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NEW PERSPECTIVES OF FETAL NUCLEAR MAGNETIC RESONANCE IMAGING IN THE DIAGNOSIS AND MANAGEMENT OF CONGENITAL DIAPHRAGMATIC HERNIA

DOCTORAL THESIS ABSTRACT

PhD coordinator:
PROF. UNIV. DR. VLĂDĂREANU RADU

PhD student:
NEȘTIANU ERICK GEORGE

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1. Congenital diaphragmatic hernia and pulmonary hypoplasia

Congenital diaphragmatic hernia (CDH) is part of a diverse group of developmental diaphragm defects that allow abdominal organs to move into the thoracic cavity. CDH has an incidence of 1 in 2500-4000 births and a mortality rate of 30-60% due to pulmonary hypoplasia. Despite advancements in antenatal screening and postnatal treatments, the mortality rate remains high, ranging from 20% to 60% [1]. Currently, the antepartum detection rate of diaphragmatic hernia is approximately 60%.

The cause of diaphragmatic hernia remains uncertain and is believed to be multifactorial, involving genetic, environmental, and nutritional factors. CDH is considered an isolated condition in about 50-60% of cases, while it is associated with other congenital anomalies in 40-50% of cases [2]. Some genetic syndromes, such as Donnai-Barrow syndrome, Tonne-Kalscheuer syndrome, and Fryns syndrome, always include CDH. In other syndromes, CDH occurs incidentally.

Targeted studies have identified the most common structural genetic abnormality as the deletion of chromosome 15q. Transmission of congenital diaphragmatic hernia, whether in consanguineous or non-consanguineous cases, appears to be autosomal recessive linked to the X chromosome. Additionally, alterations in the retinoid-signaling pathway may play a role in CDH development, as vitamin A deficiency has been experimentally shown to contribute to its occurrence [3].

CDH results from changes in essential components of the diaphragm, namely the transverse septum and pleuroperitoneal membrane. The key ultrasonographic signs include the visualization of abdominal organs migrating into the thoracic cavity and the deviation of the mediastinum contralateral to the hernia. In mild cases where the defect is small and fewer abdominal organs are herniated, the condition may be identified later.

In terms of prognosis, cases with isolated CDH have better survival than those with CDH associated with other chromosomal pathologies, even if these are related to single gene alterations or occur in complex genetic syndromes. The coexistence of malformations involving the cardiovascular system makes the prognosis even more reserved.

By far the most important prognostic factor is the degree of lung hypoplasia. Pulmonary hypoplasia is an abnormality defined by morphologically and functionally incomplete development of the lung. It is characterized by both reduced lung tissue and reduced blood flow that would allow the newborn to breathe on its own.

The exact incidence of CDH is not well established, with some studies reporting 1.4/1000 of all births and between 9.9 to 1.1/1000 live births [4]. The Fetal Medicine Foundation estimates the prevalence to be 1 in 50,000 births. Although the etiology of this condition is not entirely known, several conditions are essential for normal lung development "in utero." These include normal rib cage conformation, the presence of fetal respiratory movements, lung fluid at positive pressure, and a normal volume of amniotic fluid [5].

Changes leading to lung hypoplasia occur in the early stages of lung development, which is divided into five developmental stages: embryonic (Day 22 - week 6), pseudoglandular (weeks 5 - 17), canalicular (weeks 16 - 25), saccular (week 24 - until birth), and alveolar (week 36 to about 8 years) [6]. Fetal respiratory movements stimulate the growth of platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), and thyroid transcription factor 1 (TTF-1) [7].

There is currently no 'gold standard' for assessing lung development. The most common criterion used is the lung-to-body weight ratio, with a normal ratio considered to be 0.012 for girls older than 28 weeks and 0.015 for those below this gestational age [8]. Intrauterine suspicion of pulmonary hypoplasia diagnosis is suggested by biometric changes observed on 2D ultrasound, including altered lung area, thoracic circumference, the ratio between thoracic and abdominal circumference, and normal biometry (CT/CA). More accurate and predictive assessments of lung hypoplasia can be obtained through lung volume assessment using 3D ultrasonography or MRI [9].

Recent scientific advancements have introduced various therapies for CDH. The modern FETO (fetal endoscopic tracheal occlusion) technique involves inserting a balloon into the fetus's trachea to produce tracheal occlusion, allowing lung fluid to accumulate and expand the lung. Surgical options include minimally invasive laparoscopy, tracheoscopy, and classical surgical techniques. Defects can be repaired using synthetic or biological patches, abdominal or thoracic muscle flaps, and biomaterials.

Postpartum ventilation of infants with pulmonary hypoplasia due to CDH is particularly challenging. Surfactant administration is not beneficial for term and preterm infants with CDH. Nitric oxide is the preferred therapy to relieve pulmonary hypertension [10]. For left ventricular dysfunction, Milrinone, a phosphodiesterase-3 inhibitor, is used, along with Sildenafil, Bosentan, PGE1 (Prostaglandin E1), PGI2 (Prostaglandin I2), and prostacyclin. The final therapeutic option for eligible children who do not respond to drug therapies is ECMO (extracorporeal membrane oxygenation).

2. Congenital diaphragmatic hernia imaging and lung hypoplasia

The most common method for examining a fetus is through ultrasonography, specifically fetal ultrasound or screening ultrasound for fetal malformations during the second trimester of pregnancy. The optimal time for this ultrasound, as recommended by the Fetal Medicine Foundation (FMF), is between 18 and 23 weeks of gestation.

