Risk Factors for Coarctation of the Aorta on Prenatal Ultrasound

A Systematic Review and Meta-Analysis

BACKGROUND: Prenatal diagnosis of coarctation of the aorta (CoA) is still challenging and affected by high rates of false-positive diagnoses. The aim of this study was to ascertain the strength of association and to quantify the diagnostic accuracy of different ultrasound signs in predicting CoA prenatally.

METHODS: Medline, Embase, CINAHL, and Cochrane databases were searched. Random-effects and hierarchical summary receiver operating characteristic model meta-analyses were used to analyze the data.

RESULTS: Seven hundred ninety-four articles were identified, and 12 (922 fetuses at risk for CoA) articles were included. Mean mitral valve diameter *z* score was lower ($P<0.001$) and the mean tricuspid valve diameter *z* score was higher in fetuses with CoA than in those without CoA ($P=0.01$). Mean aortic valve diameter *z* score was lower in fetuses with CoA than in healthy fetuses ($P\leq0.001$), but the ascending aorta diameter, expressed as *z* score or millimeters, was similar between groups ($P=0.07$ and 0.47, respectively). Mean aortic isthmus diameter *z* scores measured either in sagittal ($P=0.02$) or in 3-vessel trachea view ($P<0.001$) were lower in fetuses with CoA. Conversely, the mean pulmonary artery diameter *z* score, the right/left ventricular and pulmonary artery/ascending aorta diameter ratios were higher ($P<0.001$, $P=0.02$, and $P=0.02$, respectively) in fetuses with CoA in comparison with controls, although aortic isthmus/arterial duct diameter ratio was lower in fetuses with CoA than in those without CoA ($P<0.001$). The presence of coarctation shelf and aortic arch hypoplasia were more common in fetuses with CoA than in controls (odds ratio, 26.0; 95% confidence interval, 4.42–153; $P<0.001$ and odds ratio, 38.2; 95% confidence interval, 3.01–486; $P=0.005$), whereas persistent left superior vena cava ($P=0.85$), ventricular septal defect ($P=0.12$), and bicuspid aortic valve ($P=0.14$) did not carry an increased risk for this anomaly. Multiparametric diagnostic models integrating different ultrasound signs for the detection of CoA were associated with an increased detection rate.

CONCLUSIONS: The detection rate of CoA may improve when a multiple-criteria prediction model is adopted. Further large multicenter studies sharing the same imaging protocols are needed to develop objective models for risk assessment in these fetuses.

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Clinical Perspective

What Is New?

- This systematic review of studies on fetuses with cardiovascular disproportion showed that those with the postnatal diagnosis of coarctation of the aorta (CoA) had significant differences in several cardiac morphological parameters in comparison with cases without CoA.
- The presence of a coarctation shelf or hypoplastic arch was associated with a significantly increased risk of CoA.
- Multiparametric diagnostic models were associated with an increased detection rate.

What Are the Clinical Implications?

- Assessment of left inflow and outflow tracts may help in stratifying the risk of CoA prenatally.
- Future large prospective studies are needed to ascertain the diagnostic performance of ultrasound in detecting CoA prenatally.

Coarctation of the aorta (CoA) is one of the most common congenital heart defects in the pediatric population, accounting for 5% to 8% of children with congenital heart defects.[1] It has been classically defined as a discrete narrowing of the aorta in the region of the ligamentum arteriosum, although more diffuse forms of the disease may involve the arch or isthmus to varying degrees.[2]

The importance of prenatal diagnosis of CoA relies on the fact that the burden of mortality and morbidity associated with this anomaly is significantly higher when prenatal detection is missed.[3] CoA does not cause fetal circulatory compromise in utero because the aortic isthmus is not an essential component of the fetal circulation; however, after birth and ductal closure, a critical coarctation will result in poor perfusion of the lower body and acidemia that, together with an increase in left ventricular afterload, might result in acute circulatory shock. Cases with a less narrow CoA can be completely asymptomatic, develop arterial collateral vessels that bypass the aortic obstruction, and remain asymptomatic until they are diagnosed with hypertension.

