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Published in:
Prenatal Diagnosis

Publication status and date:
Published: 01/11/2024

DOI (link to publisher):
10.1002/pd.6672

Document Version
Publisher's PDF, also known as Version of record

Prenatal Diagnosis

WILEY

PRENATAL DIAGNOSIS

REVIEW OPEN ACCESS

Fetal Speckle Tracking Echocardiography Measured Global Longitudinal Strain and Strain Rate in Congenital Heart Disease: A Systematic Review and Meta-Analysis

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Received: 7 June 2024 | **Revised:** 23 August 2024 | **Accepted:** 4 September 2024

Funding: The authors received no specific funding for this work.

Keywords: fetal echocardiography | fetal imaging | fetal ultrasound | prenatal | ultrasonography

ABSTRACT

Fetal two-dimensional speckle tracking echocardiography (2D-STE) is a novel technique that provides information on fetal heart function by measuring global longitudinal strain (GLS) and global longitudinal strain rate (GLSR). These features assess the longitudinal deformity of the fetal cardiac wall. 2D-STE is shown to be of prognostic value in children and adults with congenital heart disease (CHD). Therefore, its importance in fetal life should also be considered. This systematic review and meta-analysis provides an overview of the literature on 2D-STE (GLS/GLSR) in fetuses with CHD, focusing on the left and right ventricles (LV/RV). Findings indicated that LV-GLS was significantly lower in fetuses with coarctation of the aorta (CoA) and Tetralogy of Fallot (ToF) compared to controls. Conversely, fetuses with a single left ventricle exhibited higher LV-GLS. RV-GLS was significantly lower in fetuses with hypoplastic left heart syndrome (HLHS) and ToF compared to controls. LV-GLSR was significantly lower in fetuses with CoA. Overall, considerable heterogeneity was observed, possibly due to differences in study design. More prospective longitudinal studies on 2D-STE in fetuses with CHD, considering heterogeneity parameters, could offer better insights into this promising technique.

1 | Introduction

Prenatal echocardiography allows structural and functional assessment of the fetal heart. While structural cardiac examination is an integral part of the routine ultrasound, myocardial function assessment is less common. Myocardial muscle fibers, arranged in a helical structure, result in a systolic twist and diastolic untwist along the ventricular axis [1–5]. Two-dimensional–Speckle Tracking Echocardiography (2D-STE) is a novel technique analyzing 2D-ultrasound cardiac recordings with software that tracks characteristic ultrasonic markers (speckles) during systole and diastole. It allows assessment of global longitudinal strain (GLS) and strain rate (GLSR), reflecting myocardial deformation during the cardiac cycle as

Summary

- **What's already known about this topic?**
  - Two-dimensional speckle tracking echocardiography (2D-STE) has shown its clinical relevance in functional heart assessment of both pediatric and adult populations.
  - Recent literature has confirmed its importance in patients with congenital heart disease (CHD) as strain and strain rate are associated with outcomes in different CHDs.
- **What does this study add?**
  - This study provides a literature overview of speckle tracking echocardiography measured strain and strain rate in fetuses with CHD. To date, no systematic review or meta-analysis has been published in this specific patient population.
  - It highlights speckle tracking echocardiography's diagnostic and monitoring potential in fetuses with CHD. Furthermore, it underscores the importance of specific factors, such as, frame rate and software, when comparing and measuring strain and strain rate measurements.

a percentage from its initial length ([systolic length-diastolic length]/diastolic length (%)) and its corresponding rate (s^{-1}) [4, 6–8]. They are the parameters of ventricular function [9].

2D-STE has shown clinical relevance in functional heart assessment in adults and children [10]. Recent reports have confirmed its importance in patients with congenital heart disease (CHD) [11]. Research in fetuses is emerging in both physiological and pathological conditions [3, 10, 12–18]. 2D-STE in fetuses has major attractions by analyzing greyscale images and being technically feasible in different fetal positions, provided the myocardium is adequately visualized. However, technical challenges include image quality, which in turn is impacted by fetal lie, acoustic shadows, and maternal factors. Additionally, the high fetal heart rate requires high frame rate (optimally $\geq$ 80 Hz) recordings to permit reliable strain analysis. Recent improvements in ultrasound devices allowing good image resolution at high frame rates have made fetal 2D-STE more technically feasible [15].

Moreover, 2D-STE can potentially detect subclinical changes in myocardial strain and strain rate in CHD fetuses, which might provide further insights into the impact of CHD on cardiac function, the impact of such differences on postnatal outcome, and to gauge the impact of prenatal or postnatal intervention [19–21]. As 2D-STE is shown to be of prognostic value in CHD in children and adults, its importance in fetal life should also be considered.

Our aim was to summarize the current knowledge on 2D-STE (GLS/GLSR) in fetuses with CHD through a systematic literature review. Additionally, a meta-analysis per CHD subtype was conducted to provide pooled estimates of mean GLS/GLSR differences between CHD fetuses and controls.

2 | Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement and the Cochrane Collaboration [22–25], and was registered in the international prospective register of systematic reviews (PROSPERO 2023 CRD42023466868).

2.1 | Data Collection

In October 2021, a systematic literature search was performed with the assistance of an information specialist of the Erasmus MC Medical Library using the following literature databases: EMBASE, Medline ALL Ovid, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials. The literature search was updated in October 2022, September 2023, and August 2024. Supporting Information S1: Appendix S1 provides an overview of the complete search strategies.

Article selection was performed by two independent reviewers (SvdW and MH). After the removal of duplicates, the articles were screened for title and abstract. The remaining articles were read and assessed for eligibility in full text. Moreover, citation tracking, including forward and backward reference searching, was performed.

Studies written in the English language, using speckle tracking (e.g., 2D-STE or Velocity Vector Imaging [VVI]) to measure or describe GLS and/or GLSR in the left ventricle (LV) and/or right ventricle (RV) in fetuses with CHD and/or congenital arrhythmia, with or without a control population, were included in this review. Reviews, case reports, and case series with less than five cases, as well as abstracts and reports without published full text manuscript (e.g., conference abstracts), were excluded.

If the two reviewers (SvdW and MH) could not come to an agreement on eligibility, a third independent reviewer (JC) was consulted. All articles that matched up to the inclusion criteria after full text examination were included in the systematic review.

2.2 | Data Extraction and Outcomes

The following study characteristics were retrieved from the included articles: author, year of publication, study type, type of CHD, ultrasound timing, study population size, gestational age (GA), fetal heart rate, ultrasound device, speckle tracking software, and frame rate.

The articles were categorized based on the examined CHD type [26], resulting in the following nine subtypes: multiple CHD/other, hypoplastic left heart syndrome (HLHS), single ventricle (SV), coarctation of the aorta (CoA), transposition of the great arteries (TGA), pulmonary atresia (PA), tricuspid valve malformation (TVM), Tetralogy of Fallot (ToF), and ductus arteriosus constriction (DAC).

Articles were checked on how certain features of CHD, such as a ventricular septal defect (VSD) or atrioventricular valve regurgitation, were considered in their speckle tracking analysis, given their potential impact on deformation outcomes [9].

The outcomes of interest of this research were the LV-GLS and/or RV-GLS and/or GLSR of fetuses with CHD and/or congenital arrhythmia using a speckle tracking technique (e.g., 2D-STE or VVI). These outcomes were reported either in quantitative values (e.g., mean, median) or descriptively (e.g., lower, higher, or equal to compared to control fetuses).

