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Oslo, Norway; Trondheim, Norway; Stockholm, Sweden; Gothenborg, Sweden; Lund, Sweden; Uppsala, Sweden; Kuopio, Finland; Turku, Finland; Helsinki, Finland; Copenhagen, Denmark; and Odense, Denmark

Background/Purpose: There is a lack of large contemporary studies on the management of congenital diaphragmatic hernia (CDH), and the prediction of mortality remains difficult. The aim of this study was to investigate the influence of perinatal factors on mortality rate in a contemporary multicenter study.

Methods: The authors conducted a retrospective multicenter cohort study. Twelve of 13 Scandinavian pediatric surgical centers participated in the study. During a 4-year period (1995 through 1998) 195 children with CDH were included. The main endpoints were hospital mortality rate and total mortality rate (before 2001). Bivariate and multivariate survival analyses were performed using Kaplan-Meier plots, Log-rank test, and Cox regression.

Results: Overall hospital mortality rate was 30%. Among 168 neonates with symptoms within 24 hours (early presenters) 35% died before discharge. All 61 deaths occurred in 157 neonates with symptoms within the first 2 hours of life. Among early presenters, 27% had prenatal ultrasound diagnosis, 26% were delivered by cesarean section, and 21% had associated major malformations. Bivariate analysis of early presenters showed increased risk of death in neonates with prenatal diagnosis, associated anomalies, right-sided diaphragmatic hernia (RCDH), low 1-minute and 5-minute Apgar scores, low birth weight, short gestational age, and cesarean delivery. Neonates with prenatal diagnosis were characterized by significantly lower Apgar scores, lower birth weight, and increased frequency of associated anomalies than those diagnosed after birth. Multivariate analysis found that prenatal diagnosis (P = .004), 1-minute Apgar (P = .001), and RCDH (P = .042) were independent predictors of total mortality rate.

Conclusions: In a series of 195 CDH patients, all 61 deaths occurred in the 157 neonates presenting with symptoms within the first 2 hours of life. Prenatal diagnosis, 1-minute Apgar score, and RCDH were significant independent predictors of total mortality.

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INDEX WORDS: Congenital diaphragmatic hernia, prenatal diagnosis, mode of delivery, cesarean section, associated anomalies, Apgar score, mortality rate, prognostic factors, multivariate analysis.

Despite many new supportive modalities for the treatment of congenital diaphragmatic hernia (CDH), the mortality rate remains high.1-4 Although an increasing proportion of patients with CDH is diagnosed by prenatal ultrasound scan,5,6 no convincing benefit of prenatal diagnosis in terms of reduced postnatal mortality has been shown.6-8 More than 2,200 studies of CDH currently are retrievable by Medline. However, the sample size is too small in the majority of these studies. A few large CDH studies have been published, but they are vitiated by very long observation periods wherein treatment protocols have changed many times.1-2,9-11 The problem of small sample size can be overcome by including data from several studies in a metaanalysis6 or a systematic review.12,13 A different approach is to conduct a registry-based study3-4,14 or a multicenter study.15-18 Several predictors of mortality have been suggested, including polyhydramnios,19 early prenatal diagnosis,19 intrathoracic stomach,20,21 intrathoracic liver,22 presence of associated anomalies,23 right-sided (RCDH) diaphragmatic hernia,24-25 and low Apgar scores.2,26 However, studies on predictors of mortality rate in CDH patients...
Table 1. Number of CDH Patients, Centers, and Birth Prevalence by Country (1995 to 1998)

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of Patients</th>
<th>Participating Centers</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>89 (46%)</td>
<td>4</td>
<td>1: 4,200</td>
</tr>
<tr>
<td>Denmark</td>
<td>49 (25%)</td>
<td>2</td>
<td>1: 5,500</td>
</tr>
<tr>
<td>Finland</td>
<td>14 (7%)</td>
<td>3*</td>
<td>1:17,200</td>
</tr>
<tr>
<td>Norway</td>
<td>43 (22%)</td>
<td>3</td>
<td>1: 5,600</td>
</tr>
<tr>
<td>Total</td>
<td>195 (100%)</td>
<td>12</td>
<td>1: 5,800</td>
</tr>
</tbody>
</table>

*One center treating about 1 to 3 patients a year did not participate.