Prenatal diagnosis of CoA allows planning delivery in a center with pediatric cardiology service, starting prostaglandin infusion immediately after birth to maintain ductal patency, and performing surgery electively. Although the current rate of mortality and morbidity for this condition is lower than in the past, lifelong follow-up is needed in view of the high rates of hypertension and need for reintervention later in life.[4]

Prenatal detection of CoA has been reported to be poor, in general, and this anomaly is usually not suspected until the third trimester of pregnancy when ventricular or vascular disproportion is detected.[5,6] However, because the fetal heart has a normal physiological right-sided dominance that increases with gestation, the use of cardiovascular disproportion alone has an overall low diagnostic accuracy that is even lower during the third trimester.

Several ultrasound signs have been proposed to potentially improve the detection rate of prenatal diagnosis for CoA.

The primary aim of this systematic review was to identify the ultrasonographic cardiovascular parameters associated with the occurrence of CoA. The secondary aim was to develop a prediction model combining these ultrasound predictors to improve the prenatal diagnosis of CoA.

METHODS

Protocol, Eligibility Criteria, Information Sources, and Search

This review was performed according to an a priori designed protocol using methods recommended for systematic reviews and meta-analysis.[7,8] Medline, Embase, CINAHL, and Cochrane databases were searched electronically on May 2, 2016 by using combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "coarctation of aorta," "prenatal diagnosis," and "ultrasound" (online-only Data Supplement Table I). The search and selection criteria were restricted to the English language. PRISMA guidelines were followed.[9]

The study was registered with the PROSPERO database (Registration number: CRD42016038845).

Study Selection, Data Collection, and Data Items

Two authors (A.F., M.M.) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus. Full-text copies of those articles were obtained, and the same 2 reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. If >1 study was published for the same cohort with identical end points, the report containing the most comprehensive information on the population was included to avoid overlapping populations. Excluded studies and the reasons for exclusions are listed in online-only Data Supplement Table II.

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale. According to the Newcastle-Ottawa Scale, each study is judged on 3 broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment outcome of interest.[10] According to the Newcastle-Ottawa Scale, a study can be awarded a maximum of 1 star for each numbered item within the Selection and Outcome categories. A maximum of 2 stars can be given for Comparability.[10]

Risk of Bias, Summary Measures, and Synthesis of the Results

We explored the strength of association between different ultrasound parameters in fetuses in comparison with those

without CoA that had their diagnosis confirmed or refuted at postnatal imaging or surgery. The analyzed population included fetuses suspected to be at risk for CoA on the basis of cardiovascular disproportion, defined as a discrepancy in size of either cardiac chambers or great vessels, detected at the scan.

The following ultrasound parameters were assessed:

- Inflow tracts: tricuspid valve (TV) *z* score, mitral valve (MV) *z* score
- Outflow tracts: aortic valve (AoV) *z* score, ascending aorta (AAo) *z* score, AAo diameter, aortic isthmus (AoI) *z* score, AoI diameter, pulmonary valve (PV) *z* score, main pulmonary artery (MPA) *z* score, MPA diameter, arterial duct (AD) *z* score, AoV growth rate, AoI growth rate.
- Ratios: Right ventricular/left ventricular (RV/LV) diameter, RV/LV length, RV/LV area, RV/LV volume, TV/MV, MV/TV, PV/AoV, AoV/PV, MPA/AAo, descending aorta/AoI angle, MPA/AoI, AoI/AD, AD/AoI diameter.
- Doppler signs: AoI pulsatility index, AoI peak systolic velocity, reversed or mixed flow at the aortic arch, bidirectional flow at the foramen ovale.
- Other signs: Persistent left superior vena cava (PLSVC), ventricular septal defect, bicuspid aortic valve (BAV), coarctation shelf, arch hypoplasia, left common carotid to left subclavian artery distance, the ratio of the aortic arch diameter at the left subclavian artery and the distance between the left carotid artery and the left subclavian artery, namely the carotid subclavian index, AAo/descending aorta angle, transverse aortic arch/descending aorta angle, AoI-AD angle.

All *z* scores, computed on gestational age (GA) and femur length, were considered suitable for inclusion.

Only case-control studies including fetuses undergoing echocardiography for suspected CoA on the basis of cardiovascular disproportion were considered suitable for the inclusion in this study.[5,6] Only full-text articles were considered eligible for the inclusion and all the studies addressing differences in ultrasonographically measured continuous variables in fetuses with CoA in comparison with those without.

