Risk factors and outcome of antenatally diagnosed congenital diaphragmatic hernia following in-utero transfer in a busy public-sector tertiary care center in North India

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Abstract

We analyzed the risk factors and outcomes of antenatally diagnosed congenital diaphragmatic hernia (CDH) from a tertiary-care children's hospital following in-utero transfer. A total of 41 antenatally detected cases of CDH were included; 30 were live-born and 11 were stillborn. The primary outcome was postnatal survival. The secondary outcome was the probable factor affecting survival. No medical termination of the pregnancy was done. The mean gestational age at diagnosis was 23 weeks. The diagnostic accuracy of antenatal ultrasonography was 40/41 (97.5%). Lung-to-head ratio (LHR) was <1 in 20 cases (survived 2), it was >1 in 10 cases (survived 8), and it was not recorded in 11 cases (survived 4). Overall survival was 14/41 (34.1%). Survival in fetuses with polyhydramnios was 0% (n=3; survived 0), associated anomalies were 33.3% (n=3; survived 1), and liver herniation was 22.2% (n=9; survived 2). Postnatally, significant risk factors included a low Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score, the need for ventilation, and neonatal intensive care unit (NICU) management. Survival in live-born cases was 14/30 (46.6%), and in operated cases, it was 14/19 (73.6%). We concluded that antenatal ultrasound had a high accuracy rate for detecting CDH. Antenatal risk factors affecting outcomes were low LHR, maternal polyhydramnios, liver herniation, and associated malformations. Postnatal risk factors included a low APGAR score, NICU admission, and a need for ventilation. The overall survival rate, as well as the survival rates for live-borns and those undergoing surgery, were 34.1%, 46.6%, and 73.6%, respectively. This data will guide clinicians in counseling the families of antenatally diagnosed CDH.

Introduction

Congenital diaphragmatic hernia (CDH) is the most common thoracic abnormality identified on prenatal ultrasound (US) examination, with an incidence of 2.3-2.6 per 10,000 births [1]. CDH carries a mortality in the range of 30-60%, higher in the antenatally diagnosed cases [1-3]. In a recently concluded multi-country study, survival has shown an improving trend, although the total percent mortality was still reported at 37.7% and 45.1% for live births [2]. There is also a large hidden mortality for CDH cases due to stillborn babies and intrauterine loss, including medical termination of pregnancy, which are often missed and excluded from the analysis of the overall mortality.

This study was aimed at analyzing the outcome of antenatally detected CDH from a tertiary-care center and to investigate the risk factors affecting neonatal and postnatal outcomes. This will help in prognostication with realistic survival rates and appropriate counselling while planning the future course of management in antenatally detected CDH.

Materials and Methods

This prospective longitudinal study was conducted jointly by the departments of Pediatric Surgery and Obstetrics and Gynecology after obtaining institutional ethical clearance (LHMC/ECHR/2018/77). The study was conducted over 3 years (2018-2021). All pregnant mothers with fetuses having antenatally detected CDH who agreed to in-utero transfer and delivery at our center were included.

Obstetric details of the mother were recorded. US findings at the first scan were noted, and the patients were kept in follow-up with serial US scans to see the evolution of the anomaly.

The antenatal prognostic factors assessed were: i) lung-to-head ratio (LHR) for CDH; ii) hydrops; iii) polyhydramnios; and iv) associated anomalies like cardiac, genitourinary, skeletal, if any. LHR was calculated as the ratio between the lung area contralateral to the CDH at the level of the atria and the head circumference in the second trimester. It was recorded by a true transverse scan of the chest- visualization of abdominal organs was performed at the same level as a four-chamber view of the heart. LHR was noted for most of the cases, except for cases that were referred late or presented late.

The postnatal prognostic factors assessed were: i) mode of delivery; ii) gestational age at delivery; iii) birth weight; iv) sex; v) type of CDH; vi) any associated anomalies; and vii) Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score at 1-min and 5-min of the neonate.

The management of newborns with CDH followed a standard protocol of pre-operative stabilization followed by surgical intervention. Details of neonatal outcome data, including outcome following surgery, neonatal intensive care unit (NICU) admission days, ventilation, and mortality with probable cause, were also noted. The survivors were followed till discharge from the hospital.

The primary outcome was postnatal survival, and the secondary outcome was probable risk factors affecting fetal and neonatal survival.

Statistical data analysis was done by comparing the distribution of categorical variables in different groups, and significance was tested using the Chi-Square test or Fisher's exact probability test if more than 20% cells had an expected frequency less than 5. The statistical agreement between the two types of diagnosis was done using the Cohen-Kappa technique. In this study, p-values less than 0.05 were considered to be statistically significant. All the hypotheses were formulated using two-tailed alternatives against each null hypothesis (hypothesis of no difference). The entire data was statistically analyzed using Statistical Package for Social Sciences (SPSS ver 22.0, IBM Corporation, Armonk, NY, USA) for MS Windows.