Table 2. Comparison of Frequencies of Prenatal Diagnosis and Hospital Mortality Rate Between the Scandinavian Countries in 168 CDH Patients With Early Symptoms (≤24 Hours of Life)

<table>
<thead>
<tr>
<th>Country</th>
<th>Prenatal Diagnosis*</th>
<th>Hospital Mortality Rate†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>22%</td>
<td>43%</td>
</tr>
<tr>
<td>Finland</td>
<td>17%</td>
<td>33%</td>
</tr>
<tr>
<td>Norway</td>
<td>29%</td>
<td>37%</td>
</tr>
<tr>
<td>Sweden</td>
<td>30%</td>
<td>31%</td>
</tr>
<tr>
<td>Total</td>
<td>27%</td>
<td>35%</td>
</tr>
</tbody>
</table>

NOTE. Chi-square test (between countries).
* P = .67.
† P = .62.

RESULTS

The number of CDH patients, number of centers, and prevalence for each country are shown in Table 1. The average number of patients treated at each center was 16 during the 4-year study period. Two hospitals treated ≥30 patients, 2 hospitals between 20 and 29 patients, 4 hospitals between 10 and 19 patients, and 4 hospitals less than 10 patients. No significant differences were found between the countries concerning prenatal detection rate and hospital mortality rate (Table 2).

Fifty-nine patients (30%) died before hospital discharge, and 2 more patients died after discharge at the ages of 3 and 10 months, respectively. All fatalities occurred in neonates presenting symptoms within the first 2 hours of life.

Hospital mortality rate in early presenters was 35% (59 of 168). The characteristics of early and late presenters are shown in Table 3. CDH was diagnosed prenatally in 27% of the early presenters. A total of 61 associated major anomalies were found in 36 early presenters. Cardiovascular anomalies were observed in 19 neonates (13 died), chromosomal abnormalities in 7 neonates (6 died), a neural tube defect in 7 neonates (all died), and major associated malformations in other organ systems in 21 neonates (13 died).

Cesarean delivery was much more likely in early presenters with prenatal diagnosis than in those without (58% v 14%; P < .001). Neonates delivered by cesarean section more frequently had associated anomalies (40% v 15%; P = .001), lower 1-minute Apgar score (4.8 v 6.1; P < .005), lower birth weight (2.71 v 3.18 kg; P = .004), and shorter gestational age (37 v 39 weeks; P = .008), but similar 5-minute Apgar score (6.2 v 6.3; P = .82). Additional data were available on 32 of 43 cesarean deliveries. Fifty percent of the cesarean sections (16 of 32) were emergency procedures because of asphyxia.
(n = 8) or other obstetric complications (n = 8), and 50% (16 of 32) were elective procedures because of prenatal diagnosis of CDH (n = 11) or obstetric reasons (n = 5). Fifty percent of the CDH patients died in both the groups (8 of 16 v 8 of 16).

Seventy-seven percent (129 of 168) of the early presenters underwent surgery with 16% (20 of 129) hospital mortality rate and 17% (22 of 129) total mortality rate. No significant difference (21% v 14%; P = .34) was found comparing hospital mortality rate in early presenters who underwent early (<24 h) and delayed surgery (≥24 h), respectively. All 27 late presenters underwent surgery and all survived. Postoperative complications are shown in Table 4.

Bivariate and multivariate analyses of the mortality factors are presented in Table 5. Bivariate Cox regression showed that the risk of dying was 3.7 times higher in neonates with prenatal diagnosis compared with those without (P < .001). The corresponding Kaplan-Meier curves are shown in Fig 1. Subgroup analysis showed significantly increased risk of total mortality (mortality before January 1, 2001) for prenatally diagnosed patients both in neonates with isolated CDH (52% v 21%; P = .001) and in neonates with associated major malformations (94% v 45%; P = .004). Presence of associated major malformation was associated with 3.3 times higher risk of total mortality compared with isolated CDH, and the corresponding Kaplan-Meier curves are presented in Fig 2. Early presenters delivered by cesarean section had 2.5 times higher risk of death compared with those delivered vaginally in the bivariate analysis. Among a subgroup of prenatally diagnosed patients subsequently undergoing planned delivery at a center, we found a significant increase in total mortality rate in the group delivered by cesarean section compared with those delivered vaginally (11 of 20 v 19 of 23; P = .049). The category of cesarean delivery was available in 14 of these 20 patients; 8 of 9 patients died in the elective cesarean delivery group compared with 4 of 5 in the emergency cesarean delivery group.

