DOCTORAL THESIS

Possibilities and limits in the diagnosis and treatment of congenital diaphragmatic hernias

-SUMMARY-

Scientific coordinator
Professor Ion Georgescu PhD

Doctoral candidate
Dr. Georgescu Raluca

Craiova
2014
Content

1. INTRODUCTION ................................................................. 3
2. MATERIAL AND METHOD .................................................... 5
3. DISCUSSION ON OUTCOMES ............................................. 8
4. CONCLUSIONS .................................................................. 26
5. BIBLIOGRAPHY ................................................................. 29
1 INTRODUCTION

Congenital diaphragmatic hernias represent one of the most severe congenital malformations, they being almost consistently associated with the pulmonary hypoplasia and the concomitance with other cardiovascular, digestive, neurologic or skeletal congenital malformations causing it to be encumbered until recently a very high mortality (70-80%), despite the fact that malformations are surgically treated in most cases.

In recent decades there were important steps in understanding the etiopathogenesis of this malformation complex, changing the therapeutic concept and thus leading to a significant improvement of prognosis and therapeutic outcomes; these advances have resulted in:

- deepening knowledge of diaphragm embryogenesis and correctly understanding the consequences that it has on the development of diaphragmatic hernia and lung function;
- prenatal diagnosis is possible with the introduction of prenatal ultrasound imaging as a routine test in monitoring pregnancy, allowing on the one hand correct information to parents about the risks and therefore the decision on the development of pregnancy and on the other hand to monitor pregnant women throughout pregnancy and mentoring them to a specialized center capable of providing maternal and newborn specialized healthcare of high level;
- conceptual change of the therapy behavior meaning that the congenital diaphragmatic hernia is not considered any more a surgical emergency, the defect repair must be preceded by preoperative respiratory resuscitation and stabilization;
- development and introduction into practice of a wide range of modern therapeutic means of preoperative respiratory resuscitation and stabilization and postoperative care (mechanical ventilation, surfactant, nitric oxide, ECMO) each with indications, contraindications and their limits.

Starting from the above mentioned, we carry out a multicenter prospective and retrospective study on a number of 49 cases of congenital diaphragmatic hernias hospitalized, monitored and surged during the last 5 years (2007 - 2012)
within the Pediatric Surgery Clinic of “Marie Curie” Children’s Hospital of Bucharest (1st lot) and within the Pediatric Surgery Clinic of No. 1 Emergency County Clinical Hospital of Craiova (2nd lot), aiming to establish an algorithm of diagnosis and treatment leading to the outcomes improvement including the disease prognosis.

I take this opportunity to thank to my scientific coordinator, Professor Ion Georgescu PhD, from the Clinic I of Surgery who accepted me as doctoral candidate, giving me the possibility to carry out this research and inspiring me courage throughout this study.

I also thank to Mr. Lecturer Sebastian Ionescu PhD, Head of the Pediatric Surgery Clinic of “Marie Curie” Children’s Hospital of Bucharest, who provided me the casuistry of the clinic and thus offering me the possibility of an ample and consistent multicenter study.

Thanks to Mrs. Dr. Stefania Tudorache for the generosity of allowing me the casuistry and her personal experience, which was extremely useful for performing and illustrating the chapter related to the prenatal diagnosis of the congenital diaphragmatic hernias.

Thanks to Mr. Prof. dr. Nemes Raducu of whose support, expertise and guidance I received throughout this research, his experience and knowledge in pediatric surgery being essential in developing this paper.
2 MATERIAL AND METHOD

This paper is a multicenter prospective and retrospective study on a number of 49 cases of congenital diaphragmatic hernias hospitalized, monitored and surged during the last 5 years (2007 - 2012) within the Pediatric Surgery Clinic of “Marie Curie” Children’s Hospital of Bucharest (1st lot) and within the Pediatric Surgery Clinic of No. 1 Emergency County Clinical Hospital of Craiova (2nd lot), aiming to establish an algorithm of diagnosis and treatment leading to the outcomes improvement, including the disease prognostic.

![Figure 1. Congenital diaphragmatic hernia – study material](image)

We mention that the study was carried out only on the cases of congenital diaphragmatic hernia of Bochdaleck type; previous hernia of Morgani – Larrey type and the hiatal hernias, rare to the newborn, without vital risk from birth, with a long evolution, sometimes until an adult age and which, excepting the evolutionary complications, are not as severe as the Bochdaleck type were excluded from this study.

