Consequences of prenatal diagnosis in perinatal management of congenital diaphragmatic hernia

Ph.D. Thesis

Dr. Ágnes Éva Harmath

Semmelweis University
Clinical Medicine Doctoral School

Advisor: Zoltan Papp MD, DSc, professor
Opponents: Lídia Balogh MD, PhD, associate professor
Ertl Tibor MD, DSc, professor
President of doctoral examination committee: Tamás Machay MD, PhD, professor
Members of doctoral examination committee: Elek Kisida MD, PhD, professor
Tibor Verebély MD, PhD, professor

Budapest
2007
INTRODUCTION

Over the past decades, notable changes have taken place in diagnosing fetal malformations including congenital diaphragmatic hernia. Development in ultrasonography has contributed to the broadening of our knowledge of fetal anatomy and physiology. The spread of examination techniques with increasingly higher resolution together with the growth of professional and practical experience enable physicians to recognize disorders in the early period of pregnancy. Despite their different embryological background but due to their similar mechanism, congenital diaphragmatic hernia, and thoracic changes of non-cardiac origin such as congenital cystic adenomatoid malformation, bronchopulmonary sequestration and fetal hydrothorax (which may pose a problem in making a differential diagnosis) may have severe consequences for fetal development and the perinatal outcome. These malformations interfere with the normal development of fetal lungs; they may lead to the development of pulmonary hypoplasia by compressing the adjacent pulmonary tissues. Such major changes may result in a shift of the mediastinum, hypoplasia of the contralateral lung and, by compressing the heart and great blood vessels, they may lead to the development of non-immune hydrops syndrome and, also, result in polyhydramnios.

Early prenatal diagnosis and relevant supplementary tests allow confirmation of possible other developmental disorders and chromosome aberrations. In addition to establishing a diagnosis, prenatal investigations are also aimed at giving an accurate prognosis. Given adequate information by genetic counselling, couples can make an informed decision about the fate of the pregnancy after an early diagnosis.

The dissertation discusses congenital diaphragmatic hernia and certain non-cardiac intrathoracic malformations that represents problems in differential diagnosis.

It is the first time in Hungary that the localization of organs herniated into the thorax has been analyzed in a large sample with due consideration to the distribution of the associated anomalies and prediction of the expected survival rate. All these data are indispensable to provide the couples with full and detailed information during prenatal care.
GOALS

In the dissertation, in which data of congenital diaphragmatic hernia cases diagnosed at the I. Department of Obstetrics and Gynecology, Semmelweis University Faculty of Medicine, Budapest over the past 15 years were analyzed, my goal was to seek answers for the following questions:

1. How often did thoracic anomalies of non-cardiac origin (congenital adenomatoid malformation, bronchopulmonary sequestration) cause difficulty in making the diagnosis?
2. In view of the age of the pregnancy, what was the proportion of diagnosed malformations and what was their lateral distribution?
3. What were the most commonly associated anomalies in congenital diaphragmatic hernia?
4. To what extent was polyhydramnios predictive of isolated congenital diaphragmatic hernia?
5. What was the outcome of pregnancies, did the survival rate change as a result of the broadening of the diagnostic and therapeutic techniques and did the laterality of diaphragmatic hernia have an influence on survival?
6. What organs were most commonly herniated into the thorax and how did they affect survival?
7. Was survival influenced by the method of delivery, birth weight or gestational age at the time of delivery?
8. How indicative was the Apgar score of the expected survival rate? Was there a relationship between the Apgar score and the method of delivery? Did the method of delivery influence early (first-day) postnatal mortality?
9. What influence has the development in neonatology over the past 15 years had on postnatal care at our department?
10. Did maternal age or the sex of the fetus play a role in the development of congenital diaphragmatic hernia?
MATERIAL AND METHODS

All cases of congenital diaphragmatic hernia diagnosed at the I. Department of Obstetrics and Gynecology, Semmelweis University Faculty of Medicine, Budapest, from July 1, 1990, until June 30, 2005 were analyzed retrospectively. Thoracic malformations of non-cardiac origin were included as anomalies for differential diagnosis.

