRITANI, 1984). Other authors have evidenced a multifactorial origin, such as the *dual-hit theory* (**Figure 01**), which attributes the lung defect to two distinct disorders: an earlier one, caused by environmental and genetic factors, which affects both lungs; and another directed only to the ipsilateral lung, due to interference of the herniated abdominal organs with fetal respiratory movements (KEIJZER; PURI, 2010).

Figure 1 – *Dual-hit hypothesis*



Fonte: adapted from Keijzer *et al*., 2000.

ENVIRONMENTAL AND GENETIC FACTORS

Since 1950, several studies have shown a relationship between changes in vitamin A metabolism and the onset of congenital diaphragmatic hernia (KEIJZER; PRAISE, 2010; POBER; RUSSELL; ACKERMAN, 2010; VEENMA; SMALL; TIBBUL, 2012; BEURSKENS; TIBBOEL, 2009). The same mechanism would explain the relationship between the appearance of congenital diaphragmatic hernia and the social consumption of alcohol in the months prior to conception and during the first trimester of pregnancy – inhibition of alcohol on the metabolism of vitamin A and consequent decrease in retinoic acid (BEURSKENS; TIBBOEL, 2009; FELIX, 2008). Mycophenolate mofetil and allopurinol have both been associated with diaphragmatic hernia by interfering with purine biosynthesis (KOZENKO *et al.,* 2011).

Obesity is also associated with a higher risk of congenital diaphragmatic hernia, probably due to insulin resistance and poor glycemic control during pregnancy. In addition, no relationship was found between maternal smoking and congenital diaphragmatic hernia (POBER; RUSSELL; ACKERMAN, 2010; VEENMA; TIBBOEL, 2012; BEURSKENS; TIBBOEL, 2009).

GENETIC FACTORS

In addition, CDH is generally understood as an isolated finding, but approximately 10% of affected patients have a diagnosis of genetic syndrome (GRAHAM; DEVINE, 2005; SLAVOTINEK, 2005). There are several possible anomalies, including chromosomal disorders, genetic syndromes and other structural anomalies (JHONSON, 1999; DAVENPORT, 1999; BUNDUKI; RWAN; ZUGAIB, 1998; HILPERT; PRETORIUS, 1990). Structural cardiac, renal, brain, or gastrointestinal defects are found in 25 to 57% of cases, and cardiovascular defects are more frequent, such as coarctation of the aorta, tetralogy of Fallot, transposition of great vessels, and pulmonary stenosis (GRAHAM; DEVINE, 2005; HILPERT; PRETORIUS, 1990). The vast majority are sporadic with no observable family association (GIBBS *et al*., 1997).

CLASSIFICATION

There are several ways to classify congenital diaphragmatic hernia: by the anatomical position of the diaphragmatic defect or by the degree of development of the affected lung.

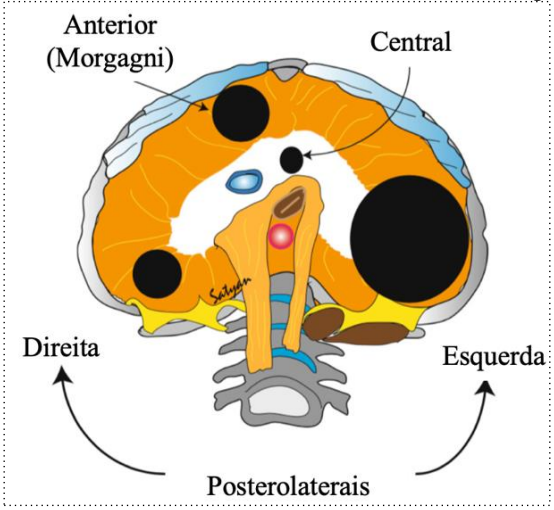
ANATOMICAL CLASSIFICATION

It is based on the location of the defect (**Figure 02**) (LEEUWEN; FITZGERALD, 2014). Posterolateral (Bochdalek) hernias are the most common type – accounting for about 70 to 75% of all congenital diaphragmatic hernias. It occurs in 85% of cases on the left side, followed by 13% that affect the right side and 2% that are bilateral (CHANDRASEKARAN *et al*., 2017; GREER, 2013; VEENMA; TIBBOEL, 2012). These hernias result from the incomplete fusion of pleuroperitoneal membranes between 8 and 10 weeks of gestation, when the intestine returns to the peritoneal cavity, with consequent persistence of the pleuroperitoneal canal (JHONSON, 1999; DAVENPORT, 1999; HILPERT; PRETORIUS, 1990; POBER; RUSSELL; ACKERMAN, 2010; LEEUWEN; FITZGERALD, 2014; TORFS *et al*., 1992).

On the other hand, non-posterolateral hernias (Morgagni's) are anterior defects of the diaphragm, with more than 90% occurring on the right (CAETANO, 2016; JHONSON, 1999). They represent 23 to 28% of cases of congenital diaphragmatic hernia, usually evolving asymptomatically in the postnatal period (CHANDRASEKARAN *et al*., 2017; POBER; RUSSELL; ACKERMAN, 2010). In addition, they result from the incomplete fusion between the sternal and costal elements of the diaphragm and usually present a hernial sac (BUNDUKI; RWAN; ZUGAIB, 1998; HILPERT; PRETORIUS, 1990).

Finally, the central hernias (*pars sternalis*) have a rare occurrence (from 2 to 7% of congenital diaphragmatic hernias) and involve the central tendon portion of the diaphragm (POBER; RUSSELL; ACKERMAN, 2010; LEEUWEN; FITZGERALD, 2014; VEENMA; TIBBOEL, 2012).

Figure 02 – Classification of HDC based on the location of the diaphragmatic defect



Fonte: adapted from Chandrasekharan *et al*., 2017.

CLASSIFICATION OF LUNG DEFECT

It takes into account the degree of lung development, since the lungs are commonly affected in individuals with congenital diaphragmatic hernia (WISEMAN; MACPHERSON, 1977). There are three types:

- Type I: severe bilateral pulmonary hypoplasia;
- Type II: unilateral pulmonary hypoplasia (ipsilateral to the diaphragmatic defect); and
- Type III: Negligible pulmonary hypoplasia (usually no change in lung function).

CLINICAL MANIFESTATIONS

The clinical presentation of congenital diaphragmatic hernia is very variable, and may even be asymptomatic at birth. The vast majority (95%) of affected newborns have respiratory distress and cyanosis during the neonatal period (RYCKMAN, 2002).

Generally, newborns develop respiratory distress immediately after delivery or within 48 hours, resulting in the so-called "honeymoon period" during which the patient remains asymptomatic (MAHESHWARI; CARLO, 2012; HARTMAN, 2005). Signs such as tachypnea, moaning, stripping, nasal flaring, and cyanosis may be observed, as well as a scaphoid abdomen or barrel chest. On examination, bowel sounds in the chest and decreased breath sounds may be heard, and the *ictus cordis* may be deviated (SCHWARTZ, 2014; MAHESHWARI; CARLO, 2012). Early dyspnea (before 6 hours of life) is considered a poor prognostic factor (MAHESHWARI; CARLO, 2012).