The following studies were excluded:

- Studies with missing prenatal information/diagnosis.
- Studies reporting the detection rate of prenatal ultrasound in diagnosing CoA at the time of the routine anomaly scan without providing a clear description of the ultrasound criteria used.
- Studies performed in the first trimester of pregnancy.
- Autopsy-based studies, because fetuses undergoing termination of pregnancy are more likely to have other associated major structural and chromosomal anomalies, thus potentially increasing the detection rate of this condition.
- Studies published before 2000 as advances in prenatal imaging techniques have improved the diagnosis of fetal cardiac anomalies.
- Studies not providing a clear classification of the anomaly
- Case reports, conference abstracts, and case series with <3 cases of CoA.

Statistical Analysis

We performed traditional head-to-head meta-analyses combining individual study´s means of the parameters obtained from fetuses with and without CoA. We used the random-effects model and computed a summary mean difference, its 95% confidence interval (CI), and the relative intrastudy heterogeneity (which was quantified using the I^2 metric). Then we used random-effects meta-analysis to compute a summary odds ratio (OR) of the likelihood of detecting categorical cardiovascular anomalies in fetuses with or without CoA.

For each anomaly, we used the hierarchical summary receiver operating characteristic model to compute summary estimates of sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR–), and diagnostic OR.[11,12] Rutter and Gatsonis hierarchical summary receiver operating characteristic parameterization was used because its hierarchical modeling strategy can be used when there is variability in threshold between studies.[13] However, when the number of studies is small, the uncertainty associated with the estimation of the shape parameter could be very high, and models may fail to converge. Thus, for all diagnostic-test meta-analyses in which <4 study estimates could be pooled, the DerSimonian-Laird random-effects model was used.

RevMan 5.3 (The Cochrane Collaboration, 2014), Stata command metandi (Stata Corp: 2013), and Meta-Disc 1.4 were used to analyze the data.

RESULTS

Study Selection and Characteristics

Seven hundred ninety-four articles were identified, 58 were assessed with respect to their eligibility for inclusion, and 12 studies were included in the systematic review (Table 1, Figure 1).[14–25] Nine hundred twenty-two fetuses undergoing echocardiography for the suspicion of CoA were included; of these, 283 (30.69%, 95% CI, 27.7–33.8) were confirmed to have a CoA postnatally.

Ventricular disproportion was defined as a ratio between the right and left ventricles >1.5, 1.6, and 1 in 3 studies, respectively, whereas the majority did not report any specific cutoff.[16,21,25] Three studies[17,19,21] reported a cutoff of ≥1.6 in the ratio between the PV and AoV. When plotted together, PV/AoV ≥1.6 was associated with a significantly increased risk for CoA (OR, 15.11; 95% CI, 6.80–33.6; $P \leq 0.001$, I^2, 0%); however, when this figure was translated into a predictive model, it gave only a moderate diagnostic accuracy and was affected by a high false-positive rate (sensitivity: 86.2%; 95% CI, 77.5–92.4; specificity: 51.8%; 95% CI, 46.1–57.4; LR+: 3.01; 95% CI, 1.09–8.33; LR: 0.20, 95% CI, 0.08–0.54; diagnostic OR: 15.1; 95% CI, 6.80–33.5).

Results of quality assessment of the included studies using Newcastle-Ottawa Scale for cohort studies are presented in Table 2.

Table 1. General Characteristics of the Studies Included in the Systematic Review

