A Population-Based Study of Congenital Diaphragmatic Hernia in Utah: 1988–1994

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Objective: To define the natural history of congenital diaphragmatic hernia and to determine the potential impact of fetal therapy.

Methods: This retrospective case series consisted of all fetuses and neonates with congenital diaphragmatic hernia born between 1988 and 1994 in the state of Utah that could be identified through genetic counseling referrals, delivery logs, and neonatal intensive care unit discharge diagnosis records. Maternal and neonatal hospital records were reviewed for antepartum, intrapartum, and postpartum variables. Based on existing recommendations, fetuses who might have benefited from fetal therapy were identified.

Results: Ninety-six cases were identified, for a frequency of one case in 2710 live births per year. Five pregnancies were terminated before 21 weeks' gestation. The overall survival rate excluding these five cases was 58.2%. Among the remaining 91 cases, survival was significantly better for infants diagnosed in the neonatal period than for those diagnosed prenatally (78% versus 35%; $P < .001$). The frequency of associated anomalies was similar for antepartum and postpartum cases. Sixty-two percent of nonsurvivors had some type of other anomaly, but no pattern was apparent. There were no accurate prenatal predictors for lethal pulmonary hypoplasia, but preterm birth and the presence of severe cardiac anomalies were predictors of neonatal death. Only two of 96 fetuses would have potentially benefited from fetal therapy.

Conclusion: The outcome of infants with congenital diaphragmatic hernia is worse with preterm birth and if diagnosed prenatally. The survival rate we found was better than that reported in earlier studies, suggesting improved perinatal and neonatal management. Fetal therapy based on current eligibility criteria would have a minimal impact on survival of fetuses with congenital diaphragmatic hernia. *(Obstet Gynecol 1996;87:959–63)*

Congenital diaphragmatic hernia, the failure of normal diaphragm fusion, has an incidence of one in 2200–5000 births[1] and may or may not be associated with other congenital anomalies. In the past 30 years, sonographic evaluation has resulted in improved antepartum detection of congenital diaphragmatic hernia and associated anomalies. Although the condition is not uniformly lethal, mortality rates range from 27.5% to greater than 85%.[2] Infants with congenital diaphragmatic hernia usually die of pulmonary hypoplasia, resulting in the inability of the lung to expand adequately to support minimal required gas exchange. With the prenatal diagnosis of congenital diaphragmatic hernia, experimental reduction of visceral contents from the chest and intrauterine repair have been attempted to permit normal antepartum lung development.[3,4]

The purpose of this study was to determine the potential effect of prenatal therapy on the neonatal outcome of fetuses diagnosed with congenital diaphragmatic hernia. We performed a population-based review of all recent cases of congenital diaphragmatic hernia in the state of Utah from 1988 to 1994. The natural histories of prenatally and neonatally diagnosed cases were compared to identify antepartum prognostic factors of neonatal outcome and the impact of these factors on neonatal survival.

Materials and Methods

All fetuses or neonates with congenital diaphragmatic hernia were identified in our referral area for 1988–1994. Records were reviewed from four tertiary care centers in Utah, all of which have neonatal intensive care units: the University of Utah Health Sciences Center, Utah Valley Regional Medical Center, Primary Children's Medical Center, and Latter Day Saints Hospital. Primary Children's Medical Center and Utah Valley Regional Medical Center are the only hospitals in this region with pediatric surgical personnel and the capability to manage infants with congenital diaphragmatic hernia in the neonatal period. These institutions

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are all located in Utah and receive referrals from the Intermountain West (Wyoming, Idaho, Nevada, Montana, and Utah).

Fetuses and neonates with congenital diaphragmatic hernia were identified through genetic counseling referrals, delivery logs, neonatal intensive care unit records, and discharge diagnosis records from each hospital. Cases diagnosed in the antepartum period were included regardless of delivery site, although the majority were delivered at tertiary care hospitals and were referred to Primary Children's Medical Center or Utah Valley Regional Medical Center for surgical evaluation. Maternal and neonatal charts were reviewed for details regarding demographics, antepartum risk factors, labor and delivery characteristics, and neonatal outcome. In addition, vital statistics of birth and death records recorded by the Utah State Department of Health were reviewed to ensure complete case identification. Despite these extensive efforts, some cases of congenital diaphragmatic hernia in this population may have escaped ascertainment. However, given the nature of referrals in this region, this number is likely to be small.

Statistical analysis used χ^2 test or unpaired t test for normally distributed data. Statistical significance was defined as $P < .05$. All statistical analyses were performed using StatView 4.1 (Abacus Concepts, Berkeley, CA).

