Congenital Diaphragmatic Hernia Management and Outcomes: A Simple Literature Review

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ABSTRACT

Background: Congenital diaphragmatic hernia (CDH) is considered as one of the most common congenital anomalies. As a result, significant literatures have been done to assess the different management procedures and outcomes of each. Assessment of these literatures will support in providing better outcomes for the patients. Objective: Aim of the study: Assessment of different management plans of CDH, and the outcomes related. In addition to providing scientific references for analyzing all the clinical studies in this field. Methods: PubMed database was used for articles selection. We included all relevant articles to our review with the following topics: Congenital Diaphragmatic Hernia, Management, Outcomes, Morbidity, and Mortality. We excluded other articles which are not related to this field. The data were extracted according to specific form to be reviewed by group members to assess the different procedures, and the outcomes. Conclusion: Congenital Diaphragmatic Hernia has high complexity regarding its management. Prenatal screening is important because early diagnosis is helpful either in family education about the condition and its prognosis or in the decision regarding prenatal intervention. Smoking and alcohol intake are modifiable risk factors of CDH and their complications like prematurity, which is associated with high incidence of morbidity and mortality. Resolution and improvement of pulmonary hypertension either with or without treatment in the first 2-3 weeks was a major indicator of good prognosis of the case. Minimally invasive techniques showed lower rate of complications than open surgeries either prenatally like FETO or postnatally like thoracoscopic CDH repair. In addition, Hernia repair after decannulation from ECMO showed lower bleeding complications than repair on ECMO.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is considered as one of the most common congenital anomalies with a frequency of 1/2200 live births. CDH can present at posterior lateral (Bochdalek 95%) and anterior (Morgagni defects). Eighty-six percent of Bochdalek defects are left-sided, 13% right-sided, and up to 2% bilateral. CDH is further classified as either isolated, syndromic or associated with other anomalies. In its isolated form, CDH leads to two neonatal problems: (1) the anatomical yet surgically correctable diaphragmatic defect; and (2) the coinciding pulmonary hypoplasia. The latter is the result of disturbed lung development, which starts in the embryonic period. As pregnancy continues, viscera herniate into the chest, and compete for space with the developing lungs. CDH lungs have fewer airway branches, smaller cross-sectional area of pulmonary vessels, structural vascular remodeling, and vasoconstriction with altered vasoreactivity. A patient with severe CDH is highly sensitive to hypoxemia, hypotension, acidosis, and even environmental stimulation, which can precipitate pulmonary vasoconstriction and shunting episodes. The broad spectrum of severity in patients with CDH is dependent on the degree of pulmonary hypoplasia and pulmonary hypertension. Presently, delivery of infants with CDH is recommended to be close to term gestation. The focus of care includes gentle ventilation, hemodynamic monitoring, and treatment of pulmonary hypertension followed by surgery for the defect. Despite advances in neonatal and surgical care, the management of congenital diaphragmatic hernia (CDH) remains challenging with no definitive standard treatment guidelines. In this paper we will be focusing upon reviewing the management, and outcome of CDH that have been reached in the last 5 years.

MATERIALS AND METHODS

Sample

PubMed was chosen as the search database for the articles selection, because it is one of the major research databases within the suite of resources that have been developed by the National Center for Biotechnology Information (NCBI). The following

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keys used for the Mesh ("Congenital Diaphragmatic Hernia/management"[Mesh] OR "Congenital Diaphragmatic Hernia/outcomes"[Mesh]) AND ("Mortality/Morbidity"[Mesh]). Inclusion criteria, the articles were selected based on the relevance to the project which should include one of the following topics, {Congenital Diaphragmatic Hernia, CDH Management, CDH Outcomes, CDH Mortality & Morbidity}. Exclusion criteria, all other articles which did not have one of these topics as their primary end point, or repeated studies.

**Analysis**
No software was used, The data extracted based on specific form that contain (Title of the study, name of the author, Objective, Summary, Results, and Outcomes), these data were reviewed by the group members to assess different management plans of CDH, and the outcomes related. Double revision of each member’s outcomes was applied to ensure the validity and minimize errors.