Author	Year	Country	Study Design	Ultrasound Signs	Reference Standard	Associated Major CHDs	GA at US	Fetuses, n	CoA, n
Arya[14]	2016	United States	Retrospective	AoI d *z* score, RV/LV d ratio, RV/LV length ratio, TV/LV area ratio, RV/LV volume ratio, DA/AoI flow ratio, DAo/AoI d ratio, MPA/AoI d ratio, LCSA, Aao/Dao angle, TAo-DAo angle	Postnatal echocardiography, surgery	Excluded	32.8±4.2	40	20
Toole[15]	2015	United States	Retrospective	TV *z* score, MV *z* score, PV *z* score AoV *z* score, AAo *z* score, TAoA *z* score, AoI *z* score, RV length, LV length, AoV/PV ratio, RV/LV area ratio, AoI/DA ratio, MV/TV ratio, PLSVC, isthmus-ductal angle, AoI PSV, AoI PI	Postnatal echocardiography, surgery	Excluded	33.9 (30.4–36.0)	62	27
Mărginean[16]	2015	Romania	Prospective	AoI *z* score, AAo *z* score, AD/AoI ratio, PA/Ao ratio, Ao d, AoI d, RV/LV ratio, PLSVC, BAV, VSD	Postnatal echocardiography, surgery	Excluded	36 (32–39)	32	9
Durand[17]	2015	France	Prospective	Ventricular and great vessels disproportion, AoV *z* score (FL and GA), AoV d (mm), PSLVC, VSD, bicuspid AoV, hypoplastic and angular AoA	Postnatal echocardiography, surgery	Excluded	36 wk±3 days	285	41
Sivanandam[18]	2015	United States	Retrospective	CSI, AoI *z* score, MV *z* score, AoV *z* score	Postnatal echocardiography, surgery	Excluded	25.6 (20–35)	31	11
Gomez-Montes[19]	2014	Spain	Retrospective	TV *z* score, MV *z* score, TV/MV ratio, PV *z* score, AoV *z* score, MPA *z* score, AA *z* score, isthmus *z* score, AD *z* score, isthmus/AD ratio, hypoplastic arch, PLSVC, midflow at AoA, bidirectional flow at FO	Postnatal echocardiography, surgery	Excluded	27.6±6.6	115	52
Rizzo[20]	2010	Italy	Prospective	PA/AO ratio	Postnatal echocardiography, surgery	Excluded	30 (26–34)	18	8
Slodki[21]	2009	Poland/United States	Retrospective	AoI d (mm), AAo d (mm), PA d (mm), PA/AoA ratio	Postnatal echocardiography, surgery	Excluded	33.0±3.8	52	12
Axt-Fliedner[22]	2008	Germany	Retrospective	PLSVC, VSD	Autopsy, postnatal echocardiography, surgery	Excluded	31 wk+4 days (13+2–38+6)	61	37

(*Continued*)

Table 1. Continued

Author	Year	Country	Study Design	Ultrasound Signs	Reference Standard	Associated Major CHDs	GA at US	Fetuses, n	CoA, n
Matsui[23]	2008	United Kingdom	Retrospective	Vascular disproportion, PLSVC, VSD, BAV, shelf, Doppler anomalies, AoI *z* score, AoI/AD ratio	Autopsy, postnatal echocardiography, surgery	Excluded	22 wk+0 days (15+4–38+4)	44	20
Head[24]	2004	United Kingdom	Retrospective	VSD, PLSVC	Autopsy, postnatal echocardiography, surgery	Excluded	Not stated	144	43
Hornung[25]	2001	United Kingdom	Retrospective	VSD, BAV	Postnatal echocardiography, surgery	Excluded	29 (16–38)	38	3

Ao indicates aorta; AAo, ascending aorta; AD, arterial duct; AoA, aortic arch; AoI, aortic isthmus; BAV, bicuspid aortic valve; CHD, congenital heart defect; CoA, coarctation of the aorta; CSI, carotid subclavian index; d, diameter; DAo, descending aorta; GA, gestational age; LCSA, left common carotid–to–left subclavian artery distance; LV, left ventricle; MV, mitral valve; PA, pulmonary artery; PI, pulsatility index; PLSVC, persistent left superior vena cava; PV, pulmonary valve; RV, right ventricle; TAoA, transverse aortic arch; TV, tricuspid valve; US, ultrasound; and VSD, ventricular septal defect.

Synthesis of the Results

The mean MV diameter *z* score was significantly lower in fetuses with CoA than in those without CoA (mean difference [MD], –0.97; 95% CI, –1.43 to –0.51; $P<0.001$), whereas the mean TV diameter *z* score was significantly higher in fetuses with CoA than in controls (MD, 0.40; 95% CI, 0.09–0.71; $P=0.01$) (Figure 2).

The mean AoV diameter *z* score for GA was significantly lower in fetuses with CoA than in healthy fetuses (MD, –1.19; 95% CI, –1.56 to –0.82; $P\leq0.001$), whereas the mean AAo diameters expressed as *z* score or mm ($P=0.07$ and 0.47, respectively; Table 3), were not different between cases and controls, although these parameters were assessed only in 2 studies. The mean AoI