Results

Ninety-six cases of fetuses or infants with congenital diaphragmatic hernia were identified in our referral area from 1988 to 1994. Over this time, there were 260,176 live births in Utah, yielding an incidence of 0.39 cases of congenital diaphragmatic hernia per 1000 live births, or one case per 2710 live births. Excluding five known cases referred from outside Utah, the corrected incidence was one per 2859 live births.

Fifty-one cases were diagnosed prenatally and 45 after birth. Five pregnancy terminations were performed shortly after second-trimester sonographic diagnosis, leaving 91 total infants. Fifty-three of these 91 survived, for an overall survival rate of 58.2%. Eighteen of 51 fetuses (35%) diagnosed prenatally survived, compared with 35 of 45 (78%) of neonates diagnosed after birth, a significant difference ($P < .001$). The time of diagnosis varied greatly both prenatally and neonatally, ranging from 17 weeks' gestation to day 70 after birth.

Obstetric and neonatal predictors of outcome were compared for four groups: 1) survivors after prenatal diagnosis of congenital diaphragmatic hernia ($n = 18$), 2) non-survivors after prenatal diagnosis of congenital diaphragmatic hernia ($n = 33$), 3) survivors after neonatal diagnosis of congenital diaphragmatic hernia ($n = 35$), and 4) non-survivors after neonatal diagnosis ($n = 10$). Representative maternal, fetal, and neonatal variables are described in Table 1. Neonatal outcome was significantly predicted by three variables: prenatal diagnosis, preterm birth, and associated anomalies.

Table 1. Fetal and Neonatal Variables for Infants Born With Congenital Diaphragmatic Hernia

Characteristic	Prenatal diagnosis		Neonatal diagnosis	
	Deaths	Survivors	Deaths	Survivors
No. identified	33*	18	10	35
Maternal age (y)	28.2 ± 1.1	26.5 ± 1.3	30.2 ± 2.2	24.9 ± 1.2
Birth weight (g)	2065 ± 194	3042 ± 119†	2453 ± 310	3126 ± 88†
Estimated gestational age (wk)				
At diagnosis	25.7 ± 0.9	30.5 ± 1.7		
At delivery	33.0 ± 1.2	38.6 ± 0.3	37.2 ± 1.5	38.6 ± 0.4
5-min Apgar score <7‡	21 (75%)	6 (33%)	8 (80%)	13 (37%)
Age at surgery (h)	13.0 ± 4.6	13.3 ± 2.5	13.0 ± 1.0	14.3 ± 1.6
Ventilator days	8.5 ± 5.6	19.3 ± 3.5	2.7 ± 1.0	10.4 ± 2.2
Hospital days	11.9 ± 7.54	5.8 ± 8.5†	2.7 ± 1.0	29.5 ± 8.5

Data are presented as n or mean ± standard error of the mean.
* Includes five fetuses terminated in the second trimester.
† $P < .05$ (unpaired t test).
‡ Apgar scores exclude five cases terminated in the second trimester.

The diagnosis of congenital diaphragmatic hernia prenatally was highly predictive of non-survival, with a 65% neonatal death rate in this group, compared with a 22% mortality rate if congenital diaphragmatic hernia was detected after birth ($P < .001$). Among fetuses diagnosed prenatally, those diagnosed at earlier gestational ages had a higher risk for neonatal death ($P < .05$). Ten women underwent sonographic evaluation before 20 weeks, and the remainder were diagnosed after 20 weeks.

Preterm birth (delivery before 37 weeks' gestation) was a significant risk factor for neonatal death independent of the gestational age at which congenital diaphragmatic hernia was diagnosed ($P < .05$). No other obstetric characteristics, including route of or indication for delivery, correlated with perinatal survival in this population. Thirty-four women underwent labor induction, and only three were preterm: one for diabetes, one for chorioamnionitis after preterm premature rupture of the membranes, and one for blood group isoimmunization. Five women underwent termination before viability and the remainder were induced at term, primarily for physician convenience to optimize the timing of neonatal surgery. Fifty-two women presented in spontaneous labor, and eight women had cesarean deliveries without labor: Two were preterm (fetal dis-

Table 2. Anomalies in Fetuses and Neonates Diagnosed With Congenital Diaphragmatic Hernia

Anomaly	Prenatal diagnosis		Neonatal diagnosis	
	Deaths	Survivors	Deaths	Survivors
None	9 (27%)	13 (72%)	2 (20%)	23 (66%)
No postmortem examination	4 (12%)	0	0	0
Cardiac anomalies	6 (18%)	2 (11%)	3 (30%)	3 (9%)
Chromosomal abnormality	7 (21%)	0	0	0
Multiple anomalies	3 (9%)	1 (5%)	4 (40%)	2 (5%)
Other associated anomalies*	4 (12%)	2 (11%)	1 (10%)	7 (20%)
Total	33	18	10	35

Data are presented as *n* (percentage for each abnormality in that specific group).