Analyzing the data in the database of the Genetic Counselling Unit I excluded cases where the parents of a fetus with congenital diaphragmatic hernia were only referred for risk assessment of their pregnancy and not for further treatment.

There were 107 cases with a diagnosis of congenital diaphragmatic hernia, which came from two databases. The majority (97 cases) included pregnant women and their fetuses of our own Department presenting for genetic counselling. The minority (10 newborns and their mothers) were referred to our department due to perinatal disorders or transferred to the Neonatal Intensive Care Centre of our Department for postnatal deteriorating condition or respiratory failure.

The patients sought counselling for pathological findings (ultrasonography or AFP levels) or maternal age. Genetic counselling in Hungary is provided in 7 centres, on a territorial basis. Our department is mainly visited by pregnant women from Budapest, and Fejér, Komárom, Nógrád and Pest Counties, but we also receive patients from all parts of Hungary.

In each case, the final diagnosis was made at our department. Investigations were done by ATL Ultramark 9 (Bothell, Washington, USA) and GE Voluson 730 (Fairfield, Connecticut, USA) ultrasound devices using a linear array, 5–7,5 MHz transducer. Thoracic position of the fetal liver or stomach was regarded as a primary disorder. The examination also included identification of the line of the diaphragm and the position of the mediastinum, measurement of amniotic fluid and detection of associated anomalies.

The diagnoses were followed by fetal echocardiography, following-up ultrasound examinations and genetic counselling. In the frame of genetic counselling, karyotyping by genetic amniocentesis (GAC) was recommended. Cytogenetic (chromosomal), biochemical
and molecular genetic tests were performed on amniotic fluid cells. At the Genetic Counselling Unit, the couples were asked to agree to deliver their infant at our department. In case the infant was delivered elsewhere (2 pregnancies) information on the way of delivery and the fate of the fetus/newborn were asked in a questionnaire. In some instances (3 pregnancies) no data about the outcome of the pregnancy was available, but in the possession of certain prenatal diagnoses, these cases were also included in the sample.

In case the pregnancies were terminated by induced abortion, we processed the fetopathological data. If the infants were delivered, only immediate perinatal care was provided at the neonatological intensive care unit (NICU). After stabilization, if an operation was feasible, the newborns were transported to a paediatric surgery centre, given perioperative care, and further surveillance there. Although surgery can be considered as part of the perinatal care, due to their special paediatric surgical nature, the operative techniques are not discussed in the present work.

In cases of postnatal diagnosis, a “scaphoid” abdomen (hollowed abdomen below the thoracic line), changes in thoracic auscultation and disturbed respiration detected in the delivery room were all suggestive of anomalies. Based on the chest X-rays, the final diagnoses were made at the intensive care unit.

To provide an accurate assessment of the herniated organs, the foetopathological data, autopsy records and operation notes were analyzed. In 9 cases, the organs located in the thorax were evaluated on the basis of perinatal ultrasonograms and X-rays. In 8 cases, the description of the organs was incomplete or not adequately detailed enough. In another case, pneumothorax, which developed prior to the operation, did not allow for the exact evaluation of the herniated organs.

Newborns who were discharged home from the care facility immediately after perinatal care were considered survivors.

The observed period was analyzed in two parts (1 July 1990 – 31 December 1997 and 1 January 1998 – 30 June 2005). Technological development over the past 15 years such as the spread of ultrasound devices with increasing, the use of surfactant and high-frequency respiration, and international changes in the timing of operations, as well as increasing
experience in diagnostics and each related discipline underlined the necessity of comparing
the findings in the aforementioned two periods.

Owing to the high incidence of the associated developmental anomalies, data of all
patients and those of the patients with associated diseases, including the time of the diagnosis,
maternal age, organs herniated into the thorax, survival and the distribution of anomalies
according to laterality and gender, were also compared..

STATISTICAL METHODS

The results are presented as absolute figures, percentages and means. Intervals and data such
as number of patients per group serving as the basis of calculations of the percentages are
shown in brackets.