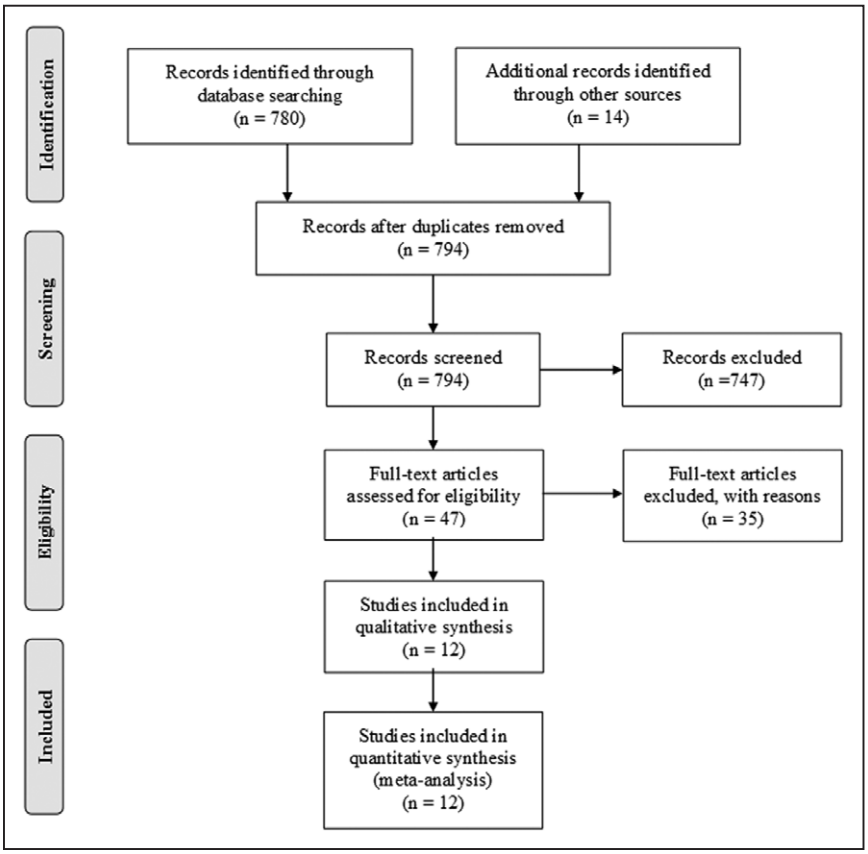

Figure 1. Systematic review flowchart.

Table 2. Quality Assessment of the Included Studies According to the Newcastle-Ottawa Scale

Author	Year	Selection	Comparability	Outcome
Arya[14]	2016	★★★	★★	★★
Toole[15]	2016	★★	★★	★★
Mărginean[16]	2015	★★★	★	★
Durand[17]	2015	★★★	★★	★★
Sivanandam[18]	2015	★★	★	★
Gomez-Montes[19]	2015	★★★	★★	★★
Rizzo[20]	2014	★★	★	★
Slodki[21]	2010	★★	★	★
Axt-Fliedner[22]	2009	★★	★	★
Matsui[23]	2008	★★★	★★	★★
Head[24]	2008	★★★	★★	★★
Hornung[25]	2002	★★	★	★

A study can be awarded a maximum of 1 star for each numbered item in the Selection and Outcome categories. A maximum of 2 stars can be given for Comparability.

diameter *z* scores measured either in sagittal view (MD, –1.24; 95% CI, –2.27 to –0.22; *P*=0.02) or in 3 vessels and trachea view (MD, 1.47; 95% CI, –2.27 to –0.68; *P*<0.001) were significantly lower in fetuses with CoA. Conversely, mean PA diameter *z* score was significantly higher in fetuses with CoA than in controls (MD, 0.73; 95% CI, 0.32–1.13; *P*<0.001) (Figure 3). Mean difference of ultrasound parameters which were reported only in single studies could not be plotted in a quantitative synthesis are reported in online-only Data Supplement Table III.

Few studies reported the ratios between different continuous cardiovascular morphological parameters, and a quantitative synthesis could be performed for only 5 parameters (Table 3). RV/LV and PA/AAo diameters were significantly higher in fetuses with CoA than in controls (MD, 0.21; 95% CI, 0.04–0.39; *P*=0.02 and MD, 0.43; 95% CI, 0.07–0.78; *P*=0.02, respectively), whereas AoI/AD diameter was lower in fetuses with CoA than in those without CoA (MD, –0.13, 95% CI, –0.19 to –0.08; *P*<0.001) (Figure 4).

The majority of the signs detected at fetal echocardiography were reported by single studies and thus could not be integrated in the quantitative synthesis (online-only Data Supplement Table IV).

