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Diagnostic accuracy of prenatal ultrasound in coarctation of aorta: systematic review and individual participant data meta-analysis

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KEYWORDS: aortic arch anomaly; coarctation of the aorta; meta-analysis; prenatal diagnosis; systematic review; ultrasound

CONTRIBUTION

What are the novel findings of this work?
Several known prenatal ultrasound parameters show an association with the postnatal diagnosis of coarctation of the aorta. However, both single parameters and models combining multiple parameters have only moderate diagnostic yield.

What are the clinical implications of this work?
The prenatal diagnosis of coarctation of the aorta using ultrasound remains challenging. Further research should focus on improving and validating models both prospectively and externally as well as evaluating the true additional value of other novel technologies.

ABSTRACT

Objective *To determine the diagnostic accuracy of prenatal ultrasound in detecting coarctation of the aorta (CoA).*

Methods *An individual participant data meta-analysis was performed to report on the strength of association and diagnostic accuracy of different ultrasound signs in detecting CoA prenatally. MEDLINE, EMBASE and CINAHL were searched for studies published between January 2000 and November 2021. Inclusion criteria were fetuses with suspected isolated CoA, defined as ventricular and/or great vessel disproportion with right dominance on ultrasound assessment. Individual participant-level data were obtained by two leading teams.*

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PRISMA-IPD and PRISMA-DTA guidelines were used for extracting data, and the QUADAS-2 tool was used for assessing quality and applicability. The reference standard was CoA, defined as narrowing of the aortic arch, diagnosed after birth. The most commonly evaluated parameters on ultrasound, both in B-mode and on Doppler, constituted the index test. Summary estimates of sensitivity, specificity, diagnostic odds ratio (DOR) and likelihood ratios were computed using the hierarchical summary receiver-operating-characteristics model.

Results *The initial search yielded 72 studies, of which 25 met the inclusion criteria. Seventeen studies (640 fetuses) were included. On random-effects logistic regression analysis, tricuspid valve/mitral valve diameter ratio > 1.4 and > 1.6, aortic isthmus/arterial duct diameter ratio < 0.7, hypoplastic aortic arch (all* $P < 0.001$*), aortic isthmus diameter Z-score of < −2 in the sagittal* ($P = 0.003$) *and three-vessel-and-trachea* ($P < 0.001$) *views, pulmonary artery/ascending aorta diameter ratio > 1.4* ($P = 0.048$) *and bidirectional flow at the foramen ovale* ($P = 0.012$) *were independently associated with CoA. Redundant foramen ovale was inversely associated with CoA* ($P = 0.037$). *Regarding diagnostic accuracy, tricuspid valve/mitral valve diameter ratio > 1.4 had a sensitivity of 72.6% (95% CI, 48.2–88.3%), specificity of 65.4% (95% CI, 46.9–80.2%) and DOR of 5.02 (95% CI, 1.82–13.9). The sensitivity and specificity values were, respectively, 75.0% (95% CI, 61.1–86.0%) and 39.7% (95% CI, 27.0–53.4%) for pulmonary artery/ascending aorta diameter ratio > 1.4, 47.8% (95% CI, 14.6–83.0%) and 87.6% (95% CI, 27.3–99.3%) for aortic isthmus diameter Z-score of < −2 in the sagittal view and 74.1% (95% CI, 58.0–85.6%) and 62.0% (95% CI, 41.6–78.9%) for aortic isthmus diameter Z-score of < −2 in the three-vessel-and-trachea view. Hypoplastic aortic arch had a sensitivity of 70.0% (95% CI, 42.0–88.6%), specificity of 91.3% (95% CI, 78.6–96.8%) and DOR of 24.9 (95% CI, 6.18–100). The diagnostic yield of prenatal ultrasound in detecting CoA did not change significantly when considering multiple categorical parameters. Five of the 11 evaluated continuous parameters were independently associated with CoA (all* $P < 0.001$*) but all had low-to-moderate diagnostic yield.*

Conclusions *Several prenatal ultrasound parameters are associated with an increased risk for postnatal CoA. However, diagnostic accuracy is only moderate, even when combinations of parameters are considered.* © *2024 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Coarctation of the aorta (CoA) accounts for 7% of cases of congenital heart disease in neonates[1–3]. Despite advances in fetal echocardiography, it continues to be one of the most challenging defects to diagnose correctly. Prenatal detection rates of the condition are low[4–7], and there are many undiagnosed neonates who leave hospital and return soon after discharge in a critical condition[8]. This is particularly true for isolated cases, in which diagnosis occurs after discharge in up to 60% of cases[9].

Prenatal diagnosis improves survival and reduces morbidity by allowing planned delivery in an appropriate center and preventing early closure of the ductus arteriosus[10–12], especially in severe cases[13]. However, prenatal diagnosis is associated with a high rate of false positives because it is based on indirect, non-specific signs, such as cardiac asymmetry with right dominance[14,15], which may result in unnecessary treatment, parental anxiety and increased medical costs. The diagnostic yield of cardiac asymmetry with right dominance is low and decreases with gestational age (GA) because the physiological asymmetry becomes more pronounced as pregnancy progresses. Thus, its positive predictive value goes from 60–86% in the second trimester to 10–41% in the third trimester[2,14]. Finally, when faced with a prenatal suspicion of CoA, the recommendation is that perinatal care takes place in a tertiary center, although most (60–80%) cases will not be confirmed after birth[9,16]. Therefore, an improved understanding of the characteristics of high-risk fetuses that actually have CoA is essential.

A recent systematic review including about 900 fetuses with a sonographic suspicion of CoA reported that mean mitral valve, aortic valve and aortic isthmus diameter *Z*-scores were lower, and the presence of the juxtaductal shelf and aortic arch hypoplasia was more common, in fetuses with confirmed CoA. However, the small number of included studies, lack of stratification by GA at ultrasound, inclusion of fetuses with other anomalies and the use of aggregate data did not allow the calculation of an objective estimation of the accuracy of prenatal ultrasound in diagnosing CoA[17].

In this context, we performed a systematic review and individual participant data (IPD) meta-analysis to elucidate the strength of association and the accuracy of different ultrasound signs in diagnosing CoA prenatally.

METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data (PRISMA-IPD) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy (PRISMA-DTA) guidance on systematic reviews.

An electronic search of MEDLINE, EMBASE and CINAHL was conducted on 2 November 2021 for

studies published between January 2000 and November 2021, and updated on 20 September 2023, utilizing combinations of the relevant medical subject heading (MeSH) terms, keywords and word variants for 'coarctation of aorta' and 'ultrasound' (Appendix S1). The search and selection criteria were restricted to the English language. The reference lists of relevant articles and reviews were searched manually for additional reports. The study was registered with the PROSPERO database (registration number: CRD42023338872). A flowchart of the identified and included studies is presented in Figure 1.

Study selection, data collection and variables

Inclusion criteria were fetuses with suspected isolated CoA, defined as ventricular and/or great vessel disproportion with right dominance on ultrasound assessment. Cases with an associated cardiac or extracardiac anomaly (including growth restriction), aneuploidy or other genetic abnormality were excluded from the analysis.

