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Prenatal Diagnosis of Congenital Diaphragmatic Hernia: Does Laterality Predict Perinatal Outcomes?

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Abstract

Objective—The objective of this study was to examine laterality as a predictor of outcomes among fetuses with prenatally diagnosed congenital diaphragmatic hernia (CDH).

Methods—This is a retrospective cohort study of pregnancies with CDH evaluated at our center from 2008 to 2016 compared cases with right-sided CDH (RCDH) versus left-sided CDH (LCDH). The primary outcome was survival to discharge. Secondary outcomes included ultrasound predictors of poor prognosis (liver herniation, stomach herniation, lung area-to-head circumference ratio [LHR]), concurrent anomalies, hydrops, stillbirth, preterm birth, mode of delivery, small for gestational age, use of extracorporeal membrane oxygenation, and length of stay. Terminations and stillbirths were excluded from analyses of neonatal outcomes.

Results—In this study, 157 (83%) LCDH and 32 (17%) RCDH cases were identified. Survival to discharge was similar (64 vs. 66.4%, $p = 0.49$) with regard to laterality. RCDH had higher rates of liver herniation (90.6 vs. 72%, $p = 0.03$), hydrops fetalis (15.6 vs. 1.3%, $p < 0.01$), and lower LHR (0.87 vs. 0.99, $p = 0.04$). LCDH had higher rates of stomach herniation (69.4 vs. 12.5%, $p < 0.01$). Rates of other outcomes were similar in univariate analyses. Adjusting for microarray abnormalities, the odds for survival to discharge for RCDH compared with LCDH was 0.93 (0.38–2.30, $p = 0.88$).

Conclusion—Compared with LCDH, fetuses with RCDH had higher rates of adverse ultrasound predictors, but equivalent survival.

Keywords

congenital; diaphragmatic hernia; prenatal diagnosis; fetal; laterality; LHR; ECMO; EXIT

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Congenital diaphragmatic hernia (CDH) is a developmental defect present in 1 to 4 per 10,000 births.[1] The diaphragmatic defect allows abdominal viscera to herniate into the thoracic space through the diaphragm,[1,2] with resultant neonatal morbidity and mortality due to lung hypoplasia and pulmonary hypertension.[3] Reported survival rates range from 69 to 93%, and is approximately 85% for cases of isolated CDH.[4] The prognosis is associated with several risk factors that can be assessed prenatally, including liver herniation,[5] stomach herniation,[6] low fetal lung volume,[7–13] and low lung area-to-head circumference ratio (LHR)[14,15] on prenatal ultrasound, as well as the presence of chromosomal abnormalities, concurrent anomalies, and hydrops fetalis.[16,17]

Right-sided CDH is less common than left-sided CDH (15 vs. 85%) and CDH laterality (right vs. left sided) may affect prognosis, although a variable relationship to neonatal outcomes has been described.[2,18,19] Compared with left-sided CDH, prior studies have shown that pregnancies complicated by right-sided CDH have worse,[8,17,20,21] improved,[22] or equivalent outcomes.[23,24] A recent large series of 330 neonates with CDH noted no difference in survival with regard to laterality.[22] Many of these studies have been limited by small numbers[17] of right-sided CDH and were potentially confounded as they were compilations from multiple institutions with different treatment strategies.[25,26] Further, most studies evaluating laterality have considered cases diagnosed with CDH after birth with limited information on antenatal ultrasound findings. A recent large series from et al included CDH cases diagnosed either prenatally (65%) or in the neonatal period (35%) and found that those with right-sided CDH were less likely to be diagnosed prenatally and have a higher need for extracorporeal membrane oxygenation (ECMO).[24] Notably, there were no differences in short-term pulmonary morbidities in this cohort series. The discrepancy in the current literature regarding the implications of CDH laterality limits the ability to counsel women prenatally about the severity of CDH, make decisions regarding pregnancy management, and predict perinatal outcomes.