Bochdalek's hernia should be suspected in neonates with the typical picture of severe respiratory distress syndrome with cyanosis, immediately after birth, associated with scaphoid abdomen, decreased or absence of breath sounds in the ipsilateral hemithorax, and diversion of heart sounds to the contralateral hemithorax (DAVENPORT, 1999; HARTMAN, 2005; MILLER; FANAROFF; MARTIN, 2002). Morgagni's hernia, on the other hand, is essentially manifested by

intestinal occlusion and growth retardation, since pulmonary hypoplasia rarely exists (DAVENPORT, 1999).

Only 5% of patients are asymptomatic during the neonatal period, and may later develop intestinal occlusion and recurrent respiratory infection (RYCKMAN, 2002).

DIAGNOSIS

The diagnosis of congenital diaphragmatic hernia can be made before or after birth. It is important to identify cases early so that screening for associated anomalies – including genetic testing – can be carried out and delivery planning in a place with a neonatal intensive care unit (ICU) available (STEINHORN, 2014; CORDIER *et al.,* 2019). Approximately 75% of cases are diagnosed in the prenatal period, usually in the second trimester of pregnancy (ZANI, A., et al., 2022; LEEUWEN; FITZGERALD, 2014; STEINHORN, 2014). In this regard, gestational age at diagnosis is an independent risk factor for prognosis for CDH (WANG *et al.,* 2019). In addition, given that cardiovascular malformations affect up to 1/3 of patients with CDH, all patients should undergo fetal echocardiography (CORDIER *et al.,* 2019).

The diagnosis is made by ultrasound, in most cases in a routine examination at 22 to 24 weeks (ZANI, A., et al., 2022; DANZER, E., et al., 2022; BENACHI *et al.,* 2014). Before 24 weeks, hernia detection is very uncommon (KUMAR, 2015). On ultrasonography, ultrasound examination shows a deviation of the mediastinum and the presence of a fluid-filled stomach near or immediately behind the heart (KOSIŃSKI; MIROSŁAW, 2017). Other suggestive alterations are polyhydramnios and the absence of gastric bulla or its presence in the thoracic cavity (LEEUWEN; FITZGERALD, 2014).

However, there are several factors that can hinder prenatal diagnosis. If the defect is located on the right, the liver may be the only abdominal organ that invades the thoracic cavity, impairing prenatal diagnosis due to its echogenicity similar to that of fetal lungs (LEEUWEN; FITZGERALD, 2014). In addition, intermittent herniation of abdominal viscera, although infrequent, can also contribute to misdiagnosis. In the case of bilateral hernias, the diagnosis may be further complicated by the absence of deviation of the heart and mediastinum or very slight deviation of these structures (GODSTEIN, 2004).

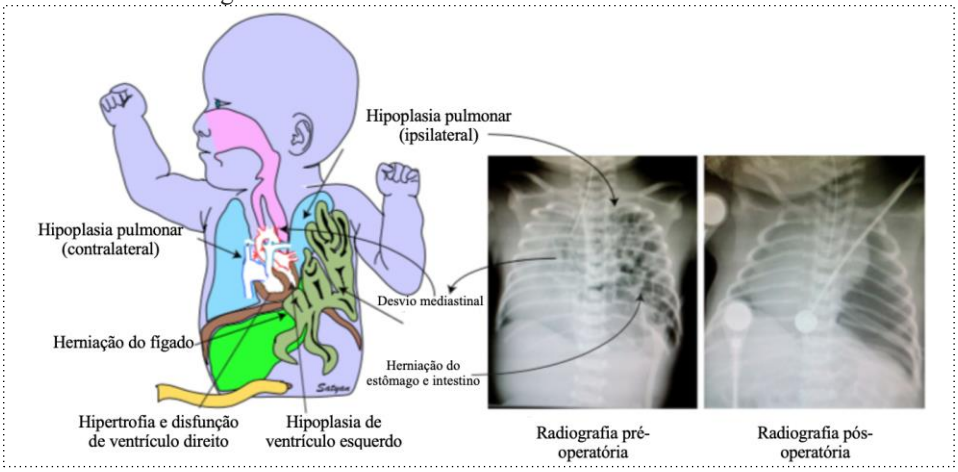
The use of color Doppler can help detect the position of the liver by visualizing the ductus venosus and the course of the intrahepatic vessels (SANANES *et al*., 2016). Magnetic resonance imaging, on the other hand, allows adequate evaluation of liver herniation and, unlike ultrasonography, is not limited by maternal obesity or oligohydramnios (KOSINSKI; MIROSŁAW, 2017). Its use is common in centers specialized in congenital diaphragmatic hernia, and it has been

shown to be effective in confirming the diagnosis and detecting associated structural defects (KOSINSKI; MIROSŁAW, 2017).

In cases in which the diagnosis prior to birth has not been made, chest and abdominal X-rays usually confirm the diagnosis by showing an opacified hemithorax, with a mass effect and contralateral deviation of the mediastinum, in addition to stomach and intestinal loops with gaseous levels in the chest (**Figure 03**) (POBER; Russell; ACKERMAN, 2010; LEEUWEN; OR, 2014).

The major differential diagnosis of congenital diaphragmatic hernia is diaphragmatic eventration, which consists of elevation of the diaphragm in a region with local fragility, but keeping the structure intact (CHANDRASEKARAN *et al*., 2017). The thin portion of the diaphragm, which is more flexible, may form a bulge with abdominal contents entering the thoracic cavity. However, the thin membrane is not always detected, and it is difficult to differentiate from diaphragmatic hernia in images obtained in the prenatal period. The eventration is usually less severe than the hernia itself, and newborns may be asymptomatic throughout childhood. (KOSINSKI; MIROSLAV, 2017).

Figure 03 - Anatomical and clinical features of CDH



Fonte: adapted from Chandrasekharan *et al.,* 2017.

MORBIDITIES

Several morbidities can afflict newborns with congenital diaphragmatic hernia. There is a high prevalence of long-term morbidities, with impaired quality of life (LEEUWEN; FITZGERALD, 2014). Not only pulmonary and gastrointestinal alterations may occur, but also those related to neurological development, growth, hearing, and the musculoskeletal system (LEEUWEN; FITZGERALD, 2014).

Most patients have some degree of lung disease (**Figure 04**) (DE BIE, F. R., et al., 2022; POBER; RUSSELL; ACKERMAN, 2010). Pulmonary hypoplasia (decreased lung mass), with a low number of bronchial divisions, respiratory bronchioles, and alveoli, is the most important morbidity of congenital diaphragmatic hernia (MAHESHWARI; CARLO, 2012). PAH may be present during

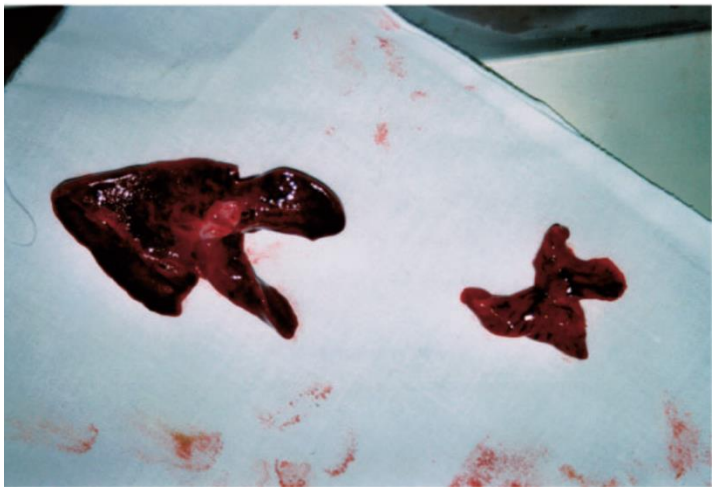
the first months of life and is associated with early mortality (LEEUWEN; FITZGERALD, 2014). Initially, hypoplasia causes restrictive lung defects, but respiratory function appears to improve considerably during childhood. (LEEUWEN; FITZGERALD, 2014).