Surfactant was used in 21%, high frequency oscillation ventilation (HFOV) in 34%, and nitric oxide (NO) in 32% of early presenters. Significantly lower 1-minute and 5-minute Apgar scores were found in neonates treated by surfactant, HFOV, and NO compared with those not treated by these modalities. Total mortality rate was 66% with and 29% without surfactant (P < .001), 60% with and 25% without HFOV (P < .001), and 58%
with and 26% without NO ($P < .001$). Nine percent were treated by ECMO. A significantly lower 5-min Apgar (4.5 vs 6.5; $P < .001$) were found in ECMO patients than in non-ECMO patients. Total mortality rate was 47% in those needing ECMO compared with 36% in those not needing ECMO ($P = .39$).

In the multivariate Cox regression model, prenatal diagnosis, associated major malformations, side of hernia, birth weight, 1-minute Apgar, and mode of delivery were entered as independent variables with total mortality rate as an endpoint. Using this model we found that the risk of dying was 2.7 times higher with prenatal diagnosis than without ($P = .002$). Furthermore, 1-minute Apgar was a significant independent predictor of total mortality rate. When the 1-minute Apgar was increased by one unit, a 17% mortality rate reduction was found ($P = .001$). The risk of mortality was significantly increased in the group with RCDH compared with LCDH ($P = .042$).

To explain why neonates with prenatal diagnosis were at increased risk of dying compared with those with postnatal diagnosis, we further explored the characteristics of the 2 groups. Neonates with prenatal diagnosis had significantly lower 1-minute Apgar scores (4.5 vs 6.3; $P < .001$), lower 5-minute Apgar scores (5.6 vs 6.6; $P < .017$), lower birth weight (2.82 vs 3.15 kg; $P = .015$), and shorter gestational age (37 vs 39 weeks; $P = .005$), and were more likely to have associated anomalies than patients with postnatal diagnosis (36% vs 16%; $P = .007$). Twelve early presenters had an early prenatal diagnosis ($< 25$ weeks), and 33 had late prenatal diagnosis ($\geq 25$ weeks). We found no significant differences in hospital mortality rate between patients with early and late prenatal diagnosis (75% vs 63%; $P = .72$). Surfactant and HFOV were applied more frequently in early presenters.

### Table 5. Predictors of Mortality in 167 CDH Patients With Early Symptoms ($\leq 24$ h)

<table>
<thead>
<tr>
<th>Factor (Category Codes: 1 vs 0)</th>
<th>Nonsurvivors (n = 60)</th>
<th>Survivors (n = 107)</th>
<th>Bivariate Hazard Ratio 95% CI $P$ Value</th>
<th>Multivariate Hazard Ratio 95% CI $P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal versus postnatal diagnosis</td>
<td>29 v 31</td>
<td>15 v 92</td>
<td>3.7 (2.2-6.2) &lt;.001</td>
<td>2.7 (1.4-5.4) .004</td>
</tr>
<tr>
<td>Associated anomaly versus isolated CDH</td>
<td>24 v 36</td>
<td>12 v 95</td>
<td>3.3 (2.0-5.6) &lt;.001</td>
<td>1.6 (0.84-2.9) .162</td>
</tr>
<tr>
<td>Right versus left-sided hernia</td>
<td>17 v 43</td>
<td>16 v 91</td>
<td>1.7 (0.94-2.9) .080</td>
<td>2.1 (1.03-4.2) .042</td>
</tr>
<tr>
<td>Birth weight (kg)*</td>
<td>2.70</td>
<td>3.26</td>
<td>0.50 (0.37-0.68) &lt;.001</td>
<td>0.74 (0.53-1.05) .092</td>
</tr>
<tr>
<td>Gestational age (wk)*</td>
<td>37</td>
<td>39</td>
<td>0.89 (0.83-0.96) .002</td>
<td>0.82 (0.73-0.93) .001</td>
</tr>
<tr>
<td>1-minute Apgar*</td>
<td>4.4</td>
<td>6.6</td>
<td>0.77 (0.70-0.85) &lt;.001</td>
<td>0.83 (0.75-0.91) &lt;.001</td>
</tr>
<tr>
<td>5-minute Apgar*</td>
<td>5.4</td>
<td>6.9</td>
<td>0.83 (0.75-0.91) &lt;.001</td>
<td>0.83 (0.75-0.91) &lt;.001</td>
</tr>
<tr>
<td>Cesarean versus vaginal delivery</td>
<td>24 v 36</td>
<td>19 v 86</td>
<td>2.5 (1.5-4.2) .001</td>
<td>1.5 (0.83-2.6) .181</td>
</tr>
<tr>
<td>Early versus delayed surgery ($\geq 24$ h)</td>
<td>7 v 15</td>
<td>27 v 80</td>
<td>1.4 (0.57-3.4) .462</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** One patient with bilateral CDH (died) was excluded from the analyses. Mortality calculations (Cox regression) based on events occurring before January 01, 2001