GLS is largely investigated prenatally due to its ease of measurement from a four-chamber view. In contrast, the global radial strain (GRS) poses challenges due to the thin fetal myocardium, whereas for the global circumferential strain (GCS), it is more difficult to determine a similar level for comparison [27]. GLS measures the systolic shortening of the endocardium, resulting in negative strain values [4, 7] and lower strain (i.e., less negative) indicates less shortening [28].

For unclear descriptive or quantitative results, the corresponding authors were contacted for additional information or raw data. Two authors responded, providing further insights or data [6, 8, 27–30].

A meta-analysis per subtype of CHD was conducted on the differences in the mean values of GLS/GLSR between fetuses with CHD and controls. Factors influencing heterogeneity, such as GA, ultrasound device, software and frame rate were identified. Study designs were compared to identify disparities and similarities. Sub-analyses were conducted on studies with comparable GA, ultrasound device, software and frame rate, aiding in understanding heterogeneity sources in this meta-analysis.

2.3 | Quality Assessment

The quality and risk of bias of the included articles were evaluated using the Newcastle-Ottawa Scale (NOS). Two independent reviewers (SvdW and MH) conducted this assessment. NOS evaluates studies based on three main categories: selection of the study group, comparability of the cases and controls, and assessment of the exposure. Articles could receive up to 9 stars, with scores categorized as follows: 0–3 stars indicated low quality with a high risk of bias, 4–6 stars indicated medium quality with moderate risk of bias, and 7–9 stars indicated high quality with low risk of bias [23, 31, 32]. Only articles with medium or high quality and moderate or low risk of bias, respectively, were included in this review.

2.4 | Statistical Analysis and Meta-Analysis

A qualitative description of the findings was provided and, if possible, quantitative descriptions were given. If applicable, comparison data on LV-GLS, RV-GLS, LV-GLSR, and RV-GLSR between fetuses with CHD and healthy controls was performed using a Welch's *t*-test, resulting in a significant or non-significant difference. The corresponding *p*-value was given. If studies did not include controls, only data on CHD fetuses were reported without comparative analysis.

Meta-analyses were conducted to provide pooled estimates of the reported differences in the mean values of GLS (%) and/or GLSR between fetuses with CHD and controls for the different CHD subtypes. A random-effects model was applied and pooled estimates were reported with a confidence interval (CI) and *p*-value. Median values of GLS or GLSR were converted to mean values when necessary, assuming that the median equaled the mean, to include this data in the meta-analysis. The I^2 statistic assessed the proportion of variation in study outcomes due to heterogeneity [33], while the Chi-squared test evaluated homogeneity to determine the comparability between studies and the impact of different factors (GA, ultrasound device, software and frame rate). IBM SPSS version 28.0.1.0 was used. A $p < 0.05$ was considered significant. To conduct a meta-analysis within a specific CHD subtype, quantitative data from at least two studies were required.

3 | Results

3.1 | Article Selection

The systematic database search yielded a total of 804 records (351 on EMBASE, 209 on Medline ALL Ovid, 241 on Web of Science Core Collection and three on the Cochrane Central Register of Controlled Trials). After removing duplicates, 416 articles remained for title and abstract screening (Supporting Information S1: Appendix S2). Of these, 95 articles were found eligible and were read in full text by SvdW and MH. Six articles were excluded because there was no GLS and/or GLSR in their outcome, 10 articles were excluded based on their study type, 37 articles were excluded as they were conference abstracts, five articles were excluded because the full text was not available, and one article was excluded for not including fetuses with CHD and/or congenital arrhythmia. This resulted in 36 articles meeting the inclusion criteria and being included in this systematic review. No additional articles were identified through citation searching. Supporting Information S1: Figure S1 provides a flowchart of the article selection process.

3.2 | Study Characteristics

Tables 1a–1e portray the study characteristics of the 36 included articles, categorized by CHD subtypes. The final quality assessment score using NOS is provided in the last column. For three studies, the NOS for case-control studies was not applicable (N/A) due to the absence of controls [46, 47, 56]. No studies were excluded based on quality assessment score. Detailed scores per category can be found in Supporting Information S1: Appendix S4.

Nine studies used a prospective study design [12, 19, 34, 36–38, 45, 51, 53], while 27 used a retrospective design [6, 8, 9, 21, 27–30, 35, 39–44, 46–50, 52, 54–59]. In total, 12 different ultrasound devices and five different speckle tracking softwares were used.

TABLE 1a | Study characteristics.

First author	Year of publication	Study type	Type of congenital heart disease (CHD)	Echocardiograms time frame (years)	Study population (CHD/control)	GA in weeks (mean ± SD [range]; median (IQR))	Heart rate (HR) (beats/min)	Ultrasound device	Speckle tracking software	Frame rate (frames/s) (Hz)	Quality assessment (NOS)
Multiple congenital heart disease (CHD)/other											
1. Barker [12]	2009	Prospective	Congenital heart disease (CHD)	N/R	48 (15/33)	24 (17–38)	N/R	N/R	Syngo VVI (Siemens)	N/R	6
2. DeVore [6]	2018	Retrospective	Congenital heart disease (CHD)	N/R	210 (10/200)	Control: 20–40 weeks CHD: N/R	Control: 144 ± 10 CHD: N/R	Voluson E10 (GE)	2D-STE (TomTec)	Control: 109 ± 23 CHD: N/R	5
3. Drop [19]	2019	Prospective	Congenital heart disease (CHD)	October 2013–September 2016	128 (23/105)	Control: 28.9 ± 5.7 CHD: 31.8 ± 6.6 $p = 0.034$	N/R	EPIQ 7 (Philips)	QLAB 10.5 (Philips)	Control: 191.0 (158.0–199.0) CHD: 197.0 (162.0–199.0) $p = 0.690$	6
4. Germanakis [34]	2012	Prospective	Congenital heart disease (CHD)	N/R	172 (28/144)	Control: 25.4 CHD: 25.7 $p = 0.852$	Control: 145 CHD: 143 $p = 0.351$	Acuson Sequoia (Siemens)	Syngo VVI (Siemens)	Control: 77 CHD: 66 $p = 0.068$	8
5. Li [35]	2023	Retrospective	Congenital heart disease (CHD) leading to LV or RV afterload increased (LVA/RVA)	July 2015–December 2018	89 (48/41) 25 LVA, 23 RVA	Control: 25.96 ± 2.92 LVA: 25.52 ± 3.08 RVA: 26.13 ± 3.71 $p > 0.05$	Control: 148 ± 7 LVA: 148 ± 10 RVA: 145 ± 10	Vivid E95 (GE)	EchoPac 201 (GE)	Control: 186 ± 47 LVA: 156 ± 42 ($p = 0.06$) RVA: 167 ± 42 ($p = 0.05$)	6
6. Lou [36]	2024	Prospective	Severe tricuspid regurgitation	June 2020–May 2022	60 (20/40)	Control: 25.6 ± 2.3 CHD: 26.2 ± 2.3	N/R	Voluson E10 (GE)	Fetal HQ (GE)	> 80	5
7. Luo [37]	2021	Prospective	Abnormal fetal heart structure, blood flow, and/or heart rhythm	July 2020–December 2020	109 (50/59)	28.0 ± 3.5 [21.6–36.6]	N/R	EPIQ 7C (Philips)	QLAB (Philips)	> 80	5
8. Willruth [38]	2012	Prospective	Left heart obstruction (LHO); tetralogy of Fallot (TOF); double outlet right ventricle (DORV)	N/R	41 (17/24)	Control: 27 (21–36) CHD: 28 (21–36)	Control: 146 (127–164) CHD: 140 (127–163)	Acuson S2000 (Siemens)	Syngo VVI (Siemens)	Control: 100 (91–143) CHD: 100 (83–167)	6

Note: Data given in mean ± SD [range] or median (IQ-range).
Abbreviation: N/R = not reported.