It is uncommon for older children to manifest symptoms at rest, but they may have decreased tolerance to physical exercise, requiring intermittent use of bronchodilators due to bronchospasms – which represents a greater risk of pulmonary decompensation due to intercurrent diseases (POBER; RUSSELL; ACKERMAN, 2010). Some studies suggest the appearance of a new worsening of lung capacity in the transition to adulthood, with obstruction of the small airways and decreased perfusion, especially in the lung ipsilateral to the congenital diaphragmatic hernia (LEEUWEN; FITZGERALD, 2014; POBER; RUSSELL; ACKERMAN, 2010).

Gastroesophageal reflux disease affects 45 to 89% of newborns with congenital diaphragmatic hernia (LEEUWEN; FITZGERALD, 2014). Associated with feeding difficulties, the disease contributes to the impaired growth of children affected by this condition, resulting in weight loss in about 69% of those up to one year of age (POBER; RUSSELL; ACKERMAN, 2010; LEEUWEN; FITZGERALD, 2014). Many children achieve good growth by two years of age, but may require pharmacological or surgical therapy for the treatment of reflux (MAHESHWARI; CARLO, 2012; LEEUWEN; FITZGERALD, 2014).

Finally, chest wall deformities are present in about half of patients with congenital diaphragmatic hernia (POBER; RUSSELL; ACKERMAN, 2010). The most common changes are the *pectus excavatum* and thoracic asymmetries, affecting 21 to 48% of survivors (LEEUWEN; FITZGERALD, 2014). Generally, they occur in patients with large diaphragmatic defects and are independent of the type of technique used in the surgical repair (RUSSEL, 2014).

Figure 04 – Comparison between hypoplastic lung and contralateral lung in fetus with CDH - autopsy image



Fonte: retirado de Giorgio *et al*., 2015.

ANTENATAL MANAGEMENT

In the last 30 years, CDH has been recognized as a syndrome, encompassing pulmonary hypoplasia and immaturity, left ventricular hypoplasia, and pulmonary arterial hypertension (COHEN-KATAN *et al*., 2009). Thus, its treatment has also undergone modifications, based on the development of new interventions and drugs that aim to attenuate the severity of the components of the syndrome or treat them in the newborn. Another major novelty was the understanding of CDH as a physiological emergency, as opposed to surgical (AIHOLE *et al*., 2018). Therefore, clinical stabilization of the patient before surgical intervention is recommended (SNOEK *et al.,* 2016b).

Management of CDH begins as soon as it is detected, either before or after birth. Planning the birth in an appropriately equipped place improves the prognosis (NEFF, 2007). Thus, patients with CDH should be referred to tertiary care centers in order to enable multidisciplinary prenatal consultations involving obstetricians, neonatologists, pediatric surgeons, and geneticists, in addition to scheduling care in units with experience in treating newborns with CDH, preferably with ECMO available (MARGOTTO, 2018; AIHOLE et al., 2018).

Since 2008, all newborns in European countries represented by the *HRC EURO Consortium* have been treated according to the protocol developed during the consortium meeting, which has undergone several modifications. After the implementation of care, mortality fell from 33% to 12%, demonstrating the importance of defining routines for patient management (REISS *et al*., 2010; SNOEK, 2016b).

ENDOSCOPIC FETAL TRACHEAL OCCLUSION (FETUS)

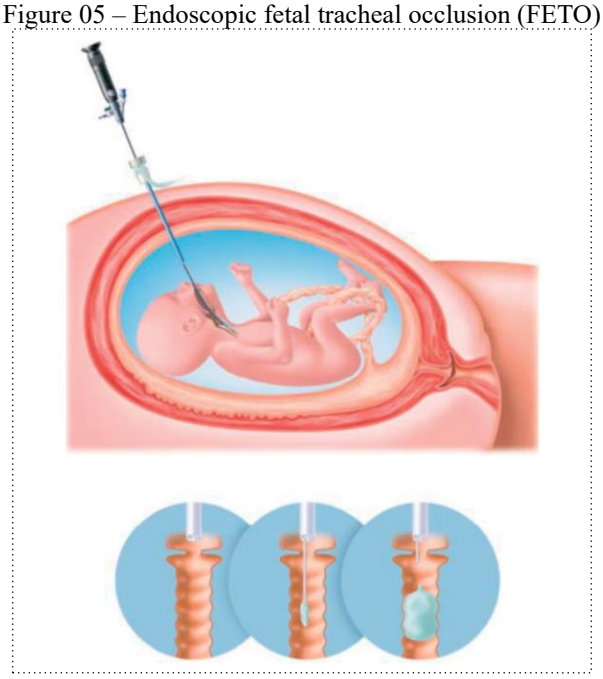
There is growing interest in antenatal interventions that can reduce the morbidity caused by CDH. In 1986, the first attempt at intrauterine repair of the hernia was performed, which basically consisted of reproducing the surgical procedure performed on newborns in fetuses, however, it resulted in very high mortality, which makes its practical application unfeasible (SANTOS *et al.* 2008).

Techniques for reversible occlusion of the fetal trachea have emerged (JANI *et al*., 2005). Harrison *et al.* (1996; 1980) were the pioneers in introducing the concept in animal models and also in applying it to human fetuses, initially using a foam *plug* (HARRISON, 1980; HARRISON, 1996). The first procedures required hysterotomy with extraction of the fetus, followed by exposure of the neck in hyperextension, dissection of the trachea and placement of occlusive clips, with subsequent replacement of the fetus in the uterine cavity (EVANS *et al.,* 1989). High rates of preterm delivery and irreversible damage to the laryngeal nerve and trachea were observed (DEPREST; THANKFUL; NICHOLAIDES, 2004). In addition, hysterotomy caused high morbidity and mortality due to preterm birth (LONGAKE *et al.*, 1991; SKARSGARD *et al.,* 1996). All the difficulties encountered

culminated in the development of FETO, an endoscopic technique of increasing importance today (VERLA; STYLE; OLUTOYE, 2018).

Fetal Endoscopic Tracheal Occlusion (FETO) is a minimally invasive percutaneous procedure that uses an endoluminal detachable inflatable balloon inserted and removed endoscopically. After ultrasound confirmation of the fetal position favorable to trocar insertion, the fetus is anesthetized by ultrasound-guided intramuscular injection, and a small cannula is placed with trocar into the amniotic cavity through the abdominal and uterine walls. The cannula is then replaced by a 1.2 mm endoscope with a catheter containing the balloon, which is introduced through the mouth of the fetus into the trachea (**Figure 05**). Finally, the balloon is inflated with isotonic magnetic resonance contrast (ZANI, A., et al., 2022; DEPREST; GRACIFUL; NICHOLAIDES, 2004).