Data needed for the study were extracted from: clinical observation sheets of the newborn departments and the surgery clinics of the two hospitals, intensive therapy sheets, operative protocols, outcomes of the biologic and/or bacteriological examinations, bulletins or protocols of the imaging examinations, protocols of necropsy and outcomes of the morphologic examinations.
All cases were sheeted, the obtained data being included in a large data base and statistically processed using the MS Excel program; when compounding the data base we followed the following parameters for each case:

- demographic data: name, surname, sex, environment of origin, domicile;
- data concerning the mother: mother’s age, occupation, educational level, consumption of toxic substances (alcohol, tobacco, professional toxic substances, etc.), number of pregnancies preceding the birth of the child with congenital diaphragmatic hernia;
- prenatal period:
  - prenatal diagnosis;
  - periodical prenatal controls;
  - fetal echography and the followed parameters: head circumference, abdominal circumference, anterior-posterior and transversal diameter of the thorax, length of the humerus and femur, presence of the pulmonary hypoplasia, liver herniation into the thorax, presence of the intrathoracic hernia sac, presence of related malformations, echocardiography for detecting the related cardiac malformations.
- Neonatal period:
  - Gestational age;
  - Weight and length, head and thorax perimeter at birth;
  - Apgar score at 1, 5, 10 and 20 minutes respectively;
  - Presence of pulmonary hypertension signals;
  - Postnatal imaging investigations: thoracic-abdominal radiography, abdominal echography, echocardiography;
  - Syndrome of respiratory distress: debut mode, clinical form: severe, medium, easy;
  - A postnatal therapeutic behavior – treatment of resuscitation and respiratory stabilization for the patient’s preoperative preparation: oral-tracheal intubation, oxygen therapy, mechanical ventilation, duration and types of the used mechanical ventilation, surfactant, nitric oxide, ECMO, continuous upper gastrointestinal suction, transfusions, antibiotics, corticosteroids, treatment of PAH;
- Surgery intervention:
  - Operative moment;
- Type or anesthesia;
- The approach path;
- Intraoperative data: topography and size of the defect, number and type of herniated viscera;
- way of closing the defect, (abdominal and / or effusion) drainage, rebuilding the wall, etc.
- intraoperative incidents and accidents;
- postoperative care:
  - postoperative mechanical ventilation: type and number of days until resuming the efficient spontaneous ventilation;
  - type of alimentation and transit resumption;
  - days of intensive therapy;
- postoperative evolution:
  - immediate and remote postoperative complications;
  - postoperative mortality and death causes;
  - remote outcomes – periodical controls, hospitalization;
3 DISCUSSION ON OUTCOMES

Congenital diaphragmatic hernias represent one of the most severe congenital malformations, they being almost constantly associated with the pulmonary hypoplasia and the concomitance with other cardiovascular, digestive, neurologic or skeletal congenital malformations causing it to be encumbered until recently a very high mortality (70-80%), despite the fact that malformations are surgically treated in most cases.

The incidence is evaluated in literature between 1/2000 – 1/5000 living newborns, with a prevalence of 2.4 – 3.8/10.000 births [26, 180]. But the real incidence of the malformation is much greater, if we also consider the dead newborns, taking into account the fact that about 1/3 of the children with congenital diaphragmatic hernias or dead newborns, but the death is usually caused by some incompatible with life anomalies [23, 24, 27].

In our study (2 lots, 49 cases in 5 years) we recorded an incidence of 1/1597 living newborns, the evaluation being carried out only for the 2nd lot (Craiova), were the studied children mostly came from the newborns in the clinics of Obstetrics and Gynecology and within the Newborns department of the County Hospital of Craiova, while for the 2nd lot (Bucharest), the incidence could not be evaluated, the lot being irregular in terms of the cases origin.

The etiopathogeny of the congenital diaphragmatic hernias is unclear and controversial: the occurrence of the diaphragmatic defect is the result of a complex of factors (food deficiencies, deficits of spontaneous regulation of the retinoic acid path, different teratogen factors or genetic factors), leading to deregulations in the formation of the primordial diaphragm in all stages of the embryogenesis: delay in closing lung pleural membranes, disorders in migrating myocytes or neuronal components of the phrenic nerve. Regarding the pulmonary hypoplasia, the main death cause, highly important in changing the therapeutic concept was proved to be the acceptance of the “dual hit” hypothesis, according to which the teratogen factors independently affect the lug morphogenesis and the occurrence of the diaphragmatic defect, such that the diaphragmatic defect become a new injury on the lug, additionally emphasizing the pulmonary hypoplasia by mass effect [180].

Isolated congenital diaphragmatic hernias are more frequent in males, 1/3 of them being severe forms, but if taking into account the so called “hidden mortality”,


the lesion is more common in females [21]. In both lots studied by us we found the prevalence of the disease in the male newborns, with a sex ratio = 2,5 on both cumulated lots and of 1,9 for 1st lot, respectively 6 for 2nd lot.

