Congenital diaphragmatic hernia: ultrasonic measurement of fetal lungs to predict pulmonary hypoplasia

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ABSTRACT

Objective The purpose of this study was to assess the value of biometric lung measurements for the prediction of severe fetal pulmonary hypoplasia in congenital diaphragmatic hernia and to determine whether a correlation between lung measurements and autopsy findings or neonatal outcome could be established.

Design Prospective study, between 1991 and 1997.

Subjects Nineteen fetuses with congenital diaphragmatic hernia.

Methods In addition to standard biometry, sonographic measurement of the transverse thoracic diameter, sagittal thoracic diameter, fetal lung diameters at the level of the four-chamber view and lung/thoracic circumference ratio were performed. These were compared with the standard curves defined by Merz and colleagues. Autopsy examinations were performed to determine lung weight, lung weight/body weight ratio and radial alveolar count.

Results Five fetuses (26%) were terminated before 24 weeks of gestation. All of these fetuses had lung measurement values below the 5th centile. Eleven of 14 fetuses (78.6%) with pulmonary hypoplasia diagnosed after 24 weeks of gestation died postnatally. The mortality rate was 70% (7/10) in the fetuses without associated anomalies. The sonographic diagnosis of fetal pulmonary hypoplasia was made in all fetuses who died postnatally. All fetuses with a lung diameter/thoracic circumference ratio below 0.09 died. Three fetuses, which had values within the normal range, survived. In contrast, measurements of the bony thorax (transverse and sagittal thoracic diameters, thoracic circumference) did not provide an indication of the presence of fetal pulmonary hypoplasia. Pulmonary hypoplasia was confirmed at autopsy in all fetuses on the basis of lung weight, lung/body weight ratio or radial alveolar count. Concomitant with pulmonary hypoplasia was polyhydramnios in ten fetuses (71.4%), mediastinal shift in 11 fetuses (78.6%), intrathoracic herniated stomach in six fetuses (42.9%) and associated malformations in four fetuses (28.6%). Postnatal mortality for these conditions was 80%, 78.6%, 100% and 100%, respectively. Postnatal mortality was 75%, 70% and 100% in the fetuses with an isolated diaphragmatic hernia.

Conclusion The results of this investigation suggest that the assessment of fetal lung diameter and the use of the lung diameter/thoracic circumference ratio are further useful prognostic parameters in the management of congenital diaphragmatic hernia.

INTRODUCTION

Despite major advances in prenatal and postnatal diagnosis and therapy, congenital diaphragmatic hernia continues to pose a major perinatal problem, with an incidence of 1 in 2200 to 1 in 5000 births and a largely unchanged perinatal mortality rate of approximately 60–80%. On the basis of data obtained by a number of prenatal ultrasound investigations the following prognostic indicators were shown to exert a negative influence on postnatal outcome: polyhydramnios, intrathoracic herniated stomach, mediastinal shift, a decreased quotient between the left and right ventricle and associated malformations in addition to the finding of diaphragmatic hernia before
25 weeks’ gestation. None of these prognostic factors has been widely accepted or applied clinically for the assessment of poor outcome.

Results of animal studies have led to the hypothesis that pulmonary hypoplasia in diaphragmatic hernia results from compression of the lung by viscera herniated into the thorax. Conversely, it has been suggested that intra-thoracic herniation occurring at an early stage of gestation may lead to the development of muscular hypertrophy of the pulmonary vascular bed, which has been associated with the risk of neonatal pulmonary hypertension. Furthermore, autopsy examinations have cited reduced bronchiolar branching, abnormal bronchiolar cartilage development, a reduced total number of alveoli in the affected lung and retarded acinar development as possible causative factors.

However, there is a lack of data on reliable prenatal diagnostic methods for the prediction of fetal pulmonary hypoplasia. The antenatal diagnosis of lung hypoplasia in congenital diaphragmatic hernia has been attempted using the lung/thorax transverse area ratio. Although these authors were able to show that, in cases of congenital diaphragmatic hernia, the lung/thorax transverse area ratio was lower than in the control group and correlated with the arterial pH, pCO₂ and preductal paCO₂ before operation, no significant differences were noted in the lung/thorax transverse area ratio between survivors and non-survivors. It has also been shown that prenatal analysis of the lung/head ratio serves as a predictor of survival in patients with congenital diaphragmatic hernia.

The aim of this study was to establish a possible correlation between prenatal measurements of the fetal bony thorax or the fetal lung and autopsy findings in congenital diaphragmatic hernia and to assess the value of these measurements as useful prognostic indicators in the prediction of severe pulmonary hypoplasia and survival. Standard curves for the growth of the fetal lung and the bony thorax recently published by Merz and co-workers serve as the basis for the present investigation.