Figure 05 – Endoscopic fetal tracheal occlusion (FETO)



Font: Deprest *et al*., 2005.

There is evidence that fetuses feel pain, so fetal anesthesia is essential to provide comfort and avoid sympathetic stimulation – which results in tachycardia, increased hormone levels, and fetal motor activity (Myers, *et al.,* 2002; CAULDWELL, 2002; ANANDA; HICKEY, 1987). Local blockade combined with sedation and fetal anesthesia has been shown to be safe and effective for performing FETO (ASUNÇÃO *et al.,* 2017). The use of tocolytic before, during, and after the procedure, as well as anesthesia, is also necessary to prevent premature delivery precipitated by uterine stimulation resulting from uterine incision and manipulation (ASUNÇÃO, *et al.,* 2017). For follow-up, periodic ultrasounds or magnetic resonance imaging (MRIs) are recommended to confirm the position of the balloon and monitor fetal lung volume and growth (DEPREST; GRACIFUL; NICHOLAIDES, 2004).

The main objective of FETO is to minimize pulmonary hypoplasia and reduce mortality in newborns with CDH, but it does not exclude the need for postnatal surgical correction of the diaphragmatic defect (KOSINSKI; MIROSŁAW, 2017 + DEPREST; GRACIFUL; NICHOLAIDES, 2004). Tracheal occlusion in the fetus results in accumulation of pulmonary fluid, which induces the expansion of lung tissue and accelerates its development (KHAN; CLOUTIER; PIEDBOEUF, 2007). In the early days of the technique's development, pregnancy was interrupted by elective cesarean section at around 37 to 38 weeks, with balloon extraction by means of the ex-uterus intrapartum theraphy (EXIT) procedure with tracheoscope, while maintaining placental circulation (JANI *et al.,* 2005; DEPREST; GRACIFUL; NICHOLAIDES, 2004). However, it has been shown that the accumulation of pulmonary fluid also causes a reduction in the number of type II pneumocytes – cells responsible for the secretion of pulmonary surfactant. (DANZER, 2008) Thus, the balloon was removed in the prenatal period, at 32 to 34 weeks of gestation, by fetal tracheoscopy or echoguided puncture of the balloon (JANI *et al.,* 2005, DEPREST; GRACIFUL; NICHOLAIDES, 2004; FLAGEOLE, 1998; PERALTA, 2011). This procedure is associated with lower morbidity and longer patient survival because it allows pulmonary recovery and improved surfactant production, reducing cases of hyaline membrane disease (DONÉ *et al.,* 2013; DEPREST; GRACIFUL; NICHOLAIDES, 2004). When labor is already at an advanced stage, the balloon can be punctured with a needle below the cricoid cartilage, in the midline, or be removed by tracheoscopy after tubal ligation of the umbilical cord (SANTOS; RIBEIRO, 2008).

Like any surgical procedure, the FETO has contraindications and can cause adverse effects, especially premature rupture of ovular membranes (RPMO) and a two-week decrease in the mean gestational age at birth. (JUNIOR *et al.,* 2016). Thus, since its inception, the correct selection of patients and their eligibility for the procedure are of vital importance (KOSINSKI; MIROSŁAW, 2017). Its indication is reserved for cases of severe isolated CDH – which has high mortality rates – clinically defined by the presence of hepatic herniation, as well as by the lung-to-head ratio (PRC) < 1.0 (SANTOS; RIBEIRO, 2008).

A meta-analysis of data from five studies using RPC ≤ 1.0 as an inclusion criterion for FETO, totaling 110 patients in the FETO group and 101 in the control group, showed a mean incidence of RPMO of 35.3% in the intervention group versus 27.8% in the control group, but with a survival rate 7 times higher in patients who received the intervention (risk of death of 89% in controls versus 50% in those submitted to FETUS) (AL-MAARY, 2016). Deprest *et al.* (2014) found RPMO in approximately 17% of cases, occurring up to three weeks after the procedure. (DEPREST *et al.,* 2014) The risk of this complication can be mitigated by using a 3.3 mm percutaneous approach instead of a 5 mm approach, with which RPMO occurred in 100% of the cases studied by Harrison *et al*. (2003) (JANI *et al.,* 2005; DEPREST; GRACIFUL; NICHOLAIDES, 2004; HARRISON, 2003).

Fetal complications may also occur, most commonly tracheobronchomegaly, which clinically has little impact on the newborn's quality of life (DEPREST, 2010).

The best results occur in procedures performed earlier, but there is an improvement in survival even when performed at 25 to 29 weeks. (RUANO *et al.,* 2013; DEPREST; GRACIFUL; NICHOLAIDES, 2004; JANI *et al.,* 2005). A prospective multicenter study conducted by the FETO *Task Group* demonstrated improved survival for left CDH – from 24.1% to 49.1% – when compared to the control group, with RPMO occurring on average thirty days after the procedure and with a mean gestational age at birth of 35.2 weeks (JANI *et al.,* 2007).

ANTENATAL CORTICOSTEROID THERAPY

In a study with an animal model, Davey *et al*. (2006) evaluated the effect of antenatal betamethasone on the pulmonary function of fetuses that had also undergone tracheal occlusion. Their results showed improvement in gas exchange, lung compliance, and ventilatory efficacy in the context of tracheal occlusion (DAVEY *et al*., 2006; DAVEY *et al*., 2007). However, Lally *et al*. (2006) conducted a randomized study with a small number of human fetuses, in which no difference was observed in relation to perinatal mortality and duration of mechanical ventilation or hospitalization between the group that received betamethasone (at 34 weeks of gestation) and the group that received placebo (LALLY, 2006). Thus, there is no evidence to justify the use of routine antenatal corticosteroids for pregnant women of fetuses with full-term CDH (VERLA; STYLE; OLUTOYE, 2018). However, it may be prudent to administer it to pregnant women of preterm fetuses with CDH, given its well-established ability to reduce morbidity in these patients (LALLY, 2006, KOSIŃSKI; MIROSŁAW, 2017).

SILDENAFIL ANTENATAL

Despite causing a large part of the morbidity and mortality of CDH, there is still no effective postnatal therapy for PAH. Therefore, the use of drugs capable of avoiding or attenuating the complications of CDH would be of great value, especially for developing countries, such as Brazil, where fetal surgery serves a very small portion of the population.

The use of sildenafil, a widely available and low-cost phosphodiesterase type five inhibitor, has shown encouraging results in animal models (VERLA; STYLE; OLUTOYE, 2018). Studies in rats have demonstrated improved fetal lung development, increased vessel density, and reduced right ventricular hypertrophy following maternal administration of high-dose sildenafil (LUONG *et al*., 2011; BURGOS *et al.,* 2016; MOUS *et al.,* 2016). Russo *et al*. (2016) conducted studies in rabbits and observed improvement in lung vasculature and airway development (RUSSO *et al*., 2016b). In addition, when combined with tracheal occlusion, sildenafil also obtained favorable results on the

lung parenchyma and vasculature (RUSSO *et al*., 2017). Kashyap *et al*. (2019) evaluated the effect of antenatal sildenafil on hemodynamics and pulmonary function of sheep fetuses with diaphragmatic hernia, and found up to four times lower pulmonary vascular resistance compared to control ($p = 0.002$), consistent with what was observed in other studies (KASHYAP, 2019).

