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Fetal Echocardiography (ECHO) in Assessment of Structural Heart Defects in Congenital Diaphragmatic Hernia Patients: Is Early Postnatal ECHO Necessary for ECMO Candidacy?

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Abstract

Purpose: The purpose of this study was to determine the accuracy of fetal echocardiogram (ECHO) for detecting cardiac structural anomalies that may impact Extracorporeal Membrane Oxygenation (ECMO) candidacy in infants with Congenital Diaphragmatic Hernia (CDH).

Methods: A retrospective review was performed on fetuses with CDH (January 2007-June 2017). Inclusion criteria were inborn and at least one prenatal and postnatal ECHO. ECHOs were evaluated for structural heart defects. Primary outcomes were accuracy of prenatal fetal ECHO and identify differences between prenatal and postnatal ECHO. Descriptive statistics and Chi-square analysis were performed.

Results: 131 inborn patients were identified. Mean gestational age of fetal ECHO was 26.6 ± 5.5 weeks. The median time to post-natal ECHO was DOL 1 [0–30]. Fetal ECHO had 92% accuracy, 83% sensitivity, 93% specificity, PPV of 95%, NPV of 92%, and a 90% accuracy for visualization of at least one pulmonary vein into the left atrium on the contralateral (non-CDH) side. Thirty-five

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percent of patients received ECMO, and 26% had an associated cardiac anomaly. All ECMO patients had an accurate structural fetal ECHO.

Conclusion: Fetal ECHO is sufficient for identifying major structural heart defects at large volume centers with trained pediatric cardiologists and may be used to guide clinical management, particularly in regards to ECMO candidacy.

Keywords

Congenital diaphragmatic hernia (CDH); Congenital heart disease; Fetal; Echocardiogram (ECHO); Extracorporeal membranous oxygenation (ECMO)

Introduction

Congenital diaphragmatic hernia (CDH) is the most common thoracic congenital anomaly and results from failure of closure of pleuroperitoneal folds during weeks 4 – 10 of gestation [1]. It is associated with other chromosomal or anatomical defects in 30% of those affected and approximately 15% of patients have congenital heart disease (CHD)[2–4]. Herniation of abdominal viscera into the thoracic cavity in CDH can cause external cardiac compression, pulmonary hypoplasia, and pulmonary hypertension leading to a high morbidity and mortality [5–7]. Thus, postnatal management of CDH may involve aggressive pulmonary and hemodynamic support to manage infants that are critically ill. This is particularly true in the immediate neonatal period, where infants can rapidly progress to severe cardiopulmonary failure within the first few hours of life. If conventional medical management fails, many tertiary institutions offer the use of extracorporeal membrane oxygenation (ECMO) to provide cardiopulmonary support for patient stabilization and also as a bridge to CDH repair [8]. Congenital heart disease is a recognized risk factor for poor prognosis in the CDH population, and while not an absolute contraindication, it should be assessed prior to ECMO initiation [3, 9].

Given that many CDH patients are now diagnosed prenatally, many infants will have undergone a fetal echocardiogram (ECHO) to evaluate for complex structural cardiac anomalies. The purpose of the fetal ECHO is determine if there are large structural cardiac anomalies, and to help provide information to determine postnatal management and candidacy for fetal intervention. This information is also used for parental counseling. The presence of major structural cardiac anomalies may exclude the candidacy of certain critically ill CDH patients for ECMO and redirection of goal of care may be appropriate in these specific situations. Thus, the purpose of this study is to determine the accuracy of fetal echocardiogram (ECHO) for detecting major cardiac structural anomalies in our CDH population in comparison to a postnatal ECHO. We hypothesize that fetal ECHO performed and interpreted by trained pediatric cardiologists whom specialize in fetal ECHO is as accurate as post-natal ECHO for detecting major cardiac structural anomalies that may impact ECMO candidacy.

Methods

A retrospective review of the electronic medical records for all fetuses diagnosed with CDH and referred to a large volume tertiary care fetal center from January 2007 to June 2017 was performed. Permission was obtained from the Institutional Review Board (H-26176). Our primary objectives were to 1) determine the accuracy of prenatal fetal ECHO and 2) identify differences between diagnoses in prenatal and postnatal ECHO.