*Mean values shown.*

**Fig 1.** Kaplan-Meier curves of 169 CDH patients symptomatic within the first 24 hours of life with and without prenatal diagnosis.

**Fig 2.** Kaplan-Meier curves of 168 CDH patients symptomatic within the first 24 hours with isolated CDH or associated anomalies.
with prenatal diagnosis than in those with postnatal diagnosis (33% vs 16%; P = .017; 47% vs 30%; P = .038). No such difference was found concerning the use of NO and ECMO in the same groups (33% vs 31%; P = .79; 4.4% vs 11%; P = .36).

Applying the risk stratification model developed by The Congenital Diaphragmatic Hernia Study Group, we divided the early presenters into 3 groups: low (0 to 33.3% predicted total mortality rate), moderate (33.4% to 66.6% predicted total mortality rate), and high (66.7% to 100% predicted total mortality rate) risk groups. Sufficient data were available on 156 of 168 early presenters. The observed total mortality rate was 17% in the predicted low-risk group, and 53% and 62% in the predicted moderate and high risk groups, respectively (Fig 3).

**DISCUSSION**

This contemporary multicenter study from Scandinavia showed survival rates in accordance with those of recent large series. There are, however, recent series reporting even higher survival rates. We speculate that very low ventilation pressures with permissive hypercapnea may have contributed to the improved survival rate. However, different frequencies of associated anomalies, different inclusion criteria, and several other factors may have influenced survival rate.

By bivariate and multivariate analyses, we found significantly increased mortality rate in neonates with prenatal diagnosis compared with those without. This observation is in accordance with those in recent large studies showing significantly increased mortality rate in CDH patients with a prenatal diagnosis compared with those without. However, some studies did not find any effect on mortality rate. There is reason to believe that increased statistical power based on a large sample was a prerequisite for this finding.

Why do neonates with prenatal diagnosis fare worse than those with postnatal diagnosis? From our data, it appears that neonates with a prenatal diagnosis of CDH are more severely affected with significantly lower Apgar scores, lower birth weight, shorter gestational age, and a higher frequency of associated abnormalities. Interestingly, increased mortality rate in neonates with prenatal diagnosis was found both in the subgroup with and without associated anomalies. In accordance with this, multivariate analysis showed that prenatal diagnosis was an independent predictor of mortality rate when adjusting for other prognostic factors. An alternative explanation for the excess mortality in patients with prenatal diagnosis has been suggested by Harrison et al: Prenatal diagnosis probably uncovers a population of fetuses with CDH who previously died in utero, were stillborn, or died immediately after birth before admission to a perinatal center. In other words, prenatal diagnosis may reduce the magnitude of hidden mortality as reported in a recent meta-analysis. These two explanations are not mutually exclusive. In the current study we did not identify early prenatal diagnosis (<25 weeks) as a negative prognostic factor, which has been reported previously. In the current retrospective study, we did not find it feasible to collect data on polyhydramnios and LHR ratio. Therefore, we were not able to relate prenatal diagnosis to polyhydramnios or lung-to-head ratio (LHR), which previously have been reported as prognostic factors in studies of CDH.

