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Perinatal Outcomes in Fetuses Prenatally Diagnosed with Congenital Diaphragmatic Hernia and Concomitant Lung Lesions: A 10-Year Review

Shelly Soni[a–c] Julie S. Moldenhauer[a–c] Natalie Rintoul[a, b, d] N. Scott Adzick[a–c] Holly L. Hedrick[a–c] Nahla Khalek[a–c]

[a]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [b]Center for Fetal Diagnosis and Treatment, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [c]Department of Surgery, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [d]Division of Neonatology, Children's Hospital of Philadelphia, Philadelphia, PA, USA

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Abstract
Aim: To describe perinatal outcomes of fetuses with a prenatal diagnosis of a concomitant lung lesion in the setting of congenital diaphragmatic hernia (CDH) and to compare outcomes with an isolated CDH control group without a lung lesion, matched by ultrasound-based prognostic markers including presence of liver herniation and lung measurements. ***Material and Methods:*** This was a retrospective case-control study, wherein all pregnancies diagnosed with CDH and concomitant lung lesions were identified between July 1, 2008, and December 31, 2018. For each case, 2 controls with isolated CDH from the same study period were selected after matching for the presence of liver herniation into the thoracic cavity and ultrasound-based lung measurements either observed over expected lung-to-head ratio (LHR) or absolute LHR with their corresponding gestational age. The outcomes analyzed in the 2 groups included survival to hospital discharge, neonatal intensive care unit (NICU) length of stay (LOS), extracorporeal membrane oxygenation (ECMO) requirement and need for supplemental oxygen (O_2) at day 30 of life. ***Results:*** A total of 21 pregnancies were identified with CDH and a concomitant lung lesion in the study period. All the lung lesions were stratified into a "low-risk category" with a congenital cystic adenomatoid malformation volume ratio of less than 1.0 at the time of presentation. None of these fetuses developed hydrops or required in utero intervention. Overall survival in the group was 80.7% (17/21) and rate of ECMO was 38.1%. Causes of mortality included pulmonary insufficiency, sepsis, renal failure, and bowel infarction. Upon comparison between the cases and controls, the 2 groups were similar with respect to pregnancy demographics. There were no fetal demises in either group. Outcomes including survival rate, NICU LOS, ECMO requirements and need for supplemental O_2 at day 30 of life, were comparable among the 2 groups. ***Conclusions:*** In our descriptive series, the presence of a concomitant, low-risk lung lesion in the setting of fetal CDH did not have a significant impact on the natural course of the disease, nor was it associated with a worse prognosis.

karger@karger.com
www.karger.com/fdt

Shelly Soni, MD
Center for Fetal Diagnosis and Treatment, Children's Hospital of Philadelphia
34th Street and Civic Center Boulevard, 5 Wood
Philadelphia, PA 19104 (USA)
shellysoni.13@gmail.com, sonis1@email.chop.edu

Introduction

Congenital diaphragmatic hernia (CDH), a developmental defect in formation of the diaphragm, is a major congenital anomaly which is associated with adverse neonatal outcomes and multiple neonatal morbidities. Survival for infants with CDH, despite advancements in neonatal care, remains at approximately 70% [1, 2]. Survival for those that require extracorporeal membrane oxygenation (ECMO) is approximately 50% [3]. Survival is dependent on the ability to oxygenate and ventilate, a function of the neonatal lung volumes and structure of the pulmonary vasculature. With an estimated prevalence of 1 in 2,200–4,000, CDH is diagnosed prenatally as early as 16–17 weeks' gestational age [4, 5]. Prognosis can be stratified by multiple sonographic variables including herniation of liver into the chest cavity as well as lung measurements such as the lung-to-head ratio (LHR) [6–9]. Pregnancies with concomitant major anomalies including complex congenital heart disease or genetic abnormalities are associated with worse prognosis [10].

Benign pulmonary lesions such as bronchopulmonary sequestration (BPS) and congenital cystic adenomatoid malformation (CCAM) are rare developmental anomalies of the respiratory tract. Their reported incidence varies from 0.15 to 1.8% [11, 12]. These lesions are nonfunctioning lung tissue and have been classified based on their location and blood supply. CCAMs communicate with the tracheobronchial tree and derive their blood supply from the pulmonary circulation [13]. BPSs have systemic arterial blood supply [14]. Sequestrations are further classified into intralobar and extralobar forms [15]. The extralobar form rarely communicates with the tracheobronchial tree and is engulfed in its own pleura. A third type of lung lesion demonstrating features of both CCAM and BPS is classified as a hybrid lesion [13]. Even though the clinical course for these lung lesions can be challenging, fetuses with smaller lesions tend to do very well. Larger lesions that produce a significant mass effect can lead to fetal hydrops or neonatal pulmonary hypoplasia. Ultrasound based CCAM volume ratio (CVR) is used as a prognostic tool in prenatally diagnosed cases, and those with a CVR >1.6 are at higher risk for the development of hydrops [13, 16].