TABLE 1b | Study characteristics.

Author	Year	Study type	Congenital heart disease (CHD)	Echocardiograms time frame (years)	Study population (CHD/control)	GA in weeks (mean ± SD [range]; median (IQR))	Heart rate (HR) (beats/min)	Ultrasound device	Speckle tracking software	Frame rate (frames/s) (Hz)	Quality assessment (NOS)
Hypoplastic left heart syndrome (HLHS)											
9. Brooks [39]	2012	Retrospective	Hypoplastic left heart syndrome (HLHS)	February 2003–March 2011	96 (48/48)	Control: 28.1 ± 6.4 CHD: 27.9 ± 6.2 $p = 0.90$	Control: 138 ± 9 CHD: 139 ± 12 $p = 0.66$	Phillips iE33, Voluson E8 (GE), Acuson S2000 (Siemens)	Syngo VVI (Siemens)	30	6
10. Cox [40]	2022	Retrospective	Left heart hypoplasia (LHH)	February 2014–January 2015	18 (9/9)	Control: 27.8 ± 5.1 CHD: 31.0 ± 4.0 $p = 0.094$	N/R	N/R	Syngo VVI (Siemens)	30	6
11. Enzensberger [41]	2022	Retrospective	Hypoplastic left heart (HLH)	August 2012–March 2018	142 (41/101)	Control: 26.0 ± 5.6 CHD: 29.1 ± 5.6	N/R	Toshiba Artida, Aplio 500 Aplio i900 (Toshiba)	2D-STE (TomTec)	N/R	6
12. Ishii [42]	2014	Retrospective	Valvar aortic stenosis/evolving HLHS	2000–2010	138 (57/81)	24.1 ± 2.4	HR did not differ between control and CHD	Acuson Sequoia (Siemens), Sonos 5500 (Philips), Philips iE33	Syngo VVI (Siemens)	30 (30–50)	5
13. Ma [43]	2022	Retrospective	Hypoplastic left heart syndrome (HLHS)	2016–2021	84 (42/42)	Control: 24.67 ± 3.34 CHD: 24.49 ± 3.88 $p = 0.31$	N/R	Voluson E10 and E8 (GE)	2D-STE (TomTec)	N/R	6
14. Miller [44]	2012	Retrospective	Hypoplastic left heart syndrome (HLHS)	October 2007–March 2011	60 (30/30)	Control: 30.5 ± 3.5 CHD: 30.6 ± 3.5	N/R	Acuson Sequoia 512 (Siemens), Philips iE33	Syngo VVI (Siemens)	25–50	6
15. Patey [45]	2024	Prospective	Hypoplastic left heart syndrome (HLHS)	2011–2020	52 (35/17)	Control: 37.9 ± 0.7 CHD: 37.5 ± 1.3	Control: 138 ± 9 CHD: 132 ± 10	Vivid-iQ/Q/E9/E95	Echopac 112 (GE)	> 100	6
16. Reitz [46]	2024	Retrospective	Critical aortic stenosis	2011–2020	23 (23/0)	26	141	Philips IU22, Epique Elite and Voluson E10 (GE)	2D-STE (TomTec)	47 (32–87)	N/A[a]
17. Wilkes [47]	2022	Retrospective	Hypoplastic left heart syndrome (HLHS)	November 2015–November 2019	60 (60/0)	28.4 (26.6–30.5)	N/R	N/R	2D-STE (TomTec)	30.6 ± 5.6	N/A[a]

Note: Data given in mean ± SD [range] or median (IQ-range).
Abbreviations: N/A = not applicable, N/R = not reported.
[a]Absence of controls.

TABLE 1c | Study characteristics.

Author	Year	Study type	Congenital heart disease (CHD)	Echocardiograms time frame (years)	Study population (CHD/control)	GA in weeks (mean ± SD [range]; median (IQR))	Heart rate (HR) (beats/min)	Ultrasound device	Speckle tracking software	Frame rate (frames/s) (Hz)	Quality assessment (NOS)
Single ventricle (SV)											
18. Brooks [48]	2014	Retrospective	Single (left) ventricle (SV)	February 2003–March 2011	77 (29/48)	Control: 28.1 ± 6.4 CHD: 26.0 ± 5.0 $p = 0.15$	Control: 138 ± 9 CHD: 139 ± 12 $p = 0.66$	Philips iE33, Voluson E8 (GE), Acuson S2000 (Siemens)	Syngo VVI (Siemens)	30	6
19. Truong [9]	2013	Retrospective	Single (left and right) ventricle (SV)	November 2007–March 2012	108 (54/54)	Control: 28.1 ± 6.3 CHD: 28.2 ± 6.3	N/R	Sequoia C512 (Siemens), Philips iE33	Syngo VVI (Siemens)	30	6
Coarctation of the aorta (CoA)											
20. Amar [49]	2024	Retrospective	Coarctation of the aorta (CoA)	October 2013–May 2022	75 (16/59)	Control (FP): 33 (26–35) CHD: 27 (22–28) $p = 0.09$	Control (FP): 146 ± 13 CHD: 151 ± 13 $p = 0.27$	Vivid E9/E95 (GE)	2D-STE (TomTec)	30	5
21. DeVore [30]	2021	Retrospective	Coarctation of the aorta (CoA)	N/R	254 (54/200)	Control: 20–40 TP: 32 + 2 ± 3 + 6 (last examination)	Control: 144 ± 10 CHD: N/R	Voluson E10 (GE)	2D-STE (TomTec)	Control: 109 ± 23 CHD: N/R	5
22. DeVore [8]	2020	Retrospective	Coarctation of the aorta (CoA)	N/R	250 (50/200)	Control: 20–40 CHD: 33 ± 3.15 [23–37]	Control: 144 ± 10 CHD: N/R	Voluson E10 (GE)	2D-STE (TomTec)	Control: 109 ± 23 CHD: > 20 frames per cardiac cycle	5
23. Liu [21]	2022	Retrospective	Coarctation of the aorta (CoA)	January 2016–June 2020	122 (62/60)	Non-CoA: 27.8 (24.5–30.4) CoA: 24.5 (23.3–26.4) $p < 0.001$	Non-CoA: 147 ± 8 CoA: 147 ± 8 $p = 0.624$	Voluson E10 (GE)	Fetal HQ (GE)	70	6
24. Miranda [27]	2017	Retrospective	Coarctation of the aorta (CoA)	January 2013–July 2014	24 (12/12)	25 + 4 (19 + 1 − 33 + 1)	Control: 129 CHD: 139 $p = 0.01$	Aplio 500 (Toshiba)	2D-STE (TomTec)	Control: 60 CHD: 54 $p = 0.31$	7
25. Moras [50]	2023	Retrospective	Shone's complex (SC) and simple-coarctation of the aorta (S-CoA)	January 2010–June 2021	Total: 109 SC: 17 S-CoA: 24 FP-CoA: 34 Control: 34	SC: 29.5 S-CoA: 30.6 FP-CoA: 30.7 Control: 29.8 $p = 0.785$	N/R	EPIQ CVx (Philips)	2D-STE (TomTec)	N/R	6
26. Zeng [51]	2017	Prospective	Small aortic isthmus at risk for coarctation (CoA)	January 2012–December 2014	96 (48/48)	Control: 30.1 ± 2.9 CHD: 30.1 ± 2.9	N/R	Acuson Sequoia 512 (Siemens)	Syngo VVI (Siemens)	40–50	7

Note: Data given in mean ± SD [range] or median (IQ-range).
Abbreviations: FP = false positive, N/R = not reported, TP = True positive.