MATERIALS AND METHODS
Detailed sonographic biometry of the bony thorax and the lung was performed in 19 fetuses with congenital diaphragmatic hernia between 19 and 38 weeks of gestation according to the reference planes described by Merz and colleagues. Sonographic examinations were carried out with the Combson 530 (Kretztechnik, Austria) 5-MHz sector probe, a Hitachi EUB 525, 5-MHz curved-array probe and a Logic 700 (General Electrics, Kranzbühler) 5-MHz curved-array probe. The evaluation was based solely on biometric data obtained at the time of the initial sonographic diagnosis. All measurements were obtained using electronic calipers on the frozen ultrasound image (1540 m/s in all cases). We performed three measurements for each parameter and calculated the average of the obtained values. To establish the reference plane for measurements of the bony thorax diameter and the lung diameter, the chest was visualized in a transverse section at the level of the four-chamber view. The transverse diameter measurement of the bony thorax included the ribs. The anterior–posterior diameter was obtained by measuring from the outer edge of the vertebra to the outer edge of the sternum. The subcutis was excluded from these measurements. Bony thorax measurements were performed to calculate the lung/thoracic circumference ratio. Calculations of the circumference of the bony thorax were made using the following formula:

\[
\text{Bony thorax circumference} = (\text{transverse} + \text{anterior–posterior bony thorax circumference}) \times 1.57
\]

For lung measurements, first the heart was visualized at the level of the four-chamber view. Second, the electronic calipers were positioned at the extension of the atrio-ventricular septum between the outside of the myocardium and the inside of the bony thorax (Figure 1). The lung diameter/thoracic circumference ratio was calculated.

As reported elsewhere by Merz and colleagues, the interobserver and intraobserver variations for all measurements were below 9% in a normal control group. Intraobserver variations of lung measurements and measurements of the bony thorax in all cases with congenital diaphragmatic hernia were studied by calculating the coefficient of variability (%). Three measurements were made for each parameter. Longitudinal measurements of the lung diameter were performed in seven fetuses. With the exception of two fetuses (for which the parents refused an autopsy), autopsy examinations were performed on all non-surviving fetuses (Figure 2) to determine the lung weight, lung weight/body weight ratio or the radial alveolar count (RAC). A lung weight/body weight ratio of ≤ 0.012 and RAC values of ≤ 4.1 were considered to be indicators of pulmonary hypoplasia. Amniotic fluid volume was estimated from the vertical measurement of the largest cord-free pool. A measurement of > 8 cm was regarded as indicative of polyhydramnios.

All fetuses were delivered by the vaginal route. Immediately after birth the fetuses were intubated by experienced pediatricians. High-frequency oscillatory ventilation or nitric oxide therapy was performed in cases of severe pulmonary hypoplasia. Surgery was carried out only in the presence of a stable fetal circulation.

RESULTS
Sonographic findings and prognostic criteria are summarized in Tables 1 and 2. With the exception of case 1 (15p deletion, ventricular septal defect, intrauterine growth restriction) all chromosomal investigations revealed a normal karyotype. The mean gestational age at the time of initial diagnosis was 30.3 weeks (range 19–38 weeks). Eighteen fetuses had left-sided posterolateral diaphragmatic hernia; right-sided diaphragmatic hernia was found in one fetus. In five of 19 fetuses (26%) the parents elected to terminate the pregnancy. All terminated fetuses were excluded from further analyses of prenatal risk factors and fetal outcome. As expected, measurements of the transverse and
anterior–posterior bony thorax diameter as well as of the bony thorax circumference were not useful in predicting pulmonary hypoplasia in cases of congenital diaphragmatic hernia and did not prove to be reliable predictors of mortality (Figure 3). However, the measurement of the bony thorax diameter is of importance in calculating the lung diameter/thoracic circumference ratio. Biometric values of the bony thorax diameter below the 5th centile were found in case 1 only. This fetus had a chromosomal anomaly with 15p deletion, a confirmed ventricular septal defect and symmetrical 3-week growth restriction. Lung diameter and the lung diameter/thorax circumference ratio were significantly below the 5th centile in all five fetuses. Excepting cases 9, 10 and 18, the lung diameter and lung diameter/thorax circumference ratio were below the 5th centile in the remaining 14 fetuses. Perinatal mortality was 100% for fetuses with values below the 5th centile, whereas the three infants who had lung diameters and lung diameter/thorax circumference ratios within the normal range survived (Figures 4 and 5). All fetuses with a lung diameter/thorax circumference ratio of less than 0.09 died (Table 1, Figure 5). Sonographic lung diameter follow-up measurements were made for seven fetuses. Although lung growth was virtually absent in the fetuses that died, one surviving infant exhibited marked lung growth (Figure 6).