The purpose of the ultrasonographic examination is to confirm normal morphology, study the normal echogenicity of the lung parenchyma, indicate the normal shape, morphology, and position of the mediastinum and heart, and note the normal shape of the diaphragm or any possible pleural effusions [11]. For the sonographic examination of the lung, it is sufficient to examine the lung in the "four-chamber" section.

Ultrasonographic diagnosis of diaphragmatic hernia is possible in 90% of cases in patients with stomach and intestinal loop herniation, but only in about 50% of cases when patients present with liver herniation. Antenatal diagnosis of pulmonary hypoplasia remains the greatest challenge for the examiner since the subsequent prognosis of the fetus depends significantly on this evaluation.

The significant disparity between the clinical significance of pulmonary hypoplasia and the imaging findings has led to the development of various ratios and measurements to better stratify the severity of the condition. Among these measurements are the following:

- Lung area to cranial circumference ratio (LHR) (poor prognosis at values less than 1).
- fetal chest circumference reduction
- chest circumference to abdominal circumference ratio less than 0.615
- femur length/abdominal circumference ratio less than 0.1615.
- an abnormally low lung-to-body weight ratio

An LRH (lung-to-head ratio) of less than 1 is associated with a poor prognosis [12]. An LRH value between 1 and 1.4 indicates the need for postpartum ECMO (extracorporeal membrane oxygenation), while an LRH value greater than 1.4 suggests a better prognosis.

Fetal MRI is considered the best method for investigating fetal pathology when ultrasound does not provide sufficient information. There has been a significant and continuous increase in the indications for this method. The most common indications for

fetal MRI include ventriculomegaly, neural tube defects (such as spina bifida), intracranial hemorrhages, lissencephaly, tumor masses in the neck, congenital diaphragmatic hernia, and abdominal masses [13].

Several standard sequences are generally used in fetal MRI, each providing specific benefits. T2-weighted sequences are commonly employed due to their high spatial resolution, which differentiates adjacent structures and blood vessels.

The optimal period for fetal MRI is between 26 and 32 weeks of gestation. In fetuses with CDH, fetal MRI provides additional information about the herniated organs and the degree of herniation. It also differentiates between liver herniation and the hypoplastic lung, which can be challenging to distinguish via ultrasound due to their similar echogenicity [14].

One of the primary uses of fetal MRI is the assessment of pulmonary hypoplasia in CDH. MRI can make volumetric determinations of the lungs and calculate the degree of pulmonary hypoplasia. Currently, the most accurate tool for predicting fetal survival is total fetal lung volume (TFLV) measured by fetal MRI [15]. A TFLV percentage below 35% is considered unfavorable and is associated with a high neonatal mortality rate.

3. Work hypothesis and general objectives

In developing this thesis, we aimed to address several questions related to CDH, focusing on modern methods of antenatal diagnosis and exploring potential new means of assessing disease severity to improve therapeutic management. Advances in medical imaging and radiology have introduced new methods for evaluating the cardiorespiratory risk associated with CDH. These advancements enable early diagnosis, which, combined with modern treatment techniques, can significantly impact therapeutic management.

As mentioned earlier, ultrasonography is the primary screening method used by gynecologists for antenatal diagnosis of CDH [16]. While it is a reliable method for detecting CDH, there are complex cases where standard ultrasonography may not provide all the necessary information, and there are instances where the diagnosis may be missed. Therefore, we decided to examine the role and benefits of MRI in diagnosing and assessing CDH. Despite being an advanced technique, MRI has been used for several years, though debates continue regarding its precise role in CDH. In Romania, its use remains relatively limited due to a lack of experienced personnel and the small number of specialized maternal-fetal medicine centers [17].

The hypotheses that guided the choice of this topic are as follows:

1. CDH is a rare pathology that isn't investigated rigorously enough by ultrasound in our country.
2. MRI investigation of CDH is not widely used in current practice due to a lack of experienced personnel and difficult access to this imaging technique.
3. When used as a diagnostic investigation, MRI can provide more information than is commonly used in current practice, and other parameters can be analyzed.

Building on these hypotheses and examining the present state of medical knowledge, we concluded that this topic holds scientific significance warranting further investigation, leading us to establish the following objectives:Clarifying the indications for MRI examination.

1. Establishing the advantages of the method.
2. Identifying the limitations of MRI exploration.
3. Analyzing the ability to assess the severity of CDH.
4. Finding new parameters that can help in diagnosis and severity assessment.
5. Diaphragmatic defect analysis.
6. Analysis of the ascending organs through the diaphragmatic defect.

The study was conducted sequentially. Due to the focus on a rare pathology, the patient groups were small and fewer parameters were analyzed at the beginning of the research. Each study in this thesis explored different elements and sought new correlations, particularly by comparing MRI and ultrasound techniques.

4. General research methodology

This is a retrospective multicenter study. Data were collected between January 2017 and December 2023 from two university hospitals in Bucharest and a private imaging center. The inclusion criteria are as follows:

- patients in whom routine fetal morphology ultrasound revealed or raised the suspicion of CDH, which was subsequently explored using MRI;
- Presence of unilateral CDH as the only malformation detectable by ultrasound and MRI;

- Single pregnancy;
- Pregnancy that occurred naturally without the use of in vitro fertilization techniques;
- Patients who underwent a single MRI during pregnancy, if multiple examinations were performed, only the first investigation was considered.

A total of 60 patients were enrolled at the time of the thesis. After applying the exclusion criteria, we were left with a group of 50 patients.

The ultrasound examinations were conducted using modern equipment adapted for the study of fetal morphology and approved by national and international guidelines provided by the International Society of Ultrasonography in Obstetrics and Gynecology (ISUOG), such as Voluson™. High-frequency probes and dedicated obstetric protocols were used. The physicians operating these machines underwent training and are accredited in morpho-fetal explorations.

