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REVIEW

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Prenatal assessment of pulmonary vasculature development in fetuses with congenital diaphragmatic hernia: A literature review

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Abstract

Pathophysiological studies have shown that pulmonary vascular development is impaired in fetuses with a congenital diaphragmatic hernia (CDH), leading to a simplified vascular tree and increased vascular resistance. Multiple studies have described prenatal ultrasound parameters for the assessment of the pulmonary vasculature, but none of these parameters are used in daily clinical practice. We provide a comprehensive review of the literature published between January 1990 and February 2022 describing these parameters, and aim to explain the clinical relevance of these parameters from what is known from pathophysiological studies. Prenatal detection of a smaller diameter of the contralateral (i.e. contralateral to the diaphragmatic defect) first branch of the pulmonary artery (PA), higher pulsatility indices (PI), higher peak early diastolic reverse flow values, and a lower vascularization index seem of added value for the prediction of survival and, to a lesser extent, morbidity. Integration within the routine evaluation is complicated by the lack of uniformity of the methods used. To address the main components of the pathophysiological changes, we recommend future prenatal studies in CDH with a focus on PI values, PA diameters and pulmonary vascular branching.

Key points

What's already known about this topic?

- In fetuses with congenital diaphragmatic hernia (CDH), assessment of the pulmonary vasculature has been suggested but is not yet routine practice in the prenatal work-up.
- Pathophysiological (animal) studies show abnormal fetal pulmonary vascular development in CDH.

What does this review add?

- This paper offers a pathophysiological explanation for the value of the different ultrasound parameters used to assess prenatal pulmonary vasculature.

- Although literature is relatively scarce and uniformity in study designs is needed to draw clear conclusions, there might be an added value of structural and/or functional evaluation of the pulmonary vasculature in fetuses diagnosed with a CDH for the prediction of postnatal survival and, to a lesser extent, morbidity.

1 | INTRODUCTION

Congenital diaphragmatic hernia is a life-threatening, rare congenital anomaly characterized by a developmental defect of the diaphragm and subsequent herniation of abdominal organs in the thorax. As the thoracic space is limited, this causes mediastinal shift resulting in impaired lung (airways and vessels) and cardiac development. After birth, the condition is then characterized by a triad of pulmonary hypoplasia, pulmonary hypertension (PH), and cardiac dysfunction.[1,2] Overall survival rates are reported between 70% and 80%, and survivors will have significant short- and long-term morbidities.[3,4]

Currently, prenatal prediction and counseling is mainly done using the degree of pulmonary hypoplasia (mild, moderate, severe or extreme), which is based on the side of the defect, and ultrasound assessment contralateral lung size, expressed as the observed-to-expected lung-to-head ratio (O/E LHR),[5] combined with liver position (intra-abdominal or intrathoracic).[3,6–8] Although these predictors have been proven to be very helpful in determining survival and the degree of morbidity,[9,10] they only asses one part of the pathophysiological triad of CDH. It goes without saying that prenatal evaluation of the two other main components of the triad may facilitate prenatal counseling but also could guide perinatal management.

The pathophysiological changes of the pulmonary vascular tree due to CDH are well described, that is, hypertrophic walls of the pulmonary arteries and a reduced number of branches.[11–13] However, an important limitation in the evaluation of the severity of impaired vascular development *before birth* is that PH can only be diagnosed *after birth* given the differences between the fetal and neonatal circulation. Before birth, the pulmonary vessels are constricted and the presence of physiological shunts makes the lungs largely bypassed.[14,15]

In healthy fetuses, there is ample literature describing the direct visualization and functional assessment of the fetal pulmonary circulation by use of two-dimensional (2D) and three-dimensional (3D) ultrasound techniques.[16,17] Structural evaluation can be done by measuring main arterial branches for which nomograms are available.[16,18–20] Functional evaluation is often done using various modalities of Doppler imaging, for example, by measurement of velocimetry indices such as the pulsatility index (PI) or peak early diastolic reverse flow (PEDRF) or by calculation of the fractional moving blood volume (FMBV).[21–27] For CDH fetuses, there have been attempts to include evaluation of the pulmonary vasculature in the prediction algorithms for responsiveness to Fetoscopic Endoluminal Tracheal Occlusion (FETO) and postnatal outcomes.[28] However, significant variations in predictive value and reproducibility issues prevent most centers from including this in their routine assessment of CDH fetuses. To gain insight into the usefulness of these ultrasound parameters for the prediction of postnatal outcomes in CDH, we provide a literature overview of the investigated parameters and correlate them to pathophysiological changes characteristic for CDH.

2 | METHODS

2.1 | Search strategy

Literature search was performed in Embase and Pubmed databases to collect all relevant articles published regarding prenatal ultrasound measurements of the pulmonary vessels in fetuses with CDH. The search strategy was developed on the 16th of December 2020 and updated on the 28th of February 2022. This was done in consultation with a research librarian with experience in developing search strategies.