Without having particular etiopathogenic connotations, we studied some data related to the mother: environment of origins, educational level, age, obstetrical antecedents (number of pregnancies, number of births), mother’s pathological antecedents, consumption of toxic substances or developing some activities in a toxic environment, level of the hospital where the birth took place, data we considered useful for being able to appreciate the way of monitoring and following the pregnancy, the existence of some potential risk factors, precocity of the diagnosis and first therapeutic gestures, etc.

Regarding the environment of origins and the educational level of the mother, we found that, as a whole, most mothers (59,18%) come from urban environment, having a lower educational level in 51% of cases, medium in 37% and high in 12% of cases. Mothers’ age covered all the fertile period (17-46 years) most cases falling in the age group of 31-35 years; but we found a number of 12 mothers aged between 36-46 years, given that data from literature appreciate a risk exceeding 50% for mothers aging more than 35 years [180]. With respect to the number of pregnancies and births, 18 mothers were primigesta, 15 secundigesta, the others being at the third (8 cases), fourth (3 cases) or even fifth (5 cases) pregnancy, and regarding the number of births in 26 cases the malformation occurred in the primiparous, in 12 cases in secundiparous and for the rest at the third birth in 10 cases and at the fifth birth in one case.

Starting from the premise that the level of the hospital where the birth take place may be decisive in terms of the possibilities of postnatal diagnosis and especially the means for establishing the level of the pulmonary hypoplasia, resuscitation and preoperative respiratory stabilization, we found that in 15 (30,6%) cases (10 of the 1st lot and 5 of the 2nd lot) the birth took place in a university clinic, in 11 (22,44%) cases in hospitals of county level, in 21 (42,85%) cases in hospitals of municipal level and in one case at domicile.

According to the literature data, the presence of congenital diaphragmatic hernia, especially of the isolated one, does not represent a contraindication for the natural birth, and our study confirms these data; thus, in 31 cases (63,26%) the birth
was natural and only in 18 cases (36.74%) the birth was carried out by caesarian surgical intervention, with obstetrical indication upon request.

The prenatal diagnosis of the congenital diaphragmatic hernias is the result of a complex of imaging investigations: fetal echography, starting with the 28th week of pregnancy, fetal echocardiography for detecting the potential related congenital cardiac malformations and the magnetic resonance. The main advantages of the prenatal diagnosis are: defining the natural history of the injury, determining the physiopathological elements affecting the clinical evolution, formulating a management strategy based on the prognostic elements, facilitate the postnatal care of the newborn and allow the mother guidance and transportation to a neonatal center of high performance, where the birth may be guided and the newborn may be resuscitated, stabilized and surged by a trained team of neonatologists, anesthetists and surgeons.

The prenatal diagnosis of the congenital diaphragmatic hernia is exclusively an imagistic one, the prenatal echography being the election method, establishing in the proportion of 50-60% of cases, having a accuracy of 40-90% [8,65]. Generally, the average age of the pregnancy when echographically detecting the congenital diaphragmatic hernia was of 24 weeks, although there were reported cases diagnosed at 11 weeks [66].

The echography may be carried out as routine obstetrical investigation or it may be imposed by the presence of the polyhydramnios. In this respect, our study revealed system deficiencies related to the evidence of pregnant women and the monitoring of pregnancy evolution, elements reflected in the fact that the prenatal diagnosis of the congenital diaphragmatic hernia was established only in 26.53% cases (9 cases in 1st lot and 4 cases in 2nd lot), especially among the pregnant women with a higher social and educational level, where the monitoring of pregnancy evolution was carried out in private medical offices, equipped with high performance echographs.

The main data which were the basis of the echographic diagnosis of the congenital diaphragmatic hernias were the presence of the stomach or intestinal loops full of liquid in the fetus' thorax on a transversal section at the level of the heart, intrathoracic heterogeneous mass, meaning the presence of intestinal loops in thorax, mediastinal shift toward the contralateral side, the stomach absence from the
abdomen (absent gas bubble of the stomach or intrathoracic present), the intrathoracic ascension of the liver and biliary vesicle.