The MRI examinations utilized 1.5 Tesla machines, as required by current protocols, using abdominal antennas. Although fetal sedation with 7.5 mg Zopiclone is still used to reduce movement artifacts, we opted for fast sequences that minimize motion artifacts and avoid sedatives as long as the examination quality was satisfactory. Various sequences can be used during the examination, with names and acronyms differing by equipment manufacturer. For simplicity, we will refer to these sequences by their generic names and acronyms.

The most common and significant sequence in fetal examination is single-shot fast spin-echo (SSFSE). It offers many advantages, particularly that in the case of motion artifacts, only the section acquired at the time of fetal movements is affected, leaving other sections uncompromised. [18]

T1-weighted images represent another common sequence used in current practice. Although less useful than SSFSE, it is still essential for obtaining a quality examination. These images are obtained using two-dimensional gradient echo sequences (2D GRE).

Diffusion-weighted sequences can be used in selected cases, showing greater utility in central nervous system explorations.

In most cases in our study, SSFSE and 2D GRE sequences were sufficient for diagnosis and risk stratification. Acquisitions were performed in all three planes (axial, sagittal, and coronal) of the fetus, with the mother positioned in dorsal or lateral decubitus.

Prior authorization for the studies was obtained from the ethics committees of the hospitals and the private center. Patient examinations were anonymized before data processing.

Numerous parameters characterizing both the mother and fetus were analyzed. These include: gestational age; affected hemidiaphragm; location of the herniation (anterior or posterior); fetal sex; direction of cardiac deviation; lung area of the contra-lateral lung to the diaphragmatic defect; cranial circumference measured in mm by MRI; individual lung volume; total lung volume, obtained by summing the left and right lung volumes; transverse diameter of the diaphragmatic defect; the antero-posterior diameter of the diaphragmatic defect; the antero- posterior diameter of each hemi-diaphragm at the anterior and posterior costo-diaphragmatic sinuses between the inner ribs; the transverse diameter of each hemi-diaphragm at the level of the lateral costo-diaphragmatic and costomediastinal sinuses; the area of the diaphragmatic defect; the area of each hemi-diaphragm in mm^2 ; the thoracic transverse diameter measured at the level of the lateral costo-diaphragmatic sinuses between the internal costal margins anterior-posterior thoracic diameter at the 4-chamber equivalent level measured from the level of the anterior edge of the vertebrae to the level of the posterior sternal surface; transverse thoracic diameter at the 4-chamber equivalent level measured between the internal edges of the ribs; thoracic area measured in mm^2 at the level of the 4 chambers in mm, following the internal edge of the chest wall, vertebrae, sternum and ribs; the thoracic circumference, measured in mm at the level of the 4 chambers, following the outer edge of the ribs, sternum, spinous and lateral processes; the thoracic volume; the organs ascending into the thoracic cavity and their number; the presence of ascites, pleurisy or pericarditis; the LHR index obtained by ultrasound; the perinatal mortality, up to the time of discharge of the newborn.

5. Severity assessment using MRI techniques

Due to the lack of a study providing standardized lung volume according to gestational age for the Romanian population, we decided to review the literature to see if the currently accepted values show a statistically significant correlation. The study aims to find reference values that correspond best to our country to be further used as references.

After calculating the total lung volume by MRI using the planimetry technique, we obtained the ratio between the observed and the expected value (severity index) for all 4 studies. We also used the mean between the four studies as another reference value. [19-22].

After calculating the severity index, patients were divided into severity categories according to the percentage of missing lung volume according to the ranges used in current practice.[23]

Patients died in 64% of cases. The correlations between severity index value and mortality were statistically significant regardless of the reference values used.

Regarding the correlation between severity categories and mortality, there is no statistically significant relationship between them, regardless of the reference values used.

The only two studies that came close to statistical significance correlation were Rypens et al. and Meyer et al.

A higher statistical significance is however observed when using the reference values provided by the Rypens et all group. It is observed that the p-value is generally lower in this case, even reaching very close to the statistical threshold of 0.05 for the maximum severity group where the p-value is observed to be 0.0502.

Moreover, another factor that attests to the superiority of the values offered by the Rypens et al. study is the r-squared parameter. A higher value indicates a better ability to predict survival in our study.

Thus, after analyzing the data, we can observe that among all the values used to predict normal fetal lung volume, the most relevant for the population of which this study is part, are those provided by the group Rypens et al.

For our population, the best reference values for normal fetal lung volume are those obtained by Rypens et al. Although all reference values showed a very good statistical correlation with mortality, when the same analysis was performed after dividing patients into groups according to severity, the values closest to statistical significance were observed when using the study by Rypens et al.

6. Differences in severity assessment between ultrasound and MRI using LHR

The aim of this study is to compare the severity assessment capabilities of ultrasound using the LHR with that of MRI. From an accessibility perspective, patients have easier access to ultrasound examinations compared to MRI examinations.

We gathered LHR index values, representing the ratio between the observed and expected LHR, for all patients from their ultrasonographic reports. This data was then analyzed for its correlation with mortality. Using MRI examinations, LHR MRI was calculated following the method described by Jani et al. [24]. Measurements of fetal head

circumference and lung area on the contralateral side of the diaphragmatic defect were taken at a section equivalent to the 4-chamber ultrasound section. The LHR MRI value was then calculated by dividing the lung area by the cranial circumference.

Based on the LHR MRI value, the ratio of the measured values to the reference values for gestational age (LHR MRI index) was calculated using data from the study by Jani et al. [25]. The analysis of the correlation between the LHR MRI index and mortality revealed a high statistical significance, consistent with literature showing a strong predictive value between these two parameters [12].