All studies in the English language concerning human populations between 1990 and February 2022 were considered eligible. The following terms and their synonyms were used as search terms: “ultrasound”, “prenatal diagnosis”, “fetal”, “CDH”, “pulmonary vasculature”, “pulmonary vessel”, “lung perfusion”. Exclusion criteria were animal studies, postnatal assessment of the pulmonary vasculature, prenatal assessment of the fetal heart and/or great arteries, and prenatal assessment of pulmonary vasculature by techniques other than ultrasound (e.g. magnetic resonance imaging). References of the retrieved articles were also screened for eligibility.

2.2 | Study selection

Two independent reviewers (KW and NCJP) screened the titles and abstracts of all retrieved articles for relevance. The full-text versions of the selected articles were retrieved and reviewed by the same authors. In case of disagreement regarding inclusion or exclusion of an article, the two reviewers discussed it until a consensus was reached.

2.3 | Data extraction

The included full-text articles were summarized regarding author, year of publication, study design, study population (number of CDH cases, type of CDH with side of the defect, fetal intervention),

parameter of interest, outcome data and results. Quality assessment of the studies was not possible due to the variety of study designs and outcome parameters.

3 | RESULTS

3.1 | Study selection

A total of 744 articles were retrieved from the different databases, after which 257 duplicates were excluded. After updating the search on 28 February 2022, 83 articles were added, and the remaining 570 studies were screened by title and abstract for eligibility. This resulted in 102 potentially relevant studies. After full text assessment, 26 studies that met our inclusion criteria were included in this review. Reasons for exclusion of articles are shown in Figure 1. Twenty-four reviews were excluded but used for reference screening. These reviews did not specifically review prenatal pulmonary vasculature assessment but were general reviews of (prenatal) CDH diagnostics and treatment.

3.2 | Main findings

As presented in Figure 1, the selected articles were divided into four categories depending on the technique and type of parameter that was investigated ("Pulmonary artery (PA) diameters", "Vascular branching", "Doppler velocimetry" or "Vascular indices"). Two articles