TABLE 1d | Study characteristics.

Author	Year	Study type	Congenital heart disease (CHD)	Echocardiograms time frame (years)	Study population (CHD/control)	GA in weeks (mean ± SD [range]; median (IQR))	Heart rate (HR) (beats/min)	Ultrasound device	Speckle tracking software	Frame rate (frames/s) (Hz)	Quality assessment (NOS)
Transposition of the great arteries (TGA)											
27. DeVore [29]	2023	Retrospective	D-transposition of the great arteries (D-TGA)	N/R	239 (39/200)	Control: 20–40 CHD: 29 [20–39]	Control: 144 ± 10 CHD: N/R	N/R	2D-STE (TomTec)	Control: 109 ± 23 CHD: N/R	5
28. Lin [52]	2022	Retrospective	Transposition of the great arteries (TGA)	August 2015–November 2019	127 (78/49) d-TGA 49, TBA 29	Control: 25.09 ± 1.13 d-TGA: 24.52 ± 2.82 TBA: 24.42 ± 1.84 $p = 0.129$	Control: 148.90 ± 7.18 d-TGA: 149.12 ± 8.43 TBA: 146.38 ± 6.46 $p = 0.257$	Voluson E8/E10 (GE)	Syngo VVI (Siemens)	60–80	6
29. Patey [53]	2021	Prospective	Simple transposition of the great arteries (TGA)	July 2014–September 2016	67 (13/54)	Control: 38 (37–39) CHD: 38 (37–38) $p = 0.129$	Control: 138 ± 9 CHD: 141 ± 11	Vivid E9 (GE)	EchoPAC 112 (GE)	> 100	6
30. Young [54]	2024	Retrospective	D-transposition of the great arteries (D-TGA) and atrioventricular canal defects (AVC)	2010–2021	72 (46/26) D-TGA: 15 AVC: 31	Control: 25.8 ± 4.2 D-TGA: 27.9 ± 2.7 AVC: 26.1 ± 3.1	N/R	N/R	2D-STE (TomTec)	> 40	6
Pulmonary atresia (PA)											
31. Cohen [55]	2019	Retrospective	Pulmonary atresia and intact ventricular septum (PA/IVS)	January 2005–October 2017	114 (57/57)	26.5 ± 5	N/R	Philips iU22, Acuson Sequoia (Siemens)	2D-STE (TomTec)	42 (30–75)	6

Note: Data given in mean ± SD [range] or median (IQ-range).
Abbreviations: d-TGA = complete transposition of the great arteries, N/R = not reported, TBA = Taussig Bing anomaly.

TABLE 1e | Study characteristics.

Author	Year	Study type	Congenital heart disease (CHD)	Echocardiograms time frame (years)	Study population (CHD/control)	GA in weeks (mean ± SD [range]; median (IQR))	Heart rate (HR) (beats/min)	Ultrasound device	Speckle tracking software	Frame rate (frames/s) (Hz)	Quality assessment (NOS)
Tricuspid valve malformation (TVM)											
32. Ishii [56]	2012	Retrospective	Ebstein malformation or congenital TV dysplasia	2004–2010	16 (16/0)	29.3 ± 5.2	N/R	N/R	Syngo VVI (Siemens)	30	N/A[a]
33. Liu [57]	2022	Retrospective	Tricuspid valve malformation (TVM)	January 2016–December 2020	168 (88/80) EA 40, TVD 48	Control: – 2nd trimester (n = 40): 24.86 ± 0.74 – 3rd trimester (n = 40): 29.60 (28.70–30.90) TVM-N: – 2nd trimester (n = 23): 24.71 ± 1.55 – 3rd trimester (n = 26): 30.25 (28.95–33.13) TVM-R/A: – 2nd trimester (n = 24): 24.26 ± 1.86 – 3rd trimester (n = 23): 31.00 (29.10–32.50)	Control: – 2nd trimester (n = 40): 151 ± 5 – 3rd trimester (n = 40): 146 ± 7 TVM-N: – 2nd trimester (n = 23): 149 ± 7 – 3rd trimester (n = 26): 148 ± 10 TVM-R/A: – 2nd trimester (n = 24): 149 ± 4 – 3rd trimester (n = 23): 146 ± 8	Voluson E10 (GE)	2D-STE (TomTec)	> 50	7
Tetralogy of Fallot (TOF)											
34. DeVore [28]	2022	Retrospective	Tetralogy of Fallot (TOF)	N/R	244 (44/200)	Control: 20–40 CHD: 28 + 5 ± 4 + 4	Control: 144 ± 10 CHD: 154 ± 11	Voluson E10 (GE)	2D-STE (TomTec)	Control: 109 ± 23 CHD: 84 ± 21	5
35. Song [58]	2021	Retrospective	Tetralogy of Fallot (TOF)	January 2014–December 2020	104 (52/52)	Control: 24.4 (23.2–26.0) CHD: 24.4 (23.2–26.5) p = 0.84	Control: 147.1 ± 6.0 CHD: 146.8 ± 7.6 p = 0.84	Voluson E10 (GE)	2D-STE (TomTec)	N/R	6
Ductus arteriosus constriction (DAC)											
36. Ma [59]	2022	Retrospective	Ductal arteriosus constriction (DAC)	January 2016–April 2022	120 (60/60)	Control: 28.30 ± 3.27 CHD: 30.74 ± 3.76	N/R	Voluson E10 and E8 (GE)	Fetal HQ (GE)	N/R	6

Note: Data given in mean ± SD [range] or median (IQ-range).
Abbreviations: EA = Ebstein anomaly, N = normal, N/A = not applicable, N/R = not reported, R/A = reduced/absent, TP = True positive, TVD = tricuspid valve dysplasia.
[a]Absence of controls.

A frame rate of >80 Hz in both CHD as controls was documented in only eight studies [19, 28, 35–38, 45, 53]. In the remaining studies, frame rates were either lower [9, 21, 27, 34, 39, 40, 42, 44, 47–49, 51, 52, 54–57], especially in fetuses with CHD [8], or not described [6, 12, 29, 30, 41, 43, 50, 58, 59]. Only three studies did not include healthy controls [46, 47, 56].