We do not yet have data on human use. However, there are no reports of severe adverse effects for human fetuses, neonates or pregnant women, making antenatal sildenafil a promising idea (VERLA; STYLE; OLUTOYE, 2018). A European group of researchers is already recruiting patients to conduct the first phase I/IIb clinical trial, called "SToP-PH", with the aim of measuring sildenafil placental transfer *in vivo* and maternal and fetal tolerance to the drug, enabling subsequent phase III (RUSSO *et al*., 2018).

RETINOIC ACID

Decreased levels of retinoic acid, a derivative of vitamin A, contribute to the emergence of HDC and PAH in humans (KUTASY *et al*., 2016). The use of this acid during pregnancy in rats has been shown to reduce the degree of pulmonary hypoplasia and vascular abnormalities in fetuses with CDH (MONTEDONICO *et al*., 2008). In addition, prenatal exposure to retinoic acid antagonists causes CDH in rat fetuses (CIPOLLONE *et al.,* 2017). Analyzing hepatic stellate cells from human fetal tissue, Loo *et al*. (2018) concluded that fetal retinoic acid stores interfere with lung growth and diaphragmatic development in humans with CDH (LOO, 2018). Despite the evidence presented, the teratogenic effects of retinoic acid preclude its clinical application in human fetuses (EASTWOOD, 2015; TZIMAS; NAU, 2001).

ROSIGLITAZONA

Gosemann *et al*. (2018) conducted a study to evaluate the effects of the administration of rosiglitazone – a thiazolidinedione used in the treatment of *diabetes mellitus* – in pregnant rats of fetuses with and without diaphragmatic hernia, concluding that the use of the substance was able to attenuate the vascular remodeling of fetuses with hernia ($p < 0.01$) (GOSEMANN, *et al.,* 2018). The authors also demonstrated that the thickening of the pulmonary arteries in CDH was accompanied by increased systemic and perivascular expression of MCP-1 compared to the control group ($p = 0.04$) (GOSEMANN, *et al.,* 2018). Thus, the suggested mechanism would be MCP-1 (monocyte chemoattractant protein 1), a powerful monocyte chemoattractant whose increase in patients with PAH is already consolidated, suggesting that rosiglitazone would act by inhibiting its expression (ITOH *et al.,* 2006; OKAWADA *et al*., 2007; REHAN *et al.,* 2010; NERI *et al*., 2011; SIMON; MARIANI, 2007; GOSEMANN, 2018).

STEM CELLS

The beneficial effect of mesenchymal stem cells on CDH has been previously reported by Yuniartha *et al*. (2014), but intravascular injection – such as the uterine vein – was the means of choice (YUNIARTHA *et al*., 2014). Due to the potential for complications such as immunodeficiency, inflammation, and microvascular embolism, Takayama *et al*. (2019), evaluated the effects of injecting human mesenchymal stem cells into the amniotic cavity of pregnant rats with induced CDH. Despite the mortality of 27.9% after the procedure, they observed larger alveolar spaces and thinner alveolar walls in the group that received the intervention ($p < 0.05$), in addition to significantly better measurements of the thickness of the media and adventitious layers of the pulmonary artery ($p < 0.001$) (TAKAYAMA, 2019). Thus, despite being in the early stages, stem cell therapy may become, in the future, a possibility to reduce the severity of CDH.

TERMINATION OF PREGNANCY AND MODE OF DELIVERY

The ideal age for terminating the pregnancy of a fetus with CDH is still controversial. The literature presents conflicting results, highlighting the lower need for ECMO when delivery occurs at 37 to 38 weeks, but lower mortality when gestational age is more advanced (ZANI, A., et al., 2022; STEVENS *et al*., 2009; HUTCHEON, 2010). In high-volume European tertiary centres, it is indicated to plan delivery at more than 39 weeks (SNOEK *et al.,* 2016).

As for the mode of delivery, the vaginal route is usually chosen, with the guarantee of all the necessary equipment for the postnatal management of the neonate. Cesarean section is reserved for obstetric indications or when fetal well-being is compromised during any stage of labor, as perinatal stress, hypoxia, and acidosis induce pulmonary vasospasm (BHATNAGA; SARIN, 2017).

POSTNATAL CLINICAL MANAGEMENT

Despite the evolution of fetal surgery, the most common treatment offered to newborns with CDH is still centered on postnatal interventions performed in the neonatal ICU. Classically, the therapy employed consists of mechanical ventilation for clinical stabilization, followed by surgical correction of the diaphragmatic defect (VERLA; STYLE; OLUTOYE, 2018). Invasive blood pressure (BP) monitoring is preferred, associated with pre- and post-ductal oxygen saturation (SatO2) and heart rate (HR) (CHANDRASEKHARAN *et al*., 2017). In addition, other interventions may also be necessary, especially for PAH therapy.

CARE IN THE DELIVERY ROOM

During the care of the newborn in the delivery room, it is essential to pay attention to the prevention of lung injuries, especially due to high airway pressures, as well as high oxygen

concentrations (DE BIE, F. R., et al., 2022; MARGOTTO, 2018). Balloon and mask ventilation should also be avoided, and most require intubation while still in the delivery room (CHANDRASEKHARAN *et al*., 2017). The use of an orogastric or nasogastric tube is recommended in all patients, aiming at bowel decompression (SANTANA, 2017).

Neuromuscular blockers should be avoided because they are associated with adverse effects such as hypoxemia (SNOEK *et al.*, 2016b). Delayed clamping of the umbilical cord is preferable, as 20 mmHg lower pulmonary arterial pressure is observed in newborns with CDH undergoing delayed clamping. It is understood that immediate clamping forces blood to circulate through a smaller vascular bed, resulting in vasospasm in the pulmonary circulation (MARGOTTO, 2018).

MECHANICAL VENTILATION

The best mode of ventilation for neonates with CDH and hypoplastic lungs is not yet known. Several centers initiate conventional ventilation and optimize peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), and respiratory rate (RR) values – alternating to high-frequency oscillatory ventilation (HFOV) if the objectives are not achieved (CHANDRASEKHARAN ET AL., 2017).

Snoek *et al*. (2016a) found no statistically significant difference in the combined outcomes of mortality and bronchopulmonary dysplasia when comparing conventional ventilation to HFOV as the initial ventilatory mode for CDH. However, patients undergoing the conventional mode were ventilated for fewer days ($p = 0.03$), required less ECMO ($p = 0.007$) and vasoactive drugs for less time ($p = 0.02$), and had fewer treatment failures ($p = 0.01$) (SNOEK, 2016a). It seems reasonable, therefore, to try conventional ventilation for patients with CDH.

A cautious approach should be followed to prevent barotrauma and volutrauma. PIP is generally maintained at < 25 cmH2O, while PEEP is maintained at ≤ 5 cmH2O, aiming for preductal SatO2 > 85%, postductal SatO2 > 70%, and carbon dioxide partial pressure (PaCO2) of 45 to 60 mmHg (WUNG *et al.,* 1995; REISS *et al.,* 2010).