The reference standard was CoA diagnosed in the neonatal period and defined as a discrete narrowing of the thoracic aorta just distal to the left subclavian artery. The index test was ultrasound assessment of the fetal heart. Different categorical and continuous sonographic parameters reported to be associated with CoA in the published literature were analyzed (Figures 2 and 3, Table S1). *Z*-scores were calculated according to GA from the charts developed by Schneider *et al.*[18] and Pasquini *et al.*[19], as they were the most widely used charts among the included studies.

Risk of bias assessment across studies and data extraction

Data were extracted and assessed by authors from two different leading teams (C.V., F.D.A., E.G.-M.). Two authors (F.D.A., C.V.), who were not involved in the original studies, independently assessed each eligible study for potential sources of bias and applicability concerns using the QUADAS-2 tool (Table S2). Any disagreement was resolved by discussion between them or with a third author (A.G.).

Study-level data extraction from the included reports and entry into a data extraction sheet were performed by two authors (C.V., E.G.-M.). Collected data included time period, targeted outcome and its incidence, evaluated parameters and selected predictors. The first and the corresponding authors were contacted to gather raw data. This information was transformed into individual participant-level data, chosen based on their availability in the included studies. If there was no response after 1 month, the same approach was reattempted twice. After checking each dataset, authors were contacted to resolve any discrepancies, and once resolved, data were merged into the IPD meta-analysis dataset.

Data analysis

The predictive accuracy of the selected sonographic signs for the detection of CoA was assessed as follows. First, for signs expressed as categorical variables

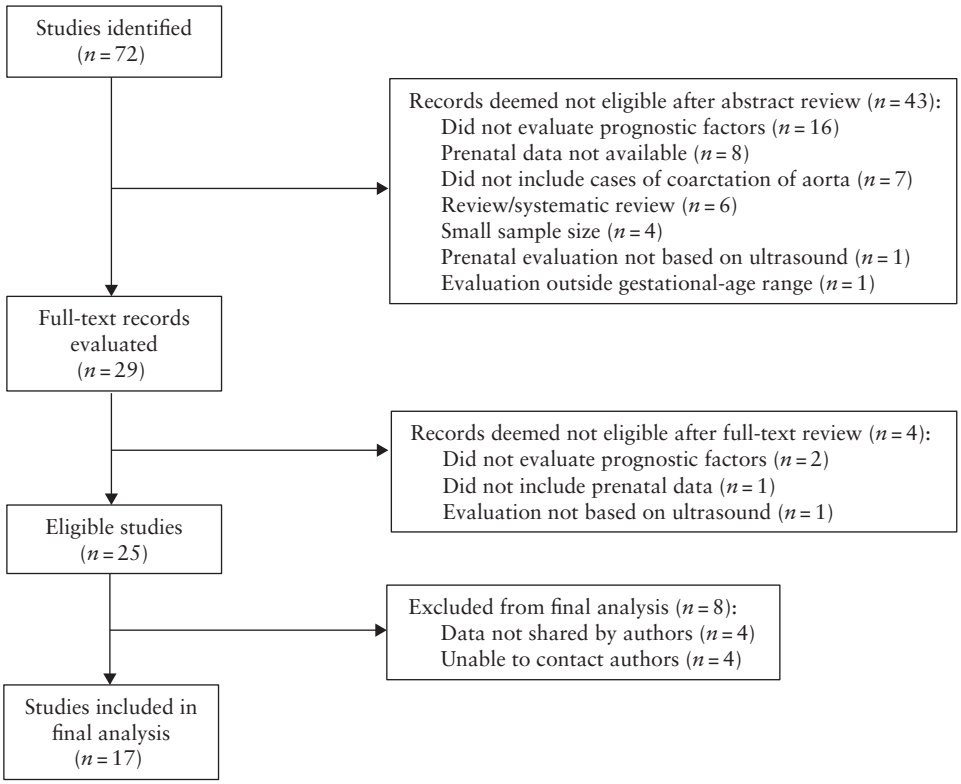

Figure 1 Flowchart summarizing identification and inclusion of studies in systematic review and meta-analysis.

(juxtaductal shelf, hypoplastic aortic arch, laminar flow, bidirectional flow at the aortic arch, bidirectional flow at the foramen ovale, redundant foramen ovale, tricuspid valve/mitral valve diameter ratio > 1.4 or > 1.6, pulmonary artery/ascending aorta diameter ratio > 1.4, aortic isthmus diameter *Z*-score < −2 in the sagittal

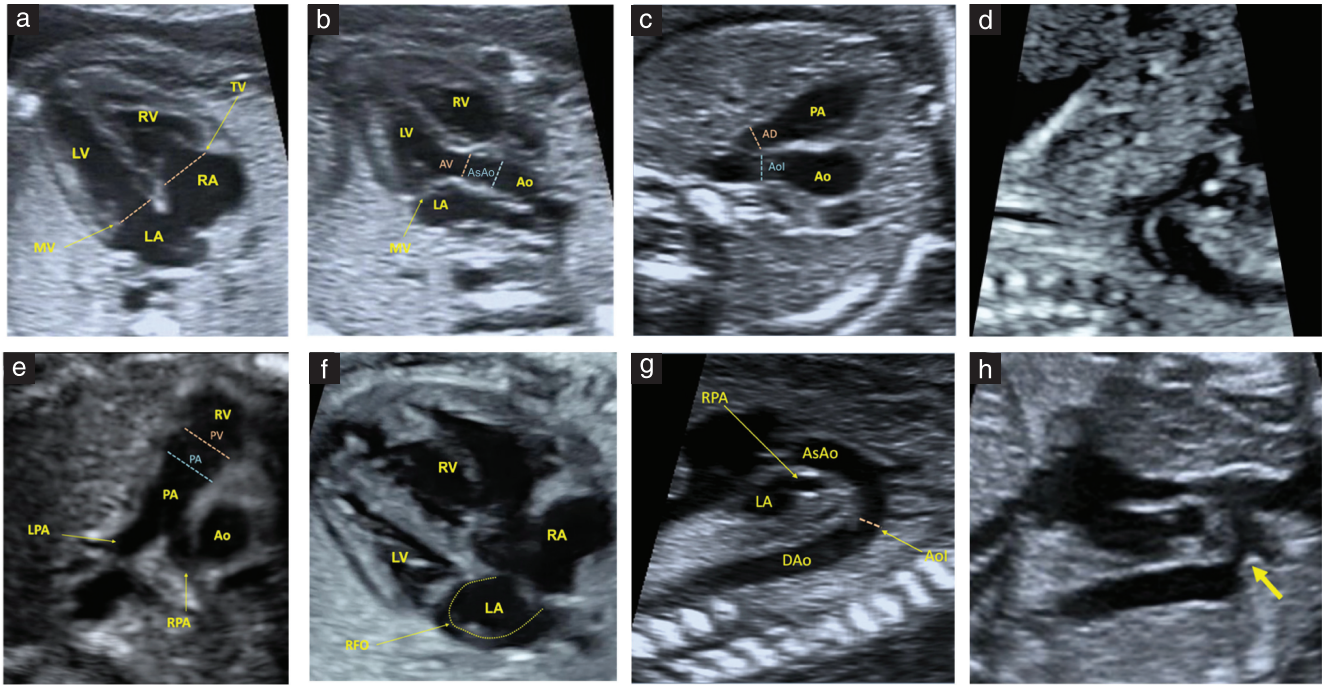

Figure 2 Ultrasound parameters obtained using B-mode that were evaluated as predictors of coarctation of aorta, including: (a) tricuspid valve (TV) and mitral valve (MV) diameters; (b) aortic valve (AV) and ascending aorta (AsAo) diameters; (c) arterial duct (AD) and aortic isthmus (AoI) diameters; (d) hypoplastic aortic arch; (e) pulmonary valve (PV) and main pulmonary artery (PA) diameters; (f) redundant foramen ovale (RFO); (g) AoI diameter in sagittal view; and (h) juxtaductal shelf (arrow). Dashed lines indicate diameters. Ao, aorta; DAo, descending aorta; LA, left atrium; LPA, left pulmonary artery; LV, left ventricle; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle.