Regarding CHD-specific features, none of the studies investigating CHD with a VSD described the methodology for handling the VSD in speckle tracking analysis [12, 19, 28, 34, 35, 38, 49, 52, 58]. One study on HLHS excluded cases with severe TR [44], while another study on SV fetuses excluded those with moderate or greater atrioventricular valve regurgitation [9]. For CoA, one study excluded fetuses with TR [51]. Three studies investigating PA, DC, and TGA analyzed the degree of TR and its relationship to GLS [52, 55, 59]. Additionally, one study on TVM graded TR severity [57]. Another study reported a lack of information regarding valve regurgitation [41]. Furthermore, one study specifically focused on fetuses with severe TR [36].

3.3 | Overview of All CHD Combined

Tables 2a–2e provide an overview of the outcomes (LV-GLS, RV-GLS, LV-GLSR, and RV-GLSR) of each study in this systematic review. Outcomes are given in quantitative values (e.g., mean ± SD and median [IQ-range]) or in a descriptive form (e.g., lower and higher). A more detailed description of the overview of all CHD combined can be found in Supporting Information S1: Appendix S5.

3.4 | Overview and Meta-Analysis of CHD Subtypes

A meta-analysis combining data from different studies could be performed for five of the nine following CHD subtypes: HLHS, SV, CoA, TGA, and ToF. In the case of the remaining four subtypes (multiple CHD/other, PA, TVM, and DAC) no meta-analysis could be performed. This was due to insufficient data (e.g., the outcome being examined in only a singular study) as seen in subtypes PA, TVM, and DAC. In the subtype multiple CHD/other, no meta-analysis was performed as these studies examined cases with a wide variety of CHD which could not easily be categorized into subtypes. Supporting Information S1: Appendix S6 shows the results of the meta-analysis visualized by forest plots.

3.4.1 | Hypoplastic Left Heart Syndrome (HLHS)

RV-GLS (six studies, $n = 452$: 205 HLHS, and 247 controls) was significantly lower in fetuses with HLHS compared to controls with a pooled mean difference of 2.39% (95% CI: 0.65–4.13, $p = 0.01$) [39–41, 43–45]. RV-GLSR (five studies, $n = 356$: 157 HLHS, and 199 controls) was not significantly different compared to controls with a pooled mean difference of 0.62 (95% CI: −0.36–1.60 and $p = 0.21$) [40, 41, 43–45]. The studies showed considerable heterogeneity, with variations in the ultrasound device, software, frame rate, sample size, and GA (Figures S2, S3).

3.4.2 | Single (Left) Ventricle (SV)

LV-GLS (two studies, $n = 185$: 83 SV, and 102 controls) was significantly higher in fetuses with a single left ventricle compared to controls with a pooled mean difference of −1.11% (95% CI: −2.30–0.09 and $p = 0.07$) [9, 48]. Heterogeneity between the studies was limited, with variations in the ultrasound device and sample size, but similarities in factors such as the software, frame rate (although both low), and GA (Figure S4).

3.4.3 | Coarctation of the Aorta (CoA)

LV-GLS (five studies, $n = 533$: 168 CoA, and 365 controls) was significantly lower in fetuses with CoA compared to controls with a pooled mean difference of 4.46% (95% CI: 1.41–7.50 and $p = 0.00$) [21, 27, 30, 49, 50]. The studies showed considerable heterogeneity, with variations in the ultrasound device, software, frame rate, sample size, and GA (Figure S5). LV-GLSR (two studies, $n = 82$: 36 CoA, and 46 controls) was also significantly lower in fetuses with CoA compared to controls with a pooled mean difference of 0.59 (95% CI: 0.47–0.72 and $p = 0.00$) [27, 50]. Heterogeneity between the studies was limited. The included studies showed variations in the ultrasound device, frame rate, sample size, and GA, but used a similar software (Figure S6).

RV-GLS (four studies, $n = 475$: 144 CoA, and 331 controls) was not significantly different in fetuses with CoA compared to controls. The pooled mean difference was −0.03% (95% CI: −4.61–4.56 and $p = 0.99$) [21, 27, 30, 49]. The studies showed considerable heterogeneity, with variations in the ultrasound device, software, frame rate, sample size, and GA (Figure S7).

3.4.4 | Transposition of the Great Arteries (TGA)

LV-GLS (three studies, $n = 347$: 67 TGA, and 280 controls) was not significantly different in fetuses with a TGA compared to controls with a pooled mean difference of 1.06% (95% CI: −0.22–2.33 and $p = 0.10$) [29, 53, 54]. Heterogeneity between the studies was limited, with variations in the ultrasound device, software, frame rate, sample size, and GA (Figure S8).

RV-GLS (four studies, $n = 445$: 116 TGA, and 329 controls) was not significantly different in fetuses with TGA compared to controls. The pooled mean difference was 1.62% (95% CI: −1.37–4.62 and $p = 0.29$) [29, 52–54]. The studies showed substantial heterogeneity, with variations in the ultrasound device, software, sample size, frame rate, and GA (Figure S9). RV-GLSR (two studies, $n = 165$: 62 TGA, and 103 controls) was also not significantly different in fetuses with TGA compared to controls. The pooled mean difference was 0.04 (95% CI: −0.28–0.35 and $p = 0.82$) [52, 53]. The studies showed substantial heterogeneity, with variations in the ultrasound device, software, sample size, frame rate, and GA (Figure S10).

TABLE 2a | Outcomes.

First author	Congenital heart disease (CHD)	Study population (CHD/control)	LV-GLS (%)		RV-GLS (%)		LV-GLSR (s^{-1})		RV-GLSR (s^{-1})	
			Control	CHD	Control	CHD	Control	CHD	Control	CHD
Multiple congenital heart disease (CHD)/other										
1. Barker [12]	Congenital heart disease (CHD)	48 (15/33)	−17.7 ± 6.4 [−32.9 to −9.2]	Descriptive (different types)	−18.0 ± 6.4 [−33.4 to −6.7]	Descriptive (different types)	−2.4 ± 1.2 [−5.9 to −0.7]	Descriptive (different types)	−1.9 ± 0.8 [−3.8 to −0.5]	Descriptive (different types)
2. DeVore [6]	Congenital heart disease (CHD)	210 (10/200)	−22.93 ± 3.52 [−30.80 to −14.59]	−19.2 ± 10.0 [−41.68 to −6.41]	*−22.70 ± 4.07 [−39.99 to −10.79]**	*−14.81 ± 11.1 [−37.13 to −2.11]**	N/A	N/A	N/A	N/A
3. Drop [19]	Congenital heart disease (CHD)	128 (23/105)	*−31.6 (−34.0 to −28.7)***	*−26.0 (−31.3 to −22.8)****	N/A	N/A	N/A	N/A	N/A	N/A
4. Germanakis [34]	Congenital heart disease (CHD)	172 (28/144)	21.9 ± 3.7	Different CHD, (descriptive)	22.0 ± 3.7	Different CHD, (descriptive)	N/A	N/A	N/A	N/A
5. Li [35]	Congenital heart disease (CHD) lead to LV or RV increased afterload	89 (48/41) 25 LVA, 23 RVA	*−27.53 (−24.33 to −29.16)*** *−26.79 ± 3.22***	*LVA: −15.97 (−12.50 to −22.52)*** *RVA: −21.52 ± 6.68***	−26.38 ± 3.97 *−26.38 ± 3.97***	LVA: −25.32 ± 6.49 *RVA: −17.64 ± 7.58***	*−2.55 (−2.28 to −2.92)*** *−2.56 ± 0.43**	*LVA: −1.34 (−1.12 to −2.16)*** *RVA: −2.11 ± 0.78**	−2.37 ± 0.44 *−2.37 ± 0.44***	LVA: −2.18 ± 0.42 *RVA: −1.62 ± 0.67***
6. Lou [36]	Severe tricuspid regurgitation	60 (20/40)	−27.73 ± 4.48	−26.24 ± 6.19	*−45.19 ± 3.49****	*−21.01 ± 5.66****	N/A	N/A	N/A	N/A
7. Luo [37]	Abnormal fetal heart structure, blood flow, and/or heart rhythm	109 (50/59)	*−19.8 ± 1.5****	*−17.1 ± 2.3****	*−18.9 ± 1.5****	*−15.5 ± 3.2****	N/A	N/A	N/A	N/A
8. Willruth [38]	Left heart obstruction (LHO)	41 (17/24)	No sig difference, (descriptive)	No sig difference (descriptive)	No sig difference (descriptive)	No sig difference (descriptive)	No sig difference (descriptive)	No sig difference (descriptive)	No sig difference (descriptive)	No sig difference (descriptive)
	Tetralogy of Fallot (TOF)/double outlet right ventricle (DORV)		No sig difference, (descriptive)	No sig difference, (descriptive)	No sig difference, (descriptive)	No sig difference, (descriptive)	No sig difference, (descriptive)	No sig difference, (descriptive)	No sig difference, (descriptive)	No sig difference, (descriptive)