The prenatal echography is also useful in the assessment of the disease evolution by using quantitative techniques for estimating the severity of the pulmonary hypoplasia, through: tridimensional estimation of the fetal pulmonary volume, calculation of the ratio between the surface of the right lung and the thoracic surface and of the ratio between the circumference of the lung and the circumference of the thorax [68, 69, 70]. Some prognostic parameters were proposed for evaluating the evolution of the fetus or newborns with congenital diaphragmatic hernia and for deciding the resuscitation and preoperative respiratory stabilization strategy:

- liver position: the intrathoracic liver presence is a sign of unfavorable prognostic, the survival rate being evaluated, depending on author, between 43 and 56% for the cases with the liver herniated intrathoracic, compared with 90-100% if the liver is located under the diaphragm;
- L/T Ratio (the ratio between the contralateral lung area and the thorax area on the transversal section) – was proposed as indicator for predicting the disease severity and the survival ratio:
  - > 0,13 – easy form – 0 mortality;
  - > 0,8 and < 0,13 – severe form – 30% mortality;
  - < 0,13 – liver herniation – lethal form – 100% mortality.
- LHR (Lung to Head Ratio) – the ratio between the contralateral lung area measured on the transversal section at the level of atria and head circumference). The survival prediction for the children with congenital diaphragmatic hernia statistically evaluated depending on LHR was of 100% for LHR > 1,35, 55% for LHR between 1,35-0,6 and 0 for LHR < 0,6. Taking into account that this ratio depends on the gestational age, it needs to calculate the O/E ratio (Observed to Expected):
  - O/E LHR < 5% - extreme pulmonary hypoplasia; 0 survival;
  - O/E LHR 15-25% - severe pulmonary hypoplasia; 15% survival;
  - O/E LHR 26-45% - moderate pulmonary hypoplasia; 30-60% survival depending on the lung size;
  - O/E LHR > 45% - moderate pulmonary hypoplasia and high survival probability.
The ultrasonography limits depends on an insufficient contrast between the fetal lung and the herniated viscera, the fetus' position and the surgeon's experience, such that, the MRI (magnetic resonance) prenatal evaluation is increasingly used as adjuvant method of the echography when it detects a complex anomaly, being a method ideally adapted for the congenital diaphragmatic hernia [71, 72]. MRI may easily indicate the liver herniation in the thorax and may be used for evaluating the pulmonary volume, for determining the pulmonary hypoplasia and as a criterion for evaluating the risk and the subsequent evolution; if the ratio between the measured volume and the expected volume is < 20%, there is a significant decrease of the postnatal survival ratio. [73, 74, 75]

Postnatal diagnosis. The newborns with typical congenital diaphragmatic hernia present respiratory distress and reactive pulmonary hypertension. The clinical table varies from the immediate respiratory distress, with a small Apgar score, to a stable initial period and the installation of the respiratory signs at 24-48 hours after the birth, or even at the occurrence of the tardive clinical signs, after months or years.

In our study, the diagnosis was established since the birth or within the first 24 hours in 85.71% cases (42 cases: 28 cases in the 1\textsuperscript{st} lot of Bucharest and all the 14 cases from the 2\textsuperscript{nd} lot of Craiova); in 3 cases of the Bucharest lot the diagnosis was established during the first year of life, and in other 4 cases, after the age of 2 years.

The fetal distress, the low Apgar score and the signs of respiratory insufficiency raise the suspicion of the diagnosis of congenital diaphragmatic hernia in most cases. The fetal distress evaluated based on the Apgar score at 1 minute after the birth was severe in 18 (40.9%) cases (8 in the 1\textsuperscript{st} lot, 10 in the 2\textsuperscript{nd} lot), moderate in 16 (36.36%) cases (14 in the 1\textsuperscript{st} lot, 2 in the 2\textsuperscript{nd} lot) and easy in 10 (22.72%) cases (8 in the 1\textsuperscript{st} lot, 2 in the 2\textsuperscript{nd} lot). The measures of resuscitation and stabilization leded to the improvement of the fetal distress, such that after 10 minutes only 2 newborns presented an Apgar score of 5, the others arising values of the Apgar score of 6 in 8 cases, 7 in 10 cases, 8 in 8 cases, 9 in 7 cases and 10 in 2 cases. The main cause of the fetal distress at birth was the respiratory insufficiency, clinically manifested dyspnea, tachypnea, circulation, pathological whistling, cyanosis and increased respiratory effort. The acute respiratory insufficiency was severe in 23 (53.48%) cases (12 in the 1\textsuperscript{st} lot and 11 in the 2\textsuperscript{nd} lot), moderate in 17 (39, 53%) and easy in 3 (6.97%) cases.
The physical examination of the newborn highlighted one or more of the characteristic objective signals: excavated abdomen due to the absence of intrathoracic herniated abdominal viscera, thorax asymmetrically relaxed, distention which is progressively accentuated, as the degluted air passes in the stomach and in the intestinal loops.