The occurrence of these benign lung lesions in conjunction with CDH has been described previously [17–21]. Intuitively, this combination could result in additional respiratory morbidity with varying degrees of respiratory distress. The actual impact of these concurrent lesions on neonatal outcomes is unclear. We report a series of 21 cases of prenatally diagnosed CDH with concurrent lung lesions (BPS, CCAM, and hybrid) and their outcomes. We also compared their outcomes with isolated CDH controls.

Materials and Methods

Study Design

All patients prenatally diagnosed with CDH along with a benign lung lesion, either CCAM, BPS or hybrid lesion, from July 1, 2008, through December 31, 2018, were identified using our institutional fetal therapy database. A retrospective chart review was performed. Controls were identified using the same institutional fetal therapy database with prenatally diagnosed isolated CDH during the same study period. For each case, 2 controls were selected with a similar gestational age at the time of their presentation to our institute and matched to liver position as well as a comparable lung measurement. Ultrasound based observed to expected (O/E) LHR was the preferred method in selecting controls. For pregnancies where O/E LHR was not available, an absolute LHR and its corresponding gestational age was used. None of the cases underwent fetoscopic endoluminal tracheal occlusion (FETO), and hence pregnancies that underwent FETO were excluded from the controls category. Data pertaining to patient demographics including maternal age, parity, race, birth weight, and mode of delivery was collected. Neonatal outcomes such as survival rate, neonatal intensive care unit (NICU) length of stay (LOS), ECMO requirement, and the need for supplemental oxygen (O_2) at day 30 of life were evaluated. CVR and an interval CVR evaluation for cases were assessed. The lung lesion diagnosis was also confirmed postnatally in 13 cases that underwent resection.

Statistical Analysis

Student's *t* test was used for continuous variables and the χ^2 test or the Fischer's exact test for categorical variables. A p value <0.05 was considered significant. Statistical analyses were performed using the statistical software STATA v.10.1 (StataCorp, College Station, TX, USA). The study was approved by the local Institutional Review Board.

Results

During the study period, a total of 292 women were evaluated for the prenatal diagnosis of CDH. Of these, 21 pregnancies (7.2% of all CDH evaluations) were also diagnosed with a concomitant lung lesion. Four of these 21 pregnancies were referred to our institution with the dual diagnosis, 4 had the referring diagnosis of a lung lesion, and the remainder were referred as isolated CDH. CDH was left-sided in 17/21 fetuses (80.9%), and liver was herniated into the chest in 12/21 pregnancies (57.1%). The average LHR for the cases at the time of their presentation was 0.95 ± 0.5 with an O/E LHR of 0.33 ± 0.1. After un-

Table 1. Description of all the pregnancies with CDH and a concurrent lung lesion