Because of the small sample sizes, the comparison of categorical variables among the
groups was done using Fisher’s exact test. Odds ratio were calculated and are presented with
95% confidence intervals (CI). P<0.05 was considered statistically significant.
RESULTS

Data of 107 newborns/fetuses receiving care at our department over the past 15 years were processed after retrospective data collection. The numbers of cases in the two halves of the aforementioned period were almost identical; in the first seven and half years, (first period 1 July 1990 – 31 December 1997) the database included 51 patients, while in the second period (1 January 1998 – 30 June 2005), 56 cases were recorded. Prenatal ultrasonography was performed in 96 cases (44 and 52); in 7 cases, congenital diaphragmatic hernia could not be confirmed postnatally. In 11 cases congenital diaphragmatic hernia was diagnosed postnatally. Associated developmental anomalies were found in 71% of the cases (71/100). In 29 patients (12 and 17 cases) the isolated form of diaphragmatic hernia was detected. The diaphragmatic hernia was considered to be isolated if it was not accompanied by changes except for pulmonary hypoplasia or polyhydramnios of average extent characteristic in such malformations (Figure 1).

1. **Figure** Except for the last column, the percentages in the table refer to the number of cases in the given period. In the last column, percentages stand for the total of the given group of patients

<table>
<thead>
<tr>
<th>Period</th>
<th>Type of malformation</th>
<th>Prenatal diagnosis</th>
<th>Postnatal diagnosis</th>
<th>Total number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≤24th gestational week</td>
<td>≥25th gestational week</td>
<td></td>
</tr>
<tr>
<td>1990–1997</td>
<td>All CDH cases</td>
<td>14 (30%)</td>
<td>25 (54%)</td>
<td>7 (15%)</td>
</tr>
<tr>
<td></td>
<td>CDH cases with associated malformation</td>
<td>12 (35%)</td>
<td>17 (50%)</td>
<td>5 (15%)</td>
</tr>
<tr>
<td>1998–2005</td>
<td>All CDH cases</td>
<td>32 (59%)</td>
<td>18 (33%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td></td>
<td>CDH cases with associated malformation</td>
<td>25 (68%)</td>
<td>10 (27%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Total number of cases</td>
<td>All CDH cases</td>
<td>46</td>
<td>43</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>CDH cases with associated malformation</td>
<td>37 (52%)</td>
<td>27 (38%)</td>
<td>7 (10%)</td>
</tr>
</tbody>
</table>

(CDH = congenital diaphragmatic hernia)

7 cases diagnosed prenatally as diaphragmatic hernia proved to be other thoracic anomalies of non-cardiac origin on postnatal examination. This resulted in a 11% (5/44) and 4% (2/52) false positive rate of prenatal diagnosis in the two and 7% (7/96) for all patients.
The difference between the two periods of interest was not significant \( p=0.24, \text{OR}: 0.31, (95\% \text{ CI}: 0.06–1.69) \).

Congenital diaphragmatic hernia was confirmed in 89 cases by both prenatal and postnatal investigations. The mean time of prenatal diagnosis was 24.8 weeks of gestation. There was a five-week difference between the means of the two periods \( 27.4 \text{ (12–39)} \) and \( 22.7 \text{ (13–36)} \) gestational weeks, respectively. A similar five-week difference \( 26.7 \text{ vs } 21.4 \text{ weeks} \) was observed for cases with associated malformations.

The malformation was diagnosed before the 24th gestational week in 52\% \( 46/89 \) of the cases. In the first and second periods, early diagnoses were made in 36\% \( 14/39 \) and 64\% \( 32/50 \) of the cases, respectively, which meant a significant difference \( p=0.01, \text{OR}: 3.18, (95\% \text{ CI}: 1.33–7.6) \). In associated malformation cases the early diagnosis rates were 41\% \( 12/29 \) and 71\% \( 25/35 \), respectively, the difference between the two periods also being significant \( p=0.02, \text{OR}: 3.54, (95\% \text{ CI}: 1.25–10.03) \).