Quantitative data synthesis was possible for 5 categorical variables: PLSVC, ventricular septal defect, coarctation shelf, hypoplastic aortic arch, and BAV. PLSVC (*P*=0.85), ventricular septal defect (*P*=0.12), and BAV (*P*=0.20) were not associated with an increased risk of CoA, whereas the presence of coarctation shelf was significantly more common in fetuses with CoA than in controls (OR, 26.0; 95% CI, 4.42–153; *P*<0.001) (Table 4, Figure 5). Last, hypoplastic aortic arch, defined as a subjective observation, was independently associated with the occurrence of CoA (OR, 38.2; 95% CI, 3.01–486; *P*=0.005)

Summary estimates of sensitivity, specificity, LR+, LR–, and diagnostic OR to predict CoA were computed by using the hierarchical summary receiver operating characteristic model for all categorical variables presented in Table 4 (Figure 6). The presence of hypoplastic aortic arch showed the overall best diagnostic performance in detecting CoA in fetuses with vascular disproportion with a sensitivity of 90.0%; 95% CI, 48.6 to 98.8; a specificity of 87.1%; 95% CI, 59.4 to 96.9; a LR+ of 6.99, 95% CI, 1.73 to 28.2; a LR– of 0.12, 95% CI, 0.014 to 0.91; and a diagnostic OR of 60.8; 95% CI, 3.16 to 1169. Coarctation shelf had a high specificity (97.7%; 95% CI, 88.0–99.9), but was affected by a low sensitivity

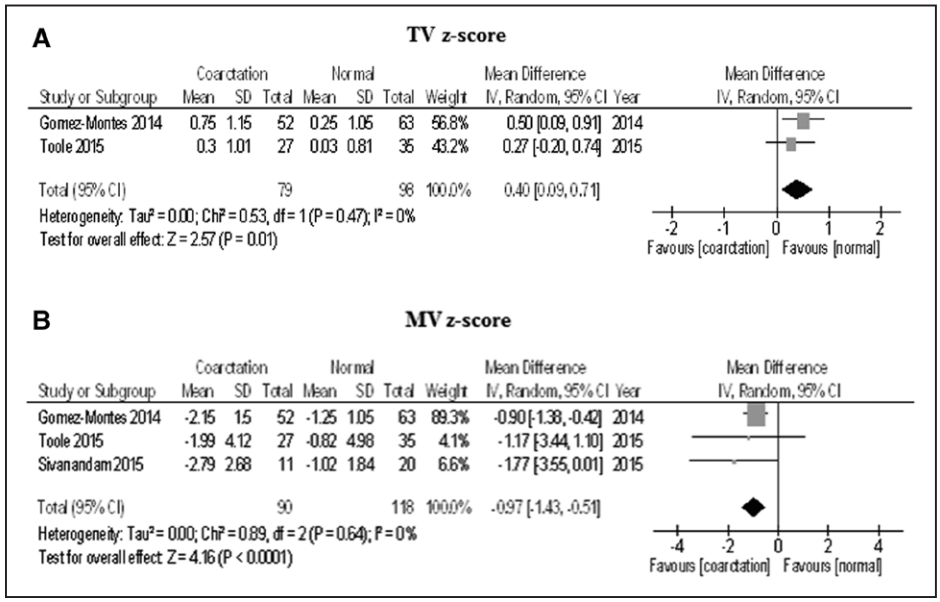

Figure 2. MD-AV valves. Results of the meta-analysis comparing the mean tricuspid valve (TV) (**A**) and mitral valve (MV) (**B**) *z* scores of fetuses with CoA in comparison with those without CoA. AV indicates aortic valve; CI, confidence limit; CoA, coarctation of the aorta; IV, inverse-variance approach; MD, mean difference; and SD, standard deviation.

Table 3. Results of the Meta-Analyses Comparing the Echocardiographic Parameters of Different Cardiac Structures in Fetuses With Diagnosis of Coarctation of the Aorta Versus Normal Fetuses