However, while a strong association was found between the LHR MRI value and mortality, no statistical correlation was observed between the LHR MRI index and mortality. Additionally, correlation analysis between severity groups using LHR MRI index values and mortality showed no statistically significant correlations and no values approaching statistical significance.

The overall survival rate was 36%, lower than that suggested by other authors. When patients were divided by severity grades, the discrepancy was noticeable depending on the assessment method. Using the classic ultrasound method, survival was 61.9% in the mildly affected group, 31.25% in the moderately affected group, and 0% in the severely affected group. Using the MRI method for calculating LHR, the survival rates were 38.3% in the mildly affected group and 0% in the other two groups.

Tracking the correlation between severity groups determined using the LHR MRI index and mortality did not show a statistically significant relationship. Analyzing the data, we can state with certainty that risk stratification using ultrasound can be done with a high degree of accuracy using both LHR values and the LHR index. Recent studies have even demonstrated the superiority of the LHR index over the simple use of LHR values [26].

Regarding the calculation of LHR using MRI, we can conclude that in its current form, it does not hold diagnostic or prognostic value. Although the mathematical calculation of LHR MRI showed a statistically significant correlation with mortality, the use of the LHR MRI index did not demonstrate such an association.

7. Assessment of the impact of diaphragmatic herniated structures and other associated conditions on survival and severity

This study aimed to evaluate MRI's effectiveness in visualizing the topography of CDH, identifying herniated organs in the chest, and quantifying the number of organs that migrated through the diaphragmatic defect. Additionally, we examined the presence of associated conditions such as pleural, pericardial, and peritoneal effusion.

For this study, MRI data were collected on the laterality and anteroposterior position of the diaphragmatic defect. Normal thoracic structures, including the heart, lungs, and vascular elements, were identified, and all abdominal structures elevated to this level were differentiated. Special attention was paid to the presence of the liver and stomach in the thoracic cavity.

The study observed a left-sided predominance of CDH in 86% of cases, with right-sided herniation in only 14% of cases [27]. Posterior defects were predominant in about two-thirds of the cases, with the remaining defects positioned anteriorly.

Analyzing the organs that ascended through the diaphragmatic defect, intestinal loops were most commonly observed, followed by colonic segments and the stomach. Intestinal loops and colonic segments were seen in all 50 cases in the study. Stomach ascension was noted in 74% of cases. Although some authors have reported a significant correlation between gastric herniation and worse postnatal prognosis, our study did not find such an association in univariate analysis with mortality.

Liver herniation was observed in 36% of subjects. While univariate statistical analysis did not show a significant correlation with mortality, a multiparametric analysis, including the severity index, revealed a statistically significant correlation, indicating that liver herniation significantly increases mortality.

MRI examination demonstrated excellent capability in delineating lung parenchyma from other herniated organs. It proved to be a high-performance technique, effectively confirming the herniation of digestive organs and identifying their components. The most significant advantage of MRI was its ability to separate the collapsed lung from other parenchymal structures.

8. Assessment of diaphragmatic defect size and its effect on prognosis and the diaphragm

This study aims to explore the ability of MRI to quantify the size of the diaphragmatic defect, providing additional prognostic information for patients. We attempted to accurately

measure the maximum anteroposterior and transverse diameters of the diaphragmatic defect. Often, direct visualization of the diaphragmatic leaflets was not clear, so we measured the area where clear ascension of intra-abdominal organs was observed.

After measuring these two diameters, the area was calculated using the classical formula for the area of an ellipse. Similarly, the area of the affected hemidiaphragm was calculated. We measured the maximum anteroposterior and transverse diameters of each hemidiaphragm at the costal-diaphragmatic sinuses.

After calculating these two areas, we determined the ratio between the area of the diaphragmatic defect and the area of the hemidiaphragm. Patients were then categorized into groups based on this ratio [28].

We found a strong correlation between both the size of the diaphragmatic defect and mortality and between the diaphragmatic index (the ratio of the diaphragmatic defect area to the affected hemidiaphragm area) and mortality. High statistical significance was observed when analyzing severity and mortality for groups A and B. Unfortunately, groups C and D did not show statistical significance in correlation with mortality [29].

Addressing the relationships between diaphragmatic impairment groups and severity index, statistically significant correlations were obtained in multiparametric analysis in nearly all cases. Groups A, B, and C showed the strongest correlations, while group D showed minimal loss of statistical significance.

The size of the diaphragmatic defect is a critical element to consider in diagnostic workup and surgery. Its predictive value has been demonstrated numerous times in the literature, and our study confirms these findings. We recommend measuring the diaphragmatic defect in each patient and calculating the diaphragmatic index. Although we did not analyze the fidelity of the measurements in this study, there is a clear correlation between imaging and intraoperative findings. We also recommend that multidisciplinary committees discuss the usefulness of 3D modeling based on MRI images. This relatively new technique may improve therapeutic management and family counseling, and it is likely to be adopted by more centers in the future.

9. Exploring individual lung volume impairment in CDH and chest biometry

In this study, we aimed to further analyze the relationship between individual lung volumes and certain pathological elements such as the size of the diaphragmatic defect, its position, and herniated organs. We began by calculating individual lung volumes using the

planimetry method. Similar to the assessment of overall pulmonary hypoplasia severity, each lung was analyzed to classify it into a severity group based on the ratio of observed values to those predicted by the literature. The same intervals as in the initial study were used.

In addition, we examined the anteroposterior and transverse diameters of each hemidiaphragm to identify potential changes in thoracic symmetry. These measurements were compared with predicted values from the literature, specifically using data from the ultrasound study conducted by the group led by Lian et al. [30].