Given the limitations in the current understanding of the impact of CDH laterality, the aim of this study was to assess infant survival among prenatally diagnosed cases of right-versus left-sided CDH, as well as differences in both antenatal ultrasound findings predicting a poor perinatal prognosis and other adverse perinatal outcomes. We hypothesized that right-sided CDH would be associated with an increased risk of infant death, presence of antenatal ultrasound findings predicting a poor prognosis, and other adverse infant outcomes.

Methods

We performed a retrospective cohort study under Institutional Review Board approval (Institutional Review Board No. 10-04093, approval on November 15, 2010) of all prenatally diagnosed cases of CDH at our institution during the study period (November 2008–June 2016). Inclusion criteria were prenatal identification of CDH, and evaluation at the University of California, San Francisco (UCSF) Fetal Treatment Center. The primary study outcome was infant survival to hospital discharge. Secondary obstetric and neonatal outcomes were considered, including antenatal ultrasound predictors of poor neonatal prognosis (liver herniation, stomach herniation, LHR,[15,27,28] concurrent anomalies, and hydrops fetalis) as well as several perinatal outcomes: stillbirth, preterm birth, mode of

delivery, small for gestational age birth weight (<10%ile for gestational age), use of ECMO, and length of neonatal intensive care unit (NICU) stay. CDH cases resulting in termination or stillbirth were excluded from analyses of neonatal outcomes. Obstetric and infant data were collected from the UCSF Fetal Treatment Center database, with supplemental information extracted from charts (T.N.S., K.G., and V.K.B.).

Demographic data were collected for all cases, including parity, maternal age, body mass index, pregnancy complications including preeclampsia, gestational diabetes mellitus, and preterm birth (< 37 weeks). Ultrasound findings included liver and stomach herniation, LHR, presence and types of additional anomalies (including single umbilical artery), polyhydramnios (defined as an amniotic fluid index of > 24 cm), hydrops fetalis (defined as ≥ 2 abnormal fetal fluid collections in the skin, abdominal cavity, pleural space, or pericardial space), and specific fetal cavity with an abnormal fluid collection. The LHR evaluates the size of the contralateral lung size and mediastinal shift and directly correlates with survival.[29] For this measurement, the lung area is measured at the level of the atria on a transverse scan of the fetal thorax. The lung area is then calculated as the product of the two longest two perpendicular linear measurements. The LHR is then calculated by a simple ratio of lung area (in square millimeters) to head circumference (in millimeters) to minimize lung size differences owing to gestational age.[30] A recent systematic review showed that the absence of liver herniation into the thoracic cavity is among the most reliable predictors of postnatal survival.[5] A single umbilical artery is associated with additional abnormalities when seen on prenatal ultrasound, is among most common additional abnormalities seen in the setting of a CDH, and may portend a worse prognosis for the fetus in the setting of a CDH.[31–33] Genetic testing data were collected for all cases in which it was performed, whether prenatal or postnatal.

LHR was measured for most cases in our cohort, although often not when patients were referred at later gestational ages or presented late to care. The initial LHR at the time of diagnosis or referral was recorded for the purposes of this study, regardless of gestational age at measurement, as this was felt to be the more accurate measurement. Stomach herniation has been associated with a worse prognosis in some studies,[34–36] and progressively aberrant stomach position (i.e., abdominal, anterior left chest, mid-posterior left chest, or retrocardiac) has been associated with neonatal mortality, use of ECMO, prolonged neonatal respiratory support, and delayed time to resolution of pulmonary hypertension in neonates with CDH.[6,37] Stomach herniation was categorized dichotomously (intrathoracic or abdominal) as the degree of stomach herniation is not routinely measured at our institution. Obstetric data collected were use of the fetal tracheal occlusion, ex utero intrapartum treatment (EXIT) procedure, stillbirth, and mode of delivery (vaginal or cesarean delivery). Neonatal data were collected from the birth hospitalization until discharge. Many cases had neonatal care at UCSF, but for those cared for at outside institutions, analyses were restricted to only known outcomes. The author, K.G., personally called either the referring physician or the obstetric patient for cases in which delivery occurred at an outside institution, to obtain information about the delivery and neonate. Postnatal data collected were gestational age at delivery, sex, use of ECMO, length of NICU stay, and survival to discharge.