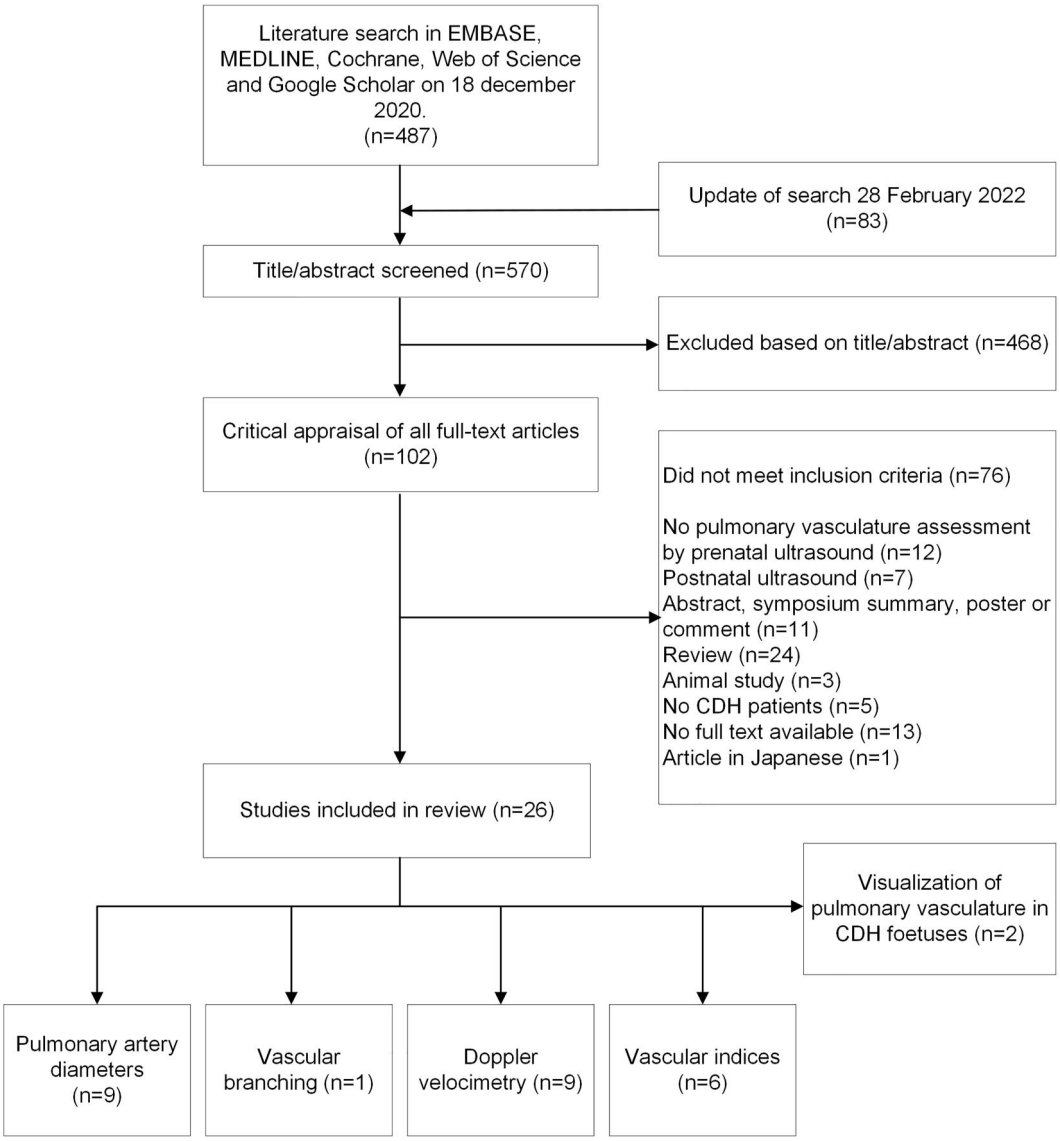

FIGURE 1 Flowchart of the search strategy and study selection process. The selected articles are subdivided into different categories according to the type of parameter that is studied. One article assessed multiple parameters and falls into two categories. CDH, congenital diaphragmatic hernia; 2D, 2 dimensional; 3D, 3-dimensional.

assessed the possibility of visualization of the pulmonary vasculature without performing any measurements and were therefore not included in the four categories. These studies showed that comparable to the assessment of pulmonary vessels in healthy fetuses, identification of the proximal fetal pulmonary vessels is primarily possible by the use of 2D power Doppler.[29,30] In line with abbreviations given in the selected articles, the parameters assessed in the pulmonary vessels ipsilateral or contralateral to the diaphragmatic defect are described as "ipsilateral [parameter]" or "contralateral [parameter]" respectively. All reported findings concern left-sided CDH (LCDH) fetuses, if it concerns right-sided CDH (RCDH), this is reported specifically.

3.3 | Pulmonary artery diameters

An overview of the articles concerning the analysis of pulmonary arterial diameters is presented in Table 1. All studies assessed right or left PA diameters just distal to the bifurcation of the main PA in the short-axis view of the main PA, the ascending aorta and superior vena cava (Supplemental figure S1).

3.3.1 | Ipsilateral pulmonary artery diameter

We found six studies evaluating the ipsilateral PA in LCDH fetuses. All six studies shared the common finding that the ipsilateral PA diameters were reduced compared to healthy controls[31–34] and compared to contralateral PA diameters.[31,32,35] In three studies, this was correlated with postnatal outcomes, observing a higher likelihood of mortality[36] and an increased risk of oxygen and ventilation requirement in neonates[31,32] with smaller ipsilateral PA diameters.

3.3.2 | Contralateral pulmonary artery diameter

Nine studies examined contralateral PA size, with the large majority only assessing LCDH.[31–39] Diameters were expressed as continuous diameters,[31–35,39] Z-scores[37] or observed/expected (O/E) values.[36,38] In all studies, the methods of measurement, that is, side and location in the artery, were the same.

Contralateral PA diameters were found to be within normal ranges[32,34] or reported to be smaller compared to healthy fetuses.[33,34,36]

Overall, smaller contralateral PA diameters were correlated with higher mortality,[31,35–38] and only one study showed the opposite ($n = 26$).[32] This correlation was found to be more evident in low birth weight (≤2500 g, $n = 15$) than in normal birth weight (>2500g, $n = 24$) fetuses.[39] In relation to morbidity, Ruano et al.[38] found a correlation between smaller contralateral PA diameters and higher incidences of severe PH in 108 neonates, which was not found in an earlier smaller study ($n = 21$) by the same authors.[36]

3.4 | Vascular branching

We found one study (Table 2) which evaluated fetal pulmonary vascular branching patterns. In this small, single-center study consisting of 32 LCDH and 10 RCDH fetuses, the total number of visible bifurcations just distal to the first bifurcation was determined in the contralateral lung by means of 2D power Doppler.[40] The main observation was that the number of visible divisions (1, 2 or 3 or more) could be a potential predictor of neonatal mortality, since a total of three or more branches was correlated with higher survival in CDH neonates.[40]

3.5 | Doppler velocimetry

An overview of the articles concerning the 2D analysis of Doppler velocimetry parameters is presented in Table 3.

Seven studies evaluated the vascular resistance by assessing the pulsatility index (PI) in the most proximal branches by identifying the typical waveform of the first PA branch after the bifurcation of the main PA (Figure 2).[21,41–47] Three of these studies reported higher contralateral PI values in CDH fetuses compared with healthy controls. In addition, they showed a significant increase throughout gestation and a negative correlation with predicted lung size (O/E LHR).[41,42,46] One of these studies also showed significantly higher PI values in the ipsilateral lung compared to the contralateral side.[42] No other studies were found that described ipsilateral PI values.