We propose that the probability of prenatal detection of CDH is increased by an increasing degree of malformation severity. This assumption is supported by our findings of significantly lower Apgar scores, lower birth weight, and shorter gestational age in the group with prenatal diagnosis compared with those without. The antenatal health care in Scandinavia routinely includes second trimester prenatal ultrasound screening. The main objective of the examination is dating of pregnancy, detection of twins, fetal biometry, and examination of the placenta and thus is not primarily aimed at detection of fetal anomalies. Prenatal detection rates of about 25% have been reported for CDH patients admitted for surgery in Scandinavia. In the current study, prenatal detection rate also was rather low. A considerable proportion of pregnancies complicated by CDH are terminated after prenatal diagnosis. Thus, the detection rate presented in this report should not be compared with detection rates published from obstetric units. Over time, increased detection rates of CDH by prenatal ultrasound scan has been documented. Only time will show whether prenatal ultrasound scan will remain a prognostic factor of clinical importance if detection rates are increased.

Perinatal management of prenatally diagnosed CDH
patients is challenging. In the current study, bivariate survival analysis showed increased mortality rate in the cesarean section group, but this finding did not reach significance in multivariate analysis. Subgroup analysis of prenatally diagnosed patients with planned delivery at a center showed a similar tendency. Few studies have evaluated the role of mode of delivery in CDH patients, and, in a review Langer concluded that there is no evidence that altering the time or mode of delivery affects outcome. In an observational German study, no difference in mortality rate between cesarean and vaginal delivery was found. The tendency toward increased mortality rates after cesarean section in the current study should be interpreted cautiously and warrants further investigation. However, the current study gave no support for routinely delivering prenatally diagnosed CDH patients by cesarean section. The use of antenatal steroids after prenatal diagnosis was not assessed in this study.

Patients with RCDH had increased mortality rates compared with those with LCDH in the multivariate Cox analysis. Although the bivariate Cox regression analysis showed no significant difference (P = .080) between the 2 groups, applying a different statistical method (χ² test) on the data provided in Table 5, a significantly increased mortality in RCDH compared with LCDH was shown (52% vs 32%; P = .037). Excess mortality rates in neonates with RCDH have been reported previously, but not by all investigators.

The current study is limited by the heterogeneity between centers in perinatal treatment strategies, a problem comparable with the interpretation of the data from the Congenital Diaphragmatic Hernia Study Group. No predetermined Scandinavian treatment protocol has been used during the study period. In general, treatment has been tailored according to the severity of the disease. Thus, the current study design does not allow analysis of the effectiveness of different treatment modalities. However, the results represent the pooled experience of the 12 centers from a well-defined geographical region during a recent 4-year period as contrasted with much longer study periods in recent large series.

All series from pediatric surgical centers are subject to some degree of hidden mortality. Hidden mortality may be caused by either termination of pregnancy, in utero fetal demise, stillbirth, or postnatal death occurring before admission to a center. In the current study, we believe that the majority of liveborn CDH patients have been included based on the public health care system in all the Scandinavian countries, but long distances between the centers in Finland, Sweden, and Norway may have contributed to hidden mortality as reported previously. The difference in prevalence may be attributable to hidden mortality, true geographical differences, or a combination of the above. Four-fold geographical differences in CDH prevalence have been reported. The current study allows no explanation for the observed differences in prevalence.

The risk stratification formula derived by the CDH study group is based on 5-minute Apgar score and birth weight, and not on prenatal diagnosis and immediate respiratory distress, which also were significant independent predictors of mortality in the same study. Applied on our population, the results were similar for the 2 groups with predicted low and moderate mortality risk. However, for the group with predicted high risk of mortality we observed a relatively lower mortality rate than reported by the CDH study group.

We think that prospective studies are needed to get reliable measurements of more sophisticated prenatal prognostic factors as LHR and polyhydramnios as well as prognostic factors based on postnatal blood gases and ventilation treatment. The multicenter strategy is valuable for both prospective and retrospective studies of CDH, and we believe this approach should be utilized more frequently in future.

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