Continuous Parameters	No. Studies (Total Sample)	Reference	n/N*	Mean Difference (95% CI)	*P* Value	I^2, %
Atrioventricular valves						
Tricuspid valve *z* score	2 (177)	15,19	79/98	0.40 (0.09 to 0.71)	0.01†	0
Mitral valve *z* score	3 (208)	15,18,19	90/118	–0.97 (–1.43 to –0.51)	<0.001†	0
Outflow tracts						
Aortic valve *z* score (based on GA)	4 (383)	15,17–19	130/253	–1.19 (–1.56 to –0.82)	<0.001†	32
Ascending aorta *z* score (based on GA)	2 (177)	15,19	79/98	–0.95 (–1.97 to 0.07)	0.07	85
Ascending aorta diameter, mm	2 (84)	16,21	21/63	–0.78 (–2.86 to 1.31)	0.47	87
Aortic isthmus *z* score (sagittal view)	4 (248)	14,15,18,19	110/138	–1.24 (–2.27 to –0.22)	0.02†	82
Aortic isthmus *z* score (3-vessel view)	3 (178)	16,18,19	72/106	–1.47 (–2.27 to –0.68)	<0.001†	74
Aortic isthmus diameter, mm	2 (84)	16,21	21/63	–0.99 (–1.21 to –0.77)	<0.001†	0
Pulmonary valve *z* score	2 (177)	15,19	79/98	0.73 (0.32 to 1.13)	<0.001†	0
Ratios						
Right ventricle/left ventricle (diameters, mm)	2 (72)	14,16	29/43	0.21 (0.04 to 0.39)	0.02†	0
Right ventricle/left ventricle (areas, mm^2)	2 (102)	14,15	47/55	0.25 (–0.01 to 0.51)	0.06	0
Pulmonary artery/ascending aorta (diameters, mm)	4 (217)	15,19–21	81/136	0.43 (0.07 to 0.78)	0.02†	90
Aortic isthmus/arterial duct (diameters, mm)	2 (161)	15,19	63/98	–0.13 (–0.19 to –0.08)	<0.001†	0
Arterial duct/aortic isthmus (diameters, mm)	2 (70)	14,16	28/42	0.24 (–0.17 to 0.65)	0.25	82

CI indicates confidence interval; CoA, coarctation of the aorta; and GA, gestational age.
*n indicates the overall number of fetuses affected by CoA; and N, the overall number of fetuses not affected by CoA.
†Statistically significant value.

(Table 4). All other parameters in isolation had an overall poor diagnostic accuracy in detecting CoA prenatally.

Multiparametric diagnostic models integrating different ultrasound signs for the detection of CoA were reported only by 4 studies[14–16,19] (Table 5). Because all these models integrate different variables with different cutoffs, it was not possible to perform a quantitative data synthesis. In the study by Toole et al[15] a multiple–risk factors model incorporating MV diameter, MV/TV ratio, isthmus/ductal diameter ratio, and isthmus–ductal angle had an area under the curve of 0.92 (95% CI, 0.80–1.00) with a sensitivity of 85% and a specificity of 60%, best predictive accuracy was accomplished by AAo *z* score + AoI *z* score (3 vessels and trachea view) before 28 weeks of gestations with an area under the curve of 0.98 (95% CI, 0.94–1.0) in the study by Gomez Montes et al.[19] In the study by Arya et al,[14] the best combination of sensitivity and specificity was accomplished by a predictive model integrating the angle between the ascending aorta and descending aorta and that between the transverse aorta and descending aorta. In the study by Mărginean et al[16] a combination of RV/LV<1.5, AoI <4.2 mm, and AD/AoI >1.4 gave the overall best predictive accuracy for CoA, although it was affected by a low sensitivity (55.56%; 95% CI, 21.2–86.3) (Table 5).

DISCUSSION

Main Findings

The findings of this systematic review show that fetuses with CoA have significant differences in several parameters, particularly in the left inflow (mean MV diameter *z* score) and outflow tracts (mean AoV and AoI diameter *z* scores, and RV/LV, PA/AAo, and AoI/AD ratios). The presence of a coarctation shelf or hypoplastic arch were associated with a significantly increased risk of CoA (OR, 26.0; 95% CI, 4.42–153 and OR, 38.2; 95% CI, 3.01–486, respectively). The prenatal detection rate of CoA was significantly increased when a multiple-criteria prediction model was adopted.

Large multicenter prospective studies including fetuses with different risk factors for CoA are needed to ascertain the actual diagnostic performance of fetal echocardiography in diagnosing CoA.