2.1 Inclusion Criteria

The clinical data of neonates with a prenatal diagnosis of left- or right-sided CDH were reviewed. Patients were included in this study if they were evaluated and found to have CDH in the fetal period, inborn at our institution, and if they had undergone at least one fetal echocardiogram and one postnatal echocardiogram. Bilateral CDH patients were excluded.

2.2. Data Collection

Prenatal data were collected from maternal medical records and included gestational age at CDH diagnosis, observed-to-expected total fetal lung volume (O/E TFLV) and percent of intrathoracic liver herniation (%LH) assessed by MRI. Fetuses with CDH seen during the study period were evaluated for chromosomal and structural heart defects. Postnatal data obtained from the medical record included gestational age at birth, birthweight, fetal ECHO, and postnatal outcomes at one year. CDH patients were classified as severe based on published parameters using MRI derived O/E TFLV and % liver herniation [10]. Severe CDH was defined as O/E-TFLV <32% and %LH >21%. Moderate CDH was defined as O/E-TFLV 32% and %LH > 21% or O/E-TFLV < 32% and %LH 21%. Mild CDH was defined as O/E-TFLV 32% and %LH 21%.

2.3 Echocardiogram data

Echocardiograms were interpreted by pediatric cardiologists trained in fetal echocardiography at the time of the study. The data were retrieved from the final report. The protocol for a complete fetal echocardiogram followed recommendations for cardiac imaging according to the American Society of Echocardiography Guidelines for Fetal Echocardiography [11]. All CDH infants referred in the prenatal period have a fetal echocardiogram in either the second or third trimester. For neonates with CDH, a postnatal echocardiogram is routinely obtained within the first forty-eight of life and follow-up echocardiograms are obtained as needed prior to discharge and post-discharge. Fetal echocardiography was considered abnormal if it led to the diagnosis of any identified structural heart disease. Major structural heart defects were classified as patients with a large ventricular septal defect (VSD), double outlet right ventricle (DORV), tetralogy of Fallot (ToF), severe or tubular coarctation of the aorta, transposition of the great arteries (TGA), Ebstein's anomaly, pulmonary or aortic valve stenosis, truncus arteriosus, single ventricle defects (hypoplastic left heart syndrome (HLHS), tricuspid atresia, etc.) and total anomalous pulmonary venous connection (TAPVC). Cardiac anatomy on postnatal echocardiography was considered to be the definitive or "gold standard" for diagnostic study comparison. Details regarding atrial septal defect (ASD), post ductal arteriosus (PDA), and patent

foreman ovale (PFO) were collected and evaluated but were not included in the final statistical analysis.

2.4 Postnatal Care and Management

The timing and mode of delivery were based on obstetrical indications and coordinated with the multidisciplinary CDH team. Postnatal management decisions regarding mechanical ventilation, use of the high-frequency oscillator, surfactant and/or inhaled nitric oxide administration, extracorporeal membrane oxygenation (ECMO) and timing for CDH repair were based on standardized institutional guidelines which have been previously reported [12, 13].

2.5 Statistical analysis

Diagnostic imaging accuracy was tested between the pre and post-natal ECHOs. The post-natal echocardiogram results were considered the definitive diagnosis. Estimates of sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were calculated and conducted according to the standards for reporting diagnostic accuracy study guidelines [14]. Confidence intervals were generated using receiver operator characteristic (ROC) curve analysis. Student's t-test, chi-square and Mann-Whitney U test were used for comparisons based on variable type and distribution, and results are presented as the median value and interquartile range or mean and standard deviation. A p-value of <0.05 and 95% CI were considered significant. All statistical analysis was performed using IBM Statistical Package for Social Sciences (IBM SPSS version 24, NY, USA).

Results

3.1 Clinical and Demographic Data

A total of 200 fetuses were identified over the study period. Of these, 131 neonates were inborn, underwent a fetal center evaluation at Texas Children's Hospital, and had at least one prenatal and one postnatal ECHO. Left-sided CDH accounted for 87% (n=114) of the population with slight predilection of the male sex at 57% (n=74, Table 1). Mean age at diagnosis and fetal center referral was 23.1 ± 5.5 weeks of gestation. The majority of patients had an intrathoracic liver (79%, n=102) and stomach (74%, n=94) noted prenatally. Using the scale of severity based on O/E TFLV and percent of liver herniation, 30% were classified as mild, 33% were classified as moderate and 38% were severe. ECMO was initiated in 35% (n=45) of the neonates (with and without cardiac defects). Overall cohort survival was 78% (n=102/131).