Diagnosis	GA at presentation, weeks	Liver position	LHR/CVR at presentation	USG O/E LHR at presentation	LHR/CVR at 30–32 weeks	GA at delivery, weeks	Outcome
Left CDH/left CCAM (lower lobe)	19.5	Down	1.09/0.09	NA	1.97/0.13	39.3	Alive at 10 years
Right CDH/right CCAM (middle lobe)	23.1	Up	0.34/0.41	NA	0.91/0.5	37.3	Deceased at DOL 1
Left CDH/right BPS (extra lobar)	21.6	Up	0.57/0.05	0.22	0.85/0.05	38	Deceased DOL 1
Left CDH/left BPS (not specified)	21.2	Up	1/0.07	0.41	NA	38.3	Alive at 9 years
Left CDH/left BPS (extra lobar)	24.2	Up	0.97/0.08	0.36	NA	40	Alive at 7 years
Left CDH/right hybrid (middle lobe)	22.3	Down	1.16/0.05	0.42	1.52/0.07	39.1	Alive at 7 years
Left CDH/left hybrid (left lower lobe)	29	Down	1.6/0.25	NA	1.5/0.16	39.1	Alive at 7 years
Left CDH/left CCAM (lower lobe)	23.3	Down	1.3/0.7	NA	NA	34	Alive at 6 years
Right CDH/right BPS (extra lobar)	29.1	Up	0.65/0.83	0.35	1.2/0.78	37.3	Alive at 6 years
Left CDH/left BPS (extra lobar)	35	Down	1.36/0.05	0.45	NA	39.1	Alive at 6 years
Left CDH/left BPS (extra lobar)	18.3	Up	0.79/0.3	0.46	1.83/0.15	39.4	Alive at 5 years
Left CDH/left BPS (not specified)	37.5	Down	2.41/0.05		NA	38.3	Alive at 5 years
Right CDH/right BPS (lower lobe)	27.1	Up	0.49/0.21	0.27	0.71/0.11	37.4	Alive at 4 years
Left CDH/left BPS (lower lobe)	22.6	Down	1.25/0.3	0.41	1.76/isoechoic	38	Alive at 4 years
Left CDH/left CCAM (lower lobe)	22.2	Down	1.25/0.05	0.43	NA	39	Alive at 4 years
Left CDH/left BPS (upper lobe)	21.3	Up	0.83/0.10	0.30	1.48/0.03	37.1	Alive at 4 years
Left CDH/left hybrid (lower lobe)	21.3	Up	0.75/0.13	0.28	1.05/0.14	38.4	Alive at 3 years
Left CDH/left BPS (lower lobe)	22.2	Up	0.59/0.20	0.20	1.15/isoechoic	38.5	Alive at 2 years
Left CDH/left CCAM (lower lobe)	22.1	Down	0.67/0.65	0.23	1.28/0.40	39	Alive at 2 years
Left CDH/left BPS (lower lobe)	21.1	Up	0.53/0.19	0.20	0.92/0.23	39	Deceased DOL 78
Right CDH/right hybrid (not specified)	20.5	Up	0.27/0.22	0.20	NA/0.20	38.1	Deceased DOL 41

GA, gestational age; CDH, congenital diaphragmatic hernia; CCAM, congenital cystic adenomatoid malformation; BPS, bronchopulmonary sequestration; LHR, lung to head ratio; O/E, observed over expected; CVR, congenital cystic adenomatoid malformation (CCAM) volume ratio. Location of lung lesion specified in parenthesis in column 1.

dergoing a detailed ultrasound examination as well as an ultrafast MRI, 12 were found to have BPS, 5 had CCAM, and 4 were diagnosed with a hybrid lesion along with CDH (Table 1). The lung lesion was ipsilateral to the CDH in the majority of fetuses 19/21 (90.5%). Out of 12 pregnancies with BPS, 5 had an extralobar form of BPS. Most of the intralobar BPS were identified in the lower lobe except 1. For all the left sided CCAMs ($n = 4$), lung lesion occupied the lower lobe. The right sided CCAM ($n = 1$) was diagnosed in the middle lobe. The exact location of lung lesion was not identified in 3 cases. The average CVR at the time of their presentation was 0.24 ± 0.2 at a mean gestational age of 24 weeks and 1 day. Thirteen cases underwent resection of these lesions at the time of CDH repair, and the diagnosis was confirmed postoperatively on pathology.

Table 1 provides a detailed description of the cases. On further evaluation, prenatal genetic testing was available in 12 of these pregnancies and all except 1 fetus demonstrated normal karyotype. A benign inversion with no known pathologic phenotypic association was identified in that fetus [46, XY, inv (2)(p11.2q13)]. Echocardiogram demonstrated a ventricular septal defect in 1 other fetus. The remainder of the cohort demonstrated normal echocardiogram evaluation. None of the fetuses developed hydrops or required in utero intervention such as a thoracoamniotic shunt or fetal surgery. The average gestational age at delivery was 38 weeks 3 days, and average birth weight was 3,246.1 g. Nine women (42.9%) delivered vaginally. There were 4 neonatal demises in the group. Primary cause of mortality in these cases was respiratory failure. Excluding these 4 neonates, the average length of hospital stay in the group was 73.6 ± 38.1 days. ECMO was utilized in 8 of the 21 infants (38.1%). No adverse maternal outcomes were identified.

All of the fetuses in the control group demonstrated a normal karyotype. A comparison of demographics, patient characteristics and outcomes between the 2 groups is provided in Tables 2 and 3. There were no fetal demises in either group. Gestational age at delivery, birth weight, and cesarean delivery rates were comparable between the 2 groups. Survival rate, NICU LOS and need for supplemental O_2 at day 30 of life was similar between the 2 groups. ECMO rates were higher for the cases when compared to controls, but the difference was not statistically significant (38.1 vs. 23.8%, respectively).