**RESULTS**
We enrolled a total 10 studies according to our inclusion, and exclusion criteria described above. 9 of them were a retrospective studies, and the last one was a literature review. All of the included study discussed various aspects about CDH; incidence, risk factors, survival rates, prognosis parameters, and results of different types of intervention. The studies characteristics are shown in Table 1.

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Study Design</th>
<th>Country</th>
<th>No. of participants</th>
<th>Objective</th>
<th>Duration of Study</th>
<th>Outcome</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partridge et al. (2014)</td>
<td>Retrospective study</td>
<td>USA</td>
<td>77</td>
<td>Evaluation of the impact of timing of CDH repair on outcomes</td>
<td>8 years</td>
<td>Outcomes were improved in CDH patients undergoing surgical repair following ECMO with significantly increased survival, lower rates of surgical bleeding, and decreased total duration of ECMO therapy compared to patients repaired on ECMO.</td>
<td>4</td>
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<tr>
<td>K. Ali et al. (2013)</td>
<td>Retrospective review</td>
<td>UK</td>
<td>61</td>
<td>Evaluation of the mortality and morbidity of infants with CDH who had undergone FETO</td>
<td>6 years</td>
<td>In infants with CDH who had been treated by FETO, premature delivery was common and associated with significantly greater mortality, with no survivors born before 33 weeks of gestation. These results emphasize the need to reduce premature delivery following FETO and are useful to inform counselling of parents.</td>
<td>5</td>
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<tr>
<td>Balayla et Abenhaim (2013)</td>
<td>Retrospective cohort study</td>
<td>USA</td>
<td>5,958</td>
<td>Evaluation of the incidence, risk factors and neonatal outcomes associated with a congenital diaphragmatic hernia (CDH).</td>
<td>8 years</td>
<td>The incidence of CDH was 1.93/10,000 births. Risk factors for the development of CDH included fetal male gender, maternal age beyond 40, Caucasian ethnicity, smoking and alcohol use during pregnancy. As compared to fetuses with no CDH, fetuses with CDH were at an increased risk of preterm birth, Intra-Uterine Growth Restriction, stillbirth, and overall infant death. The 1-year mortality was 45.89%.</td>
<td>6</td>
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<tr>
<td>DeKoninck et al. (2014)</td>
<td>Retrospective review</td>
<td>Belgium and Spain</td>
<td>76</td>
<td>Reporting a recent update on fetuses with right-sided congenital diaphragmatic hernia (RCDH) in the era of fetal surgery.</td>
<td>10 years</td>
<td>Right-sided CDH seems to have a poorer outcome than that reported for fetuses with left-sided CDH with similar lung size before birth. Survival rates after expectant management with observed/expected lung-to-head ratio values ≤45 and ≤30% were 17 and 0%, respectively. In those undergoing fetal surgery (observed/expected lung-to-head ratio ≤45%) there was an apparent increase (42%).</td>
<td>7</td>
</tr>
<tr>
<td>S.C. Fallon et al. (2013)</td>
<td>Retrospective study</td>
<td>USA</td>
<td>148</td>
<td>Examination of the institutional outcomes of early CDH repair on ECMO.</td>
<td>10 years</td>
<td>Early decannulation from ECMO and early repair was associated with decreased ECMO duration, decreased circuit complications, and a trend towards improved survival.</td>
<td>8</td>
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<tr>
<td>Lusk et al. (2014)</td>
<td>Retrospective cohort study</td>
<td>USA</td>
<td>140</td>
<td>Description of the natural history of pulmonary hypertension and the risk of death and pulmonary morbidity associated with the persistence of pulmonary hypertension through the neonatal hospitalization for these infants.</td>
<td>10 years</td>
<td>The majority of infants with CDH resolve PH between 1 and 3 weeks of life. At 2 weeks of age, severity of PH by echocardiogram strongly predicts short-term pulmonary morbidity and death. Further evaluation of physiological alterations during that time may lead to novel therapies for severe CDH.</td>
<td>9</td>
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The study's inclusion criteria. The incidence of ETO infants was 48%. 84% of the survived infants were delivered after 35 weeks of gestation. 31 infants were repaired on ECMO, survival was related to gestational age at delivery and the duration of FETO. Their survival rate was 18%. 23 of 24 infants who had emergency balloon removal were born before 35 weeks of gestation. Survival was related to gestational age at delivery and the duration of FETO. Infants born prior to 35 weeks of gestation compared to those born at 35 weeks or more required a longer duration of ventilation (median 45 days versus 12 days) and a greater proportion had surgery for Gastro Esophageal Reflux (50% versus 9%).