Note: Data given in mean ± SD [range] or median (IQ-range).
Abbreviations: N/A = not applicable, sig = significant.
*$p < 0.05$, **$p < 0.01$, ***, $p < 0.001$.

TABLE 2b | Outcomes.

Author	Congenital heart disease (CHD)	Study population (CHD/control)	LV-GLS (%)		RV-GLS (%)		LV-GLSR (s^{-1})		RV-GLSR (s^{-1})	
			Control	CHD	Control	CHD	Control	CHD	Control	CHD
Hypoplastic left heart syndrome (HLHS)										
9. Brooks [39]	Hypoplastic left heart syndrome (HLHS)	96 (48/48)	−16.7 ± 3.2	N/A	*−17.9 ± 3.1***	*−14.8 ± 4.0****	N/A	N/A	N/A	N/A
10. Cox [40]	Left heart hypoplasia (LHH)	18 (9/9)	−14.56 ± 2.01	−13.69 ± 1.12	−13.74 ± 2.51	−13.80 ± 2.33	−1.29 ± 0.22	−1.40 ± 0.24	−1.23 ± 0.29	−1.34 ± 0.17
11. Enzensberger [41]	Hypoplastic left heart (HLH)	142 (41/101)	N/A	N/A	−16.80 ± 0.16	−15.65 ± 0.58	N/A	N/A	−1.29 ± 0.03	−1.25 ± 0.05
12. Ishii [42]	Valvar aortic stenosis/evolving HLHS	138 (57/81)	15.2 ± 2.7	3.3 ± 3.1 (biventricular outcome) 1.0 ± 1.1 (univentricular outcome)	Descriptive, graph	8.9 ± 2.5 (biventricular outcome) 8.2 ± 2.5 (univentricular outcome)	N/A	N/A	N/A	N/A
13. Ma [43]	Hypoplastic left heart syndrome (HLHS)	84 (42/42)	N/A	N/A	*−21.60 ± 1.74****	*−15.58 ± 3.33****	N/A	N/A	*−1.95 ± 0.63****	*−1.40 ± 0.35****
14. Miller [44]	Hypoplastic left heart syndrome (HLHS)	60 (30/30)	N/A	N/A	*−4.1 ± 3.99***	*−1.9 ± 1.13***	N/A	N/A	−1.02 ± 0.58	−1.1 ± 0.45
15. Patey [45]	Hypoplastic left heart syndrome (HLHS)	52 (35/17)	−12.79 ± 5.78	N/A	−14.53 ± 4.05	−13.22 ± 5.66	−1.51 ± 0.46	N/A	−1.56 ± 0.18	−1.53 ± 0.53
16. Reitz [46]	Critical aortic stenosis	23 (23/0)	N/A	−1.57 ± 2.24	N/A	−10.37 ± 4.67	N/A	N/A	N/A	N/A
17. Wilkes [47]	Hypoplastic left heart syndrome (HLHS)	60 (60/0)	N/A	N/A	N/A	−17.9 (−21.2 to −14.7) (overall) −17.1 (−20.7 to −14.3) (no genetic condition) −20.9 (−22.6 to −18.3) (genetic condition)	N/A	N/A	N/A	N/A

Note: Data given in mean ± SD [range] or median (IQ-range).
Abbreviation: N/A = not applicable.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

TABLE 2c | Outcomes.

Author	Congenital heart disease (CHD)	Study population (CHD/control)	LV-GLS (%)		RV-GLS (%)		LV-GLSR (s^{-1})		RV-GLSR (s^{-1})	
			Control	CHD	Control	CHD	Control	CHD	Control	CHD
Single ventricle (SV)										
18. Brooks [48]	Single (left) ventricle (SV)	77 (29/48)	−16.7 ± 3.2	−17.3 ± 4.3	N/A	N/A	N/A	N/A	N/A	N/A
19. Truong [9]	Single (right and left) ventricle (SV)	108 (54/54)	−15.6 ± 3.3	−17.1 ± 5.0	−16.5 ± 3.9	−16.2 ± 4.8	−1.5 ± 0.4	−1.6 ± 0.5	−1.6 ± 0.4	−1.4 ± 0.5
Coarctation of the aorta (CoA)										
20. Amar [49]	Coarctation of the aorta (CoA)	75 (16/59)	−22.38 ± 4.35	−22.04 ± 3.80	*−22.23 ± 2.73****	*−19.18 ± 2.94****	N/A	N/A	N/A	N/A
21. DeVore [30]	Coarctation of the aorta (CoA)	254 (54/200)	−22.93 ± 3.52 [−30.80 to −14.59]	−20.59 ± 10.44	−22.70 ± 4.07 [−39.99 to −10.79]	−19.65 ± 7.01	N/A	N/A	N/A	N/A
22. DeVore [8]	Coarctation of the aorta (CoA)	250 (50/200)	*−22.93 ± 3.52 [−30.80 to −14.59]***	*−20.935 ± 83.48****	*−22.70 ± 4.07 [−39.99 to −10.79]****	*−18.57 ± 6.84****	N/A	N/A	N/A	N/A
23. Liu [21]	Coarctation of the aorta (CoA)	122 (62/60)	*−21.04 ± 2.76*** (Non-CoA)*	*−17.25 ± 2.40****	−20.71 ± 2.51 (Non-CoA)	−20.08 ± 2.20	N/A	N/A	N/A	N/A
24. Miranda [27]	Coarctation of the aorta (CoA)	24 (12/12)	*−17.398 ± 5.6***	*−10.003 ± 3.499***	−13.1 ± 3.16	−15.827 ± 5.008	*−1.54 ± 0.59**	*−1.009 ± 0.34**	−1.368 ± 0.53	−1.601 ± 0.500
25. Moras [50]	Shone's complex (SC) and simple-coarctation of the aorta (S-CoA)	Total: 75 SC: 17 S-CoA: 24 Control: 34	*−25.6 ± 3.6****	*SC: −13.3 ± 2.1**** *S-CoA: −17.0 ± 2.2****	N/A	N/A	*−1.9 ± 0.3****	*SC: −1.1 ± 0.1**** *S-CoA: −1.3 ± 0.2****	N/A	N/A
26. Zeng [51]	Small aortic isthmus at risk for coarctation (CoA)	96 (48/48)	*Descriptive**	*Sig lower compared to control* (descriptive)*	*Descriptive**	*Sig lower compared to control* (descriptive)*	*Descriptive**	*Sig lower compared to control* (descriptive)*	*Descriptive**	*Sig lower compared to control* (descriptive)*

Note: Data given in mean ± SD [range] or median (IQ-range).
Abbreviations: FP = false positive, N/A = not applicable, sig = significant.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

TABLE 2d | Outcomes.

