Abstract. Aim: To evaluate the influence of gender in neonates with congenital diaphragmatic hernia (CDH) on survival and to assess the necessity of extracorporeal membrane oxygenation (ECMO) therapy. Patients and Methods: All parturients with newborns suffering from CDH were included. A total of 425 infants with CDH were analyzed. The primary outcome parameters evaluated were the necessity of ECMO and the survival. Secondary outcome parameters were the mode of delivery, the arterial umbilical cord pH value, the Apgar score, and the postpartum day of death. Cases with incomplete data were excluded. Results: An analysis of the gender distribution of neonates in our study revealed that more males (n=248) than females (n=177) suffered from CDH. This represented a male versus female gender ratio of 58.4% to 41.6%, a significantly different ratio from that for neonates without CDH (p=0.003). Comparing both groups, statistical analysis showed no significant differences in mode of delivery, arterial umbilical cord blood pH, Apgar score, or CDH-relevant parameters of postpartum survival, including the need for ECMO therapy. Conclusion: CDH occurred significantly more frequently in male newborns. However, there were no significant differences in postnatal survival nor in the necessity of ECMO therapy.

Congenital diaphragmatic hernia (CDH) is a life-threatening condition and the most frequent malformation accompanied by pulmonary hypoplasia (1). A persistent gap in the diaphragm leads to intrathoracically herniated visceral organs, which constrain lung development. The dimension of pulmonary hypoplasia determines perinatal mortality, and morbidity and thus the primary neonatal outcome, assuming that severe defects such as chromosomal abnormalities and other grave malformations have been ruled out (2-4). Antenatal diagnosis is crucial for appropriate medical advice and planning of ongoing therapeutic approaches. It has been shown in various investigations that in neonates who do not respond to conventional therapy, extracorporeal membrane oxygenation (ECMO) therapy improves survival (5-7). Generally accepted as prognostic factors in fetuses with CDH are the side of herniation and the liver position (8-11). Throughout the past decade, various further prognostic factors have been detected to predict neonatal outcome, such as mediastinal shift (12), presence of a polyhydramnio (13), intrathoracic stomach (14, 15), visceral herniation (16), and underdevelopment of the left side of the heart (17). In clinical routine, sidedness of hernia, liver herniation and pulmonary hypoplasia are particularly being used as predictors of perinatal outcome. The most commonly used method is the measurement of the lung area to head circumference ratio (LHR) via ultrasound examination (8, 11, 18, 19), although the predictive value of this sonographic parameter is still a matter of ongoing debate (19-21). Determination of fetal lung volume by magnetic resonance imaging (MRI) has been implemented in clinical routine, as various investigations showed that this diagnostic approach constitutes a valuable prognostic tool (18, 22-25). Various studies showed that fetal gender influences perinatal outcome in general. Abnormal fetal heart rate patterns during birth (26-28), preterm delivery (29-31), placental dysfunction (32), true umbilical cord knots (33, 34) as well as placental abruption and stillbirth (35, 36) have been shown to be more frequent in pregnancies with male fetuses. The association of male gender with pulmonary hypoplasia after premature rupture of membranes at less than

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28 weeks of gestation (37) in particular indicates that fetal gender could also potentially impact the outcome in fetuses with CDH.

For these reasons, this study evaluated whether or not fetal sex has an influence on survival rates and the necessity of ECMO therapy in neonates.

**Patients and Methods**

In this retrospective investigation, all parturients of the Department of Obstetrics and Gynecology, University Medical Center Mannheim, Germany between March 2001 and August 2010 with newborns suffering from CDH, were included. Aside from fetal gender, the following demographic parameters were analyzed: maternal age, gestational age at birth, number of pregnancies, parity, and birth weight. Concerning CDH, time of diagnosis (before or after birth), the side of hernia, and the liver placement were recorded. The distribution of the fetal gender was compared with gender distribution of all births throughout the above mentioned time period at our University Medical Center. The study’s primary outcome parameters were the necessity of ECMO therapy and survival. The secondary outcome parameters were: the mode of delivery, the arterial umbilical cord the blood pH value, the Apgar score, and the day of death after birth. Cases with incomplete data regarding outcome were excluded.