Diaphragmatic hernia was postnatally diagnosed in 11 \( 7 \text{ and 4} \) cases. Seven cases were diagnosed in the first seven and half-year period, while 4 cases were found in the second one. Left-sided diaphragmatic hernia was diagnosed in 85 \( 85\% \) cases, right-sided hernia in 10 \( 10\% \) and bilateral lesions in 5 \( 5\% \) cases, respectively. Changes in rates of right-sided diaphragmatic hernia were detected between the two periods. In the first seven and half years, only 3 \( 7\%, 3/46 \) cases whereas in the second seven and half years, 7 \( 13\%, 7/54 \) cases of right-sided hernia were detected \( p=0.34, \text{OR}: 2.14, (95\% \text{ CI}: 0.52–8.79) \). There were no isolated disorders in patients with right-sided or bilateral lesion.

Associated anomalies were observed at similar rates \( 74\% (36/46) \text{ and } 69\% (37/54) \), respectively] in the two periods \( p=0.66; \text{OR}: 0.77; (95\% \text{ CI}: 0.32–1.84) \). Multiple anomalies were detected in 51 \( 72\% \) cases. The incidence rate \( 59\% (20/34) \text{ vs. } 84\% (31/37) \] was significantly higher in the second period \( p=0.03; \text{OR}: 3.62; (95\% \text{ CI}: 1.19–10.97) \). The disorders of heart development \( 44\%, 31/71 \) and thoracic anomalies \( 28\%, 20/71 \) were the most common among them.

Polyhydramnios and oligohydramnion affected 23\% \( 20/89 \) and 3\% \( 3/89 \) of all cases, respectively. Anomalies of amniotic fluid quantity were found in 249\% \( 17/71 \) of the cases with associated malformations. Oligohydramnion was exclusively found in cases with associated anomalies. The majority \( 70\%, 14/20 \) of cases with polyhydramnios were also
detected in associated malformations. In isolated congenital diaphragmatic hernia, polyhydramnios was confirmed in only 6 cases 21%, 6/29).

Altogether there were 52 deliveries, 5 cases of intrauterine or sub partu death while in 40 cases the pregnancy was terminated by induced abortion. Of cases with associated malformations, 30 pregnancies ended with delivery, 5 cases resulted in intrauterine or sub partu death, while in 34 cases the pregnancy was terminated with induced abortions. In two cases, the outcome of the pregnancy was unknown. In the case of isolated diaphragmatic hernia, abortion was induced in 21% (6/29) of the pregnancies; in the case of early diagnosis this rate was 67% (6/9). Induced abortions took place in 85% (39/46) of all of the cases diagnosed before the 24th gestational week, and if there were associated anomalies, the rate of induced abortions amounted to 89% (33/37).

After perinatal care, 27% (14/52) of the newborns were discharged home from the hospital. Survival rates were 26% (8/31) and 29% (6/21) in the two periods, but this difference was not statistically significant [p=0.99; OR: 1.15; (95% CI: 0.33–3.99)]. No survivors were found in cases when the diagnosis was made before the 24th gestational week (these 4 infants died within 48 hours of delivery). In isolated diaphragmatic hernia, the survival rate was 46% (10/22). In one case no information was available about the outcome of the pregnancy.

In the case of associated malformations, 13% (4/30) of the newborns were discharged home after perinatal care. In the surviving newborns malrotation and intrauterine growth retardation were detected in two cases each. In one child, malrotation was associated with pulmonary hypoplasia. If malformations were diagnosed postnatally, the survival rate was 46% (5/11); six of the patients died within the first two postpartum days.

If the malformation affected the right side, the survival rate was 17% (1/6). Intrauterine growth retardation was the only associated anomaly in the single survivor, the diaphragmatic hernia was detected postnatally. The survival rate in isolated left-sided malformations was 46% (10/22). There were no survivors in bilateral diaphragmatic hernia.