EXOGENOUS SURFACTANT

Although they have similar surfactant dosages in relation to healthy newborns, the kinetics are altered in neonates affected by CDH (COGO, *et al.,* 2003). However, there is no evidence of benefit in the administration of exogenous surfactant for this population, resulting in an increase in the need for ECMO, the incidence of chronic lung disease, and the mortality rate (VAN MEURS, 2004; LALLY, 2004).

ECMO

When available, ECMO can be used temporarily to provide respiratory support to infants affected by severe CDH, which is the most common indication for ECMO in neonates today (VERLA; STYLE; OLUTOYE, 2018; BROGAN *et al.* 2017). Despite the divergence of data on its benefit, ECMO may be a great alternative therapeutic option when conventional approaches fail, given that neonates with CDH have hyperreactivity of the pulmonary vasculature, which makes them more susceptible to exacerbation of PAH due to hypoxia or hypercapnia (RAFA; SCHAIBLE, 2019).

ECMO support is usually limited to two or three weeks in duration (VERLA; STYLE; OLUTOYE, 2018; BEALS *et al.,* 1992). Its function consists only of stabilizing the patient while PAH improves, providing clinical conditions for surgery (VERLA; STYLE; OLUTOYE, 2018). It may be indicated for patients who persist with low preductal SatO2 and labile hemodynamics, despite optimized ventilation, adequate inotropic support, and use of a pulmonary vasodilator (RAFAT; SCHAIBLE, 2019).

Chandrasekaran *et al*. (2017) also advocate that candidates have CDH not associated with lethal abnormalities, and that they are born at least 34 weeks of gestation or that they weigh more than 2 kg (CHANDRASEKARAN *et al*., 2017). Kipfmueller *et al*. (2019) suggest the use of *Score for Neonatal Acute Physiology-II* (SNAP-II) – which evaluates BP, blood pH, PaO2:FiO2 ratio, body temperature and occurrence of seizures – to facilitate risk stratification of neonates with CDH and the indication of ECMO therapy, after demonstrating that the value obtained in the score is a predictive factor for mortality (with 81.8% sensitivity and 79.7% specificity) and need for ECMO (with 90.7% sensitivity and 63.8% specificity). To this end, the authors calculated the value of the score assigned to 101 newborns with CDH between 2009 and 2017 at the 12th hour of life and analyzed the results in a ROC curve. The cut-off points obtained were ≥ 22 for the need for ECMO and ≥ 28 for predicting death (KIPFMUELLER *et al.,* 2019).

Table 1 – SNAP-II Score

Mean Arterial Pressure	> 30 mmHg	0 point
	20 to 29 mmHg	9 points
	< 20 mmHg	19 points
Lower temperature	> 35.6°C	0 point
	35.0 to 35.6°C	8 points
	< 35.0°C	15 points
pO2:FiO2	> 2.49	0 point
	1.00 to 2.49	5 points
	0.30 to 0.99	16 points
	< 0.30	28 points
Lower serum pH	≥ 7.20	0 point
	7.10 to 7.19	7 points
	< 7.10	16 points
Multiple seizures	No	0 point
	Yes	19 points
Urine output (mL/Kg/h)	≥ 1.0	0 point
	0.1 to 0.9	5 points
	< 0.1	18 points

Fonte: Kipfmueller, et al., 2019

Importantly, the need for ECMO is a marker of worse prognosis, with a survival rate of approximately 50%, considerably lower than the 70 to 90% observed in neonates who do not require support (HARICHARAN *et al.,* 2009; KAYS *et al*., 2014; SEETHARAMAIAH *et al*., 2009). Prolonged need for ECMO is also associated with higher morbidity and mortality (SEETHARAMAIAH *et al*., 2009).

As for the types of ECMO, venovenous ECMO seems to be the best option for newborns with CDH, as it allows oxygenated blood to circulate through the pulmonary capillaries – which would result in greater pulmonary vasodilation, in addition to maintaining pulsatile flow of oxygenated blood capable of increasing coronary perfusion and improving cardiac function (DIMMITT *et al*., 2001; GUNER *et al*., 2009). However, it is still not possible to rule out that the flow of oxygenated blood through the pulmonary vessels results in worsening of inflammation due to the formation of oxygen free radicals (RAFAT; SCHAIBLE, 2019). When there is cardiovascular involvement, however, venoarterial ECMO is preferable because it reduces the overload on the right ventricle (MCHONEY; HAMMOND, 2018).

Venovenous ECMO can be performed by ultrasound-guided percutaneous technique, with insertion of a double-lumen catheter into the internal jugular vein. As a result of the larger diameter of the catheter – around 12 Fr – the venovenous technique is indicated for infants weighing more than 2.5 kg (RAFAT; SCHAIBLE, 2019). On the other hand, venoarterial ECMO usually involves cannulation of the right common carotid artery and the right internal jugular vein, which causes the risk of carotid stenosis or occlusion in up to half of the patients after removal of the cannula (RAFAT; SCHAIBLE, 2019; BUESING, 2007). However, it can be performed with a cannula of up to 8 Fr, making it the preferable technique for smaller newborns (MCHONEY; HAMMOND, 2018).

A systemic review conducted by Puligandla *et al*. (2015) found no difference between the types of ECMO, but concluded that the mode of insertion of the cannula seems to lead to the preponderant use of the venoarterial variant, in addition to its already consolidated benefit in the presence of severe cardiac dysfunction (PULIGANDLA *et al.,* 2015).

After two days of tolerating very low flow to ECMO – approximately 30 mL/kg – weaning is initiated. Initially, campleation is attempted for ten to fifteen minutes, with the aim of achieving adequate oxygenation and ventilation with fraction of inspired oxygen (FiO2) ≤ 50%. In case of failure, one can choose to extend the support for a few more days. Duration longer than 21 days with failure usually leads to palliative treatment and contraindicates surgery (RAFAT; SCHAIBLE, 2019).

TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

In addition to being one of the preponderant factors for mortality, PAH secondary to CHD is usually associated with left ventricular hypoplasia, as well as right ventricular hypertrophy and insufficiency, making it refractory to conventional treatment (HARTING, 2017; CHANDRASEKHARAN *et al*., 2017). Several groups study the vascular changes that occur in the lungs of neonates with CDH to design alternative therapeutic strategies, but the molecular pathophysiology of vascular remodeling is still not understood (HARTING, 2017). For evaluation, echocardiography is the best non-invasive test available, and it is indicated in the first 24 hours of life (SUDA *et al*., 2000).