**Partridge et al.** examined the impact of timing of CDH repair on outcomes in a large cohort of patients. This is one of the biggest controversies in CDH management. The study was done retrospectively in 2014 using the records of 77 CDH patients who got treated at Children’s Hospital of Philadelphia. Of the 77 CDH patients who required ECMO support during the study dates, 16 patients did not survive to repair, 3 patients were repaired prior to cannulation, 41 patients were repaired during ECMO, and 17 patients were repaired after decannulation from ECMO. Survival was 67%, 43.9%, and 100% for those repaired prior to, during, or post ECMO, respectively. The survival associated with repair after decannulation was statistically significant. Operative bleeding requiring transfusion occurred in 12 patients repaired on ECMO, while no significant bleeding occurred in patients repaired after decannulation.

**Ali et al.** determined the impact of premature delivery on the survival rate of CDH infants who had undergone fetal endoscopic tracheal occlusion (ETO). They also determined the association between premature delivery and morbidity. They used data of all infants with isolated CDH born at King's College Hospital (KCH), London who had undergone FETO. The study period was 6 years. The survival rate of the 61 FETO infants was 48%. 84% of the survived infants were delivered after 35 weeks of gestation. 31 of the total number were delivered before 35 weeks of gestation. Their survival rate was 18%. 23 of 24 infants who had emergency balloon removal were born before 35 weeks of gestation. Survival was related to gestational age at delivery and the duration of FETO. Infants born prior to 35 weeks of gestation compared to those born at 35 weeks or more required a longer duration of ventilation (median 45 days versus 12 days) and a greater proportion had surgery for Gastro Esophageal Reflux (50% versus 9%).

**Balayla et al.** established the incidence rate of CDH and evaluated the maternal/gestational risk factors associated with the development of the condition. They also quantified specific outcome risks associated with this condition. This retrospective cohort study was done during 8 years using the records of all births and fetal deaths in the United States from 1995 to 2002.32,145,448 births during study period met the study’s inclusion criteria. The incidence of CDH was 1.93 per 10,000 births. Risk factors for the development of CDH included fetal male gender, maternal age beyond 40, Caucasian ethnicity, smoking and alcohol use during pregnancy. As compared to fetuses with no CDH, fetuses with CDH were at an increased risk of preterm birth, Intra-Uterine Growth Restriction, stillbirth, and overall infant death. The 1-year mortality was 45.89%.
Koninck et al.\textsuperscript{7} evaluated retrospectively a decade of fetal intervention for CDH (2002–12). They reviewed all consecutive cases prenatally diagnosed with Right sided CDH at two fetal surgery centers in Belgium and Spain. 10 out of 86 fetuses with Right CDH had associated abnormalities. Of 76 isolated pregnancies, 8 women opted for termination of pregnancy. 19 pregnancies were expectantly managed and delivered at a mean gestational age of 36 weeks. Survival at discharge was 53\% (10/19), one being oxygen dependent. In the fetal surgery group (n = 48), mean gestational age at delivery was 34.5 weeks. In their recent experience not previously published (n = 23) survival rate was 52 and 39\% were oxygen dependent at discharge. The found data showed a 42\% survival rate in 57 fetuses. They concluded that Right-sided CDH seems to have a poorer outcome than that reported for fetuses with left-sided CDH with similar lung size before birth. Lung size on magnetic resonance imaging, and an interval of >24 hours between reversal of tracheal occlusion and delivery were predictors of outcome.

Early repair on ECMO theoretically allows for restoration of normal thoracic anatomy but entails significant bleeding risks. So, Fallon et al.\textsuperscript{8} examined the institutional outcomes of early CDH repair on ECMO. It is a retrospective review done in 2013. During 10 years period (2001-2011), 148 patients have presented to Texas Children's Hospital with the diagnosis of congenital diaphragmatic hernia. 53 patients required the use of ECMO during their hospitalization.