3.2 Fetal and Postnatal Echocardiography in the CDH cohort

Mean age at fetal ECHO was 26.4 ± 4.7 weeks, with 61% (n=80) occurring in the 2nd trimester and 39% (n=51) occurring in the 3rd trimester. Fifty-three percent (n=69) of fetuses were found to have an abnormal fetal ECHO including effects related to CDH such as dextroposition and mildly hypoplastic heart structures on the side of the diaphragm lesion. Twenty-seven fetuses (21%) had findings of one or more structural cardiac defects. CHDs diagnosed or deemed "highly suspicious for" on fetal ECHO included VSD (n=15), DORV

(n=4), HLHS (n=3), coarctation of the aorta (n=4), ToF (n=6), TAPVC (n=3) and Shone's syndrome (n=1) as illustrated in figure 1. Of note, VSDs were accounted for individually, but were only noted as isolated defects in six fetuses.

In comparison, congenital heart defects were diagnosed on postnatal ECHO in 18% (n=23) of CDH neonates at a median age of postnatal ECHO of 1 [0 – 30] day of life. A total of n=35 structural cardiac defects were confirmed or diagnosed on postnatal ECHO in comparison to the n=36 on fetal ECHO (figure 2). Three VSDs present on fetal ECHO of three separate patients were no longer distinguishable on postnatal ECHO and two additional VSDs were reported that were not noted on fetal ECHO. Additionally, two prenatal diagnoses of TAPVC and one prenatal diagnosis of coarctation of the aorta were rescinded on postnatal ECHO.

The most commonly diagnosed CHD on both fetal and postnatal ECHO was VSD with a 73% sensitivity, 98% specificity, 85% positive predictive value and an 86% diagnostic accuracy on Fetal ECHO (Table 2). DORV, HLHS, ToF, and Shone's syndrome were accurately diagnosed in all cases with no false negatives noted for any of these cardiac diagnoses. All three cases of severe or tubular coarctation of the aorta determined on postnatal ECHO were diagnosed on prenatal ECHO. However, there was one false positive diagnosis of coarctation of the aorta on prenatal echo resulting in a sensitivity of 75%, but a specificity of 98%. When evaluating for visualization of the pulmonary vasculature, at least one pulmonary vein was visualized on the affected side of the diaphragm lesion in 84% of the cases. TAPVC was falsely positive in two cases. Overall for all major defects evaluated, fetal ECHO was found to have 92% accuracy, 75% sensitivity, 100% specificity, positive predictive value of 100%, and negative predictive value of 91% [CI=0.781–0.971].

3.3. Comparison of Cohort Outcomes

The majority of fetuses were delivered at term with a mean GA at delivery of 36.6 ± 6 weeks with no significant difference when comparing the CDH with heart disease to the isolated CDH cohort. Neonates with CDH at comparable gestational ages with structural heart defects were significantly smaller (2.4 vs 2.9 kg, $p=0.003$, Table 3). ECMO was performed in 17% (n=6) of the CDH patients with heart anomalies. The cardiac diagnoses were VSD (n=5) or coarctation of the aorta (n=1). Diagnosis was accurate on fetal ECHO in all cases of neonates who underwent ECMO (n=45), with or without congenital heart disease, excluding ASDs. There was no significant difference in timing of repair or length of time spent on ECMO in those with congenital cardiac anomalies. Survival however was significantly lower in those with congenital cardiac anomalies (52% vs. 83%, $p=0.004$).