ECMO. According to previously published guidelines, in all neonates with CDH, ECMO therapy was applied when necessary (6, 38-40). Endotracheal intubation was implemented immediately after birth in all neonates and conventional ventilation was accomplished. ECMO therapy was initiated in neonates with a postductal pO2 less than 50 mm Hg and a preductal saturation below 95% for more than 4 hours, or with a postductal pO2 less than 40 mmHg and preductal saturation below 80 mmHg for more than 2 hours. Throughout ECMO therapy, heparin (Liquemin N5000; Roche, Basel, Switzerland) was applied intravenously at 400 IU/kg/day. Decannulation, ligation of the jugular vein and reconstruction of the common carotid artery were performed in one surgical session. ECMO therapy was not initiated with proof of ongoing hemorrhage or detection of severe coagulopathy, severe concomitant anomalies, and lactate levels ≥20 mmol/l.

**Statistical analysis.** All data were recorded in an Excel datasheet. After careful check for faulty entries and extreme values, the data were transferred into the Statistical Package for the Social Sciences (SPSS, 2006, Inc., Chicago, IL, USA) environment for statistical analysis. Quantitative data are presented as median and range, qualitative data as frequencies. Group-wise comparisons were performed using either the Mann-Whitney U-test or the binominal test. All tests were two-sided. p-values ≤0.05 were considered significant.

**Results**

A total of 425 newborns with CDH were included in the study. The distribution of gender for all births throughout the examined time period showed a male versus female gender ratio of 51.9% to 48.9%. Analysis of the gender distribution of neonates with CDH revealed that there were more male infants with CDH (n=248) than female infants (n=177)
Diagnosis of CDH 0.322  
Survival 0.278  
ECMO 0.702  
Herniation of liver 0.664  
Location of herniation 0.957

Difficulties still remain in assessing precise prenatal abnormalities (2, 3). With the improvement of ventilation techniques and the increasing prenatal detection of CDH (41), accompanied by delivery in specialized centers, the prognosis of CDH has improved over the past decade (42-45). Difficulties still remain in assessing precise prenatal prognostic parameters. Predicting perinatal outcomes in infants with CDH remains a challenge.

The most commonly used method is the sonographic measurement of LHR (8, 11, 18, 19). Many studies report improved survival with increasing LHR; on the other hand, it is proven that LHR changes with advancing gestational age (46). For this reason, the observed-to-expected LHR was implemented, which has been proven a reliable parameter throughout pregnancy for prediction of subsequent survival (47). The determination of fetal lung volume by MRI was also proven to be a valuable predictor of postpartum fetal outcomes (22, 24, 25, 38, 39). A limitation of this diagnostic approach is the high cost and, partially, the lack of patient compliance. 3D Sonography is a promising alternative in the determination of fetal lung volume and might consequently serve as a good predictor of fetal outcome. However, compared to MRI, the existing data on 3D sonography are still not as convincing (48). Some of the longest known and still most influential predictors of fetal outcome are sidedness of hernia and liver herniation (8-11).

Although several investigations demonstrated that fetal sex had an influence on parameters concerning fetal outcomes, until now the influence of fetal gender on clinical outcomes is still unclear.

Various authors stated that abnormal fetal heart rate patterns during labour and fetal distress are more frequent in male fetuses (26-28, 49, 50). Lieberman et al. found a 70% increase in caesarean deliveries due to fetal distress in parturients carrying male fetuses (28). The authors also stated that male infants delivered by cesarean section for fetal distress had lower Apgar scores than female fetuses delivered for the same indication.

Medical literature cites a number of instances in which male fetuses are more prone to developmental problems. Placental disorders such as placental insufficiency (32) and placenta previa were found to be more common among male fetuses. Severe twin–twin transfusion syndromes were more common in pregnancies with monozygotic male twins (51). Furthermore, several authors reported that placental abruption and stillbirth (35, 36), umbilical cord abnormalities (33, 34), fetal macrosomia and shoulder dystocia (52, 53) are associated with male sex. Various investigations showed that preterm birth (29-31) and prolonged pregnancies (54) also occur more often in parturients carrying male fetuses. Considering fetuses with CDH, an association between male gender and pulmonary hypoplasia after second-trimester premature rupture of membranes at <28 weeks of gestation was found (37). In an investigation by Vergagni et al., two thirds of the infants who developed pulmonary hypoplasia were male. Stocks et al. (55) also discovered that in preterm infants, the airway function was diminished in boys compared to girls, a finding consistent with other observations.