The relationship between the lung volume, the lung index of the lung ipsilateral to the diaphragmatic breach, and the contralateral lung index on survival showed high statistical significance. However, when a multiparametric analysis of these two values versus survival was performed, the statistical significance for the ipsilateral lung index was lost, while the contralateral lung index remained strongly significant. This suggests that the contralateral lung index is a more critical factor in determining survival.

Statistically significant relationships were also observed when analyzing the correlation between left and right lung volumes with the global severity index, and between individual lung indices and the global severity index. Uniparametric and multiparametric analyses demonstrated that a greater difference between the transverse diameters of the hemidiaphragms had a high statistical significance in correlation with mortality. Additionally, the relationship between the difference in transverse hemidiaphragm diameters and mediastinal laterolateral deviation with severity was investigated. A strong statistical correlation was found, indicating that greater mediastinal deviation increases the degree of severity [31].

This study has demonstrated several critical elements related to the morphopathogenesis and progression of CDH. One key finding is that the lung volume contralateral to the diaphragmatic breach has a greater impact on predicting mortality and determining the degree of severity. The underlying pathophysiologic mechanisms for these phenomena remain unclear and require further investigation.

The study also confirmed the presence of certain alterations in usual thoracic biometric parameters, particularly demonstrating an important relationship between the transverse thoracic diameter and the degree of severity. Moreover, a significant relationship was found between the degree of mediastinal deviation and the severity index. These findings highlight the complex interactions between lung volumes, thoracic asymmetry, and mediastinal structures in the progression and severity of CDH.

10. General discussion of the thesis

Despite its rarity, CDH is a complex disease with a significant impact on patients. As emphasized throughout this thesis, many aspects of the disease are well understood and utilized in current practice. Antenatal diagnosis is becoming more frequent and reliable, with undiagnosed cases generally stemming from unmonitored pregnancies. Major improvements have been observed not only in the diagnosis but also in the development of numerous parameters to help clinicians more accurately assess the severity and prognosis of CDH. Ultrasound is mainly used in current practice due to its quick and accessible nature in most clinics and hospitals. However, there is an increasing need to complement initial ultrasound examinations with modern MRI techniques, which offer significant benefits both in confirming the diagnosis and providing valuable supplementary information for clinicians [32].

Risk stratification is one of the most debated topics in the antenatal exploration of CDH. Recent years have seen a decrease in morbidity and mortality due to better diagnosis, improved ante- and post-natal protocols, and advanced antenatal operative and therapeutic techniques. This progress is encouraging and indicates tangible improvements in diagnostic and therapeutic approaches for CDH patients. The most crucial aspect in severity assessment is using appropriate reference values. Anthropometric differences between regions can significantly alter the severity assessment, and correct classification into severity groups can change therapeutic management both antenatally and postnatally. It is advisable to conduct a dedicated study in our country to establish reference values for fetal lung volumes according to gestational age [12,33-35].

Another crucial factor in risk stratification is the analysis of herniated organs, particularly the presence of the liver. The liver's presence is a major negative prognostic factor, critical for antenatal therapeutic management and surgical preparation. Some authors suggest quantifying the amount of liver ascending into the thorax, as it could be an even more important prognostic parameter than total lung volume. This raises questions about whether a large volume of herniated liver results from a small lung volume or vice versa. These questions need further exploration to better understand CDH [36,37].

The presence of other abdominal organs ascending through the diaphragmatic defect, especially the stomach, is also vital for operative preparation. The prognostic value of stomach ascension is debated in the literature. Some believe it's enough to note the stomach's ascension, while others consider its position relative to the heart more important. Another

group suggests quantifying the stomach's volume. The common view is that the stomach's position reflects changes that impact severity more than the stomach itself. Future studies should explore these aspects in larger patient groups and include postnatal correlation of antenatal ultrasonographic and MRI findings with surgical or anatomopathologic outcomes [23,38,39].

Specific ultrasound methods for assessing severity, such as the LHR ratio, are used, though not as accurate as 3D ultrasound or MRI. MRI will never replace ultrasound as a screening method, but ultrasound alone is insufficient for a complete malformational workup. These imaging techniques complement each other, each providing unique information about patients.

The primary cause of CDH is a diaphragmatic defect, which can only be accurately assessed by MRI, as ultrasound cannot precisely describe its position and size. Further studies are needed to understand the ability to assess the defect accurately and its dynamics throughout gestation. The most important aspect is correlating MRI findings with intraoperative findings. Our study showed MRI's ability to describe the defect's position and size, though operative protocols could not be obtained for further correlation. Changes in thoracic biometry related to severity and mortality were observed, indicating potential future elements for risk stratification, especially in ultrasound explorations. In MRI or 3D ultrasound, calculating total lung volumes for risk assessment and subsequent therapeutic decisions is recommended.

Management and therapeutic decisions should always be tailored to the patient. The information provided by current imaging scans, whether ultrasound or MRI, is indispensable and should be obtained as soon as possible after pathology discovery. The timing of the pathology may influence the multidisciplinary committee's decision to terminate the pregnancy or attempt a fetoscopic procedure.

11. General conclusions of the thesis

MRI examination has shown an excellent ability to complete the fetal malformation workup in patients with CDH. We believe that all patients suspected of this pathology should be further investigated by MRI for diagnostic confirmation. Even if ultrasonographic examinations are satisfactory, highlighting diaphragmatic organs and accurately calculating the LHR, an MRI examination is still recommended to complete the diagnosis and assess

lung volumes. We recommend fetal MRI in all cases, as it represents an essential investigation in the complete workup of patients suffering from CDH.