Intestine in the chest was the most common disorder. The affected part of the intestines was specified in 71 cases. In the documentation of another 10 patients, the general term “intestine” was used. Examining the distribution of the small and large intestines, the presence of isolated herniation of the small intestine (21/71) was significantly more frequent than that of the large intestine (2/71) [p<0.0001, OR: 14.49, (95% CI: 3.25–64.66)]. Isolated herniation of the large intestine was always detected in cases with associated anomalies. Most
often (in 48 cases), both the small and large intestines were situated above the diaphragmatic line. Herniation of the liver, stomach and spleen was found at almost equal frequency. Analysing the data of the 29 live-born patients, the cumulative survival rates in hepatic, gastric and splenic herniations into the chest were 7% (2/29), 18% (5/29) and 24% (7/29), respectively. Among the survivors, a 25% incidence rate was found for liver, stomach and spleen hernias into the chest in the first period of the study while in the second period, 60% (3/6) of patients had the stomach and 83% (5/6) of the spleen herniated. No case of hepatic herniation was found among survivors in the second period. In 74% (17/23), 70% (16/23) and 61% (14/23) of the live-born patients who died later, it was the stomach, large intestine and liver, and spleen that herniated into the thorax in the first period of the study. In the second period, however, the incidence of herniation of the small intestine and liver, large intestine and spleen and stomach was found to be 93% (11/15), 53% (8/15) and 40% (6/15), respectively. Accessory spleen, kidney, adrenal gland, pancreas and gall bladder superior to the line of the diaphragm were found in 20% of the cases, with no survivors among them.

The pregnancy ended by caesarean section in 27 (53%) and by vaginal delivery in 24 (74%) cases, respectively. In one case in the first period no data were available about the method of delivery. Vaginal deliveries occurred at a similar rate in the two periods (12/31 39% vs. 12/21 57%). Although there was a 20% increase in the rate with respect to the relative number of cases in the period of interest, the difference was not statistically significant [p=0,26, OR: 2,11, (95% CI: 0,68–6,52)]. Pregnancies were delivered in 58% and 43% in the two periods, respectively [p=0, 40, OR:0,54, (95% CI: 0,18–1,66)].

There were 11 surviving patients out of the infants delivered by caesarean section while out of the cases with vaginal delivery there were only 3 surviving patients [p=0,03, OR: 4,81, (95% CI: 1,15–20,17)]. In the first period, the survival rates after caesarean section and vaginal delivery were 39% (7/18) and 8% (1/12), respectively [p=0,10, OR: 7,0, (95% CI: 0,77–66,84)]. In the second period, the prospective data were 44% (4/9) and 17% (2/12) [p=0,33, OR: 4,0, (95% CI: 0,54–29,82)]. The mean birth weight in the first period was 2489 grams (1400–3500 grams) while in the second one it was found to be 2417 grams (850–3750 grams). The mean weight of infants born by vaginal delivery was significantly smaller (>500 g) in the second period of the study. The mean gestational age at birth in the first and second periods was 36.6 (27–41 weeks) and 37.1 (25–41 weeks) weeks, respectively. No caesarean sections were performed before the 32nd gestational week.
Analyzing the relationship between survival and time way of delivery it was observed that a third (3/10) of the mature newborns born by vaginal delivery survived, while there were no survivors among premature infants (0/14) \([p=0.06, \text{ OR: } 0.07, (95\% \text{ CI: } 0.003–1.63)]\). For caesarean section, survival rates of mature and premature infants were 47\% (9/19) and 25\% (2/8) \([p=0.40, \text{ OR: } 0.37, (95\% \text{ CI: } 0.06–2.32)]\), respectively, which corresponds to a 15–25\% advantage for caesarean section as opposed to vaginal delivery.

Ninety-four per cent (49/52) of the live newborns were delivered at our department. In one case from the first period no detailed data which in another two cases only some of the data were available.