Categorical variables were compared with the Fisher's exact or chi-square test as appropriate, and median values of nonparametric continuous variables were compared using Wilcoxon's rank-sum test. Multivariate logistic regression was used to generate odds ratios, adjusting for potential confounding variables. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using STATA (version 11.0, College Station, TX).

Results

A total of 189 CDH cases during the study period were identified, of which 157 (83%) were left sided and 32 (17%) were right sided. Table 1 displays the maternal demographics of our cohort by CDH laterality, with no differences observed between groups in parity, age, preeclampsia, gestational diabetes mellitus, use of assisted reproductive technologies, or obesity. No differences were observed in indications for induction.

Considering antenatal ultrasound predictors of poor neonatal prognosis, compared with left-sided CDH cases, right-sided CDH had higher rates of liver herniation (90.6 vs. 72%, p = 0.03), hydrops fetalis (15.6 vs. 1.3%, p < 0.01), ascites (18.8 vs. 1.9%, p < 0.01), pleural effusion (15.6 vs. 1.9%, p < 0.01), and a lower median LHR (0.87 vs. 0.99, p = 0.04) (Table 2). In contrast, left-sided CDH had higher rates of stomach herniation (69.4 vs. 12.5%, p < 0.01). No difference in rates of abnormal fetal/neonatal microarray results were observed in right- versus left-sided CDH (12.5 vs. 8.9%, p = 0.36), nor were there differences in rates of single umbilical artery (3.1 vs. 4.5%, p = 0.99), tracheal occlusion (10.5 vs. 6.4%, p = 0.39), or EXIT procedure (9.1 vs. 1.9%, p = 0.14). All fetuses delivered by EXIT also had tracheal occlusion performed. There were no differences in survival by laterality among those with tracheal occlusion compared with those without tracheal occlusion. Only two thoracoamniotic shunts were performed, and both were performed in cases with right-sided lesions.

The primary outcome, infant survival to hospital discharge, was similar (64 vs. 66.4%, p = 0.49) with regard to laterality. A multivariate logistic regression adjusting for chromosomal abnormalities yielded an adjusted odds ratio of 0.93 (95% confidence interval 0.38–2.30, p = 0.88) for infant survival to hospital discharge. Secondary obstetric and neonatal outcomes were comparable among right- versus left-sided CDH cases including neonatal gender, stillbirth, preterm birth, gestational age at delivery, mode of delivery, small for gestational age, ECMO use, and length of NICU stay (Table 3). We performed a multivariate regression analysis of antenatal ultrasound markers with poor perinatal outcome using laterality as a confounder and found an increased odds of neonatal death with liver herniation, lung area-to-head ratio <1, and additional anomalies.

Discussion

This study presents the results of an 8-year review of 189 CDH pregnancies, comparing 32 right-sided and 157 left-sided cases of CDH. When compared with left-sided CDH, fetuses with right-sided CDH were more likely to have liver herniation, ascites, pleural effusion, and

hydrops, and to have a lower LHR with no difference in infant survival to discharge or other perinatal outcomes. In contrast, left-sided CDH had higher rates of stomach herniation.