46 CDH patients received ECMO support with an overall survival of 53\%. 29 patients (11 early/18 late) were repaired on ECMO, while 17 patients had repair post-decannulation from ECMO. Survival was 73\%, 50\%, and 64\% for those repaired early, late, or post-decannulation, respectively. Patients who were repaired early on ECMO had a similar survival, despite their significant worse prenatal factors. The group of patients who were decannulated 6 days earlier had significantly lower circuit complications comparing to patients repaired on ECMO. Therefore, early repair after early decannulation from ECMO was associated with decreased ECMO duration, decreased circuit complications, and a trend towards improved survival.

Lusk et al.\textsuperscript{9} conducted a retrospective cohort study on infants with CDH who were treated at the University of California San Francisco Benioff Children’s Hospital between 2002 and 2012. They evaluated the natural history of pulmonary hypertension in infants with CDH, based on routine echocardiography over the first 6 weeks of life. They also evaluated pulmonary hypertension on routine echocardiography at various time points as a biomarker for predicting the risk of death and short-term pulmonary morbidity among infants with CDH. They found that of the 140 infants who are with ≥1 echo, 98 resolved their pulmonary hypertension prior to death/discharge. Mean time to resolution was 18 days (median 14 days, Inter Quartile Ranges: 8, 21 days). Those with persistence of pulmonary hypertension had a higher rate of extracorporeal membrane oxygenation and death, and fewer ventilator-free days. Persistence of pulmonary hypertension at 14 days predicted mortality and adverse respiratory outcome. They concluded that the majority of infants with CDH resolve pulmonary hypertension between 1 and 3 weeks of life. At 2 weeks of age, severity of pulmonary hypertension by echocardiogram strongly predicts short-term pulmonary morbidity and death. Further evaluation of physiological alterations during that time may lead to novel therapies for severe CDH.

Javier et al.\textsuperscript{10} compared the periods before and after the ECMO program was established in Pontificia Universidad Católica Hospital, Santiago, Chile. It is a retrospective study done using the data of all newborns with severe hypoxic respiratory failure (HRF) admitted in NICU between 1996 and 2009. Data from 259 infants were analyzed. 100 of them were born in the pre-ECMO period and 159 born after the ECMO program was established. Survival significantly increased from 72\% before extracorporeal membrane oxygenation to 89\% during the ECMO period. ECMO survival rate to discharge was 85\%. The conclusion of their analysis was that the establishment of an ECMO program was associated with a significant increase in the survival of newborns more than or equal to 35 weeks old with severe hypoxic respiratory failure.

Zani et al.\textsuperscript{11} reviewed and commented on the main aspects and controversies of postnatal CDH repair, such as timing of surgery, the different surgical approaches and patch repair, and comment on different surgical practices reported in the literature. It was published in 2014. At last, they strongly encouraged the minimally invasive way of intervention over open procedures.

Bebbington et al.\textsuperscript{12} compared test characteristics of ultrasound and magnetic resonance imaging (MRI)-derived parameters in predicting newborn survival in cases of isolated left-sided congenital diaphragmatic
hernia (CDH). They used the Children’s Hospital of Philadelphia database of the period from 2001 to 2010. They involved and studied retrospectively 85 cases. All had detailed prenatal evaluation, prenatal care, delivery and postnatal care at a single institution. They concluded that ultrasound parameters function at a similar level, whereas MRI determined parameters appear to offer better predictive value.

**Bialkowski et al.** assessed the acute effects of IV sildenafil infusion on myocardial function, pulmonary artery pressure (PAP), and oxygenation in infants with CDH. The study was done in Royal Children’s Hospital, Melbourne in 2013. A total of 9 infants received IV sildenafil after CDH repair but before enteral feeding. Their cardiopulmonary functionality was monitored closely to be analyzed and studied. The result of the study that IV sildenafil infusion was associated with improved oxygenation.

**Discussion:**

CDH is a developmental defect that results in partial or complete absence of the diaphragm. The defect in the diaphragm allows abdominal contents to herniate into the chest creating a mass effect that impedes lung development during a critical stage of normal lung development. The pathophysiology of CDH relates to the resultant pulmonary parenchymal and vascular hypoplasia. Pulmonary hypoplasia is not only a problem because of the small size. The lung structure is abnormal as well. A patient with severe CDH is highly sensitive to hypoxemia, hypotension, acidosis, and even environmental stimulation, which can precipitate pulmonary vasospasm and shunting episodes. The broad spectrum of severity in patients with CDH is dependent on the degree of pulmonary hypoplasia and pulmonary hypertension.