Results

A total of 41 fetuses satisfying the inclusion criteria were delivered at our center; 30 were liveborn and 11 stillborn. No medical termination of pregnancy was done. The mean gestational age at diagnosis was 23 weeks (range 18 weeks-34 weeks). All patients except one were diagnosed after 20 weeks of gestation. Diagnostic accuracy of antenatal US was 40/41 (97.5%). Survival in liveborn was 14/30 (46.6%). Survival in operated cases was 14/19 (73.6%).

Comparison of factors affecting liveborn (n=30) *vs.* stillborn (n=11)

Distribution of characteristics such as sex, gestational period of detection, initial diagnosis, and side involved did not differ significantly between the liveborn and stillborn cases ($p>0.05$) (Table 1).

Distribution of neonatal and maternal characteristics such as LHR, associated anomalies, and polyhydramnios differed significantly between the group of cases who survived *vs.* the stillborn ($p<0.05$) (Table 1). LHR was <1 in 20 patients, out of which only 2 survived; LHR was >1 in 10 patients, out of which 8 survived, and LHR was not recorded in 11 patients, and 4 of these survived ($p<0.024$) (Table 1).

Comparison of factors affecting the survived (n=14) *vs.* the expired (n=16) amongst 30 liveborn

Gestational period of detection (> or < than 20 weeks), mode of delivery, *i.e.*, normal *vs.* caesarean, and birth weight were not significant between the two groups ($p>0.05$) (Table 2). Whereas APGAR score (> or < than 7), need for ventilation, and NICU admission significantly affected survival ($p<0.05$) (Table 2). All 30 liveborn babies had left-sided CDH, and there was no patient with bilateral CDH. Liver herniation was present in 9 patients, out of whom 2 patients (22.2%) survived, whereas liver herniation was absent in 21 patients, and 12 of these survived ($p<0.01$).

Discussion

This prospective longitudinal study was focused on the identification of risk factors and realistic outcomes of antenatally detected isolated CDH with in-utero transfer by eliminating the delay in treatment during postnatal transport to a tertiary care center. Our overall survival of antenatally diagnosed CDH cases was low (34.1%), although the survival improved drastically when only liveborn CDH patients were considered, especially those who could reach the stage of surgery (73.6%). The range of survival rate for antenatal CDH reported in different series varies between 30-60% (Table 3) [4-7]; ours being at the lower end of the spectrum, probably because we were non-selective and included all cases of antenatally diagnosed CDH. A large number of patients with low LHR were included in the study, and a significant number of liveborn babies died before undergoing surgery, indicating lung hypoplasia and poor lung maturation. However, it can clearly be observed that the survival rate improved dramatically for patients who reached the stage for surgical repair, indicating a high proportion of hidden mortality in antenatally diagnosed CDH cases. The known prenatal factors predicting outcome are associated anomalies, neonatal intensive care unit *vs.* isolated CDH, lung hypoplasia and total lung volume, liver herniation, and size/side of the defect [4]. Associated malformations were noted in 21.95% of cases, which was similar to the incidence reported by Barriere *et al.* and Van den Hout *et al.* [4,5]. In our study, associated malformations were significantly associated with poor survival. The incidence of liver herniation noted was 21.95%, which was also similar to other reported studies [4,5]. Currently, fetal magnetic resonance imaging (MRI) is applied to measure fetal lung volume, which may have a significant relation with lung development. Additionally, polyhydramnios was noted in

19.5% of our cases, similar to the study by Sperling *et al*. (28%), and was associated with a poor outcome [7]. All the cases in our study (100%) were left-sided CDH. Although right-sided CDH is considered prognostically poor compared to left-sided CDH, Sperling *et al.* reported similar survival of left-sided and right-sided CDH in their series [7]. The survival was poor in patients with liver herniation, a known risk factor, which also corroborated with other published reports [4-7].

Table 1. Analysis of clinical parameters between the liveborn and stillborn groups.

Parameters		Liveborn (n=30)		Stillborn (n=11)		p
		n	%	n	%	
Sex	Male	22	73.3	6	54.5	0.252^{NS}
	Female	8	26.7	5	45.5	
Initial presentation	<20 weeks	1	3.3	0	0.0	0.999^{NS}
	>20 weeks	29	96.7	11	100.0	
Mode of delivery	Normal vaginal	26	86.7	0	0.0	--
	LSCS	4	13.3	0	0.0	
	Stillborn	0	0.0	11	100.0	
Initial diagnosis	CDH	30	100.0	11	100.0	0.999^{NS}
	Other	0	0.0	0	0.0	
Lung-to-head ratio	Not known	9	30.0	2	18.2	0.024*
	<1	11	36.7	9	81.8	
	>1	10	33.3	0	0.0	
Associated anomalies	Yes	3	10.0	6	54.5	0.006**
	No	27	90.0	5	45.5	
Side involved	Left	30	100.0	11	100.0	0.999^{NS}
	Right	0	0.0	0	0.0	
	Bilateral	0	0.0	0	0.0	
Polyhydramnios	Yes	3	10.0	5	45.5	0.022*
	No	27	90.0	6	54.5	

LSCS, lower segment cesarean section; CDH, congenital diaphragmatic hernia; NS, statistically non-significant; p-value by Chi-Square test; p<0.05 is considered to be statistically significant. *p<0.05; **p<0.01.