Discussion

This study investigates the diagnostic accuracy of fetal ECHO and its utility in the pre and post-natal period of neonates with CDH particularly as it relates to use for ECMO candidacy. Similar to studies reported in the literature [15–17], the results of this study demonstrates high diagnostic accuracy, sensitivity and specificity of fetal ECHO to diagnose significant cardiac defects in a population of fetuses with both left and right CDH (excluding ASDs and minor cardiac lesions). Additionally, no patient that underwent ECMO in this

cohort, regardless of presence of cardiac anomaly, had findings different on postnatal ECHO when compared to prenatal ECHO. This implies that a quality fetal ECHO performed by image trained pediatric cardiologists may be used as a surrogate for postnatal echo in the early hours or perhaps first few days of the neonatal period to rule out or rule in cardiac anomalies that may exclude a patient from ECMO candidacy.

In the fetal period, ECHO is used to assess the structural integrity of the heart as well as the effects of structural compression from the CDH (i.e. small aortic arch, cardiac position, etc.). Structural heart defects can occur in up to 15% of CDH patients [3]. First introduced clinically in the 1980s [17, 18], fetal ECHO is now widely used and has aided in multidisciplinary treatment planning and prenatal counseling. In the postnatal period, ECHO is standard of care to evaluate for definitive diagnosis of cardiac defects and to assess and estimate the severity of pulmonary hypertension [19, 20]. Traditionally, the first ECHO obtained is to confirm cardiac anatomy and then repeat ECHOs are obtained to assess cardiac function after neonatal stability is established pre- and post-repair [21]. Several studies report [22, 23] institutional protocols of conducting ECHOs within 24 hours of birth and weekly ECHOs for the duration of the hospitalization.

Previously, use of fetal ECHO was precluded owing to the variability of reported diagnostic accuracy, sensitivity and specificity of the exam [16, 24]. This variability has been attributed to several factors including sonographer and ECHO interpreter (pediatric cardiologist) experience, transducer frequency, maternal body habitus, gestational age, and fetal position [25, 26]. However, recent studies in the cardiac literature have been favorable regarding fetal ECHO accuracy. Zhang et al. demonstrated on their meta-analysis that sensitivity is improved during the second trimester and third trimester and that fetal ECHO has been highly effective for diagnosis [17].

CDH is now the most common indication for ECMO in neonates with respiratory failure [27]. ECMO is often initiated in the early neonatal period and the majority of CDH neonates on ECMO are cannulated within the first 48 hours of life. During this period of instability, performing a bedside ECHO may not be technically possible in a CDH patient who may already be in a pulmonary hypertensive crisis. The question for this study is whether an immediate post-natal ECHO is absolutely necessary in unstable CDH patients whom have had a fetal ECHO that shows no significant cardiac lesion. The results of current study suggest that a fetal ECHO interpreted by a pediatric cardiologist whom specializes in fetal ECHO is sufficient in determining whether there may be a cardiac lesion that may be a contraindication to ECMO initiation. While co-existing congenital cardiac lesions are not an absolute contraindication to ECMO, the extracorporeal life support organization (ELSO) guidelines for neonatal respiratory ECMO do list a lethal anomaly as an absolute contraindication and patients with disease states with a high probability of poor prognosis as a relative contraindication [28]. The conditions which may give pause to ECMO therapy would mainly be patients where significant pulmonary hypertension would preclude cardiac repair, i.e., single ventricle physiology or pulmonary atresia, and this is where the fetal ECHO appears to be sufficient in making that determination. Thus, in an unstable patient with a finding of a significant cardiac defect contraindicative to ECMO therapy on prenatal ECHO, there would be pause in ECMO initiation until confirmation on postnatal ECHO.

The high sensitivity and specificity findings in our study serve to further validate the accuracy of second and third trimester fetal ECHO studies when performed by a fetal trained pediatric cardiologist. With an optimal fetal ECHO study there can be more flexibility of timing to postnatal ECHO which can be scheduled after the initial patient stabilization.

This study is limited by the retrospective nature of the review. Additionally, it is important to note that the findings are specific to our institution and reproducibility across other institutions has yet to be tested. As a single center study there is likely selection bias within the patient population. Additionally, all of the pediatric cardiologists who perform fetal ECHO have had dedicated training in this area, and the findings from this study in the ability to discern structural cardiac defects may not be applicable in hospitals or programs where there are not trained fetal ECHO pediatric cardiologists. There are also well established limitations of fetal echocardiography to detect small septal defects, minor valve anomalies, abnormalities of pulmonary venous return, and postnatal patent foramen ovale, patent ductus arteriosus, or coarctation of the aorta. As a result, a normal echocardiogram does not guarantee the absence of a congenital cardiac anomaly and we would still recommend a formal post-natal ECHO once the patient has stabilized.