Table 2. Demographics and patient characteristics of cases and controls

	Cases (n = 21)	Controls (n = 42)	p value
Maternal age, mean ± SD, years	29.4±5.8	31.0±6.6	0.34[0]
Parity (multiparous), n (%)	17 (80.9)	23 (54.8)	0.05[1]
Hispanic race, n (%)	5 (23.8)	7 (16.7)	0.51[1]
Gestational age at presentation, mean ± SD, weeks	24.1±4.9	25.1±3.8	0.35[0]
Left sided CDH, n (%)	17 (80.9)	40 (95.2)	0.32[1]
Liver herniation into thoracic cavity, n (%)	12 (57.1)	24 (57.1)	1.0[1]
LHR, mean ± SD	0.95±0.5	1.05±0.4	0.25[0]
O/E LHR, mean ± SD	0.33±0.1	0.34±0.1	0.59[0]
Gestational age at delivery, mean ± SD, weeks	38.3±1.3	38.4±1.1	0.90[0]
Birth weight, mean ± SD, g	3,246.1±424.4	3,156.6±488.9	0.48[0]
Cesarean delivery, n (%)	12 (57.1)	15 (35.7)	0.12[1]

CDH, congenital diaphragmatic hernia; LHR, lung to head ratio; O/E, observed over expected; g, grams. [0] Compares mean differences using Student's t test. [1] Compares the association between the two groups using Fisher's exact test.

Table 3. Outcomes of cases and controls

	Cases (n = 21)	Controls (n = 42)	p value
Survival, n (%)	17 (80.9)	34 (80.9)	1.0[1]
ECMO rates, n (%)	8 (38.1)	10 (23.8)	0.25[1]
Hours on ECMO, mean ± SD	501.6±218.7	518.3±204.4	0.87[0]
NICU LOS, mean ± SD, days	65.3±40.9	69.4±48.5	0.74[0]
NICU LOS for survivors, mean ± SD, days	73.6±38.1	72.4±50.0	0.93[0]
Median age of death for non-survivors, days	21	35.5	0.87[2]
Umbilical artery pH, mean ± SD	7.15±0.19	7.19±0.16	0.26[0]
5-min Apgars	7.0	8.0	0.42[2]
O_2 requirement at day 30 of life, n (%)	15 (71.4)	31 (73.8)	1.0[1]

ECMO, extracorporeal membrane oxygenation; NICU, neonatal intensive care unit; LOS, length of stay. [0] Compares mean differences using Student's t test. [1] Compares the association between the two groups using Fisher's Exact test. [2] Compares the difference between the two groups using non-parametric Kruskal-Wallis test.

Discussion

In this retrospective case-control study, cases with CDH and concomitant lung lesions were similar to those with isolated CDH with respect to perinatal outcomes. The presence of these low-risk benign lung lesions did not impact the survival rate, NICU LOS, or the respiratory morbidity in cases of CDH. This information adds to previously reported series with similar findings.

Embryologically, the diaphragm is formed from its components including the septum transversum and the pleuroperitoneal membranes by 8 weeks of gestation [22]. About 85–90% of CDHs are left-sided, as was seen in our series. Lung lesions may have a variable time range for formation and expansion, encompassing 7–17 weeks [13]. Both the anomalies have different pathogenesis, and CDH may be associated with genetic abnormalities, whereas a lung lesion is generally not [17]. There is an increased association of other congenital anomalies specifically cardiac with CDH as well as BPS [17, 21, 23]. The exact incidence of a concomitant lung lesion and CDH is unknown. Some small case series have reported a high association of CDH with BPS, especially the extralobar form. Savic et al. [18] described a 3% incidence of CDH with intralobar sequestration and about 27% with extralobar sequestration. A few other case series have also described a common association of BPS and CDH, with an incidence of 15–30% [20, 21, 24]. Our series did not find the same degree of association between the two anomalies, with a 7.2% incidence rate of their coexisting diagnosis including CCAM

diagnoses as well. However, it is prudent to obtain a detailed ultrasound examination for either of the diagnoses in search for the other. As evidenced by the referring diagnosis, it is often difficult to identify both thoracic pathologies as the majority of referral indications were for one diagnosis, 80.7% of the referred cases (17/21), and only 4 patients were referred with a dual diagnosis. The authors have speculated that manifestations of a sequestration might serve as an anatomical barrier and interfere with the fusion of diaphragm and closure of the pleuroperitoneal canal [25]. This would be plausible in the CDH cases with ipsilateral lung lesions. The majority of CDH cases in our series had ipsilateral lung lesions (19/21).