Several studies have aimed to predict postnatal outcome in CDH fetuses, that is, mortality or morbidity.[43,44,46,47] A higher mortality was observed in CDH fetuses who showed contralateral PI values outside normal ranges.[43,46,47] One of these studies was conducted in a cohort of 41 LCDH fetuses with severe pulmonary hypoplasia (O/E LHR below 26%) treated with (FETO).[43] The other two studies both evaluated LCDH fetuses which were not treated with FETO, either with severe, moderate or mild pulmonary hypoplasia ($n = 69$),[46] or only in mild and moderate cases ($n = 70$).[47] Assessment of contralateral PI was found predictive for morbidity amongst CDH patients in two studies amongst 26 and 70 LCDH fetuses, respectively (Table 2).[44,47] A higher PI value showed an association with the development of PH ($n = 70$).[47]

Evaluation of vascular reactivity of the fetal pulmonary vessels in response to increased fetal blood oxygenation was performed by measuring the PI before and after maternal hyperoxygenation (delta PI). This was assessed in two studies ($n = 38$ and $n = 40$) by Done et al. in the late second and mid-third trimesters (Table 2).[45,48] They reported a lower contralateral delta PI after maternal hyperoxygenation in non-survivors compared with survivors.[45,48] They also reported an association between lower delta PI and the occurrence of PH and neonatal oxygenation index. In addition, a lower delta PI in the late second trimester, but not in the mid-third trimester, was associated with a longer duration of high frequency oscillatory ventilation. Since the exact period of inclusion of patients in the

TABLE 1 Overview articles – Diameters of pulmonary arteries.

Parameter	Author	Year	No of CDH cases	Side of CDH			Subgroup	Isolated/complex	GA US (weeks + days)	Outcome parameters	Results
				Left	Right	Bil					
Branch diameters (observed)	Sokol	2002	26	26	0		-	Isolated	16–41	1. Survival 2. Morbidity (oxygen and ventilation requirement, >28 days hospital stay)	1. Cont-PA diameter smaller in survivors 2. Ipsi-PA diameter smaller in CDH and correlated with morbidity
	Sokol	2006	20	17	2	1	-	18 isolated 2 complex	18–37	1. Survival 2. Morbidity (oxygen and ventilation requirement, >28 days hospital stay)	1. Cont-PA diameter larger in survivors 2. Ipsi-PA diameter smaller in CDH and correlated with morbidity
	Katayama	2008	4	4	0		-	Isolated	26–38	Diameter values	Diameters correlated to GA, ratios are constant, ipsi-PA diameter smaller than average, Cont-PA diameter normal
	Beljiqi	2010	6	6	0		-	Isolated	Unknown	Diameter values	Diameters correlated to GA, ratios are constant, ipsi-PA diameter smaller than average, Cont-PA diameter normal
	Okazaki	2011	19	19	0		Liver-up	Unknown	32-34—2 days post-partum	Survival	Cont-PA diameters larger in survivors. Cont- and ipsi-PA diameters in survivors increase from third trimester to birth. Poor outcomes in PA diameters <2 mm, but better outcomes if growth is seen.
	Takahashi	2011	39	39	0		Low birth weight (LBW, ≤2500g) versus normal birth weight (NBW, >2500g)	Isolated	32–34	Survival	Diameters in LBW larger in survivors, Cont-PA diameters in LBW also larger at day 0 and day 2. Fetal PA diameters <2 mm and/or at day 0 <3 mm did not survive.
	Derderian	2016	26	17	9		Severe CDH (median LHR 0.7) FETO ($n = 5$)	Isolated	23.3 ± 3.0 (SD)	1. Survival	Cont-PA diameters larger in survivors, Cont-PA with Z-score <1.2 did not survive
Branch diameters (O/E)	Ruano	2008	21	19	2		-	Isolated	22–36	1. Survival 2. PH 3. Diameter values in CDH	1. O/E PA diameters larger in survivors 2. O/E PA diameters not associated with PH 3. Overall O/E PA diameters are reduced in CDH
	Ruano	2012	108	82	26		-	Isolated	26–30	1. Survival 2. Severe PH	1. O/E PA diameters larger in survivors 2. O/E PA diameters smaller in severe PH

Abbreviations: Bil, bilateral; CDH, congenital diaphragmatic hernia; Cont-PA, contralateral pulmonary artery; FETO, Fetoscopic Endoluminal Occlusion; GA, gestational age; GA US, gestational age at ultrasound scan in weeks + days; Ipsi-PA, ipsilateral pulmonary artery; O/E, observed/expected; O/E LHR, observed-to-expected lung-to-head ratio; PH, pulmonary hypertension.

TABLE 2 Overview articles - Vascular branching.

Parameter	Author	Year	No of CDH cases	Side of CDH			Subgroup	Isolated/ complex	GA US (weeks + days)	Outcome parameters	Results
				Left	Right	Bil					
Branch number	Mahieu-Caputo	2004	42	32	10		-	Isolated	28–37	Survival	Higher survival when ≥3 branches

Abbreviations: Bil, bilateral; CDH, congenital diaphragmatic hernia; GA, US; gestational, age at ultrasound scan in weeks + days.

second study[45] by this group was not specified in the article, duplication of included patients with their previous study[48] cannot be ruled out.