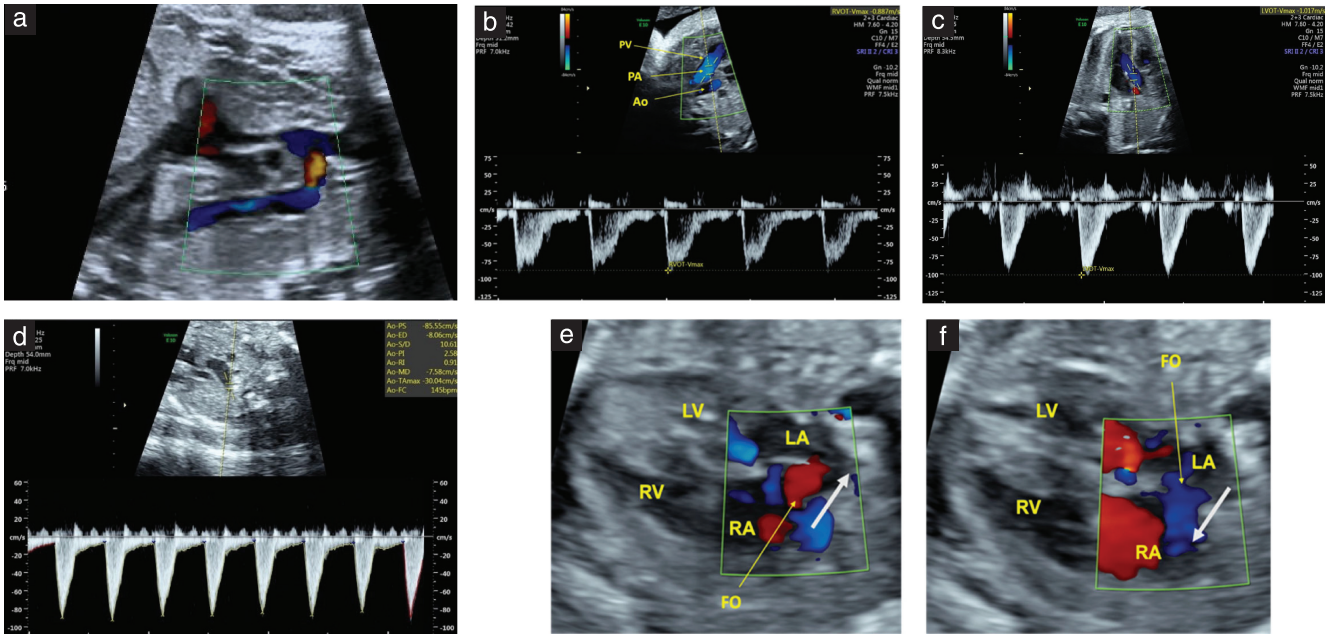

Figure 3 Color (a,e,f) and pulsed (b–d) Doppler parameters that were evaluated as predictors of coarctation of aorta, including: (a) bi-directional flow at aortic arch; (b) main pulmonary artery (PA) peak velocity; (c) ascending aorta peak velocity; (d) laminar flow in aorta; and (e,f) bidirectional flow at foramen ovale (FO) (arrows indicate flow direction). Ao, aorta; LA, left atrium; LV, left ventricle; PV, pulmonary valve; RA, right atrium; RV, right ventricle.

or three-vessel-and-trachea (3VT) view and aortic isthmus/arterial duct diameter ratio < 0.7), we computed summary estimates of sensitivity, specificity, diagnostic odds ratio (DOR) and positive (LR+) and negative (LR−) likelihood ratios. DOR is the ratio of the odds of the test being positive in a disease state relative to the odds of the test being positive in a non-disease state. DOR ranges from zero to infinity, with higher values indicating better discriminatory test performance and a DOR of 1 indicating that the test does not discriminate between people with and those without the disease[20]. For all computations, the hierarchical summary receiver-operating-characteristics (HSROC) model was adopted[21]. However, if the number of studies is small, the uncertainty associated with the estimation of the shape parameter can be high and models may fail to converge. Thus, for all meta-analyses in which fewer than four center estimates could be pooled, the DerSimonian–Laird random-effects model was used.

Second, the diagnostic performance of two sets of combinations was evaluated: (1) the most frequently used sonographic signs (tricuspid valve/mitral valve diameter ratio > 1.4; pulmonary artery/ascending aorta diameter ratio > 1.4; aortic isthmus diameter *Z*-score < −2 in the 3VT view) and GA at evaluation (dichotomized into < 28 weeks *vs* ≥ 28 weeks)[22] and (2) sonographic signs with the highest diagnostic yield on univariate analysis in the meta-analysis (tricuspid valve/mitral valve diameter ratio > 1.6; hypoplastic aortic arch; aortic isthmus diameter *Z*-score < −2 in the 3VT view) and dichotomized GA at evaluation. The performance was assessed by computing summary estimates of sensitivity, specificity, DOR, LR+ and LR− for the presence of all four characteristics included in the model, three or four characteristics, two characteristics and only one characteristic (*vs* none).

Third, for the sonographic parameters expressed as continuous variables (tricuspid valve diameter, mitral valve diameter, pulmonary valve diameter, aortic valve diameter, pulmonary artery peak velocity, ascending aorta peak velocity, ascending aorta diameter, aortic isthmus diameter in the 3VT and sagittal views, arterial duct diameter, aortic isthmus/ascending aorta diameter ratio), a receiver-operating-characteristics (ROC) curve was computed by calculating the false-positive and true-positive rate of CoA empirically at every value of each sonographic parameter.

In order to identify the highest diagnostic accuracy of GA at scan, several cut-offs were explored (specifically, 24, 28 and 32 weeks' gestation), with results largely overlapping across the chosen cut-offs. Thus, given the large heterogeneity in terms of the timepoint of ultrasound across the different studies (at diagnosis, last scan before delivery), and to avoid redundancy in tables and results, we decided to show only the 28-week cut-off. More specifically, the role of GA was investigated using different analytical approaches. First, it was dichotomized into < 28 weeks *vs* ≥ 28 weeks and was always included among the predictors of the models assessing the diagnostic accuracy of 1, 2 or 3–4 parameters to predict CoA. Second, dichotomized GA was included in each meta-analysis (performed through random-effects logistic regression) predicting the likelihood of CoA for each single-unit increase in the selected ultrasound parameter.

Fourth, we evaluated the association between CoA and each ultrasound sign, either taken as a single parameter or considered in combination with others. For the 12 signs expressed as categorical variables, the unit of the meta-analyses were single comparisons of subjects with (exposed group) *vs* without (unexposed group) each ultrasound sign to predict CoA. For the 11 signs expressed as continuous variables, the unit of the meta-analyses was an increase or decrease in the likelihood of detecting coarctation for each single-unit increase in a parameter.