Because catecholamines – especially dopamine – can increase systemic and pulmonary vascular resistance, and if preductal SatO2 remains between 80 and 95%, it is recommended to maintain infants' BP at normal levels for gestational age, even if their increase could minimize *the right-to-left shunt (SNOEK, 2016b).*

Despite being used deliberately in some centers, inhaled nitric oxide (iNO) still has debatable usefulness. Its action consists of selective pulmonary vasodilation, relaxing the smooth muscles of the pulmonary vascular network, with a short half-life and rapid onset of action (AGUIAR, 1998). Its use reaches 60% in case series in the literature, but recent studies have not yet been able to prove its value (PUTNAM *et al.,* 2016; HERICH *et al*., 2019). In newborns with PAH, iNO is able to improve oxygenation and reduce the need for ECMO, but the same benefit is not conclusive in cases of CDH (BARRINGTON *et al*., 2017). As a result of pulmonary hypoplasia, little iNO reaches the alveoli, which justifies the low response in newborns with CDH, and is usually indicated as a transitional therapy for ECMO candidates (MARGOTTO, 2018). Herich *et al*. (2019) analyzed the benefit of iNO in 265 neonates with CDH, of whom only 82 had an adequate response to the drug. However, the group that improved also showed a lower need for ECMO ($p = 0.0054$), endured a longer time until ECMO started ($p = 0.005$), and had lower mortality ($p = 0.0396$) (HERICH *et al*., 2019).

In addition to antenatal use, the applicability of sildenafil is also evaluated in the postnatal clinical management of PAH due to CDH. There is evidence to show improved oxygenation and reduced mortality from PAH in centers that do not have iNO or ECMO. However, there are no clinical trials that justify its use in newborns with CDH (BAQUERO *et al*., 2006; VARGAS-ORIGEL, 2010).

Milrinone, a phosphodiesterase 3 inhibitor, has been touted as an alternative to treat iNO-resistant PAH. Although it is a drug known to be beneficial for treating children in the postoperative period of cardiac surgery, its value for PAH secondary to CDH is not known (HOFFMAN, 2002). Several case series have shown the effectiveness of intravenous milrinone in the treatment of iNO-resistant PAH (PATEL, 2012; BASSLER *et al*., 2006; MCNAMARA, 2013). However, a recent retrospective analysis of 24 patients did not show any benefit of the substance on the oxygenation index, nor on pulmonary arterial pressure or left ventricular measurements (MEARS; YANG; YODER, 2019). Randomized controlled trials are still required to define their role.

SURGICAL TREATMENT

The need for surgery in newborns with CDH is well established, and its indication is almost universal to affected neonates (CLIFTON; WULKAN, 2017). However, it is currently understood that surgical repair of the diaphragmatic defect and the consequent repositioning of the abdominal viscera causes a considerable decrease in pulmonary *compliance*, which is characteristically affected by CDH (JANI *et al*., 2006; GOINCOUR *et al*., 2005; MAHIEU-CAPUTO *et al*., 2001). However, it has also been shown that the removal of herniated viscera from the chest favors lung development, which extends up to eight years of age, and can reverse pulmonary hypoplasia in the postnatal period (VERLA; STYLE; OLUTOYE, 2018). Thus, the benefits of surgery are poorly understood, but the literature argues for its long-term importance, even if the immediate benefit to the patient is modest, since PAH and hypoxemia do not respond in the short term (TSAO; LALLY, 2011; CHANDRASEKHARAN *et al*., 2017).

It is essential to establish the ideal time to perform the surgical approach. Emergency surgery is no longer indicated, since delaying it allows for increased pulmonary *compliance*, improving postoperative outcomes (JANI, 2006). The CDH EURO Consortium Consensus indicates surgery after hemodynamic stabilization, clinically defined by normal BP for gestational age, preductal oxygen SatO2 between 85 and 95% with FiO2 < 50%, lactate < 3 mmol/L, and urine output > 1 mL/kg/hour (SNOEK, 2016b). Permissive hypercapnia should be adopted, with a target PaCO2 of 45 to 60 mmHg, in addition to the prevention of volutrauma and barotrauma during ventilation, maintaining PIP < 25 cmH2O and PEEP of 2 to 5 cmH2O (BOLOKER *et al*., 2002; TRACY *et al*., 2010). Parameters should remain stable for at least 24 hours (DAVENPORT, 1999). The procedure is

contraindicated for very unstable neonates, who have no chance of recovery or adaptation to pulmonary pressures (CLIFTON; WULKAN, 2017).

The surgery consists of the reduction of the abdominal viscera and primary closure of the diaphragmatic defect, requiring the use of prostheses in large hernias (ARCA *et al*., 2003; MOSS; CHEN; HARISSON, 2011). Traditionally, transabdominal diaphragmatic herniorrhaphy has shown good results. However, it is commonly very long, causes major tissue trauma, and is associated with prolonged hospital stay and higher complication rates (QIN, 2019).

Recently, thoracoscopy repair has become the main method for surgical treatment of CDH (CHAN, 2011; OOR, 2016). The minimally invasive technique allows a better visual field for the surgeon while reducing tissue damage, and is increasingly used in practice. It is also able to reduce postoperative pain and the incidence of complications (QIN; REN; MA, 2019). A meta-analysis showed a significant reduction in mortality rates in the postoperative period of surgery minimally (relative risk of 0.26 and $p = 0.006$), but higher recurrence when compared to the open technique (relative risk 3.42 and $p < 0.00001$) (ZHU, 2016). In addition, several case series show similar data regarding recurrence (GENDER, 2011; LANDSDALE, 2010; TSAO; LALLY, 2011).

Despite this, infants with CDH are smaller, have lower body weight, have pulmonary hypoplasia and increased pulmonary vascular resistance, as well as may have associated cardiac malformations – which can pose great challenges to the anesthetic procedure (ZANI *et al*., 2017; HERATI *et al*., 2011). The pressure resulting from artificial pneumothorax and the need for some degree of lung collapse to maintain the surgeon's visual field make anesthesia even more difficult (DAI *et al*., 2016). Even in this regard, a recent study comparing postoperative anesthetic management after abdominal repair and after thoracoscopy repair showed shorter duration of mechanical ventilation ($p = 0.012$), antibiotic use ($p = 0.001$), and hospitalization ($p = 0.016$) in patients undergoing thoracoscopy (QIN; REN, MA; 2019).

Larger defects are approached with better quality in an open technique with continuous and uninterrupted suturing of the prosthesis to the diaphragm (CLIFTON; WULKAN, 2017). Thoracoscopy is ideal for repairing defects through primary raffia, and the use of small prostheses is allowed in the absence of sufficient muscle tissue – as long as the quality of the repair is not compromised to avoid laparotomy (KEIJZER; PURI, 2010). New evidence shows superiority of the use of flaps over prostheses over total (7% versus 10%) and symptomatic (0% versus 3%) recurrence (DEWBERRY *et al*., 2019).

In addition, thoracoscopy can cause pulmonary hypertension and hemodynamic instability during the intraoperative period, and is preferable for small defects and/or mild PAH (BADILLO; INGALEWSKI, 2014). Prolonged surgeries should be avoided, prioritizing a surgeon trained for intracorporeal nodes (CLIFTON; WULKAN, 2017). The duration of the procedure reflects the

learning curve in endoscopic techniques, with total time gradually decreasing during the gain of experience and more refined techniques (CHO, 2009).

Pneumothorax and pleural effusion are possible early postoperative complications, which require thoracic drainage to centralize the mediastinum, as well as to improve venous return and ensure adequate systemic perfusion (SCHLAGER *et al*., 2017). However, chest tube should not be routinely placed, as it can cause contralateral lung distension or pneumothorax due to exaggerated expansion of the hypoplastic lungs (WUNG *et al*., 1995; CLOUTIER *et al*., 1993). Consideration should also be given to the possibility of abdominal compartment syndrome following sudden reduction of the abdominal viscera (CLIFTON; WULKAN, 2017).