The intraobserver coefficient of variability was 6.9% for the circumference of the bony thorax, 7.8% for the lung diameter/thoracic circumference ratio and 8.7% for the lung.

The autopsy examination yielded right lung weights below the normal range, a lung/body weight index below

### Table 1: Fetal biometric measurements and pathological correlation

<table>
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<tr>
<th>Case</th>
<th>Gestational age (weeks)</th>
<th>LD</th>
<th>TTD</th>
<th>STD</th>
<th>TC</th>
<th>LD/TC ratio</th>
<th>Right lung weight (g)</th>
<th>RAC</th>
<th>LW/BW ratio</th>
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<tr>
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LD, lung diameter; TTD, transverse thoracic diameter; STD, sagittal thoracic diameter; TC, thoracic circumference; RAC, radial alveolar count; LW, lung weight; BW, body weight; *no pathological examination.
0.01 and/or an RAC of below 2 for all fetuses. RAC estimations were available in only five cases, because this was not routinely obtained by the Department of Pediatric Pathology. Autopsy was refused in two cases by the parents (Table 1).

The sonographic intrauterine prognostic parameters are shown in Table 2. Polyhydramnios was detected in only one case before 24 weeks of gestation. This fetus, however, had associated cleft lip, mandible and palate. Ten out of 14 (71.4%) pregnant women demonstrated polyhydramnios after 24 weeks of gestation. In cases with isolated diaphragmatic hernia, polyhydramnios occurred in eight out of ten fetuses (80%). Perinatal mortality was 80% and 75%, respectively, in the presence of this marker. Polyhydramnios was observed in two of the three surviving infants.

Intrathoracic stomach herniation was detected in three cases before, and in six out of 14 cases (42.9%) after, 24 weeks of gestation. Intrathoracic stomach herniation was observed in four out of ten (40%) of the fetuses without malformations. Perinatal mortality in both groups was 100% in the presence of this marker. Intrathoracic visualization of the stomach was not achieved in the three surviving infants.

Mediastinal shift was demonstrated in all cases, with a perinatal mortality of 78.6%. Perinatal mortality was 70% in the group without malformations.
Associated malformations were identified in three cases before 24 weeks of gestation (one Arnold–Chiari malformation; two bilateral hydronephrosis) and in four of 14 cases after 24 weeks of gestation. Malformations in these four fetuses included a cardiac defect in two cases (including one case with chromosomal anomaly) and malformations of the central nervous system in the remaining two fetuses. All four infants died during the neonatal period. None of the surviving infants had associated malformations.

DISCUSSION

The pathophysiology of congenital diaphragmatic hernia represents a highly complex process. In addition to embryonic lung development, gastrointestinal, cardiac and renal organ systems have important roles in this process. Intra-thoracic herniation of abdominal viscera occurring in the pseudoglandular and canalicular stage of development results in a disturbance of bronchogenesis and a subsequent reduction in the number and size of terminal bronchioles and alveoli. Results of animal studies have confirmed that this, in turn, leads to a marked decrease in lung volumes and lung weights. In congenital diaphragmatic hernia, vascular muscularization extends into the preacinar area. These findings have recently been supported by results obtained in a rat model. The progressive disturbance of pulmonary development in the terminal phase (24–40 weeks of gestation) results in an inadequate differentiation of squamous epithelia from alveolar epithelial cells of types I and II. The poor differentiation from type II pneumocytes leads to a decrease in surfactant secretion and to a subsequent reduction in lung surface tension. The outlined abnormal lung development is, however, not evenly distributed throughout the lung and affects not only lung morphology but, in particular, the functional areas (airways, blood vessels, air exchange, surface and surfactant system). The described histomorphometric findings are considered to be responsible for the postnatal increase in respiratory resistance as well as for the frequently noted development of therapy-resistant pulmonary hypertension. These findings therefore constitute one of the major reasons for the high neonatal mortality rate.

Even though three infants in this study had intrauterine lung diameters within the lower normal range, adequate oxygenation was achieved, owing to the presence of sufficient functional lung tissue and adequate respiratory and surgical therapy. The further development of all three infants was uneventful.