For the Romanian population, the predicted lung volume values according to gestational age provided by the team led by Rypens et al. have proven to be reliable. Compared to other reference values explored in this thesis, these are the closest to our population, providing the most accurate severity assessments. This does not demonstrate the inferiority of other studies but rather highlights the importance of using reference values tailored to the target population. In the future, conducting a study to establish baseline values for our population will be a critical step in improving the diagnostic quality of MRI, allowing for the most accurate severity assessments.

The main advantage of MRI is its excellent ability to measure lung volumes, providing a highly accurate assessment of the patient's severity. This is a significant advantage over standard ultrasound. Recent advancements in ultrasound techniques have led to the development of 3D ultrasound exploration methods, such as the VOCAL technique, which allows for the calculation of lung volumes. However, these techniques are currently less accessible in our country compared to MRI. Over time, 3D ultrasound may become more accessible, but MRI will still offer additional benefits, such as the ability to calculate the liver volume ascending through the diaphragmatic breach, a critical parameter for assessment.

One common limitation of MRI is its limited accessibility due to the small number of centers offering this examination. However, the number of physicians using this examination has been increasing in recent years. MRI examinations are time-consuming and prone to motion artifacts, but modern acquisition techniques have shortened examination periods and greatly reduced motion artifacts.

MRI's ability to assess the size and position of the diaphragmatic defect has been demonstrated. Although characterizing the diaphragmatic defect is not yet part of the standard assessment protocol, it should still be investigated. The best way to describe the diaphragmatic breach in terms of size is still unclear, and there is no standardized classification. Future studies should focus on developing standardized methods for measuring and grading these defects, correlating imaging findings with surgical or pathologic findings. These efforts could significantly impact therapeutic management both antenatally and postnatally.

Another important finding from this thesis is the greater significance of lung volume contralateral to the diaphragmatic defect in determining the degree of severity. This

phenomenon is not fully understood and requires further exploration. Future studies might change antepartum therapeutic procedures, such as the FETO technique, if it is shown that improving single lung volume yields greater benefits. With advancements in fetoscopic techniques and new therapeutic materials, single main bronchial obstruction may become possible.

Chest biometry is another element significantly affected by CDH. Higher values compared to reference values were generally observed, likely due to abdominal organs exerting passive pressure on the rib cage, causing its expansion. The transverse thoracic diameter appears to be the best biometric index for assessing patient severity, with significant correlations with both mortality and severity index.

In conclusion, although CDH has been known for a long time, there is still much room for improvement in its diagnosis and treatment. It is a rare disease, but a major cause of morbidity and mortality, with patients potentially experiencing sequelae years after surgery. This thesis demonstrates the evolution of diagnostic techniques and the improvement of therapeutic approaches, leading to increased survival rates. However, further exploration is needed to address insufficiently studied elements and improve therapeutic management.

Selective Bibliography

[1] Juretschke LJ. Congenital diaphragmatic hernia: update and review. J Obstet Gynecol Neonatal Nurs 2001;30:259–68.

[2] Longoni M, Pober BR, High FA. Congenital Diaphragmatic Hernia Overview. GeneReviews® [Internet] Seattle (WA): University of Washington, Seattle; 1993-2024 Available from: Https://WwwNcbiNlmNihGov/Books/NBK1359/ 2006.

[3] Ishaq MU, Kunwar D, Qadeer A, Komel A, Safi A, Malik A, et al. Effect of vitamin A on maternal, fetal, and neonatal outcomes: An overview of deficiency, excessive intake, and intake recommendations. Nutrition in Clinical Practice 2024;39:373–84. https://doi.org/10.1002/ncp.11096.

[4] Hamidi H, Weerakkody Y. Pulmonary hypoplasia. Radiopaedia.org, Radiopaedia.org; 2011. https://doi.org/10.53347/rID-13372.

[5] PORTER HJ. Pulmonary hypoplasia. Arch Dis Child Fetal Neonatal Ed 1999;81:F81–3. https://doi.org/10.1136/fn.81.2.F81.

[6] Warburton D, El-Hashash A, Carraro G, Tiozzo C, Sala F, Rogers O, et al. Lung Organogenesis. Curr Top Dev Biol 2010;90:73–158. https://doi.org/10.1016/S0070-2153(10)90003-3.

[7] Inanlou MR, Baguma-Nibasheka M, Kablar B. The role of fetal breathing-like movements in lung organogenesis. Histology and Histopathology Cellular and Molecular Biology, Doi: 1014670/HH-201261 2005:1261–6.

[8] WIGGLESWORTH JS. Pathology of the lung in the fetus and neonate, with particular reference to problems of growth and maturation. Histopathology 1987;11:671–89. https://doi.org/10.1111/j.1365-2559.1987.tb02682.x.

[9] Triebwasser JE, Treadwell MC. Prenatal prediction of pulmonary hypoplasia. Semin Fetal Neonatal Med 2017;22:245–9. https://doi.org/10.1016/j.siny.2017.03.001.

[10] (NINOS) TNINOSG. Inhaled Nitric Oxide and Hypoxic Respiratory Failure in Infants With Congenital Diaphragmatic Hernia. Pediatrics 1997;99:838–45. https://doi.org/10.1542/peds.99.6.838.

[11] Salomon LJ, Alfirevic Z, Berghella V, Bilardo CM, Chalouhi GE, Da Silva Costa F, et al. ISUOG Practice Guidelines (updated): performance of the routine mid-trimester fetal ultrasound scan. Ultrasound in Obstetrics & Gynecology 2022;59:840–56. https://doi.org/10.1002/uog.24888.