Some of the meta-analyses included observational studies with severely unbalanced exposed and unexposed groups. In these cases, the best performing methods are the Mantel–Haenszel odds ratio (OR) without zero-cell continuity correction, logistic regression and an exact method[23,24]. Mantel–Haenszel ORs cannot be computed in studies reporting zero events in both groups; however, the exclusion of such studies may lead to loss of information and the potential inflation of the magnitude of the pooled exposure effect[25]. Therefore, to keep all studies in the analyses, we performed all meta-analyses using individual data random-effects logistic regression, with single center as the cluster unit, and adjusting for GA at diagnosis (< 28 weeks *vs* ≥ 28 weeks) and left superior vena cava (presence *vs* absence), since it has been described as an independent risk factor for CoA[26]. The pooled datasets with individual data were reconstructed using published 2 × 2 tables. If a meta-analysis showed one of the overall pooled arms with no events, we used exact logistic regression.

Assessment of potential publication bias was not performed because of the small number of studies and events included. Formal tests for funnel plot asymmetry cannot be used when the total number of studies included for each outcome is less than 10 because their power is too low to distinguish chance from real asymmetry. Stata 14 (Stata Corp., College Station, TX, USA: 2013) and Meta-Disc 1.4 were used to analyze the data.

RESULTS

Study selection and characteristics

The systematic literature search identified 72 original studies, of which 25 were considered eligible. Reasons for exclusion of identified studies are presented in Table S3. After applying the eligibility criteria and scrutinizing original data files and publications, a total of 17 studies originating from 13 centers were selected to be included in the IPD meta-analysis, with a total of 940 fetuses with suspected CoA (Figure 1). After removing fetuses with additional cardiac findings (exclusive of persistent left superior vena cava), extracardiac anomalies and/or aneuploidies, 640 fetuses were included in the analysis, of

which 365 (57.0%) had a confirmed postnatal diagnosis of CoA and 275 (43.0%) had confirmation of a normal aortic arch. A summary of the data extraction sheet of the included studies is given in Table S4. Baseline characteristics of the study population are presented in Table 1. The mean GA at ultrasound assessment was 31.07 ± 5.52 weeks. Most of the studies were of high quality and there was a low risk of bias and a low level of concern regarding the applicability of the studies (Table S2).

Synthesis of results

On random-effects logistic regression analysis, tricuspid valve/mitral valve diameter ratio > 1.4 and > 1.6 were both independently associated with CoA, with an OR of 5.13 (95% CI, 2.64–9.98) ($P < 0.001$) and 7.58 (95% CI, 3.59–16.0) ($P < 0.001$), respectively. Likewise, an aortic isthmus diameter *Z*-score of < −2 measured in the sagittal (OR, 5.66 (95% CI, 1.80–17.9), $P = 0.003$) and 3VT (OR, 6.39 (95% CI, 3.59–11.4), $P < 0.001$) views, pulmonary artery/ascending aorta diameter ratio > 1.4 (OR, 2.50 (95% CI, 1.01–6.18), $P = 0.048$), aortic isthmus/arterial duct diameter ratio < 0.7 (OR, 7.29 (95% CI, 3.36–15.8), $P < 0.001$), presence of hypoplastic aortic arch (OR, 18.6 (95% CI, 9.07–38.03), $P < 0.001$) and bidirectional flow at the foramen ovale (OR, 2.03 (95% CI, 1.17–3.54), $P = 0.012$) were independently associated with CoA. Redundant foramen ovale was inversely associated with CoA (OR, 0.25 (95% CI, 0.07–0.92), $P = 0.037$), while the associations with the presence of a juxtaductal shelf ($P = 0.5$), laminar flow ($P = 0.5$) and bidirectional flow at the aortic arch ($P = 0.4$) did not reach statistical significance (Table S5).

Table 2 reports the summary estimates of diagnostic accuracy for the different categorical ultrasound parameters reported to be associated with CoA. A tricuspid valve/mitral valve diameter ratio > 1.4 had a sensitivity of 72.6% (95% CI, 48.2–88.3%), specificity of 65.4% (95% CI, 46.9–80.2%), DOR of 5.02 (95% CI, 1.82–13.9), LR+ of 2.10 (95% CI, 1.32–3.34) and LR− of 0.42 (95% CI, 0.21–0.84), while the respective figures for a tricuspid valve/mitral valve diameter ratio > 1.6 were 47.9% (95% CI, 30.4–65.9%), 88.2% (95% CI, 72.1–95.6%), 6.85 (95% CI, 2.73–17.2), 4.05 (95% CI, 1.82–9.01) and 0.59 (95% CI, 0.43–0.80). A pulmonary artery/ascending aorta diameter ratio > 1.4 had a sensitivity of 75.0% (95% CI, 61.1–86.0%) and a specificity of 39.7% (95% CI, 27.0–53.4%) for the detection of CoA. An aortic isthmus diameter *Z*-score of < −2 in the sagittal view had a sensitivity of 47.8% (95% CI, 14.6–83.0%), specificity of 87.6% (95% CI, 27.3–99.3%), DOR of

Table 1 Characteristics of study population according to whether coarctation of aorta (CoA) was confirmed postnatally

Characteristic	*Centers* (n)	*Confirmed CoA*	*Normal aortic arch*
Tricuspid valve diameter *Z*-score	8	0.00 (−0.68 to 0.70)	−0.17 (−1.23 to 0.51)
Mitral valve diameter *Z*-score	8	−2.00 (−3.09 to −0.90)	−1.80 (−2.81 to −0.90)
Tricuspid valve/mitral valve diameter ratio	8	1.40 (1.24 to 1.61)	1.35 (1.17 to 1.56)
Pulmonary valve diameter *Z*-score	8	1.00 (0.13 to 1.70)	0.95 (0.17 to 1.92)
Aortic valve diameter *Z*-score	9	−1.07 (−2.24 to −0.20)	−0.68 (−1.56 to 0.06)
Ascending aorta diameter *Z*-score	11	−1.40 (−2.66 to −0.50)	−1.36 (−2.13 to −0.56)
Main pulmonary artery diameter *Z*-score	3	0.84 (0.10 to 1.50)	0.50 (−0.33 to 1.23)
Pulmonary artery/ascending aorta diameter ratio	5	1.53 (1.36 to 1.80)	1.45 (1.29 to 1.60)
Aortic isthmus diameter *Z*-score			
Three-vessel view	11	−2.00 (−3.00 to −0.93)	−1.55 (−2.45 to −0.44)
Sagittal view	6	−1.60 (−2.40 to −0.70)	0.78 (−1.00 to 1.53)
Juxtaductal shelf	7	32/175 (18.3)	39/147 (26.5)
Hypoplastic aortic arch	9	114/270 (42.2)	41/183 (22.4)
Pulmonary artery peak velocity	3	90 (75 to 101)	69 (49 to 97)
Ascending aorta peak velocity	5	80 (68 to 100)	80 (75 to 100)
Laminar flow	7	56/96 (58.3)	204/254 (80.3)
Aortic arch flow	9		
Antegrade		62/82 (75.6)	231/266 (86.8)
Mixed		5/82 (6.1)	13/266 (4.9)
Reversed		15/82 (18.3)	22/266 (8.3)
Flow at foramen ovale	8		
Right to left		250/268 (93.3)	105/121 (86.8)
Left to right		3/268 (1.1)	0/121 (0)
Bidirectional		15/268 (5.6)	16/121 (13.2)
Redundant foramen ovale	5	34/234 (14.5)	12/103 (11.7)
Gestational age at delivery (weeks)	3	39.0 (38.0 to 40.0)	39.0 (38.0 to 39.3)
Neonatal sex	10		
Female		124/294 (42.2)	86/231 (37.2)
Male		170/294 (57.8)	145/231 (62.8)
Birth weight (g)	6	3210 (2860 to 3540)	3140 (2740 to 3460)
Surgical repair	3	114/121 (94.2)	0 (0)

Data are given as median (interquartile range) or *n*/*N* (%).