Author	Congenital heart disease (CHD)	Study population (CHD/control)	LV-GLS (%)		RV-GLS (%)		LV-GLSR (s^{-1})		RV-GLSR (s^{-1})	
			Control	CHD	Control	CHD	Control	CHD	Control	CHD
Transposition of the great arteries (TGA)										
27. DeVore [29]	D-transposition of the great arteries (D-TGA)	239 (39/200)	−22.93 ± 4.07	−21.84 ± 8.10	−22.7 ± 4.07	−19.18 ± 11.07	N/A	N/A	N/A	N/A
28. Lin [52]	Transposition of the great arteries (TGA)	127 (78/49) d-TGA 49, TBA 29	N/A	N/A	*−18.73 ± 3.69***	*d-TGA: −14.35 ± 3.20*** TBA: −13.04 ± 3.40****	N/A	N/A	*−1.64 ± 0.51***	*d-TGA: −1.45 ± 0.64** TBA: −1.27 ± 0.48***
29. Patey [53]	Simple transposition of the great arteries (TGA)	67 (13/54)	−14.72 ± 4.1	−13.13 ± 2.47	*−13.98 ± 4.2***	*−15.95 ± 2.33***	−1.91 ± 0.67	−1.63 ± 0.31	−1.73 ± 0.4	−1.86 ± 0.44
30. Young [54]	D-transposition of the great arteries (D-TGA) and atrioventricular canal defects (AVC)	72 (46/26) d-TGA 15, AVC 31	−22.6 ± 4.33 *−22.6 ± 4.33****	−22.9 ± 4.29 (d-TGA) *−26.9 ± 4.03**** *(AVC)*	−22.1 ± 4.48 *−22.1 ± 4.48****	−21.3 ± 4.29 (d-TGA) *−26.6 ± 4.03 (AVC)****	N/A	N/A	N/A	N/A
Pulmonary atresia (PA)										
31. Cohen [55]	Pulmonary atresia and intact ventricular septum (PA/IVS)	114 (57/57)	*−23.7 ± 2.0****	*−17.4 ± 1.7****	*−24.6 ± 2.5****	*−11.6 ± 3.8****	*−1.42 ± 0.20****	*−1.01 ± 0.21****	*−1.53 ± 0.29****	*−0.75 ± 0.67****

Note: Data given in mean ± SD [range] or median (IQ-range).
Abbreviations: d-TGA = complete transposition of the great arteries, N/A = not applicable, sig = significant, TBA = Taussig Bing anomaly.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

TABLE 2e | Outcomes.

Author	Congenital heart disease (CHD)	Study population (CHD/control)	LV-GLS (%)		RV-GLS (%)		LV-GLSR (s^{-1})		RV-GLSR (s^{-1})	
			Control	CHD	Control	CHD	Control	CHD	Control	CHD
Tricuspid valve malformation (TVM)										
32. Ishii [56]	Ebstein malformation or congenital TV dysplasia	16 (16/0)	N/A	Unclear results, (descriptive)	N/A	N/A	N/A	N/A	N/A	N/A
33. Liu [57]	Tricuspid valve malformation (TVM); *2nd trimester*	168 (88/80) EA 40, TVD 48	*−24.59 ± 3.48****	*−19.78 ± 2.73**** *(TVM-N)* *−14.41 ± 2.20**** *(TVM-R/A)*	*−23.55 ± 2.93****	*−16.09 ± 2.57**** *(TVM-N)* *−12.54 ± 2.67**** *(TVM-R/A)*	*−2.26 ± 0.51****	*−1.79 ± 0.57**** *(TVM-N)* *−1.52 ± 0.44**** *(TVM-R/A)*	*−2.09 ± 0.56****	*−1.63 ± 0.40**** *(TVM-N)* *−1.36 ± 0.48**** *(TVM-R/A)*
	Tricuspid valve malformation (TVM); *3rd trimester*	168 (88/80) EA 40, TVD 48	*−24.23 ± 3.80****	*−16.36 ± 1.93**** *(TVM-N)* *−13.95 ± 2.75**** *(TVM-R/A)*	*−22.67 ± 4.62****	*−14.98 ± 1.98**** *(TVM-N)* *−12.87 ± 2.14**** *(TVM-R/A)*	*−2.35 ± 0.70****	*−1.40 ± 0.66**** *(TVM-N)* *−1.28 ± 0.48**** *(TVM-R/A)*	*−2.18 ± 0.78****	*−1.23 ± 0.44**** *(TVM-N)* *−1.23 ± 0.39**** *(TVM-R/A)*
Tetralogy of Fallot (TOF)										
34. DeVore [28]	Tetralogy of Fallot (TOF)	244 (44/200)	*−22.93 ± 3.52 [−30.80 to −14.5]****	*−20.94 ± 9.63****	*−22.70 ± 4.07 [−39.99 to −10.79]**	*−21.07 ± 8.86**	N/A	N/A	N/A	N/A
35. Song [58]	Tetralogy of Fallot (TOF)	104 (52/52)	*−27.39 ± 4.38****	*−22.57 ± 2.91****	*−28.71 ± 4.48****	*−24.27 ± 3.18****	*−2.68 ± 0.71****	*−2.06 ± 0.64****	*−3.06 ± 0.97****	*−2.20 ± 0.56****
Ductus arteriosus constriction (DAC)										
36. Ma [59]	Ductal arteriosus constriction (DAC)	120 (60/60)	*−23.81 ± 2.01****	*−19.52 ± 3.24****	*−21.59 ± 2.51****	*−13.39 ± 3.17****	N/A	N/A	N/A	N/A

Note: Data given in mean ± SD [range] or median (IQ-range).
Abbreviations: EA = Ebstein anomaly, N = normal, N/A = not applicable, R/A = reduced/absent, TVD = tricuspid valve dysplasia.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

3.4.5 | Tetralogy of Fallot (TOF)

LV-GLS and RV-GLS (two studies, n = 348: 96 ToF, and 252 controls) were significantly lower in fetuses with ToF compared to controls. The pooled mean differences were 3.69% (95% CI: 0.98–6.41 and p = 0.01) and 3.26% (95% CI: 0.55–5.98 and p = 0.02), respectively [28, 58]. Heterogeneity was substantial. The studies showed variations in the sample size, frame rate, and GA, but used similar ultrasound devices and software (Figures S11, S12).