[12] Lipshutz GS, Albanese CT, Feldstein VA, Jennings RW, Housley HT, Beech R, et al. Prospective analysis of lung-to-head ratio predicts survival for patients with prenatally diagnosed congenital diaphragmatic hernia. J Pediatr Surg 1997;32:1634–6. https://doi.org/10.1016/S0022-3468(97)90471-1.

[13] Gatta G, Di Grezia G, Cuccurullo V, Sardu C, Iovino F, Comune R, et al. MRI in Pregnancy and Precision Medicine: A Review from Literature. J Pers Med 2021;12:9. https://doi.org/10.3390/jpm12010009.

[14] Marlow J, Thomas J. A review of congenital diaphragmatic hernia. Australas J Ultrasound Med 2013;16:16–21. https://doi.org/10.1002/j.2205-0140.2013.tb00092.x.

[15] Gerards FA, Twisk JWR, Tibboel D, van Vugt JMG. Congenital Diaphragmatic Hernia: 2D Lung Area and 3D Lung Volume Measurements of the Contralateral Lung to Predict Postnatal Outcome. Fetal Diagn Ther 2008;24:271–6. https://doi.org/10.1159/000151675.

[16] Guibaud L, Filiatrault D, Garel L, Grignon A, Dubois J, Miron MC, et al. Fetal congenital diaphragmatic hernia: accuracy of sonography in the diagnosis and prediction of the outcome after birth. American Journal of Roentgenology 1996;166:1195–202. https://doi.org/10.2214/ajr.166.5.8615269.

[17] Leung JWT, Coakley F V., Hricak H, Harrison MR, Farmer DL, Albanese CT, et al. Prenatal MR Imaging of Congenital Diaphragmatic Hernia. American Journal of Roentgenology 2000;174:1607–12. https://doi.org/10.2214/ajr.174.6.1741607.

[18] Yamashita Y, Namimoto T, Abe Y, Takahashi M, Iwamasa J, Miyazaki K, et al. MR imaging of the fetus by a HASTE sequence. American Journal of Roentgenology 1997;168:513–9. https://doi.org/10.2214/ajr.168.2.9016238.

[19] Rypens F, Metens T, Rocourt N, Sonigo P, Brunelle F, Quere MP, et al. Fetal Lung Volume: Estimation at MR Imaging—Initial Results. Radiology 2001;219:236–41. https://doi.org/10.1148/radiology.219.1.r01ap18236.

[20] Meyers ML, Garcia JR, Blough KL, Zhang W, Cassady CI, Mehollin-Ray AR. Fetal Lung Volumes by MRI: Normal Weekly Values From 18 Through 38 Weeks' Gestation. American Journal of Roentgenology 2018;211:432–8. https://doi.org/10.2214/ajr.17.19469.

[21] Osada H, Kaku K, Masuda K, Iitsuka Y, Seki K, Sekiya S. Quantitative and Qualitative Evaluations of Fetal Lung with MR Imaging. Radiology 2004;231:887–92. https://doi.org/10.1148/radiol.2313021689.

[22] Sefidbakht S, Dehdashtian A, Bagheri F, Rahimirad N, Keshavarz P, Bijan B. Standard Normal Fetal Lung Volume by MRI Measurement. Iranian Journal of Radiology 2020;17. https://doi.org/10.5812/iranjradiol.97847.

[23] Cordier A-G, Russo FM, Deprest J, Benachi A. Prenatal diagnosis, imaging, and prognosis in Congenital Diaphragmatic Hernia. Semin Perinatol 2020;44:51163. https://doi.org/10.1053/j.semperi.2019.07.002.

[24] Jani JC, Peralta CFA, Nicolaides KH. Lung-to-head ratio: a need to unify the technique. Ultrasound in Obstetrics & Gynecology 2012;39:2–6. https://doi.org/10.1002/uog.11065.

[25] Jani J, Nicolaides KH, Keller RL, Benachi A, Peralta CFA, Favre R, et al. Observed to expected lung area to head circumference ratio in the prediction of survival in fetuses with isolated diaphragmatic hernia. Ultrasound in Obstetrics and Gynecology 2007;30:67–71. https://doi.org/10.1002/uog.4052.

[26] Senat M -V., Bouchghoul H, Stirnemann J, Vaast P, Boubnova J, Begue L, et al. Prognosis of isolated congenital diaphragmatic hernia using lung-area-to-head-circumference ratio: variability across centers in a national perinatal network. Ultrasound in Obstetrics & Gynecology 2018;51:208–13. https://doi.org/10.1002/uog.17463.

[27] Irish MS, Holm BA, Glick PL. Congenital Diaphragmatic Hernia. Clin Perinatol 1996;23:625–53. https://doi.org/10.1016/S0095-5108(18)30199-4.

[28] Holden KI, Ebanks AH, Lally KP, Harting MT. The CDH Study Group: Past, Present, and Future. European Journal of Pediatric Surgery 2024;34:162–71. https://doi.org/10.1055/s-0043-1778021.

[29] Shinno Y, Terui K, Endo M, Saito T, Nakata M, Komatsu S, et al. Optimization of surgical timing of congenital diaphragmatic hernia using the quantified flow patterns of patent ductus arteriosus. Pediatr Surg Int 2021;37:197–203. https://doi.org/10.1007/s00383-020-04788-9.

[30] Lian X, Xu Z, Zheng L, Zhu Z, Ejiwale T, Kumar A, et al. Reference range of fetal thorax using two-dimensional and three-dimensional ultrasound VOCAL technique and application in fetal thoracic malformations. BMC Med Imaging 2021;21:34. https://doi.org/10.1186/s12880-021-00548-w.