6.48 (95% CI, 1.07–39.3), LR+ of 3.86 (95% CI, 0.57–26.0) and LR− of 0.60 (95% CI, 0.35–1.02), while the respective figures for an aortic isthmus diameter *Z*-score of < −2 in the 3VT view were 74.1% (95% CI, 58.0–85.6%), 62.0% (95% CI, 41.6–78.9%), 4.68 (95% CI, 2.01–10.9), 1.95 (95% CI, 1.22–3.12) and 0.42 (95% CI, 0.25–0.69). The presence of a hypoplastic aortic arch on ultrasound assessment had a sensitivity of 70.0% (95% CI, 42.0–88.6%), specificity of 91.3% (95% CI, 78.6–96.8%) and DOR of 24.9 (95% CI, 6.18–100), while the presence of a juxtaductal shelf had a sensitivity of 26.4% (95% CI, 15.6–41.1%) and a specificity of 79.9% (95% CI, 56.1–92.6%). Figure S1 shows the HSROC of tricuspid valve/mitral valve diameter ratio > 1.4 and > 1.6, and Figure S2 shows the HSROC of aortic isthmus diameter *Z*-score < −2 in the sagittal and 3VT views. Color Doppler parameters showed a low diagnostic accuracy for CoA. Laminar flow in the aorta had a sensitivity of 50.4% (95% CI, 32.0–68.7%) and a specificity of 40.4% (95% CI, 20.6–63.9%). Bidirectional flow at both the aortic arch and the foramen ovale had a low diagnostic accuracy for CoA.

The strength of association between the different categorical ultrasound parameters explored and the presence of CoA is summarized in Table S5. The diagnostic performance of prenatal ultrasound in detecting CoA did not change significantly when considering multiple categorical parameters (Tables 3 and S6).

Table 2 Summary estimates of sensitivity, specificity, diagnostic odds ratio (DOR) and positive (LR+) and negative (LR−) likelihood ratios of categorical ultrasound parameters in prediction of coarctation of aorta

Parameter	*Centers (fetuses)* (n)	*Sensitivity (95% CI) (%)*	*Specificity (95% CI) (%)*	*DOR (95% CI)*	*LR+ (95% CI)*	*LR− (95% CI)*
TV/MV diameter ratio > 1.4	7 (242)	72.6 (48.2–88.3)	65.4 (46.9–80.2)	5.02 (1.82–13.9)	2.10 (1.32–3.34)	0.42 (0.21–0.84)
TV/MV diameter ratio > 1.6	7 (242)	47.9 (30.4–65.9)	88.2 (72.1–95.6)	6.85 (2.73–17.2)	4.05 (1.82–9.01)	0.59 (0.43–0.80)
Pulmonary artery/ascending aorta diameter ratio > 1.4	4 (110)	75.0 (61.1–86.0)	39.7 (27.0–53.4)	2.05 (0.82–5.09)	1.33 (1.02–1.74)	0.66 (0.36–1.20)
Aortic isthmus diameter *Z*-score < −2 (sagittal view)	5 (187)	47.8 (14.6–83.0)	87.6 (27.3–99.3)	6.48 (1.07–39.3)	3.86 (0.57–26.0)	0.60 (0.35–1.02)
Aortic isthmus diameter *Z*-score < −2 (3VT)	9 (365)	74.1 (58.0–85.6)	62.0 (41.6–78.9)	4.68 (2.01–10.9)	1.95 (1.22–3.12)	0.42 (0.25–0.69)
Aortic isthmus/arterial duct diameter ratio < 0.7	6 (277)	87.6 (80.6–92.7)	39.9 (31.9–48.2)	4.53 (2.15–9.54)	1.48 (1.28–1.71)	0.35 (0.20–0.61)
Juxtaductal shelf	6 (256)	26.4 (15.6–41.1)	79.9 (56.1–92.6)	1.43 (0.48–4.26)	1.32 (0.56–3.12)	0.92 (0.73–1.16)
Hypoplastic aortic arch	5 (268)	70.0 (42.0–88.6)	91.3 (78.6–96.8)	24.9 (6.18–100)	8.10 (3.31–21.0)	0.32 (0.14–0.74)
Laminar flow	5 (178)	50.4 (32.0–68.7)	40.4 (20.6–63.9)	0.69 (0.23–2.10)	0.85 (0.52–1.38)	1.23 (0.65–2.30)
Bidirectional flow at aortic arch (*vs* unidirectional flow)	7 (201)	54.0 (34.4–73.1)	52.0 (31.1–72.9)	1.47 (0.63–3.47)	1.15 (0.85–1.57)	0.92 (0.64–1.31)
Bidirectional flow at foramen ovale (*vs* unidirectional, right-to-left flow)	5 (188)	53.0 (25.0–80.0)	63.0 (34.4–84.3)	1.92 (0.42–8.75)	1.43 (0.62–3.29)	0.74 (0.36–1.72)
Redundant foramen ovale	3 (147)	27.8 (9.7–53.5)	60.5 (51.5–69.0)	0.43 (0.12–1.52)	0.74 (0.40–1.35)	1.32 (0.97–1.80)

DerSimonian–Laird random-effects model was used when data were available from fewer than four centers, while hierarchical summary receiver-operating-characteristic model was used when data were available from four or more centers. 3VT, three-vessel-and-trachea view; MV, mitral valve; TV, tricuspid valve.

Table 3 Summary estimates of sensitivity, specificity, diagnostic odds ratio (DOR) and positive (LR+) and negative (LR−) likelihood ratios of models including selected ultrasound parameters and gestational age at evaluation in prediction of coarctation of aorta

Model	*Centers (fetuses)* (n)	*Sensitivity (95% CI) (%)*	*Specificity (95% CI) (%)*	*DOR (95% CI)*	*LR+ (95% CI)*	*LR− (95% CI)*
Model 1						
1 parameter	5 (108)	65.4 (53.8–75.8)	16.7 (5.64–34.7)	0.38 (0.14–1.07)	0.79 (0.63–0.99)	2.08 (0.88–4.89)
2 parameters	5 (107)	67.5 (56.3–77.4)	20.8 (7.13–42.2)	0.55 (0.19–1.57)	0.85 (0.66–1.10)	1.56 (0.68–3.61)
3–4 parameters	5 (95)	68.2 (57.2–77.9)	50.0 (18.7–81.3)	2.15 (0.61–7.58)	1.36 (0.72–2.58)	0.64 (0.32–1.27)
4 parameters	1 (33)	13.0 (2.78–33.6)	100 (69.2–100)	3.59 (0.17–76.1)	3.21 (0.18–56.9)	0.89 (0.73–1.10)
Model 2						
1 parameter	5 (197)	41.6 (32.9–50.8)	41.7 (30.2–53.9)	0.51 (0.28–0.91)	0.71 (0.54–0.95)	1.04 (1.03–1.91)
2 parameters	5 (149)	29.8 (21.2–39.6)	66.7 (51.0–80.0)	0.85 (0.40–1.78)	0.89 (0.54–1.49)	1.05 (0.83–1.34)
3–4 parameters	6 (140)	30.5 (21.9–40.2)	85.7 (69.7–95.2)	2.63 (0.93–7.13)	2.13 (0.90–5.05)	0.81 (0.67–0.98)
4 parameters	2 (3)	NA	NA	NA	NA	NA