Table 2. Analysis of factors affecting outcome between the survived and the expired groups of liveborn patients.

Factors assessed		Survived (n=14)		Expired (n=16)		Total (n=30)		p
		n	%	n	%	n	%	
Gestational period at diagnosis	<20 weeks	1	100.0	0	0.0	1	100.0	0.467^{NS}
	>20 weeks	13	44.8	16	55.2	29	100.0	
Mode of delivery	Normal	13	50.0	13	50.0	26	100.0	0.602^{NS}
	LSCS	1	25.0	3	75.0	4	100.0	
Birth weight	>2.5 kg	7	46.7	8	53.3	15	100.0	0.626^{NS}
	1.5-2.5 kg	7	50.0	7	50.0	14	100.0	
	<1.5 kg	0	0.0	1	100.0	1	100.0	
APGAR score	<7	0	0.0	6	100.0	6	100.0	0.019*
	≥7	14	58.3	10	41.7	24	100.0	
Pre-op ventilation required	Yes	5	26.3	14	73.7	19	100.0	0.007**
	No	9	81.8	2	18.2	11	100.0	
NICU admission	Yes	0	0.0	13	100.0	13	100.0	0.001***
	No	14	82.4	3	17.6	3	100.0	
Liver herniation	Yes	2	22.2	7	77.7	9	100.0	0.001*
	No	12	57.1	9	42.8	21	100.0	

LSCS, lower segment cesarean section; APGAR, Appearance, Pulse, Grimace, Activity, and Respiration; NICU, neonatal intensive care unit; NS, statistically non-significant; p-value by Chi-Square test; p<0.05 is considered to be statistically significant; *p<0.05; **p<0.01; ***p<0.001.

Table 3. Comparison of results of antenatally diagnosed congenital diaphragmatic hernia in different studies.

Studies	Survival (%)	Polyhydramnios (%)	Liver herniation(%)	Associated malformations(%)
Barriere *et al.*[4]	60	-	42	14
van den Hout *et al.*[5]	67	-	45	13
Wright *et al.*[6]	30	-	-	46
Sperling *et al.*[7]	64	28.7	70	17.2
Current study	34	19.5	21.95	21.95

There exists a significant association between low LHR, especially observed *vs.* expected (O/OE) LHR, and poor survival, as it reflects lung hypoplasia [8,9]. We also found a significant association of low LHR and poor survival; however, a more detailed and objective study in detecting O/E LHR could perhaps highlight greater insight into a more significant association between LHR and outcomes. Mortality in CDH is often due to persistent pulmonary hypertension, which is difficult to predict prenatally [4]. The benefit of fetal therapy in the form of tracheal balloon occlusion for moderate to severe antenatally diagnosed CDH, which is available in a few specialized centers in Europe and the USA [10], has not yet been proven for wider adaptation. The known postnatal predictors of outcome are APGAR score, low birthweight, major cardiac anomaly, chromosomal anomaly, and severe pulmonary hypertension on first echocardiogram [11]. Mode of delivery and birth weight did not significantly affect our survival, but low APGAR score, need for ventilation, and need for NICU care did significantly affect the survival of our CDH patients. Chandrasekaran *et al*. reported 78% survival in postnatal CDH from a single center in India, similar to our survival of patients who underwent surgery (73.6%) [12]. Wright *et al.* from the UK reported an overall 1-year survival of 42%, with 30% survival for antenatally diagnosed CDH [6]. Articles with reported higher survival rates have often excluded stillborn and medical termination of pregnancy and only included liveborn in their analysis, thereby skewing the outcome percentage [4,7]; nonetheless, we included all such cases, reflecting a more accurate and realistic outcome.

There were a few limitations of our study, like LHR, O/OE LHR, and fetal MRI assessment were missing in a large number of patients, a lack of a detailed genetic study, and a lack of a facility for fetal intervention in high-risk CDH cases. Nonetheless, the results of this study will go a long way to help in realistic counselling of the family with identification of risk factors affecting outcome for antenatally diagnosed CDH. Despite advances in fetal management, the mortality remains high; therefore, currently, no clear recommendation is available for fetal intervention, which remains experimental. The concept of in-utero transfer is a very promising step to improve outcomes, especially in high-risk preterm or low birth weight fetuses with poor LHR, as it allows for immediate and timely expert care for the associated lung hypoplasia, avoiding the adverse effects from delay in reaching tertiary care center during transportation from the referral center.

Conclusions

Antenatal US is highly accurate in detecting CDH. The overall low rate of survival (34.1%) of antenatally diagnosed CDH could be attributed to non-selective inclusions of cases. The identified antenatal risk factors affecting outcome were low LHR, maternal polyhydramnios, liver herniation, and associated malformations; postnatal risk factors were low APGAR score, need for NICU admission, and ventilation. The survival rate improved in live born (46.6%) and were even better in those who underwent surgery (73.6%) indicating better lung development. Results of this study will be invaluable for clinicians involved in counseling and prognostication of antenatally diagnosed CDH.

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