As far as the mean Apgar scores are concerned, the results were almost the same in all of the newborns in both periods of the study, independently of the method of delivery. The infants born by caesarean section scored 2–2 points higher on average. The Apgar scores were analyzed with regard to both the time and method of delivery. Only vaginal deliveries were recorded before the 32\textsuperscript{nd} gestational week. The 1 and 5 minute mean Apgar scores were significantly higher in the second period of the study (1.5 vs. 3.7 és 1.5 vs. 4.3). For infants born in the 32\textsuperscript{nd}–36\textsuperscript{th} gestational weeks, practically the same means were observed in both study periods, independently of the way of delivery. After the 37\textsuperscript{th} gestational week, the newborns delivered by caesarean section had a 1.5–2 point higher Apgar score on average in both periods.

Considering the whole period of the study, there was no significant difference in the death rates on the first postnatal day with regard to the method of delivery. Of those died within 24 hours of delivery, eleven and nine children were born by spontaneous vaginal delivery and caesarean section, respectively. Isolated anomalies occurred in 4 cases: 2 of the infants were born by vaginal delivery in the 25–26\textsuperscript{th} gestational weeks, while the other 2 children were delivered by caesarean section in the 32\textsuperscript{nd} and 39\textsuperscript{th} gestational weeks. In addition to the spleen and intestines, the left adrenal gland was also herniated into the thoracic cavity in one of the newborns delivered spontaneously. In the other infant, the left lobe of the liver was the only herniated structure. In both cases born by caesarean section, several organs (liver, stomach, spleen, small intestines or the liver, stomach, small and large intestines) were herniated into the thorax.

In the neonatal intensive care unit, conventional respiration and high-frequency respiration were started in 36 (25 and 11) and 10 (2 and 8) cases, respectively. The rate of
high-frequency respiration support rose sharply, from 8% (2/27) to 42% (8/19) \( [p=0.009, \text{OR: 9.09, (95% CI: 1.65–49.99)}] \). The use of surfactant almost doubled in view of the patients requiring respiratory support (11% 3/27 vs. 21% 4/19) \( [p=0.42, \text{OR: 2.13 (95% CI: 0.42–10.89)}] \). In the second period, there was a decrease in the proportion of newborns referred to other centres within 24 hours of delivery: compared to the 39% referral rate of the first period, one-third of the newborns were taken to intensive care centres of paediatric surgery in the early postnatal period \( [p=0.77, \text{OR: 0.79, 95% CI: 0.25–2.53)}] \).

Operations were performed in 22 (14 and 8) cases, usually on the 3rd day of life (57.8 hours; 2 days and 10 hours) on average. Analysing the two periods of the study separately, we found a two-day difference in the average starting times of the interventions (33 hours and 82.5 hours after delivery in the first and second periods 82.5 hours (3 days és 11 hours), respectively). Classifying patients according to the method of delivery, we found that in the first period spontaneously delivered newborns were operated on earlier than their counterparts born by caesarean section. In the second period, this difference was reversed: newborns delivered by caesarean section were operated on almost two days earlier on average. In the 29 cases of isolated anomalies, surgical intervention was performed in 14 children. The number of surviving children having been operated for an isolated anomaly was identical in both periods. Children with isolated anomalies born by caesarean section were all discharged home. Patients with isolated anomalies born by vaginal delivery under the overall period of study had a survival rate of 50%. In the postoperative period, 75% of the deceased infants died in the first 48 hours.

The mean maternal age was 27.4 (15–47) years, with no significant differences between the two periods of the study 27.1 vs 27.6 years). The mean maternal age was nearly two years higher in isolated and postnatally diagnosed anomalies. If all the cases were regarded, congenital diaphragmatic hernia most often occurred in the 25–29 year age group. Except for one case, isolated malformation hernia did not occur in mothers over 35 years of age. On the other hand, 18% (6/34 18% and 7/37 19%) of the affected cases also had associated malformations and were detected in that age group. In young maternal age (under 20 years) both isolated cases and cases with associated anomalies could be detected.