Model 1: tricuspid valve/mitral valve diameter ratio > 1.4, pulmonary artery/ascending aorta diameter ratio > 1.4, aortic isthmus diameter *Z*-score < −2 in three-vessel-and-trachea view (3VT) and gestational age < 28 weeks. Model 2: tricuspid valve/mitral valve diameter ratio > 1.6, hypoplastic aortic arch, aortic isthmus diameter *Z*-score < −2 in 3VT and gestational age < 28 weeks. DerSimonian–Laird random-effects model was used when data were available from fewer than four centers, while hierarchical summary receiver-operating-characteristics model was used when data were available from four or more centers. NA, not assessed.

Table 4 Results of meta-analysis evaluating association of selected continuous ultrasound parameters with coarctation of aorta

Parameter	*Centers (fetuses)* (n)	*AUC (95% CI)*	*Pooled OR (95% CI)**	P
Aortic isthmus/ascending aorta diameter ratio	8 (401)	0.42 (0.36–0.67)	0.36 (0.07–1.89)	0.2
Tricuspid valve diameter *Z*-score	8 (417)	0.56 (0.50–0.62)	1.17 (0.95–1.44)	0.14
Mitral valve diameter *Z*-score	8 (418)	0.46 (0.40–0.52)	0.57 (0.46–0.70)	< 0.001
Pulmonary valve diameter *Z*-score	8 (385)	0.49 (0.43–0.56)	1.13 (0.90–1.40)	0.3
Aortic valve diameter *Z*-score	9 (439)	0.43 (0.37–0.48)	0.61 (0.49–0.75)	< 0.001
Pulmonary artery peak velocity *Z*-score	3 (55)	0.49 (0.33–0.65)	0.99 (0.96–1.03)	0.6
Ascending aorta peak velocity *Z*-score	5 (151)	0.52 (0.42–0.61)	0.99 (0.98–1.01)	0.9
Ascending aorta diameter *Z*-score	11 (504)	0.44 (0.39–0.49)	0.56 (0.46–0.67)	< 0.001
Aortic isthmus diameter *Z*-score (3VT view)	11 (518)	0.38 (0.33–0.43)	0.56 (0.46–0.67)	< 0.001
Aortic isthmus diameter *Z*-score (sagittal view)	6 (325)	0.28 (0.21–0.35)	0.49 (0.36–0.68)	< 0.001
Arterial duct diameter *Z*-score	9 (425)	0.45 (0.40–0.51)	1.19 (0.96–1.48)	0.12

*Random-effects logistic regression, with study site as cluster unit, predicting likelihood of coarctation of aorta for 1-unit increase in ultrasound parameter. All models were adjusted for gestational age at evaluation (< 28 weeks *vs* ≥ 28weeks) and presence of left superior vena cava. AUC, area under the receiver-operating-characteristics curve; OR, odds ratio; 3VT, three-vessel-and-trachea view.

Table 4 shows the strength of association and the diagnostic accuracy of the different continuous ultrasound parameters in detecting CoA prenatally. Mitral valve diameter *Z*-score (OR, 0.57 (95% CI, 0.46–0.70), $P < 0.001$), aortic valve diameter *Z*-score (OR, 0.61 (95% CI, 0.49–0.75), $P < 0.001$), ascending aorta diameter *Z*-score (OR, 0.56 (95% CI, 0.46–0.67), $P < 0.001$) and aortic isthmus diameter *Z*-score measured in the 3VT (OR, 0.56 (95% CI, 0.46–0.67), $P < 0.001$) and sagittal (OR, 0.49 (95% CI, 0.36–0.68), $P < 0.001$) views were inversely associated with CoA. Aortic isthmus/ascending aorta diameter ratio ($P = 0.2$), tricuspid valve diameter *Z*-score ($P = 0.14$), pulmonary valve diameter *Z*-score ($P = 0.3$), pulmonary artery peak velocity *Z*-score ($P = 0.6$), ascending aorta peak velocity *Z*-score ($P = 0.9$) and arterial duct diameter *Z*-score ($P = 0.12$) were not associated with CoA.

Mitral valve and tricuspid valve diameter *Z*-scores had an area under the ROC curve (AUC) of 0.46 (95% CI, 0.40–0.52) and 0.56 (95% CI, 0.50–0.62), respectively, in detecting CoA prenatally, while aortic valve and pulmonary valve diameter *Z*-scores had an AUC of 0.43 (95% CI, 0.37–0.48) and 0.49 (95% CI, 0.43–0.56), respectively. Ascending aorta diameter *Z*-score had an AUC of 0.44 (95% CI, 0.39–0.49), while aortic isthmus diameter *Z*-score measured in the sagittal and 3VT views had an AUC of 0.28 (95% CI, 0.21–0.35) and 0.38 (95% CI, 0.33–0.43), respectively.

Unavailable data

We were unable to gather data from 8/25 (32%) eligible studies. Half of these studies were not included because we were unable to get in contact with the authors, despite making multiple attempts (Table S3). In the remaining four studies, the authors were not able or willing to share their data because of the time lapse between the original and the current studies, data sharing policies or logistical issues. Furthermore, we were unable to compare the main IPD results with those of the excluded studies because of the differences in the evaluated parameters, cut-offs and combinations among them. A summary of the excluded eligible studies is presented in Table S7. The main study characteristics were similar to those of the included studies. Excluded studies were based at single referral centers, focused on retrospective cohorts or developed multivariate models in settings with an incidence of the evaluated outcome (postnatal CoA) of around 50%. Reported outcomes were also similar, with most multivariate models achieving a sensitivity of 80–90% and specificity of 70–80%. Therefore, we hypothesize that our results would not have changed significantly if we had included these studies.

DISCUSSION

Summary of main findings

The findings of this study show that several fetal echocardiographic parameters are associated with an increased risk of postnatal CoA. Lower mitral valve diameter *Z*-score, aortic valve diameter *Z*-score, ascending aorta diameter *Z*-score, aortic isthmus diameter *Z*-score and aortic isthmus/arterial duct diameter ratio, greater tricuspid valve/mitral valve diameter ratio and pulmonary artery/ascending aorta diameter ratio and presence of a hypoplastic aortic arch or bidirectional flow at the foramen ovale were all independently associated with an increased risk for CoA. However, when translating these figures into diagnostic accuracy, ultrasound showed only a moderate performance in detecting CoA prenatally.