*Other associated anomalies include hemivertebrae, pulmonary sequestration, cleft palate, renal aplasia and other renal abnormalities, Meckel diverticulum, hydrocephalus, pyloric stenosis, polysplenia, Ladd bands, duodenal web, and microphthalmia.

tress at 32 weeks; abruptio placentae at 27 weeks), two had fetal distress at term, two had repeat cesarean deliveries, and two women had cesareans with no identifiable indication. No information on labor was available for two women.

Lower birth weight (correlating with preterm birth) was associated with neonatal death, as were 5-minute Apgar scores of less than 7 (prenatal survivors versus nonsurvivors, $P = .005$; neonatal survivors versus nonsurvivors, $P = .017$). There were four sets of twins, all in the prenatally diagnosed group, and two of these pregnancies were complicated by stuck-twin syndrome.

Table 2 shows the various types of anomalies identified in the four groups. Detailed postnatal anatomic information was not available for four cases because of second-trimester termination or lack of an autopsy. Overall, associated anomalies were detected in 45 of 92 cases (47%), but survival was greater in those cases in which no associated anomalies were found (62% versus 23%; $P = .002$). Of fetuses identified prenatally with congenital diaphragmatic hernia, 22 had no other associated anomalies; 13 of 18 survivors had no anomalies, compared with nine of 33 nonsurvivors (72% versus 27%; $P < .001$). A spectrum of anomalies was found in fetuses with sonographically detected congenital diaphragmatic hernia, and no specific pattern was identified. Discrepant findings between the prenatal sonogram and neonatal examination were evident in 11 of 51 cases. In general, anomalies not detected sonographically were relatively minor and difficult to detect prenatally (eg, cleft palate), although serious cardiac anomalies were not detected in four cases. As with those cases of congenital diaphragmatic hernia identified in the prenatal period, anomalies were commonly found in survivors diagnosed with congenital diaphragmatic hernia after birth, which correlated with survival. Twenty-three of 35 survivors had no anomalies, compared with two of ten neonates who died (66% versus 20%; $P = .01$).

Neonatal death (excluding terminations) was common among fetuses diagnosed prenatally with both congenital diaphragmatic hernia and congenital heart disease (eight of 16, 50%). Heart defects in these neonates included left heart hypoplasia, ventricular septal defect, double-outlet right ventricle, and coarctation of the aorta. In three nonsurviving neonates who had prenatal diagnosis of congenital diaphragmatic hernia, cardiac abnormalities, including double-outlet right ventricle, atrial septal defect, and situs inversus, were not detected. Three surviving neonates had congenital diaphragmatic hernia and cardiac defects, including ventricular septal defect, atrial septal defect, and DiGeorge syndrome. Three nonsurviving infants had congenital heart disease diagnosed after birth, and these defects included patent ductus arteriosus, single ventricle, and tetralogy of Fallot. Two surviving infants were diagnosed with congenital heart defects after birth, and these neonates had patent ductus arteriosus and ventricular septal defect, with atrial septal defect and coarctation of the aorta. Except for the two neonates who died with congenital diaphragmatic hernia and hypoplasia of the left heart, there was no clear pattern of cardiac defects that correlated with survival or death.

Karyotypic abnormalities and genetic syndromes were relatively common in our cases (12 of 96, 12.5%). Seven fetuses had abnormal karyotypes (four with trisomy 18, one 46,XX t(1:18), one 46,XX t(4q+:11q−), and one mosaic trisomy 16). All were detected prenatally, and none survived. Five genetic syndromes were diagnosed in the postpartum period after not being suspected prenatally (DiGeorge, Fryn, Cornelia de Lange, Apert, and Goldenhar syndromes), and there were five other cases with multiple anomalies not meeting the criteria for known genetic syndromes.

There were only two fetal deaths. One fetus died as a result of twin-twin transfusion syndrome at 30 weeks, and the second fetus had trisomy 18 and died at 36 weeks. Three neonates were not resuscitated at the parents' request. These included an infant with prenatally diagnosed multiple anomalies delivered at 32 weeks' gestation, one with trisomy 18 delivered at 32 weeks, and one delivered after preterm labor at 21 weeks as a result of twin-twin transfusion syndrome.