Six studies assessed the PEDRF in the proximal branches of the pulmonary arteries just distal from the first bifurcation of the main PA.[21,41–44,46,49] Both the ipsilateral and contralateral PEDRF showed a significant increase throughout gestation and a negative correlation with lung growth—expressed by the O/E LHR.[42,46] No differences in PEDRF values were observed between the ipsilateral and contralateral lungs in LCDH fetuses.[42]

Contralateral PEDRF outside normal ranges combined with an abnormal contralateral PI appeared to provide additional discriminative value for lower survival in the group of 41 LCDH fetuses with severe pulmonary hypoplasia treated with FETO.[43] This correlation was not found in a larger cohort of 69 LCDH cases without FETO, with either severe, moderate, or mild lung hypoplasia.[46] A study by Cruz-Martinez et al. showed an association between either high PI or peak-early diastolic reversed flow (PEDRF) with increased duration of ventilation, type of ventilation, duration of parental nutrition and length of stay in the intensive care unit amongst 26 LCDH neonates.[44]

An absent or reversed waveform of the end-diastolic blood flow (EDF) in the contralateral PA in fetuses with moderate or mild lung hypoplasia seemed to correlate with higher mortality ($n = 69$).[46]

Two studies reported other parameters for prenatal assessment of PA flow, that is, acceleration time/ejection time (AT/ET) ratio and time velocity integral (TVI) of the PA. TVI was suggested to be lower in CDH fetuses compared to healthy fetuses[41] and low AT/ET ratios might be correlated with lower survival in CDH fetuses.[50]

3.6 | Vascular indices

An overview of the articles concerning the analysis of vascular indices is presented in Table 4. Volume and/or flow analysis of pulmonary vessels (a combination of arteries and veins) is possible by use of 3D techniques and/or several 2D offline software applications.[38,51–54] In a cohort of both LCDH and RCDH fetuses ($n = 35$) an increase in contralateral vascularization index (VI), expressed as the Doppler-color percentage within a selected region of the contralateral lung, was found up to 4 weeks after FETO which remained stable up to 6 weeks after the intervention.[51] This increase in VI was not seen in 37 fetuses without FETO.

Three consecutive studies by the same group showed a positive association between the VI and increased survival.[38,51,52] In one study, they analyzed the flow index (FI) and vascular flow index (VFI) of both the ipsilateral and contralateral lungs combined, which also seemed positively correlated with survival.[52] In a cohort of 35 fetuses who underwent FETO, a significantly larger increase in VI was observed in survivors compared to non-survivors.[51]

Higher contralateral or ipsilateral VI, FI and VFI were found to be negatively correlated with the development of neonatal PH ($n = 108$ and $n = 21$).[38,52]

Contralateral FMBV, an offline calculation of the percentage of Power Doppler pixels in a 2D cross-sectional plane of the lung, appeared to be lower in 95 LCDH fetuses compared to controls and to be positively correlated with the O/E LHR.[53] FMBV was also shown to be negatively correlated with PI and PEDRF values.[53] However, variability in FMBV, measured before and after maternal hyperoxygenation in 5 LCDH fetuses, appeared to be high between individuals as well as within the same fetus throughout gestation.[54] In one study amongst 62 LCDH fetuses with severe lung hypoplasia, a significant association was seen between an increase in FMBV after FETO and higher neonatal survival.[55]

4 | DISCUSSION

This study provides an extensive overview of CDH-related changes in the fetal lung vasculature that can be detected by prenatal ultrasound. Congenital diaphragmatic hernia fetuses show smaller ipsilateral[31–34] and normal to smaller contralateral PA diameters[32–34,36] compared with healthy controls. In addition, contralateral PA PI and PEDRF values appear to be higher in CDH fetuses compared with healthy controls and are inversely correlated with lung size.[41,42,46] Smaller diameters,[31,35–39] higher PI values,[43,46,47] higher PEDRF values[43] of the first branch of the contralateral PA, lower VI percentages[38,51,52] and a reduction in vascular branching pattern[40] in the contralateral lung seem associated with higher mortality in CDH patients. Higher contralateral PI or PEDRF and a lower VI can be predictive of more development of PH,[38,45,47,48,52] and increased

TABLE 3 Overview articles - Doppler velocimetry.