Implications for clinical practice and research

The prenatal diagnosis of CoA remains challenging[27], and both false-negative and false-positive cases are of concern. Diagnosis is inherently difficult due to the lack of knowledge of the true origin of the disease and is instead based on the subsequent cardiac changes[28]. Manifestations in the second trimester are usually subtle, whereas, in the third trimester, normal evolution of mild physiological

asymmetry may preclude diagnosis, or, conversely, entities such as blood-flow redistribution may mimic CoA[29]. Furthermore, the third-trimester scan is not universally recommended and is usually focused on growth evaluation rather than anomaly detection[17]. This supports our finding, also described in the literature, that the earlier the suspicion for CoA, the more likely it is to be confirmed, as it probably represents a more severe form of the disease with manifestations earlier in pregnancy[22]. However, we could not fully evaluate the value of screening for CoA in the second and third trimesters, as some of the included centers evaluated the scan at which CoA was first suspected, whereas others focused solely on the last scan before delivery, without taking into account the moment of suspicion.

Many isolated parameters have been reported to be associated with CoA in retrospective series, including those related to cardiac asymmetry as well as anomalies of the aortic arch. Our findings are in agreement with those of most of these studies as well as a recent systematic review[17], confirming that cardiac asymmetry (reflected by an increased tricuspid valve/mitral valve diameter ratio and a lower aortic isthmus/arterial duct diameter ratio) and a narrow aortic arch (lower aortic isthmus, aortic valve and ascending aorta diameter *Z*-scores, and presence of hypoplastic aortic arch) are associated with a postnatal diagnosis of CoA. Of note, other proposed parameters targeting vascular function, such as Doppler analysis of aortic arch flow and the presence of a posterior or juxtaductal shelf, did not prove to be effective after adjusting for GA at evaluation and the presence of a persistent left superior vena cava. Evaluation of the aortic arch flow using Doppler[30] and other imaging modalities, such as computational fluid dynamics[31] and fetal cardiac magnetic resonance imaging (MRI)[32], has been shown to improve the fetal diagnosis of CoA by allowing evaluation of hemodynamics as well as aortic arch anatomy. The low diagnostic power of Doppler parameters in our study could be explained by considering the following three points: first, most studies used ultrasound evaluation at the first suspicion, in which function may not yet be affected; second, milder forms of prenatal CoA may not be associated with vascular dysfunction at any point in pregnancy; and, third, we could evaluate only some of these parameters in a relatively small number of cases. Therefore, it is possible that flow evaluation could be of use in the diagnosis of CoA.

On the other hand, we have observed that the presence of a redundant foramen ovale was associated with a lower risk of CoA. This parameter is often found in fetuses with cardiac asymmetry and right dominance (mainly after 28 weeks) in which CoA is not confirmed after birth, probably owing to a restriction to the blood flow into the left ventricle because a large part of the left atrial cavity is occupied by the foramen ovale flap[33,34].

Advanced imaging techniques, such as speckle-tracking analysis, have been shown to improve prenatal diagnosis by evaluating heart geometry[35], demonstrating that aortic arch angles may improve diagnostic accuracy. However, these findings have not been replicated in other settings[32], in line with some postnatal studies, which showed that aortic size is more important than shape when considering when to intervene again[36]. Our study focused solely on 'conventional' ultrasound and did not have sufficient data for angle evaluation; therefore, these parameters require further investigation.

Multivariate models have been proposed in an attempt to improve diagnostic accuracy over single parameters, with excellent diagnostic rates and most sensitivity and specificity values exceeding 80% reported in the literature[22,30,31,37–48]. In our study, models combining different parameters were not as successful. The presence of three sonographic parameters at an early GA had a high specificity (100%) at the expense of low sensitivity (13%) and, when there were two or three sonographic parameters, sensitivity improved to a modest 68%, but specificity was halved. A major issue in regression models is collinearity between the assessed variables. We addressed this issue by including a large sample size and combining parameters that were conceptually different; however, the risk of collinearity could not be eliminated completely. Furthermore, a recent study evaluating *Z*-score reproducibility found excessive variability between readers despite good intraobserver agreement for some variables, such as aortic isthmus diameter[49]. Our findings should be interpreted with caution, as model development was not the objective of this study. However, they should serve as a warning about the possible limitations of the developed models. To our knowledge, only two models have been validated prospectively to date[42,50], and all models currently lack external validation.

Finally, regardless of the current limitations associated with obtaining a correct prenatal diagnosis of CoA, it should be borne in mind that, in CoA, false positives are preferable to false negatives. In this sense, the presence of asymmetry of the chambers and/or great vessels should raise suspicion of CoA and prompt further evaluation to refine diagnosis.

Strengths and limitations

To the best of our knowledge, this is the first IPD meta-analysis exploring the strength of association and diagnostic accuracy of prenatal ultrasound signs in detecting CoA. A thorough literature search, the large number of ultrasound parameters assessed, strict inclusion of cases presenting solely with isolated four-chamber or great-vessel disproportion and the computation of both the strength of association and diagnostic accuracy of different ultrasound signs in accurately diagnosing CoA are the main strengths of this study. Lack of evaluation of some proposed parameters and longitudinal evaluation of the sonographic parameters explored, heterogeneity in GA at assessment (which precluded a comprehensive assessment of the diagnostic accuracy of each parameter in detecting CoA in different GA windows) and dissimilarity in the imaging protocols to assess fetuses suspected of having CoA represent the main weaknesses of this review.

Conclusions

According to the results of this IPD meta-analysis, the most commonly evaluated prenatal sonographic parameters are associated with CoA. However, their predictive capacity is only moderate, even when used in combination. Future research should focus on improving and validating models both prospectively and externally as well as evaluating the true additional value of computational fluid mechanics, novel non-standard modalities, such as Doppler and speckle-derived myocardial mechanics and fluid vector flow analysis and fetal cardiac MRI.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Hierarchical summary receiver-operating-characteristics (HSROC) curves for diagnostic performance of tricuspid valve/mitral valve (TV/MV) diameter ratio > 1.4 (a) and TV/MV diameter ratio > 1.6 (b) for detection of coarctation of aorta. Curves from HSROC model contain a summary operating point (■), representing summarized sensitivity and specificity point estimates for individual study estimates. - - - -, 95% CI.

Figure S2 Hierarchical summary receiver-operating-characteristics (HSROC) curves for diagnostic performance of aortic isthmus diameter *Z*-score < −2 in sagittal view (a) and in three-vessel-and-trachea view (b) for detection of coarctation of aorta. Curves from HSROC model contain a summary operating point (■), representing summarized sensitivity and specificity point estimates for individual study estimates. - - - -, 95% CI.

Appendix S1 Search strategy

Table S1 Evaluated prognostic parameters

Table S2 QUADAS-2 evaluation of risk of bias and applicability

Table S3 Excluded studies and reason for exclusion

Table S4 Main characteristics of included studies[15,22,30,37–42,50–57]

Table S5 Results of meta-analysis evaluating association between selected single categorical ultrasound parameters and gestational age with presence of coarctation of aorta

Table S6 Results of meta-analysis evaluating association between combinations of selected categorical ultrasound parameters and gestational age with presence of coarctation of aorta

Table S7 Main characteristics of eligible studies that were not included in systematic review and meta-analysis[31,43–48,58]

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Precisión diagnóstica de la ecografía prenatal en la coartación aórtica: revisión sistemática y metaanálisis de datos de participantes individuales

RESUMEN

Objetivo. Determinar la precisión diagnóstica de la ecografía prenatal en la detección de la coartación aórtica (CoA).