CDH is associated with significant morbidity and mortality related to pulmonary hypoplasia and pulmonary hypertension. On the one hand, the presence of an additional lung lesion may add to morbidity by contributing to the development of pulmonary hypoplasia. Especially CDH cases with contralateral lung lesions can result in bilateral pulmonary hypoplasia. Conversely, theoretically a lung lesion might serve as a hurdle and restrict the migration of abdominal contents through the diaphragmatic defect. This protective effect was supported in the study by Cruz et al. [21] secondary to less severe pulmonary hypoplasia in cases with CDH and concomitant lung lesions. Similar suggestions were made by Grethel et al. [20], though the results were inconclusive. They reported a case series of 14 patients with CDH and a concomitant BPS with a documented survival rate of 50%. Survival for our cohort of CDH with lung lesion was higher and comparable to the group of neonates with isolated CDH. The improvement in the survival rate in our series can likely be attributed to the overall improvement in CDH survival rate due to evolving management strategies in the neonatal period [26, 27]. The 2 groups were comparable with respect to other prognostic factors such as liver herniation and ultrasound-based lung measurements. Other factors that significantly influence outcomes such as presence of major congenital heart disease and genetic abnormalities were not seen in the cases and were excluded from the controls.

The finding of liver herniation is an important prenatal predictor which is associated with increased neonatal morbidity and mortality as well as increased need for ECMO [8, 28]. In our series, controls were carefully selected after matching for liver position with respect to the cases. Multiple methods have been described to perform fetal lung measurements [29]. An ultrasound estimation of contralateral lung area measured at the level of the four-chamber view of the heart standardized to the head circumference defined as LHR is a reliable method but is gestational age dependent. Lower LHR has been associated with a worse neonatal outcome [30]. LHR has now been modified as a measure of gestational age and defined as observed over expected (O/E) which has been validated as a useful marker in predicting neonatal morbidity and mortality [31]. We preferred O/E LHR to select our controls in order to eliminate the bias secondary to gestational age dependence. Absolute LHR along with respective gestational age was used in cases where O/E LHR was not available.

Similarly, a prognostic tool has been developed for lung lesions called the CCAM volume ratio (CVR) [11, 13]. A CVR ≥1.6 is considered "high-risk" and associated with an increased risk of hydrops, whereas that of less than 1 is considered "low-risk." The majority of these low-risk lung lesions will regress spontaneously as the pregnancy progresses and will have a favorable prognosis. Very few will continue to grow causing a mass effect in the thorax, which could lead to hemodynamic instability, cardiac failure, and fetal hydrops. The lung lesions in our cohort were small in size, with CVRs less than 1 and an average CVR of 0.2. Also, minimal interval growth was identified on follow-up scans, and there was no development of hydrops. Another interesting finding was that the lung lesion was ipsilateral to the CDH in more than 90% of the cases.

We identified higher ECMO rates in our cases, though the difference between the 2 groups was not significant. ECMO is a rescue therapy used for neonates with severe CDH and worsening pulmonary hypertension. CDH is the most common indication for the use of ECMO in the neonatal period [30]. The literature reports about a 30% rate of ECMO use for isolated CDH [32, 33]. We discuss the risks associated with ECMO requirement such as bleeding from anticoagulation during the counseling session for prenatal diagnosis of CDH.

We acknowledge the limitations of the study related to the case-control design including selection bias which may be associated with this type of methodology. Because of an extremely low incidence of this diagnosis, the sample size is small. The wide-ranging time interval of case collection may also have an influence on outcomes with the evolving neonatal care and improvement in survival rates. The strengths include a high-volume single-center study with consistent and standardized antenatal and neonatal management.

CDH is a severe disease in and of itself. With the presence of an additional associated diagnosis, families face a more difficult situation. This series explains that the presence of a concomitant low-risk lung lesion in CDH did not have an impact on the natural course of the disease and should help in counseling these patients including making a decision about the course of pregnancy.

Statement of Ethics

The subjects have given their written informed consent, and the study protocol was approved by the institute's committee on human research. The IRB number for the study is 19-016700.

Disclosure Statement

The authors have no conflicts of interest.

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Author Contributions

Study concept and design: N.K. and S.S. Data collection and analysis: S.S. Manuscript development: S.S. Critical review of manuscript: J.S.M., N.R., N.S.A., H.L.H., and N.K.

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