Balayla and Abenhaim paper evaluated the incidence and maternal risk factors associated with the development of CDH. They found that male fetuses showed a greater incidence but the difference in gender survival at the first year of life was not statistically significant. They also found that fetuses with CDH appear to be from older mothers (>40 years). In addition, they found that maternal smoking and alcohol intake are also risk factors for developing CDH. Their results also showed that CDH is a potential risk factor of adverse fetal and neonatal outcomes, such as, preterm birth, Intra-Uterine Growth Restriction, stillbirth, and infant death. As implied earlier, CDH is a risk factor for pulmonary hypertension and together can lead to poorer prognosis of the case and increase the risk of morbidity and mortality. This was mentioned clearly in Lusk et al. paper. They found that persistence of pulmonary hypertension in infants with CDH after 2-3 weeks of age is abnormal and associated with a worse prognosis with respect to survival and adverse short-term pulmonary outcomes. This information could guide clinicians in early prognostication and target infants for early, specific interventions to optimize pulmonary vascular outcomes. Speaking of which, in Bialkowski et al. group investigated the cardiorespiratory effects of intravenous sildenafil in CDH and they found that IV sildenafil infusion was associated with significantly improved oxygenation.

Balayla et Abenhaim paper illustrated the need for prompt fetal and maternal antenatal screening, and the importance of addressing maternal modifiable behaviors. In order to improve prenatal counseling for families, Bebbington et al. group compared test characteristics of ultrasound and magnetic resonance imaging (MRI)-derived parameters in predicting newborn survival in cases of isolated left-sided CDH. The parameters used in the study will not only help in the counseling. They also will help in selection of fetuses that may benefit from prenatal interventions, and will guide the planning for postnatal care. Varieties of measures have been proposed as antenatal predictors of survival in CDH. Lung size (lung-head ratio, LHR) was the most important and the most accurate parameter used in the study. Ultimately, they found that ultrasound parameters function at a similar level, whereas MRI determined parameters appear to offer better predictive value.

**DeKoninck et al.** study discussed the different outcomes and treatment response between right and left CDH. The majority of fetuses with congenital diaphragmatic hernia (CDH) defects are located on the left (85%). The right-sided defects are (15%) and bilateral (<1%) defects are less frequent. Despite the rarity of the right sided CDH patients, they managed to find 68 cases with isolated CDH. They found that Right-sided CDH seems to have a poorer outcome than that reported for fetuses with left-sided CDH with similar lung size before birth. Survival rate after expectant management with Observed/Expected Lung-to-Head Ratio (O/E- LHR) value ≤30% was 0%. In those with O/E- LHR value ≤45, their survival rate was higher (17%) but patients who are from the same group (O/E- LHR≤45) and underwent fetal surgery (such as FETO), there was an apparent increase in the survival rate (42%).

Speaking of fetal surgeries and intervention, we have to start mentioning the important debates in CDH management. FETO is an endoscopic fetal surgery called fetal endotracheal occlusion and it is done by insertion of a balloon into the trachea to occlude it most preferably at around 27th week of gestation. The idea behind it is to prevent outward movement of pulmonary fluid. The retention of lung fluid may...
improve lung expansion and even possibly promote reduction of the viscera into the peritoneal cavity. The placement of a “tracheal clip” may accelerate lung growth and avoid the development of fatal pulmonary hypoplasia. Moreover, as mentioned in Ali et al. paper, endoscopic techniques showed lower rates of preterm labor and other complications than open fetal surgery. Ali et al. study evaluated the influence of premature delivery on the prognosis and the survival of the CDH infants who underwent fetal endotracheal occlusion (FETO). They found that the majority of CDH infants who had undergone FETO delivered prematurely and the survival rate in those born prematurely compared to those born at term was significantly lower, particularly if delivery was prior to 34 weeks of gestation. The influence of premature delivery on survival rates of CDH infants is similar to that reported in “non FETO” CDH infants. Therefore, their results emphasize the need to reduce premature delivery following FETO and they are useful to inform counseling of parents.