Métodos. Se realizó un metaanálisis de datos de participantes individuales para informar sobre la fuerza de la asociación y la precisión diagnóstica de diferentes indicios ecográficos en la detección prenatal de la CoA. Se realizaron búsquedas en MEDLINE, EMBASE y CINAHL de estudios publicados entre enero de 2000 y noviembre de 2021. Los criterios de inclusión fueron fetos con sospecha de CoA aislada, definida como una desproporción ventricular y/o de grandes vasos con dominancia derecha en la evaluación ecográfica. Los datos individuales de los participantes fueron obtenidos por dos equipos destacados. Se utilizaron las directrices PRISMA-IPD y PRISMA-DTA para extraer los datos, y la herramienta QUADAS-2 para evaluar la calidad y la aplicabilidad. El estándar de referencia fue la CoA, definida como el estrechamiento del arco aórtico, diagnosticado tras el nacimiento. Los parámetros más comúnmente evaluados en ecografía, tanto en modo B como en Doppler, constituyeron la prueba índice. Se calcularon estimaciones resumidas de la sensibilidad, la especificidad, la razón de momios del diagnóstico (RMD) y los cocientes de probabilidad mediante el modelo jerárquico resumido de las características operativas del receptor.

Resultados. La búsqueda inicial encontró 72 estudios, de los cuales 25 cumplían los criterios de inclusión. Se incluyeron 17 estudios (640 fetos). En el análisis de regresión logística de efectos aleatorios, la relación entre el diámetro de la válvula tricúspide y la válvula mitral >1,4 y >1,6, la relación entre el diámetro del istmo aórtico y el conducto arterial <0,7, el arco aórtico hipoplásico (todos P<0,001), la puntuación estándar (Z-score) del diámetro del istmo aórtico <−2 en los planos sagital (P=0,003) y de tres vasos-tráquea (P=0,001), la relación entre el el diámetro de la arteria pulmonar y el de la aorta ascendente >1,4 (P=0,048) y el flujo bidireccional en el agujero oval (p = 0,012) se asociaron de forma independiente con la CoA. El agujero oval redundante se asoció inversamente con la CoA (P=0,037). En cuanto a la precisión diagnóstica, la relación entre el diámetro de la válvula tricúspide y la válvula mitral >1,4 tuvo una sensibilidad del 72,6% (IC 95%, 48,2–88,3%), una especificidad del 65,4% (IC 95%, 46,9–80,2%) y una RMD de 5,02 (IC 95%, 1,82-13,9). Los valores de sensibilidad y especificidad fueron, respectivamente, del 75,0% (IC 95%, 61,1–86,0%) y del 39,7% (IC 95%, 27,0–53,4%) para la relación entre el diámetro de la arteria pulmonar y la aorta ascendente >1.4, del 47,8% (IC 95%, 14,6–83,0%) y del 87,6% (IC 95%, 27.3–99,3%) para una puntuación estándar del diámetro del istmo aórtico <−2 en el plano sagital y del 74,1% (IC 95%, 58,0–85,6%) y 62,0% (IC 95%, 41,6–78,9%) para una puntuación estándar del diámetro del istmo aórtico <−2 en el plano de tres vasos-tráquea. El arco aórtico hipoplásico tuvo una sensibilidad del 70,0% (IC 95%, 42,0–88,6%), una especificidad del 91,3% (IC 95%, 78,6–96,8%) y una RMD de 24,9 (IC 95%, 6,18–100). El rendimiento diagnóstico de la ecografía prenatal en la detección de la CoA no cambió significativamente al considerar múltiples parámetros categóricos. Cinco de los 11 parámetros continuos evaluados se asociaron de forma independiente con la CoA (todos P<0,001), pero todos tuvieron un rendimiento del diagnóstico de bajo a moderado.

Conclusiones. Varios parámetros ecográficos prenatales se asocian a un mayor riesgo de CoA postnatal. Sin embargo, la precisión del diagnóstico es sólo moderada, incluso cuando se consideran combinaciones de parámetros.

产前超声对主动脉缩窄的诊断准确性：系统综述和个体参与者数据荟萃分析

摘要

目的 确定产前超声检测主动脉缩窄（CoA）的诊断准确性。

方法 对个体参与者的数据进行荟萃分析，以报告不同超声征象在 CoA 产前检测方面的关联强度和诊断准确性。检索了 2000 年 1 月至 2021 年 11 月期间在 MEDLINE、EMBASE 和 CINAHL 上发表的研究。纳入标准为疑患孤立性 CoA 的胎儿；其定义为经超声评估，心室和/或大血管比例失调，右侧占优势。两个领导小组获取了个体参与者数据。数据根据 PRISMA-IPD 和 PRISMA-DTA 指南进行提取，质量和适用性采用 QUADAS-2 工具进行评估。参考标准是 CoA，定义为出生后确诊的主动脉弓狭窄。指标检验采用 B 型超声和多普勒超声最常用的评估参数。使用层次综合接受者操作特征模型计算了灵敏度、特异性、诊断比值比（DOR）和似然比的汇总估计值。

结果 初步搜索共获得 72 项研究，其中 25 项符合纳入标准。共纳入 17 项研究（640 个胎儿）。根据随机效应逻辑回归分析结果，三尖瓣/二尖瓣直径比＞1.4 和＞1.6、主动脉峡部/动脉导管直径比＜0.7、主动脉弓发育不良（所有情况均 P＜0.001）、矢状切面（P=0.003）和三血管气管切面（P<0.001）主动脉峡部直径 Z 评分＜-2、肺动脉/升主动脉直径比>1.4（P=0.048）和卵圆孔双向血流（P=0.012）与 CoA 独立相关。卵圆孔未闭与 CoA 呈反相关（P=0.037）。关于诊断准确性，三尖瓣/二尖瓣直径比>1.4的敏感性为 72.6%（95% CI，48.2-88.3%），特异性为 65.4%（95% CI，46.9-80.2%），DOR 为 5.02（95% CI，1.82-13.9）。肺动脉/升主动脉直径比>1.4 的敏感性和特异性分别为 75.0%（95% CI，61.1-86.0%）和 39.7%（95% CI，27.0-53.4%）；矢状切面主动脉峡部直径 Z 评分< -2 的敏感性和特异性分别为 47.8%（95% CI，14.6 - 83.0%）和 87.6%（95% CI，27.3 - 99.3%）；三血管气管切面主动脉峡部直径 Z 评分< -2 的敏感性和特异性分别为 74.1%（95% CI，58.0-85.6%）和 62.0%（95% CI，41.6-78.9%）。主动脉弓发育不良的敏感性为 70.0%（95% CI，42.0-88.6%），特异性为 91.3%（95% CI，78.6-96.8%），DOR 为 24.9（95% CI，6.18-100）。当考虑多个分类参数时，产前超声检测 CoA 的诊断率没有显著变化。在研究评估的 11 个连续参数中，5 个与 CoA 独立相关（所有情况均 P<0.001），但所有参数的诊断率均为较低或中等。

结论 一些产前超声参数与产后 CoA 风险增加有关。然而，即使结合多个参数进行评估，也只有中等的诊断准确性。

SYSTEMATIC REVIEW