3.4.6 | Pulmonary Atresia (PA)

A meta-analysis could not be performed in this CHD subtype as only one study examined GLS and/or GLSR in fetuses with PA. In this study, significantly lower LV-GLS, RV-GLS, LV-GLSR, and RV-GLSR were seen in fetuses with PA compared to controls [55].

3.4.7 | Tricuspid Valve Malformation (TVM)

Two studies investigated GLS and/or GLSR in fetuses with TVM [56, 57]. One of these studies did not include healthy controls [56]. Therefore, a meta-analysis could not be performed for this CHD subtype. Another study showed significantly lower LV-GLS, RV-GLS, LV-GLSR, and RV-GLSR in fetuses with TVM compared to controls in both second and third trimesters [57].

3.4.8 | Ductus Arteriosus Constriction (DAC)

A meta-analysis could not be performed for this CHD subtype as only one study examined GLS and/or GLSR in fetuses with DAC. In this study, significantly lower LV-GLS and RV-GLS were seen in fetuses with DAC compared to controls. The study did not examine GLSR in fetuses with DAC [59].

3.5 | Influence of Heterogeneity Factors

Sub-analyses of studies examining CHD subtypes (HLHS, CoA, and TGA) revealed that factors such as the GA, software, ultrasound device, and frame rate contribute to heterogeneity. For HLHS, lower I^2 values in sub-analyses of studies with comparable GA and software indicated reduced heterogeneity, though substantial heterogeneity remained due to the differences in ultrasound devices, frame rate, and sample sizes. Similar trends were observed in CoA and TGA, where sub-analyses of studies with comparable frame rate and GA, similar software, or a similar ultrasound device led to reduced but still substantial heterogeneity. These findings indicate that, while certain factors influence heterogeneity, substantial heterogeneity remains due to unresolved differences in other contributing factors. Supporting Information S1: Appendix S7 shows the results of the sub-analyses.

4 | Discussion

This systematic review provides an overview of the current literature on 2D-STE (GLS/GLSR) in fetuses with CHD. Overall, divergent results have been found. These divergent outcomes may be attributed to several heterogeneity factors in the study designs.

Firstly, CHD is not one entity but a diverse spectrum of conditions, each with a distinct potential impact on cardiac function. Understanding the CHD-specific pathophysiology helps explain the observed differences in LV/RV GLS and/or GLSR.

In HLHS, the RV is enlarged with increased preload. The combined cardiac output in fetuses with HLHS is lower than normal [60–62], and can be achieved with less deformation of a larger ventricle. Additionally, the RV becomes more spherical with a relative shift toward circumferential deformation dominance [39], potentially accounting for the significantly lower RV-GLS observed in our meta-analysis [39, 43, 44]. Conversely, in the single left ventricle, a higher LV-GLS was seen, which might be explained by the hypothesis that the LV is better predisposed to adapt to a univentricular circulation, since it was primed to accommodate the systemic circulation [48]. In cases of CoA, our hypothesis suggests that the observed lower LV-GLS and LV-GLSR may be attributed to both a decreased preload resulting from reduced shunting at the atrial level and an increased afterload due to partial LV outflow obstruction [21]. As prenatal diagnosis of CoA is challenging, assessing myocardial deformation might aid in distinguishing between fetuses with and without CoA [8]. In ToF, it is theorized that an increase in aortic flow might induce a cerebral vasoconstrictive response, consequently increasing afterload [63]. Furthermore, the smaller combined outflow surface might play a role in the observed lower LV-GLS and RV-GLS.

Secondly, the heart undergoes a substantial evolution and maturation throughout gestation, influencing contractility and thereby potentially affecting 2D-STE parameters [10, 64]. In the third trimester, pulmonary blood flow increases, resulting in a higher LV preload, while RV afterload increases due to ductal restriction [10, 65]. Both increased LV preload and RV afterload might result in lower GLS and/or GLSR. Studies investigating the effect of GA on LV-GLS and RV-GLS and GLSR showed a significant decrease in the deformation parameters with an increase in gestational age [9, 16, 66, 67]. However, GA in our review ranged from 20 to 40 weeks of gestation, which may have contributed to the conflicting results observed across the studies. Nevertheless, two studies that found significantly lower GLS and/or GLSR in CHD fetuses versus controls, reported that this relationship was applicable in all gestational ages. This suggests that speckle tracking values may vary quantitatively with gestational age, but the relationship between CHD and controls remains the same [55, 58].

Finally, varying study sizes (from 16 to 254 fetuses), different frame rates influencing the temporal resolution, and speckle tracking reliability and different ultrasound device generations (e.g., Voluson E8 and E10), ultrasound brands, and speckle tracking software (each with different algorithms) may have

contributed to the significant heterogeneity in the results observed.

While our review demonstrates that 2D-STE is becoming more technically feasible in different fetal CHD, it also urges for standardized prenatal acquisition and analysis protocols taking these factors as the CHD type, gestational age, ultrasound device, software, and frame rate into account in order to facilitate comparison and explore the potential added value of STE in prenatal diagnosis and counseling of CHD.

As the fetal heart function undergoes substantial changes in the first days after birth, it is noteworthy that only two of the studies evaluated this important transition and change in cardiac function using 2D-STE [45, 53].

4.1 | Strengths and Limitations

The strength of this systematic review is the extensive and recent search in different databases, including all CHD subtypes. Additionally, a meta-analysis could be performed for five of the nine CHD subtypes. Therefore, this systematic review and meta-analysis provides a complete and up to date overview of all information on speckle tracking (GLS and GLSR in LV and RV) in fetuses with CHD, serving as a base for further and more standardized research on the subject.

A limitation of this study is that the articles in this systematic review were published over a span of 15 years, from 2009 to 2024. During this time, there have been substantial developments in ultrasound technology and speckle tracking software, as observed in our heterogeneity analysis, making older publications less comparable with more recent ones. While 2D-STE is supposed to be less angle dependent than the Doppler ultrasound, there remain doubts on whether 2D-STE is totally independent of fetal heart position [68, 69]. Our systematic review did not permit the analysis of the effect of fetal heart position on 2D-STE in CHD. Lastly, a heart rate dependent frequency ≥40 frames per cardiac cycle is believed to be more appropriate than a fixed frequency of ≥80 Hz. Because of the lack of individual fetal heart rate data, this could not be incorporated in our review.

5 | Conclusion

This systematic review has provided an overview of the literature presented on 2D-STE parameters, LV-GLS and RV-GLS, and/or GLSR, in fetuses with CHD, compared to healthy fetuses. Divergent results were found, which can be explained by CHD-specific pathophysiology and differences in study design.

5.1 | Future Research and Clinical Implications

2D-STE can yield reliable measurements of strain and strain rate if a standardized technical approach is maintained using a uniform software and ensuring adequate frame rates. For future research, more prospective longitudinal studies investigating LV-GLS and RV-GLS and GLSR in fetuses with CHD might provide more insights into this promising echocardiographic technique if heterogeneity parameters are taken into account. Moreover, 2D-STE may offer diagnostic and clinical benefits in specific cases, such as aortic coarctation. The potential impact of ventricular deformation on prenatal and postnatal outcomes merits further prospective study.

Acknowledgments

The authors wish to thank the information specialists of the Erasmus MC Medical Library for developing and updating the search strategies.

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are available on request from the corresponding author.

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Supporting Information

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