Analyzing all cases, the proportion of boys was 9–10% higher (54 boys and 44 girls). Differences than that of girls were found in isolated cases and cases with associated anomalies. The proportion of boys was higher in isolated malformations.
CONCLUSIONS

1. Although not significantly, but the rate of false positive cases of diaphragmatic hernia has decreased over the past decade and a half, even though the difference was not statistically significant. Over 70% of the false positive cases proved to be thoracic malformations of non-cardiac origin, the majority being congenital cystic adenomatoid malformations.

2. Due to technological development and broadening experience, congenital diaphragmatic hernias can be diagnosed prenatally in 85–90% of the cases. In the past 15 years, a significant increase was observed in diagnosing the malformation before the 24th gestational week. The earliest diagnosis can be made in the 12th gestational week while the average time of detection was in the 22.7th gestational week.

3. Most often it was heart developmental anomalies that were associated with congenital diaphragmatic hernia. The number of central nervous system anomalies decreased. The rate of thoracic anomalies, especially that of severe pulmonary hypoplasia showed a parallel increase to the rise in the incidence of cases associated with multiple anomalies.

4. Polyhydramnios was usually found together with associated anomalies, therefore it is not the polyhydramnios but the associated anomaly that can have a negative effect on the prognosis.

5. According to these data, there was no significant improvement in survival rates between the two periods of the study (26% vs 29%). It was related to the high (71%) proportion of associated anomalies than to lack of proper perinatal diagnostics or treatment. Early diagnosis (prior to the 24th gestational week) enabled the couples to make a decision of their own; they opted for pregnancy termination in 80% of the cases and over 65% even in isolated anomalies.

In bilateral malformations, live birth and survival cannot be expected. In cases affected by associated anomalies, the survival rates are expected to be approximately 15–20%. The poor prognosis in right-sided anomalies is due to the high rate of associated anomalies. The best prognosis can be expected in cases with a left-sided isolated hernia.

The survival rate in postnatally diagnosed cases was the same as that of the pregnancies with isolated diaphragmatic hernias. Although the number of cases in the individual groups was low, our data confirmed that the survival rates were basically influenced by the associated malformations in the case of diaphragmatic hernias.
6. Analyzing the survival rates of live-born infants in liver, spleen and stomach herniations, the best prognosis was expected in case the spleen was herniated into the thorax. In liver herniation, the survival rate dropped back to a quarter, while, if the stomach was located in the chest, the survival rate fell by almost half in such deliveries. No survival was expected if a “rare” organ was located above the diaphragmatic line. I observed that isolated herniation of the small intestines was more common than isolated herniation of part of the large intestines, the latter exclusively occurring in cases affected by associated anomalies.

7. The results showed that newborns delivered by caesarean section after the 37th gestational week had the best prognosis, which was not significantly influenced by birth weight (if it reached the 10 weight percentile). In infants delivered by caesarean section, postnatal stabilization was more easily achieved and the operation could be done earlier. Prematurity was one of the factors of survival; according to our data, the expected survival rate of newborns with congenital diaphragmatic hernia delivered before the 34th gestational week was low.

8. An increase in mean Apgar scores was expected in the 32nd–36th gestational weeks, independently of the method of delivery. In view of the fact that the highest Apgar scores were registered among the surviving mature infants delivered by caesarean section, it can be concluded that the Apgar score may predict the prognosis. Early postnatal mortality (within 24 hours of delivery) was basically influenced by the number of organs herniated into the chest cavity and also the number of associated anomalies. Multiple herniation of organs into the thoracic cavity significantly worsened the prognosis. Prematurity and multiple herniation into the thorax meant an extremely poor prognosis even in isolated congenital diaphragmatic hernia. The method of delivery, however, did not influence early mortality rate.

9. Common use of high-frequency respiration contributed to the increase in survival rates by preventing hyperventilation.

10. In cases when herniation was associated with other anomalies, the maternal age was not higher than the overall mean maternal age, thus it can be concluded that maternal age was
not a factor affecting the severity of the malformation. Young maternal age had no influence on whether the anomaly was isolated or associated with other malformations. Regarding of all cases, congenital diaphragmatic hernia occurred in 10% more frequently proportions in boys than in girls. Isolated diaphragmatic hernia was more commonly diagnosed than usual in boys.