PROGNOSIS

Despite medical advances in the management of congenital diaphragmatic hernia, its morbidity and mortality remain high (BROWNLEE, 2009). The prognosis depends on several factors, such as the association with chromosomal disorders, the presence of malformations – especially cardiac malformations, but also the severity of pulmonary hypoplasia and the position of the liver (GRAHAM; DEVINE, 2005). In addition, the prognosis is impaired when the hernia occurs on the right and there is hepatic herniation (KOSINSKI; MIROSŁAW, 2017). Survival in right hernias reaches 50%, while in left hernias it reaches 75% (FISHER *et al*., 2008). In addition, a delivery performed in a non-specialized center and requiring transport to a referral hospital worsens mortality. (KALANJ, 2016) The quality of care during this transfer may impact survival, as suggested by Reuter *et al*. (2019), who, in their research, found no association between place of birth and death, even though 38.6% of the studied population came from other regions (REUTER, 2019).

Hinton *et al*. (2017) demonstrated that the average survival of patients with CDH has improved, however, survival suffers from notable disparities in relation to poverty levels, also acting unevenly between ethnicities (HINTON *et al*., 2017).

The severity of congenital diaphragmatic hernia is related to the size of the herniated viscera and the height at which the herniation occurred during pregnancy. Thus, the earlier the onset and the greater the size of the effect, the worse the prognosis is attributed (HARTMAN, 2005). When herniation occurs in the pseudoglandular period, there is a decrease in the number of bronchi and bronchioles, in addition to a reduction in the vascular bed. However, when it appears in the alveolar period – which begins in the twenty-fourth week – there is a decrease in the number and size of the alveolar sacs, with impaired development of the peri-acinar blood vessels (BUNDUKI; RWAN; ZUGAIB, 1998). Two studies conducted by the Congenital Diaphragmatic Hernia Study Group demonstrated that defect size, low Apgar score at 5 minutes, and birth weight are predictors of worse

prognosis (DE COPPI, DEPREST, 2017; CONGENITAL DIAPHRAGMATIC HERIA STUDY GROUP, 2001).

For cases of isolated congenital diaphragmatic hernia, the most accepted parameter for estimating the prognosis is the evaluation of the amount of lung tissue in the fetal thorax, represented as the ratio between lung area and head circumference (DEPREST, 2014). However, lung growth follows a different rhythm from cephalic growth, and therefore the proportion expressed as a percentage of normal – observed/expected – was adopted to correct the values obtained according to gestational age (DEPREST, 2014). Currently, the ratio between the observed and expected (O/E) value of the lung area over the head circumference, represented by PRC – "lung-to-head ratio", is the most accepted and validated parameter for estimating the size of fetal lungs measured by ultrasonography (JANI *et al.,* 2007). The calculation is performed by dividing the area of the lung contralateral to the defect by the circumference of the head, followed by dividing the result obtained by the expected value (JANI *et al*., 2007). In normal children, PRC increases with gestational age, but when the observed values are compared to what is expected, the proportions appear to remain constant during pregnancy (ANTOLIN *et al*|, 2016)| Know *Et. Al.* (2007) observed the survival rate of 329 fetuses with isolated left congenital diaphragmatic hernia and found a survival rate of 18% (when RPC O/E < 25%), 66% (when RPC O/E 26 to 45%), as well as 26 to 45% and 89% (when RPC O/E > 45%).

A PRC < 0.6 has been associated with zero chance of survival, while values > 1.35 have been associated with survival. The ratio between 1.35 and 0.6 shows a survival rate of 61% (CHANDRASEKHARAN *et al*., 2017). Evaluating observed/expected values, results < 25% indicate severe hernia, with survival of 10% when associated with hepatic herniation and 25% if the liver is in the abdominal cavity. In addition, values lower than 15% and the presence of the liver in the thoracic cavity indicate 100% mortality (CHANDRASEKHARAN *et al*., 2017). Stomach herniation, in turn, has also been associated with a worse prognosis (GALLOT *et al*., 2007; MULASSERY, 2010; BEAUMIER *et al*., 2015).

Another method to assess prognosis is by assessing the presence or absence of hepatic herniation as a marker of postnatal survival (JAN *et al*., 2007). Liver measurement, obtained by magnetic resonance imaging, can be used to calculate the ratio of herniated liver to thoracic volume. Low values in the PRC combined with liver herniation represent high mortality and early neonatal morbidity (JANI *et al*., 2007). Several predictors of pulmonary hypoplasia and PAH have been described (HEDRICK *et al*., 2007). For example, the McGoon Index, obtained by ultrasonography, and the Modified McGoon Index, by magnetic resonance imaging, are calculated from the sum of the diameters of the right and left pulmonary arteries measured at the bifurcation, then divided by the diameter of the aorta (KOSINSKI; MIROSŁAW, 2017). Hedrick *Et. Al* (2007) showed that the liver

was an important predictor of the need for ECMO and that survival was affected by the presence of hepatic herniation (45% when present, versus 93% in its absence). Russian *Et. Al.* (2016) advocate the use of lung size and the presence of liver herniation to define the need for ECMO.

Clinical parameters associated with worse prognosis are low Apgar score at birth, presence of persistent neonatal PAH, and need for ECMO (CHANDRASEKARAN, *et al*., 2016; DOS SANTOS, 2003; HEIWEGEN *et al*., 2017). A recent Indian study also pointed to the presence of shock and the need for high ventilation parameters during the first 24 hours as important factors of worse prognosis (CHAUDHARY *et al*., 2019).

Table 2: Sonographic predictors of prognosis

Lung-to-head ratio	> 1.35	100% survival	
	0.6 to 1.35	61% survival rate	
	< 0.6	0% survival rate	
Observed/Expected RPC	< 25%	HDC grave	10% survival with hepatic herniation
			25% survival without hepatic herniation
	< 15%	100% mortality when associated with hepatic herniation	

Cast iron: Chandrasekharan, et. al., 2017

CONCLUSION

With the knowledge gained from new research and with the evolution of therapeutic techniques, new opportunities for intervention on long-known conditions are created. This phenomenon is quite evident in relation to CDH, which is no longer a surgical emergency and has started to arouse interest in intervention methods capable of reducing its morbidity and mortality, acting in the pre- and postnatal periods.

The objective of this study was to foster knowledge on the subject, bringing data from the medical literature that could support decision-making in the face of a patient affected by CDH. In addition, we sought to bring to light topics that are not widely known about CDH in the medical field, such as endoscopic fetal tracheal occlusion and the new uses proposed for substances commonly prescribed for other pathologies.

However, there are still large unanswered questions in the literature on the subject. From the pathophysiology that is poorly understood at the molecular level to the lack of large clinical trials on new therapeutic approaches, it is evident that there is a need for even more studies in the area, especially considering the formulation of treatment protocols that can guide health professionals in the management of this condition that, although rare, inflicts a high cost on the health system and on the quality of life of patients. but that there are still no effective and widely available specific treatments.

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