Accurate prenatal markers are critical for predicting prognosis in cases of CDH for both patients and providers. Previous studies have evaluated several parameters for predicting survival, but the impact of laterality has shown conflicting results.[22] This study uniquely investigates several ultrasound findings with regard to CDH laterality. Despite an increased association of right-sided CDH with known antenatal predictors of poor neonatal outcomes, there was no difference in neonatal morbidity or mortality in our cohort. This may be because these markers of a poor prognosis are more important than laterality of the lesion, or because other factors such as lung volume are more impactful. Several studies have shown that the percentage of liver herniation and total fetal lung volume as determined by either prenatal magnetic resonance imaging (MRI), and not CDH laterality, are important predictors of morbidity and mortality among neonates with CDH.[38–40] MRI evaluations of total lung volume are not, however, routinely performed in the evaluation of prenatally diagnosed CDH at our center. Similarly, there were no differences in obstetric or neonatal outcomes by CDH laterality including gestational age at delivery, small for gestational age, length of NICU stay, need for ECMO, and survival to discharge. This is consistent with other series examining the impact of laterality of CDH on perinatal outcomes.[22]

Several studies have used the observed-to-expected LHR as a method to correct for changes in lung area measurements through gestation.[15,27,28,41] Importantly, the exact gestational age at which the initial ultrasound was performed was not available in our cohort to calculate the observed-to-expected LHR and this calculation is not part of our routine practice. The LHR is used exclusively at our institution given the measurement was initially developed and validated internally and has performed well at the prediction of adverse outcomes within our population. As such the observed-to-expected LHR is not available as a measurement of disease severity by laterality.

In our cohort, right-sided CDH was associated with an increased incidence of fetal pleural effusions and ascites. There was no difference in other fetal fluid collections (pericardial effusion, skin edema, or polyhydramnios) by CDH laterality. These findings are consistent with previous reports showing that some fetal fluid collections are more common with right-sided CDH, yet do not necessarily portend a poor prognosis,[42] When comparing outcomes for right- versus left-sided CDH in the presence of hydrops fetalis, there was no difference in neonatal outcomes. The definition, pathogenesis, and natural history of hydrops fetalis in right-sided CDH remain poorly defined, and it is possible that intrathoracic or intra-abdominal compression resulting from CDH leads to abnormal fluid collections without the same implications as in other etiologies of nonimmune hydrops fetalis.[43] This may partially explain why there is no difference in adverse neonatal outcomes including stillbirth and infant survival to hospital discharge with regard to laterality, despite an increased rate of hydrops fetalis. Further, the existing literature on this topic is confounded by the use of fetal intervention in utero.[42,44] Only two thoracoamniotic shunts were performed in our cohort, and both were done in fetuses with right-sided CDH and hydrops fetalis.[45]

The strengths of this study are the relatively large size of the CDH cohort from a tertiary care center and the extensive prenatal ultrasound data available for analyses. However, there are several limitations to note. The data from this study come from a single institution with a standardized approach to neonatal management of these infants[46] and as a result, extrapolating these findings to other settings may be limited. It is unknown if laterality impacted patient or provider decisions in pregnancy management (e.g., termination of pregnancy, comfort care). We noted a lower rate of additional fetal anomalies in our cohort (16.9%) compared with others (57–63%).[22] This may be an effect of our prenatally diagnosed cohort as prior studies have demonstrated a lower detection rate for additional anomalies with prenatal versus postnatal diagnosis of CDH.[25,47] We may have also been underpowered in our analyses of adverse neonatal outcomes, as not all postnatal outcomes were available for our entire cohort. Furthermore, our neonatal outcomes were limited to the initial hospitalization following birth. There is limited morbidity data available in our study for comparison by CDH laterality, such as on long-term treatment for pulmonary hypertension, need for tracheostomy, timing and type of surgical repair, discharge with supplemental oxygen, and long-term neurodevelopmental outcomes. This is an important limitation to acknowledge, as Partridge et al showed that compared with those with right-sided CDH, those with left-sided lesions had an earlier surgical repair, initiation of enteral feeds, day of life when full feeds were achieved, shorter duration of nitric oxide use, less long-term sildenafil use, need for tracheostomy, and supplemental oxygen at discharge.[22] Finally, for those infants delivered at other institutions, differences in neonatal management could have affected neonatal outcomes, and these effects are difficult to capture.