PRACTICAL CONCLUSIONS

1. Being aware that prenatal diagnosis may be false positive in 7–10% of the cases, special attention has to be payed to the recognition of malformations of non-cardiac origin. At genetic counselling, we must always bear in mind the chances of false positive prenatal diagnosis despite the most modern sonographic background and highly experienced personnel.

2. Even with regular prenatal care, about 10% of cases of congenital diaphragmatic hernia are discovered only postnatally, during delivery room care. In addition to looking for the symptoms of congenital diaphragmatic hernia, we must be prepared to intubate the newborn immediately, if necessary. If a child is not delivered in perinatal centre, it should be transferred to a neonatal intensive care centre with a paediatric surgical unit immediately, in case of suspected congenital diaphragmatic hernia.

3. Considering the 44–54% association rate of cardiac developmental disorders in the prenatally diagnosed malformations, fetal echocardiography is absolutely required.

4. The simultaneous diagnosis of congenital diaphragmatic hernia and polyhydramnios requires detailed fetal ultrasonography to detect further possible anomalies.

5. In the case of a positive prenatal diagnosis elective caesarean section is recommended after the 37th gestational week to ensure the most optimal conditions for the newborn to survive.

6. Surfactant therapy improves the prognosis of premature infants with respiratory distress syndrome and improves pulmonary function of mature newborns with decreased respiratory surface due to congenital diaphragmatic hernia, and decreases the demand for respiratory support.
LIST OF PUBLICATIONS

Journal articles pertaining to the thesis

Articles published in international journals


Articles published in Hungarian journals


Book chapters


OTHER PUBLICATIONS

Articles published in international journals


Articles published in Hungarian journals


Book chapters


Abstracts published in journals


Number of all publications: 29 (impact factor: 8,973)
Number of publications with first authorship: 10 (impact factor: 3,438)
Abstracts published in journals: 26 (impact factor: 15,389)
Book chapters: 5
Cumulative impact factor: 24,362
Congenital diaphragmatic hernia (CDH) has an incidence of between one in 2000–5000 live births. The hidden mortality associated with CDH includes spontaneous abortions and stillbirths as well as therapeutic abortions (often for other identified anomalies). The management of CDH has been intensely debated since Ladd and Gross stated in 1940 that early surgery was the proper treatment for these patients. Controversies have surrounded ideal preoperative management, timing of surgery, and indeed whether surgery should be offered to all. Prenatal diagnostic rates vary from 10–90% depending on local antenatal ultrasound screening protocols. Prenatal diagnosis allows for counselling of parents and planned management but does not predict outcome. To assess the prognosis of prenatally diagnosed congenital diaphragmatic hernia (CDH) during the years 1995–2000 in order to improve prenatal counselling.

Methods. Retrospective study of all 31 cases of women with prenatally diagnosed CDH. George Graham, Patricia Connor Devine, Antenatal Diagnosis of Congenital Diaphragmatic Hernia, Seminars in Perinatology, 10.1053/j.semperi.2005.04.002, 29, 2, (69-76), (2005). Crossref. Darrell L. Cass, Fetal Surgery for Congenital Diaphragmatic Hernia: The North American Experience, Seminars in Perinatology, 10.1053/j.semperi.2005.04.010, 29, 2, (104-111), (2005). Crossref. Congenital diaphragmatic hernia is a fetal defect that develops during the formation of the diaphragm; this is the muscle that separates the chest cavity from the abdominal cavity. The diaphragm is the muscle that helps us to breathe, so it is a critical component of the respiratory system. In a diaphragmatic hernia, the diaphragm which develops at about 8 to 10 weeks of pregnancy does not completely form, and an opening remains between the chest and the abdominal cavities. In many cases CDH is diagnosed during a prenatal ultrasound. If not diagnosed prenatally, the condition may be found soon after birth when the baby has trouble breathing. Less frequently, a diaphragmatic hernia is found in an older child. How is CDH treated?