Conclusion

Fetal echocardiograms performed by image trained pediatric cardiologists have a high diagnostic accuracy for significant cardiac lesions in neonates prenatally diagnosed with CDH. If the fetal ECHO is suboptimal due to maternal body habitus or fetal position, we would continue to recommend a postnatal ECHO within 24 hours of life. However, in the setting of the critically ill infant with CDH, a quality fetal ECHO (performed by image trained pediatric cardiologists) is a valuable and sufficient tool that can be referred to in the postnatal period to evaluate for ECMO candidacy and postpone the post-natal ECMO until the patient has achieved a period of stability.

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Figure 1: Percentage distribution of Cardiac Defects

*VSD=ventricular septal defect, DORV=double outlet right ventricle, ToF=Tetrology of Fallot, HLHS=hypoplastic left heart syndrome, TAPVC=total anomalous pulmonary venous connection

Figure 2: Diagnosis of Cardiac Defect on Fetal and Postnatal ECHO

*VSD=ventricular septal defect, DORV=double outlet right ventricle, ToF=Tetrology of Falot, HLHS=Hypoplastic left heart syndrome, TAPVC=Total anomalous pulmonary venous connection, ASD=atrial septal defect

Table 1:

Clinical Cohort & Demographics

Side of CDH	n=131
Left	87%
Right	8%
Bilateral	5%
Race	
Caucasian	50%
African American	9%
Hispanic	29%
Asian	6%
Other	6%
Sex	
Male	57%
Female	43%
Gestational Age at Diagnosis (weeks)	23.1 ± 5.5
Liver “up”	79%
Stomach “up”	74% (97/118)
Gestational Age at Fetal ECHO, weeks	26.4 ± 4.7
Infants with associated anomalies, major cardiac defects	17.6%
Gestational Age at Birth (weeks)	36.6 ± 6.1
**Median age at postnatal ECHO, days [range]	1[0–30]
Need for ECMO	35%
Survival	78%

* All values listed as percentage and mean ± standard deviation unless otherwise stated; ECHO=echocardiogram.

** Of note, the range of postnatal ECHO was 0 to 30 days of life which accounts for three infants that underwent their first ECHO at our institution at day of life 7, 11, and 30.

Table 2:

Diagnostic Test Evaluation of Fetal Echocardiography in CDH

	Diagnostic Accuracy	Sensitivity	Specificity	NPV	PPV	CI (low)	CI (up)
Ventricular Septal Defect (VSD) (n= 17)	86%	73%	98%	95%	89%	0.75	0.977
Double Outlet Right Ventricle (DORV) (n=4)	100%	100%	100%	100%	100%	0.99	0.99
Hypoplastic Left Heart Syndrome (HLHS) (n=3)	100%	100%	100%	100%	100%	0.99	0.99
Tetralogy of Fallot (ToF) (n=6)	100%	100%	100%	100%	100%	0.99	0.99
Coarctation of the Aorta (n=3)	98%	75%	98%	98%	50%	0.98	0.99
Visualization of pulmonary veins on affected side (1 or more)	90%	91%	81%	97%	54%	0.438	0.939
Presence of any structural heart defect	92%	83%	93%	92%	95%	0.781	0.971

* NPV=negative predictive value, PPV=positive predictive value, CI=confidence interval

Table 3:

Outcome Comparison for CDH infants with CHD

	CHD (n=23)	No CHD (n=105)	p-value
GA at birth	37.2 ± 2.32	36.5 ± 6.5	0.598
Birthweight	2437 ± 0.6	2888 ± 0.6	0.003
ECMO	27% (n=6)	37% (n=39)	0.266
Median Time on ECMO [IQR]	7 [4, 11]	10 [6,17]	0.374
Repair on ECMO	27.8%	33%	0.423
Survival	52.2%	83%	0.004

* All values listed as percentage and mean ± standard deviation unless otherwise stated; CDH=congenital diaphragmatic hernia, CHD=congenital heart defect, ECMO=extracorporeal membrane Oxygenation, GA=gestational age, IQR=interquartile range