Of the 51 fetuses identified before delivery, 22 (43%) had isolated congenital diaphragmatic hernia (ie, no other ultrasound abnormalities) and would have been considered candidates for fetal therapy. Fifteen of these 22 fetuses survived and thus would not have had an improved survival with antepartum intervention. Only

seven fetuses with isolated congenital diaphragmatic hernia detected prenatally died, and these might have survived as a result of fetal therapy. Of these seven, diagnoses were made at 20, 22, 26, 27, 28, 29, and 30 weeks' gestation. In the review by Harrison et al,[5] only fetuses identified with isolated congenital diaphragmatic hernia before 24 weeks' gestation were eligible for prenatal intervention. Therefore, given these eligibility criteria, only two of 96 fetuses in our study might have benefited from fetal therapy.

Discussion

This study is the most detailed population-based study of congenital diaphragmatic hernia to date. Previous reviews of congenital diaphragmatic hernia usually focused on specific patient populations, including cases identified antenatally after referral to high-risk centers,[5–9] as neonates,[10–14] or in autopsy studies.[15,16] Recently, several reports[17–20] have been published to clarify the natural history of the disease through identification of all cases, whether diagnosed prenatally or after birth. An important feature of our study is the large number of cases identified through a comprehensive population-based review, with reports of subsequent outcome.

Our overall survival rate of about 58% is higher than that in most earlier studies, but is similar to two recent reports.[2,19] This improvement in outcome likely reflects the impact of regionalization of high-risk perinatal and neonatal care, along with improved neonatal care. Notably, only a few of these infants underwent extracorporeal membrane oxygenation, a modality used routinely for neonates with congenital diaphragmatic hernia in some centers. Even with improved survival, there were specific risk factors for poor neonatal outcome. Infants diagnosed after birth had a better survival rate than those with a prenatal ultrasound diagnosis. This difference likely reflects the fact that fetuses identified earlier developed congenital diaphragmatic hernia in the second trimester, with subsequent marked compromise of fetal lung development and more severe pulmonary hypoplasia.

Our study confirms the poor survival for infants with congenital diaphragmatic hernia when associated anomalies are present. In our study, we included all anomalies regardless of severity, because the actual severity of each anomaly is difficult to judge, particularly for cardiac conditions. It is noteworthy that any associated anomaly predicted a poorer prognosis regardless of the time of diagnosis; these anomalies often are not diagnosed prenatally. However, the prenatal diagnosis of associated congenital heart disease is particularly ominous. Although concurrence of congenital diaphragmatic hernia and congenital heart disease does forbode a poorer prognosis, lethality is not the rule. Patients should be advised that not all such cases have a poor outcome; even though severity of the cardiac defect does tend to correlate with mortality, survival is possible.

As in other studies,[2,6,20] chromosomal abnormalities were common, especially trisomy 18, justifying karyotype analysis when congenital diaphragmatic hernia is diagnosed prenatally. Five different genetic syndromes were also diagnosed postnatally after being unsuspected in the antenatal period. However, a large number of fetuses with associated anomalies had no identifiable syndromes or chromosomal abnormalities, underscoring the poor sensitivity of sonographic diagnosis for the definitive identification and characterization of associated anomalies in fetuses with congenital diaphragmatic hernia.

Preterm birth and low birth weight are significantly associated with poor neonatal outcome and are important predictors of outcome. Combined prematurity and pulmonary hypoplasia, secondary to congenital diaphragmatic hernia and associated anomalies, commonly leads to neonatal death despite neonatal intensive care by experienced practitioners. Hydramnios has been associated with poor outcome in some,[4,6,7,17] but not all[8,19] previous reports. Our preterm births were not associated uniformly with polyhydramnios, and we suggest that preterm birth with pulmonary hypoplasia is the true risk factor. Therefore, efforts to prolong pregnancy are probably justified.

Differences in survival rates among previous studies[17,19,20] could be due to differences and improvements in neonatal care across different time periods. Survival clearly has improved in the more recent studies. Our findings and improved survival rates undoubtedly reflect these advances. In addition, some reports did not address or define ascertainment of associated anomalies. We used a more liberal definition of associated anomalies, whereas others excluded anomalies thought to be complications of a herniated gut.

We believe our experience indicates that current prenatal interventions based on the eligibility criteria of Harrison et al[5] are unlikely to affect substantially the overall survival rates for fetuses and neonates diagnosed with congenital diaphragmatic hernia. Clinically evident congenital diaphragmatic hernia can be diagnosed at almost any gestational or neonatal age. The most noticeable void in our current understanding of congenital diaphragmatic hernia is the inability to distinguish those fetuses with marked pulmonary hypoplasia from those with adequate lung development for postnatal adaptation. Our data indicate that pulmonary hypoplasia can develop even if congenital diaphrag-

matic hernia is diagnosed late in gestation, and survival can occur even with early diagnosis of congenital diaphragmatic hernia and no specific therapeutic intervention. Improved ability to diagnose pulmonary hypoplasia and new and more effective therapies will be required to improve outcome.

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