In the prenatal setting, ultrasound features are critical to counseling patients about prognosis and management. Right-sided CDH in our study was associated with more of the ultrasound findings that are established predictors of poor neonatal outcomes, compared with left-sided CDH. Nonetheless, neonatal morbidity and mortality remained similar with regard to laterality. This may be the result of other markers or clinical factors being more impactful on CDH prognosis than laterality itself. Future studies should investigate the impact of laterality on perinatal outcomes in other cohorts of prenatally diagnosed CDH cases, examine which factors are the most important predictors of perinatal outcomes, and focus on potential differences in long-term morbidity or mortality by CDH laterality that were not captured by the present study.

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Table 1

Maternal demographics of the cohort by CDH laterality

Variable	Right-sided CDH (*n* = 32)	Left-sided CDH (*n* = 157)	*p*-Value
Nulliparity	80.8 (21/26)	69.6 (80/115)	0.18
Maternal age, y	30.5 (19–41)	31 (18–43)	0.67
Preeclampsia	9.7 (3/31)	4.8 (7/147)	0.24
Gestational diabetes mellitus	16.1 (5/31)	11.5 (17/148)	0.32
Assisted reproductive technology	9.4 (3/32)	3.2 (5/155)	0.14
Obesity	9.4 (3/32)	9.7 (15/155)	0.63

Abbreviation: CDH, congenital diaphragmatic hernia.

Note: Data presented as % (*n*/total) or median (range). Fisher's exact test used for statistical comparisons.

Table 2

Antenatal ultrasound predictors of poor neonatal prognosis by CDH laterality

Variable	Right-sided CDH (*n* = 32)	Left-sided CDH (*n* = 157)	*p*-Value
Lung area-to-head circumference ratio	0.87 (0.47–3)	0.99 (0.3–3)	**0.04**
Liver herniation	90.6 (29/32)	72 (113/157)	**0.03**
Stomach herniation	12.5 (4/32)	69.4 (109/157)	<**0.01**
Anomalies			
Cardiac anomaly	12.5 (4/32)	15.1 (23/152)	0.99
Any additional anomaly	15.6 (5/32)	17.2 (27/157)	0.53
Hydrops fetalis	15.6 (5/32)	1.3 (2/157)	<**0.01**
Abnormal fluid in only one fetal compartment	3.1 (1/32)	3.2 (5/157)	0.99
Ascites	18.8 (6/32)	1.9 (3/157)	<**0.01**
Pleural effusion	15.6 (5/32)	1.9 (3/157)	<**0.01**
Pericardial effusion	0 (0/32)	0.6 (1/157)	0.99
Skin edema	3.1 (1/32)	0.6 (1/157)	0.33
Polyhydramnios	31.3 (10/32)	28.7 (45/157)	0.83

Abbreviation: CDH, congenital diaphragmatic hernia.

Note: Data presented as % (*n*/total) or median (range). Fisher's exact test or Wilcoxon's rank-sum test as appropriate.

Table 3

Obstetric and neonatal outcomes by CDH laterality

Variable	Right-sided CDH (*n* = 32)	Left-sided CDH (*n* = 157)	*p*-Value
Stillbirth	3.2 (1/31)	2.6 (4/152)	0.61
Termination of pregnancy	10.5 (2/19)	12.2 (13/107)	0.84
Survival to discharge	64 (16/25)	66.4 (83/125)	0.49
Preterm birth	29.2 (7/24)	18.3 (20/120)	0.18
Gestational age at delivery, wk	38.1 (29–40)	38 (30–41)	0.79
Vaginal delivery	75 (18/24)	64.1 (66/103)	0.22
Small for gestational age birth weight	5 (1/20)	7.4 (8/108)	0.58
Extracorporeal membrane oxygenation	8.7 (2/23)	16.5 (20/121)	0.27
Length of NICU stay, d	26.5 (0–82)	24 (0–160)	0.06

Abbreviations: CDH, congenital diaphragmatic hernia; NICU, neonatal intensive care unit.

Note: Data presented as % (*n*/total) or median (range). Fisher's exact test or Wilcoxon's rank-sum test as appropriate.