The sonographic intrauterine detection of pulmonary hypoplasia has thus far been reported primarily in connection with a previous premature rupture of the amnion, urogenital malformations, skeletal dysplasia, or intrauterine growth restriction. These authors did not perform lung measurements in the prenatal assessment of pulmonary hypoplasia, but based their evaluations on measurements of the thoracic circumference and the ratio of thoracic circumference to abdominal circumference. The biometric assessment of the fetal lung has to date consisted solely of lung circumference measurements or of measurements of the distance between
the left and right lung performed laterally at the level of the atrioventricular valve. Our results show that severe lung hypoplasia in congenital diaphragmatic hernia can be predicted with a high degree of reliability using the described measurement technique. The intrauterine diagnosis of lung hypoplasia was associated with a neonatal mortality rate of 100% in our study population. Detailed morphometric studies in infants who died postnatally, as well as in animal models, have demonstrated both lungs to be hypoplastic, although the ipsilateral lung was shown to be significantly more severely damaged. The severity of hypoplasia of the contralateral lung therefore plays a decisive role with regard to survival. In our population all biometric measurements were obtained from the contralateral lung, in view of the fact that sonographic visualization of the ipsilateral lung is not readily achieved in congenital diaphragmatic hernia.

The use of the lung diameter and the quotient of lung diameter and bony thorax circumference are particularly useful in the prediction of pulmonary hypoplasia. For all 16 intrauterine diagnoses, pulmonary hypoplasia was confirmed at autopsy on the basis of lung weights, lung/body weight ratio and/or RAC. Maeda and co-workers firmly stated that pulmonary hypoplasia was confirmed at autopsy on the basis of lung weights, lung/body weight ratio and/or RAC. The use of the lung/thorax transverse area ratio in cases of congenital diaphragmatic hernia was lower than in the control group and correlated with biological markers of neonatal oxygenation, no significant differences were noted in this ratio between survivors and non-survivors. In contrast, two studies of the same group described the ratio of right lung area to head circumference as a predictor of postnatal survival and severe pulmonary hypoplasia. In the first study, all fetuses with a ratio of less than 0.6 died postnatally; those with a ratio between 0.6 and 1.35 had a survival rate of 61%, while all fetuses with a ratio of greater than 1.35 survived. Similar results were obtained in a following prospective study by Lipshutz and colleagues. Despite the small number of cases in our study as well as those of other authors, initial results indicate a possible relationship between the absence of lung growth and poor fetal outcome. Further work on serial lung measurements for the assessment of lung growth needs to be done in the future. The importance of intrauterine lung biometry as a prognostic indicator in congenital diaphragmatic hernia is further emphasized by initial postnatal thorax radiographs. For example, Saifuddin and associates reported an unfavorable prognosis in the absence of radiographic evidence of the ipsilateral lung and of a contralateral aerated lung. On the other hand, biometric assessments of the bony thorax based on the transverse and anterior-posterior diameter, or on the calculation of the bony thorax circumference, have not provided diagnostic information on the risk of fetal pulmonary hypoplasia.

Of further interest are the methods for fetal lung volume measurements using three-dimensional sonography recently described by Lee and colleagues and Pöhls and colleagues. Although these techniques enable more accurate volumetric measurements of the fetal lung to be made, no results have yet been published on their use as predictors of congenital diaphragmatic hernia.

Various studies have attempted a prediction of pulmonary hypoplasia in fetuses with congenital diaphragmatic hernia based on sonographic criteria. Although Thorpe-Beeston and co-workers could not establish a relationship between the presence of polyhydramnios, fetal breathing, mediastinal shift and pulmonary hypoplasia, these parameters were shown to exert a significant influence on perinatal mortality in a recently published retrospective multicenter cohort study. Ventricular disproportion represented by an underdevelopment of the left side of the fetal heart has been suggested as a possible diagnostic indicator of pulmonary hypoplasia. Furthermore, recent Doppler ultrasonographic studies on the fetal pulmonary vascular system and fetal breathing have identified these factors as possible useful predictors of the presence of severe pulmonary hypoplasia. Using color Doppler ultrasonography, Badalian and co-workers have assessed the breathing activity of 16 fetuses with congenital diaphragmatic hernia. The authors observed significantly shorter expiration times and a lower inspiration/expiration ratio in the group of infants who died postnatally compared to the group of surviving infants.

Mortality rates reported in the literature ranging from 30–90% emphasize the pronounced difference in results obtained by studies in the areas of prenatal medicine, neonatology and surgery. The conflicting results appear to be primarily due to differences in the selection of the patient population and might further be attributable to the application of more advanced therapeutic concepts.

In summary, our results suggest that the sonographic prenatal assessment of the lung diameter and the lung diameter/thorax circumference ratio permits a relatively reliable intrauterine diagnosis of severe pulmonary hypoplasia. Our data further indicate a strong correlation between the presence of severe pulmonary hypoplasia, autopsy findings and an extremely poor neonatal outcome. On the other hand, the prognosis appears to be more favorable for infants with confirmed congenital diaphragmatic hernia and lung measurements within the normal range.

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REFERENCES