[31] Amodeo I, Borzani I, Corsani G, Pesenti N, Raffaeli G, Macchini F, et al. Fetal MRI mediastinal shift angle and respiratory and cardiovascular pharmacological support in

newborns with congenital diaphragmatic hernia. Eur J Pediatr 2022;181:323–34. https://doi.org/10.1007/s00431-021-04207-8.

[32] Politis MD, Bermejo-Sánchez E, Canfield MA, Contiero P, Cragan JD, Dastgiri S, et al. Prevalence and mortality in children with congenital diaphragmatic hernia: a multicountry study. Ann Epidemiol 2021;56:61-69.e3. https://doi.org/10.1016/j.annepidem.2020.11.007.

[33] Semánová C, Szőllősi GJ, Ilyés I, Cardon G, Latomme J, Iotova V, et al. Differences in Anthropometric Parameters of Children in Six European Countries. Children 2023;10:983. https://doi.org/10.3390/children10060983.

[34] Snoek KG, Reiss IKM, Greenough A, Capolupo I, Urlesberger B, Wessel L, et al. Standardized Postnatal Management of Infants with Congenital Diaphragmatic Hernia in Europe: The CDH EURO Consortium Consensus - 2015 Update. Neonatology 2016;110:66–74. https://doi.org/10.1159/000444210.

[35] Gallot D, Coste K, Francannet C, Laurichesse H, Boda C, Ughetto S, et al. Antenatal detection and impact on outcome of congenital diaphragmatic hernia: A 12-year experience in Auvergne (France). European Journal of Obstetrics & Gynecology and Reproductive Biology 2006;125:202–5. https://doi.org/10.1016/j.ejogrb.2005.06.030.

[36] Shah NR, Criss CN, Burgi K, Matusko N, Geiger JD, Perrone EE, et al. Thoracoscopic Patch Repair of Congenital Diaphragmatic Hernia: Can Smaller Incisions Treat Larger Defects? J Pediatr Surg 2023. https://doi.org/10.1016/J.JPEDSURG.2023.09.040.

[37] Ito M, Terui K, Nagata K, Yamoto M, Shiraishi M, Okuyama H, et al. Clinical guidelines for the treatment of congenital diaphragmatic hernia. Pediatrics International 2021;63:371–90. https://doi.org/10.1111/ped.14473.

[38] Basta AM, Lusk LA, Keller RL, Filly RA. Fetal Stomach Position Predicts Neonatal Outcomes in Isolated Left-Sided Congenital Diaphragmatic Hernia. Fetal Diagn Ther 2016;39:248–55. https://doi.org/10.1159/000440649.

[39] Cordier A -G., Jani JC, Cannie MM, Rodó C, Fabietti I, Persico N, et al. Stomach position in prediction of survival in left-sided congenital diaphragmatic hernia with or without fetoscopic endoluminal tracheal occlusion. Ultrasound in Obstetrics & Gynecology 2015;46:155–61. https://doi.org/10.1002/uog.14759.

List of published scientific papers

1. **Neştianu EG**, Popescu S, Alexandru DO, Giurcăneanu L, Vlădăreanu R. Thoracic Biometry in Patients with Congenital Diaphragmatic Hernia, a Magnetic Resonance Imaging Study. Diagnostics 2024;14:641. 1-14.
   Diagnostics indexed: Web of Science, Scopus, PubMed, Embase; F.I. 3,6
   https://doi.org/10.3390/diagnostics14060641;
   https://www.mdpi.com/2075-4418/14/6/641

2. **Neştianu EG**, Brădeanu CG, Alexandru DO, Vlădăreanu R. The Necessity of Magnetic Resonance Imaging in Congenital Diaphragmatic Hernia. Diagnostics 2022;12:1733. 1-12.
   Diagnostics indexed: Web of Science, Scopus, PubMed, Embase; F.I. 3,6
   https://doi.org/10.3390/diagnostics12071733
   https://www.mdpi.com/1729030

3. **Neştianu EG**, Brădeanu CG, Drăgan I, Vlădăreanu R. The Benefits of MRI in the Prenatal Diagnosis of Congenital Diaphragmatic Hernia. Maedica - A Journal of Clinical Medicine 2021;16. 368-374.
   Maedica - A Journal of Clinical Medicine - indexed: PubMed, EBSCO; F.I.
   http://doi.org/10.26574/maedica.2021.16.3.368
   https://www.maedica.ro/articles/2021/3/2021_16(19)_No3_pg368-374.pdf

4. **Neştianu EG**, Brădeanu-Guramba C, Vlădăreanu R, Vlădăreanu S. Advances in the prenatal investigation of the fetus using MRI. GinecologiaRo 2021;2:32. 44-49 https://doi.org/10.26416/Gine.32.2.2021.5007.
   http://www.revistaginecologia.ro/index.php/arhiv/372

5. **Neştianu EG**, Brădeanu CG, Drăgan I, Vlădăreanu R. Imagistic Correlations Between Ultrasound and MRI Examination of the Fetus With Congenital Diaphragmatic Hernia. World Journal of Pharmaceutical and Medical Research 2021;4: 43–53.
   https://www.wjpmr.com/home/article_abstract/3392

6. **Neștianu EG**, Guramba-Brădeanu C, Dima V, Bohilțea RE, Varlas V, Veduța A, et al. Natural history of a complex congenital diaphragmatic hernia. Romanian Medical Journal 2021;68:75–78.
https://doi.org/10.37897/RMJ.2021.S5.13.
https://rmj.com.ro/articles/2021.S5/RMJ_2021_Suppl5_Art-13.pdf