Parameter	Author	Year	No of CDH cases	Side of CDH			Subgroup	Isolated/ complex	GA US (weeks + days)	Outcome parameters	Results
				Left	Right	Bil					
PI	Chaoui	1999	2	2	0		-	Isolated	20–23	Doppler values	PI higher in CDH compared to healthy fetuses
	Moreno-Alvarez	2008	36	36	0		-	Isolated	20–29	Correlation with O/E LHR	PI has a strong negative correlation with O/E LHR
	Cruz-Martinez	2010	41	41	0		FETO	Isolated	24–28	Survival	PI reduced in survivors, PI Z-score </> 1.0 predicts survival in group O/E LHR <26%
	Cruz-Martinez	2013	26	26	0		FETO	Isolated	26–33	Neonatal morbidity	Abnormal PI (Z-score >1.0) associated with increase in duration of mechanical ventilation, conventional ventilation, INO, higher numbers of HFV, oxygen >28 days, GER, duration of parenteral nutrition
	Cruz-Martinez	2016	90	90	0		-	Unknown	21–37	Learning curve PI measurement	Competence was achieved by 53 cases performed for the PI measurement
	Done	2011	38	30	8		Severe CDH Maternal hyper-oxygenation, FETO	Isolated	27–34	1. Survival 2. PH	1. Larger ΔPI after maternal hyper-oxygenation in survivors, all cases underwent FETO 2. Smaller ΔPI after maternal hypderox-ygenation correlated with neonatal PH, all cases underwent FETO
	Done	2015	40	33	7		Maternal hyper-oxygenation, (Partially) FETO	Isolated	26–36	1. Survival 2. Neonatal lung function (best oxygena-tion index, alveolar-arterial oxygen gradient <24 h of life, PH first 28 days of life)	1. Larger ΔPI after maternal hyper-oxygenation in survivors. No differ-ence in ΔPI between FETO and non-FETO group 2. Larger ΔPI correlated with better neonatal lung function
	Cruz-Martinez	2019	69	69	0		-	Isolated	20–38	1. Longitudinal changes in PI 2. Survival	1. GA related increase in PI 2. PI (Z-score >2.0) associated with survival
	Basurto	2021	70	70	0		-	Isolated	22.5–29.6	1. Survival 2. PH	1. PI reduced in survivors 2. PI higher in neonatal PH
PEDRF	Chaoui	1999	2	2	0		-	Isolated	20–23	Doppler values	PEDRF normal in CDH
	Moreno-Alvarez	2008	36	36	0		-	Isolated	20–29	Correlation with O/E LHR	PEDRF has a strong negative correlation with O/E LHR, especially in O/E LHR <26%

(Continues)

TABLE 3 (Continued)

Parameter	Author	Year	No of CDH cases	Side of CDH			Subgroup	Isolated/ complex	GA US (weeks + days)	Outcome parameters	Results
				Left	Right	Bil					
	Cruz-Martinez	2010	41	41	0		FETO	Isolated	24–28	Survival	PEDRF reduced in survivors, PEDRF Z-score <−3.5 or >3.5 predicts survival in group O/E LHR <26% with PI Z-score >1.0
	Cruz-Martinez	2013	26	26	0		FETO	Isolated	26–33	Neonatal morbidity	Abnormal PEDRF (Z-score >3.5) associated with increase in duration of mechanical ventilation, conventional ventilation, INO, higher numbers of HFV, oxygen >28 days, GER, duration of parenteral nutrition
	Cruz-Martinez	2016	90	90	0		-	Unknown	21–37	Learning curve PEDRF measurement	Competence was achieved by 63 cases performed for the PEDRF measurement
	Cruz-Martinez	2019	69	69	0		-	Isolated	20–38	1. Longitudinal changes in PEDRF 2. Survival	1. GA related increase in PEDRF 2. PEDRF (Z-score >2.0) not associated with survival.
EDF	Cruz-Martinez	2019	69	69	0		-	Isolated	20–38	Survival	Cases with absent/reversed EDF died. Absent/reversed EDF predicts survival in group O/E LHR >26%
AT/ET	Fuke	2003	10	9	1		-	Isolated	20–39	Survival	Cont-AT/ET <-2SD in survivors
TVI	Chaoui	1999	2	2	0		-	Isolated	20–23	Doppler values	TVI lower in CDH compared to healthy fetuses

Abbreviations: AT/ET, acceleration time/ejection time; Bil, bilateral; CDH, congenital diaphragmatic hernia; EDF, end diastolic blood flow; FETO, fetoscopic tracheal balloon occlusion; GA US, gestational age at ultrasound scan in weeks + days; GER, gastroesophageal reflux; HFV, high-frequency ventilation; INO, inhaled nitric oxide; O/E LHR, observed-to-expected lung-to-head ratio; PEDRF, peak early diastolic reverse flow; PH, pulmonary hypertension; PI, pulsatility index; SD, standard deviation; TVI, time velocity integral.