Speaking of controversies, A. Zani A et al. 11 paper discussed many aspects about different CDH surgical interventions and the question was “which is better (open or minimally invasive repair?)”. Zani A et al. 11 concluded that the main novelty in the surgical treatment is related to the use of minimally invasive techniques. Minimally invasive procedures carried out either via the chest or via the abdomen, have similar advantages in terms of decreased postoperative pain and improved wound cosmesis. However, several cases showed that thoracoscopic repair increase the risk of intraoperative acidosis and hypercapnia as well as higher hernia recurrence rate. On the other hand, in laparoscopic repair, the main disadvantages are the difficulty in visualizing the diaphragmatic defect and in reducing of the herniated organs.

In the past, surgeons used to operate CDH as emergency repair immediately after birth. Lately, they have tended to be patient for one day or two of close observation and stabilization. It was also mentioned in Lusk et al. 9 paper that pulmonary hypertension severity decreases with time which causes a little bit of improvement in lung functionality especially oxygenation. One of the interventional techniques that has been used in order to achieve more stabilization is ECMO. ECMO stands for extracorporeal membrane oxygenation. The ECMO machine is similar to the heart-lung by-pass machine used in open-heart surgery. It pumps and oxygenates a patient's blood outside the body via a large cannula, allowing the heart and lungs to rest. When the patient is connected to an ECMO, blood flows through tubing to an artificial lung in the machine that adds oxygen and takes out carbon dioxide. Then, the blood is warmed to body temperature and pumped back into the body 18.

Javier KA et al. 10 Study evaluated the impact of ECMO on the survival and outcome of newborn infants with severe hypoxemic respiratory failure among multiple conditions groups. They found that the establishment of an ECMO program was associated with a significant increase in the survival of newborns more than or equal to 35 weeks old with severe hypoxic respiratory failure. The CDH group had the greatest benefit in terms of increased survival. Nevertheless, the optimal timing of repair for CDH in patients requiring ECMO is controversial 9. Hernia repair during ECMO may improve respiratory function by restoring normal anatomy. However, there is increased risk of complications, particularly, surgical bleeding because of the requirement for systemic anticoagulation during ECMO support. Partridge et al. group tackled this issue and measured the different outcomes from the timings of the repair whether it was prior to, during, or after decannulation from ECMO 4.

The outcomes showed an improvement in CDH patients undergoing surgical repair following ECMO with significantly increased survival. It also resulted in lower rates of surgical bleeding, and decreased total duration of ECMO therapy compared to patients repaired on ECMO. So, it is recommended for patients who can be successfully weaned from ECMO, to delay their repair and make it after decannulation from ECMO in order to achieve reduced operative morbidity and increased survival 8.

In conclusion, prenatal counseling for parents is too important in order to prepare the families for any outcome of the condition and every level of severity. It should be done by educating the parents adequately about all the modifiable risk factors that might contributed in the occurrence of the hernia, for example, maternal smoking and alcohol intake. These risk factors should be stopped immediately to prevent further damage such as premature delivery, which is a contributor to the high incidence of morbidity and mortality observed in this condition. Also, they should be stopped to reduce the risk of recurrence in future pregnancies. One of the prenatal screening modalities for CDH that should be standardized is Ultrasound. Ultrasound can detect CDH to some extent and measure the LHR, which is one of the major prediction’s parameters of CDH prognosis and survival. Early detection is not important only for the counseling. In addition, it gives the surgeons the opportunity for early intervention such as FETO. FETO is minimally invasive procedure and this type of procedures is recommended to some extent because as implied earlier in some of the studies, it is highly
beneficial with lower complications rate than open fetal surgery. The key here is to prevent prematurity following FETO because it was common and associated with significantly greater mortality especially before 34th week of gestation.

Limitations and Strengths:
The number of the included studies is large which provided us a broad spectrum of results and points to discuss. We covered high number of controversies and debates. During the selection, we double-reviewed the studies and we made sure that the studies included we included are fit to be considered as major study, despite some of them were finalized upon small sample size which might provide bias to the review. This can be related to the rarity of the condition. In addition, we used the filter of the search engine to limit the result to the last 5 years only.

The absence of clear guidelines regarding CDH management motivates us to conduct further studies about every single type of intervention.

REFERENCES