Table II. Characteristics of relevant parameters in congenital diaphragmatic hernia (CDH) (n=425), p-values ≤0.05 were considered significant.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n (%)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of CDH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before birth</td>
<td>183 (74%)</td>
<td>141 (80%)</td>
</tr>
<tr>
<td>After birth</td>
<td>54 (21%)</td>
<td>30 (17%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>12 (5%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Location of herniation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left side</td>
<td>188 (76%)</td>
<td>140 (79%)</td>
</tr>
<tr>
<td>Right side</td>
<td>56 (23%)</td>
<td>35 (20%)</td>
</tr>
<tr>
<td>Both sides</td>
<td>3 (1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Herniation of liver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (liver up)</td>
<td>110 (44%)</td>
<td>80 (45%)</td>
</tr>
<tr>
<td>No (liver down)</td>
<td>63 (26%)</td>
<td>50 (28%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>75 (30%)</td>
<td>47 (27%)</td>
</tr>
<tr>
<td>ECMO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>109 (44%)</td>
<td>73 (41%)</td>
</tr>
<tr>
<td>No</td>
<td>134 (54%)</td>
<td>102 (58%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>176 (71%)</td>
<td>134 (76%)</td>
</tr>
<tr>
<td>No</td>
<td>72 (29%)</td>
<td>43 (24%)</td>
</tr>
<tr>
<td>Death after birth (in days)</td>
<td>14 (0-360)</td>
<td>10 (0-231)</td>
</tr>
</tbody>
</table>

ECMO: Extracorporeal membrane oxygenation.

(58.4%:41.6%). This allocation was significantly different (p=0.003) from the gender distribution in neonates without CDH. Table I illustrates demographic characteristics by gender. Table II shows CDH-relevant parameters of neonatal outcomes, including necessity of ECMO and survival. These parameters revealed no significant differences between the sexes. Results for mode of delivery, postpartal pH and Apgar scores are given in Table I. Comparing both groups overall, statistical analysis showed no significant differences except for birth weight.

Discussion

In neonatal fetal medicine, gender differences in outcomes are often observed. This study aimed to analyze the gender of neonates with CDH as an independent prognostic factor. Perinatal outcome among neonates with CDH depends primarily on the dimension of lung hypoplasia and persistent pulmonary hypertension, assuming there are no accompanying severe defects such as chromosomal abnormalities (2, 3). With the improvement of ventilation techniques and the increasing prenatal detection of CDH (41), accompanied by delivery in specialized centers, the prognosis of CDH has improved over the past decade (42-45). Difficulties still remain in assessing precise prenatal
However, in our investigation on newborns with CDH, these findings were not reproduced. There were a significantly higher frequencies of CDH in male infants compared to healthy neonates, but fetal gender did not have an impact on either perinatal morbidity nor on necessity of ECMO. The results of our investigation comparing the gender distribution of healthy neonates and newborns with CDH did match with findings of other investigations (56-59). The only difference found between both sexes was birth weight, a distribution that is well documented (60, 61).

It has been shown in various investigations that in neonates who do not respond to conventional therapy, ECMO therapy improves survival (5-7). The multiple-institution Congenital Diaphragmatic Hernia Study Group recorded a survival rate of 38.5% in neonates in whom, without ECMO, mortality was predicted to be greater than 80% (7). As already mentioned above, in all neonates here, endotracheal intubation was performed directly after delivery and mild conventional ventilation was applied.

Due to increased risk, especially of hemorrhage and brain damage, ECMO therapy remains a controversial issue. The estimated necessity of ECMO therapy proposed in our study cannot generally be assigned to other centers. Although the inclusion and exclusion criteria used at our institution correspond to classic objective criteria for instituting ECMO therapy (6, 40), procedures may differ among the different tertiary care centers.

Conclusion

In this study CDH occurred significantly more frequently in male infants, however, this had no bearing on postpartum mortality or necessity of ECMO.

References


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