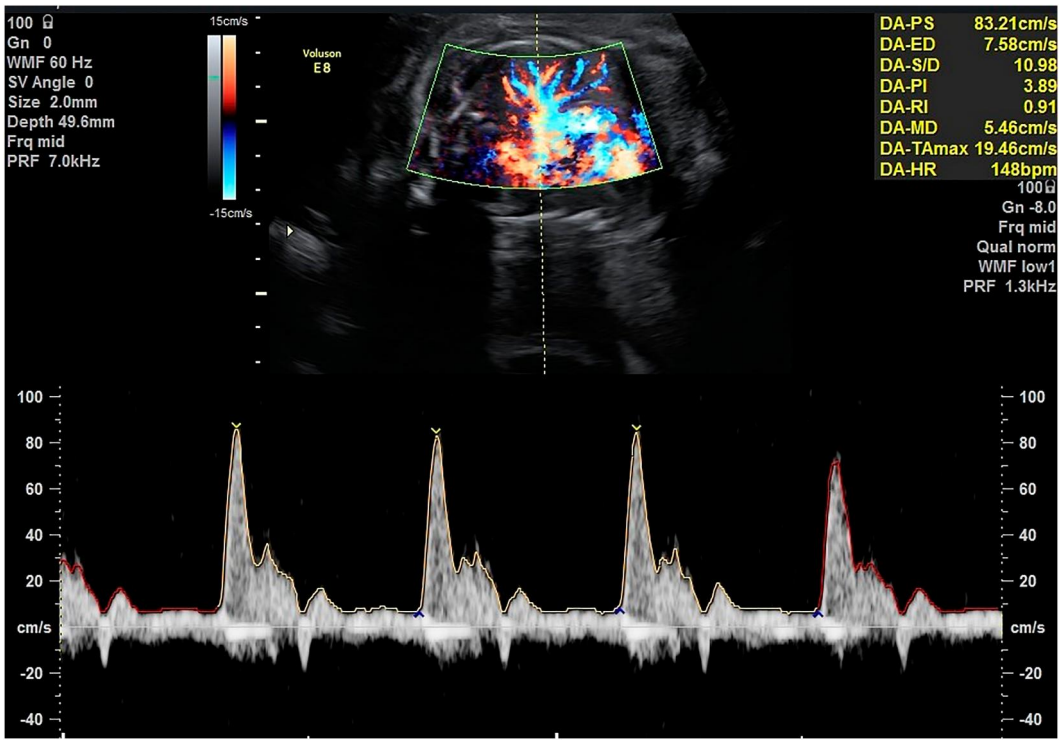

FIGURE 2 An example of the typical waveform in the most proximal branch of the pulmonary artery used for the assessment of the pulsatility index (PI), peak early-diastolic reverse flow, the waveform of the end-diastolic blood flow, acceleration time/ejection time ratio and time velocity integral. Ultrasound image from the Erasmus University Medical Center.

duration of ventilation, type of ventilation, increased duration of parental nutrition and longer length of stay in the intensive care unit.[44,47]

The development of PH associated with CDH is thought to be the result of (I) a disordered process of vascular maldevelopment and remodeling of the vascular bed, which leads to (II) a reduction in the pulmonary vascular cross-sectional area and (III) an altered vascular reactivity.[56]

The disordered process of vascular remodeling in CDH is characterized by changes in the phenotype of vascular cell types in the lung, altered proliferation of cells and defective cellular communication.[57] Vascular smooth muscle cells (SMCs) may differentiate prematurely and distribute more distally, resulting in a more contractile phenotype of the pulmonary vascular tree.[13] In addition, an increased pericyte coverage was observed in the large pulmonary vessels of mice, which also contributes to a higher contractility of these vessels.[11] A third component was shown in lamb and mouse CDH models, where SMCs and pericytes showed defective communication with endothelial cells, which might be at the basis of the altered phenotype and aberrant distribution of perivascular cells.[11,58] The more contractile phenotype of the vessels may be reflected by an increased resistance of the fetal vascular bed and could be measured by the PI together with a reduced cross-sectional area. It is debatable whether PI in the main branch of the PA reflects higher resistance downstream of the vascular tree, as prenatally the ductus arteriosus diverts blood flow away from the pulmonary vascular bed, which can cause alterations in the resistance measured just before the duct, that is, in the main branch of the PA.

Vascular maldevelopment and remodeling leads to a reduced total cross-sectional area of the pulmonary vascular tree, observed in animal CDH models (mouse, rat, rabbit and lamb) as well as human CDH neonates. There is a clear reduction in the number of vessels and a more primitive vascular tree of the lung, as shown by reduced branching of especially the smaller arteries.[11,58–61] Also, an increased coverage by perivascular cells is seen that differentiate into vascular SMCs, resulting in pulmonary vessels with an increased vascular wall thickness.[11,62] As a consequence, a significantly decreased internal diameter of pulmonary arteries was found in a study with nitrofen-induced CDH in rat pups compared to non-CDH pups.[63] Smaller lumina of pulmonary veins have also been observed in human neonates with CDH complicated by PH compared to patients with sudden infant death syndrome as age-matched controls.[64] Additional studies that directly measured luminal diameters in human neonates are scarce. Based on these findings, there seems to be a pathophysiological reason to evaluate PA diameters in CDH fetuses and to use these measurements in an attempt to predict the degree of pulmonary vascular dysfunction. The simplified vascular network could also support lower vascular volumes observed with ultrasound VI measurements.

TABLE 4 Overview articles—Vascular indices.

Parameter	Author	Year	No of CDH cases	Side of CDH			CDH subgroup	Isolated/ complex	GA US (weeks + days)	Outcome	Results
				Left	Right	Bil					
VI	Ruano	2006	21	19	2		-	Isolated	23–33	1. Survival 2. PH	1. Higher Cont-VI and VI in both lungs in survivors 2. Lower Cont-VI and VI in both lungs in neonatal PH, reduction in VI correlated to severity of PH (severe, moderate or absent)
	Ruano	2012	72	50	22		FETO	Isolated	30–36	1. Survival 2. Change in VI before-after FETO	1. Higher increase after FETO in Cont-VI in survivors, 4 weeks after FETO Cont-VI 2. Cont-VI increases significantly after FETO
	Ruano	2012	108	82	26		-	Isolated	26–30	1. Survival 2. PH	1. Higher Cont-VI in survivors, highest predictive value (compared to LHR, O/E LHR, lung volumes, diameters) 2. Smaller Cont-VI in PH
FI	Ruano	2006	21	19	2		-	Isolated	23–33	1. Survival 2. PH	1. Cont-FI not different between survivors/non survivors, FI in both lungs reduced in survivors 2. Cont-FI not different between PH/no PH, FI in both lungs reduced in PH
VFI	Ruano	2006	21	19	2		-	Isolated	23–33	1. Survival 2. PH	1. Higher Cont-VFI and VFI in both lungs in survivors 2. Lower Cont-VFI and VFI in both lungs in neonatal PH, reduction in VFI correlated to severity of PH (severe, moderate or absent)
FMBV	Cruz-Martinez	2010	62	62	0		FETO	Isolated	26–36	Survival	Higher FMBV after FETO in survivors compared to non-survivors, no difference before FETO between both groups.
	Moreno-Alvarez	2010	95	95	0		-	Isolated	27.9 ± 2.5 (SD)	1. FMBV values in CDH 2. Correlation with O/E LHR	1. FMBV lower in CDH compared to controls 2. FMBV positively correlated to O/E LHR
	DeKoninck	2014	5	5	0		Maternal hyper-oxygenation	Isolated	28.6 (IQR: 1.9)	Variability FMBV in response to maternal hyperoxygenation	Large variability in FMBV between and within fetuses

Abbreviations: Bil, bilateral; CDH, congenital diaphragmatic hernia; FETO, fetoscopic tracheal balloon occlusion; FI, flow index; FMBV, fractional moving blood volume; GA, gestational age; GA US, gestational age at ultrasound scan in weeks + days; O/E LHR, observed-to-expected lung-to-head ratio; PH, pulmonary hypertension; SD, standard deviation; VFI, vascular flow index; VI, vascularization index.

Ultrasonographic assessment of vascular branching patterns in CDH fetuses remains limited, however, since we can only visualize the most proximal branches with power Doppler.

Vascular reactivity is difficult to assess prior to birth given the vasoconstrictive state of the fetal lungs. Expression of the vasoconstrictor endothelin-1 (ET-1) was increased in PA endothelial cells and SMCs in lungs of surgically induced CDH lambs and nitrofen-induced CDH rat pups.[58,62,65] Plasma ET-1 levels were also increased in human CDH neonates with PH compared to CDH patients without PH, indicating that ET-1 can possibly be used as a predictive marker for vasoconstriction.[66,67] Functional testing such as maternal hyperoxygenation tests would make sense to study vasoconstriction, but are limited by its clinical applicability and the absence of normograms.[48]

This review was limited by a lack of uniformity between the methods used in the included studies, which hinders the recommendations for the integration of these parameters within routine prenatal evaluation of CDH. Standardized prenatal settings for 3D power Doppler indices and clear definitions of postnatal outcomes, for example, a uniform classification of PH, will contribute to the interpretation and applicability of promising prenatal ultrasound parameters. We studied only ultrasound techniques and did not include other imaging modalities such as magnetic resonance imaging (MRI). At this time fetal MRI is not yet capable of evaluating the fetal vasculature, but could be of added value in the future if more developed.[68]

The majority of the included studies on PI and PEDRF values concern CDH cases with severe pulmonary hypoplasia, and only one study was found that evaluated these parameters exclusively in moderate and mild cases.[47] For future studies, it would be important to report on CDH fetuses with less severe pulmonary hypoplasia as well as to make more generalizable statements for CDH fetuses. Also, the characteristics of the end diastolic blood flow were assessed only in one study, yet there appears to be a strong correlation with survival.[46] This observation certainly warrants further investigation in larger series and also its use in predicting postnatal morbidity. The available studies primarily focus on the assessment of arterial function, but we hypothesize that the assessment of venous functional parameters may provide important additional insights concerning vascular development in CDH. The entire vascular tree is affected in CDH and pulmonary veins can be visualized rather easily by prenatal ultrasound. Another potentially interesting, but underexposed part of the structural assessment appeared to be the number of branches of the pulmonary vascular tree.[59] In this review, only one study suggested this as a promising marker as it reported that a reduction in branching pattern was associated with higher mortality. Potentially, other Doppler techniques such as SlowflowHD™ (Voluson E10 BT19; GE Healthcare, Zipf, Austria) might identify the entire vascular tree, including the aberrant developing smaller capillaries, and add to the assessment of the branching number in the peripheral lung.[69]

5 | CONCLUSION

In conclusion, based on the available evidence, we acknowledge an added value of assessing the pulmonary vasculature in CDH fetuses for the prediction of survival and, to a lesser extent, morbidity, although its integration within the routine evaluation is complicated by the lack of uniformity of the methods used. To address the main components of the reported pathophysiological changes, we recommend future prenatal studies in CDH to focus on PI values, PA diameters and pulmonary vascular branching.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are available on request from the corresponding author.

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