Strengths and Limitations

Retrospective design, small number of included cases, different GA at scan, imaging protocols adopted, and lack of definition of the optimal cutoff for many

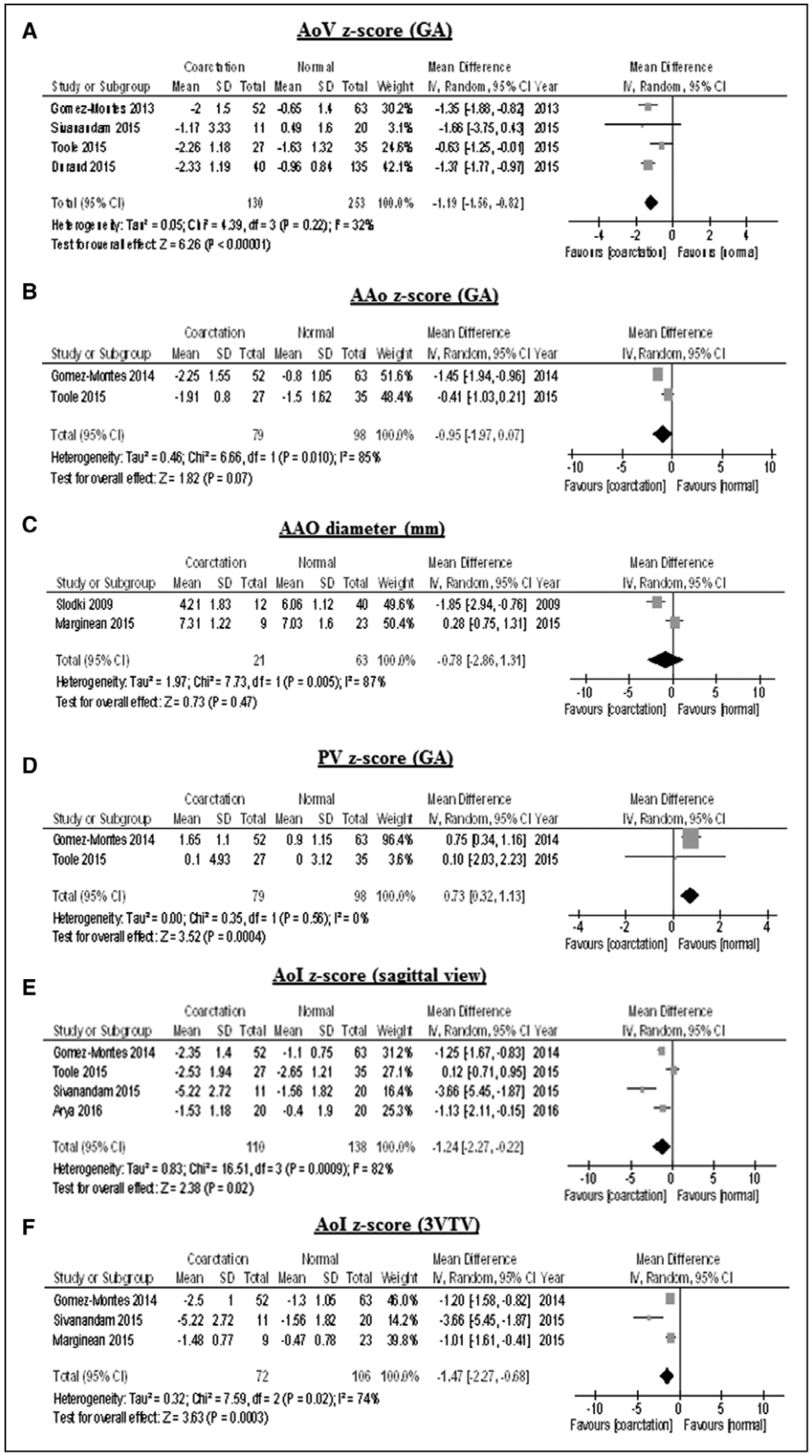

Figure 3. MD-outflow tracts. Results of the meta-analysis comparing the mean aortic valve (AoV) *z* score (**A**), ascending aorta (AAO) *z* score (**B**), ascending aorta (AAO) diameter (mm) (**C**), pulmonary valve (PV) *z* score (**D**), and aortic isthmus (AoI) *z* score in the sagittal view and 3 vessels and trachea view (3VTV), respectively (**E** and **F**) of fetuses with CoA in comparison with those without CoA. CI indicates confidence limit; CoA, coarctation of the aorta; GA, gestational age; IV, inverse-variance approach; MD, mean difference; and SD, standard deviation.

of the included variables represent the major limitation of this systematic review. Because the included cases are fetuses at high risk of CoA, it is possible that the figures we reported may not reflect the actual association between a given sign and the occurrence of the disease. The majority of the ultrasound signs associated with CoA were reported only by single studies and thus a comprehensive quantitative data

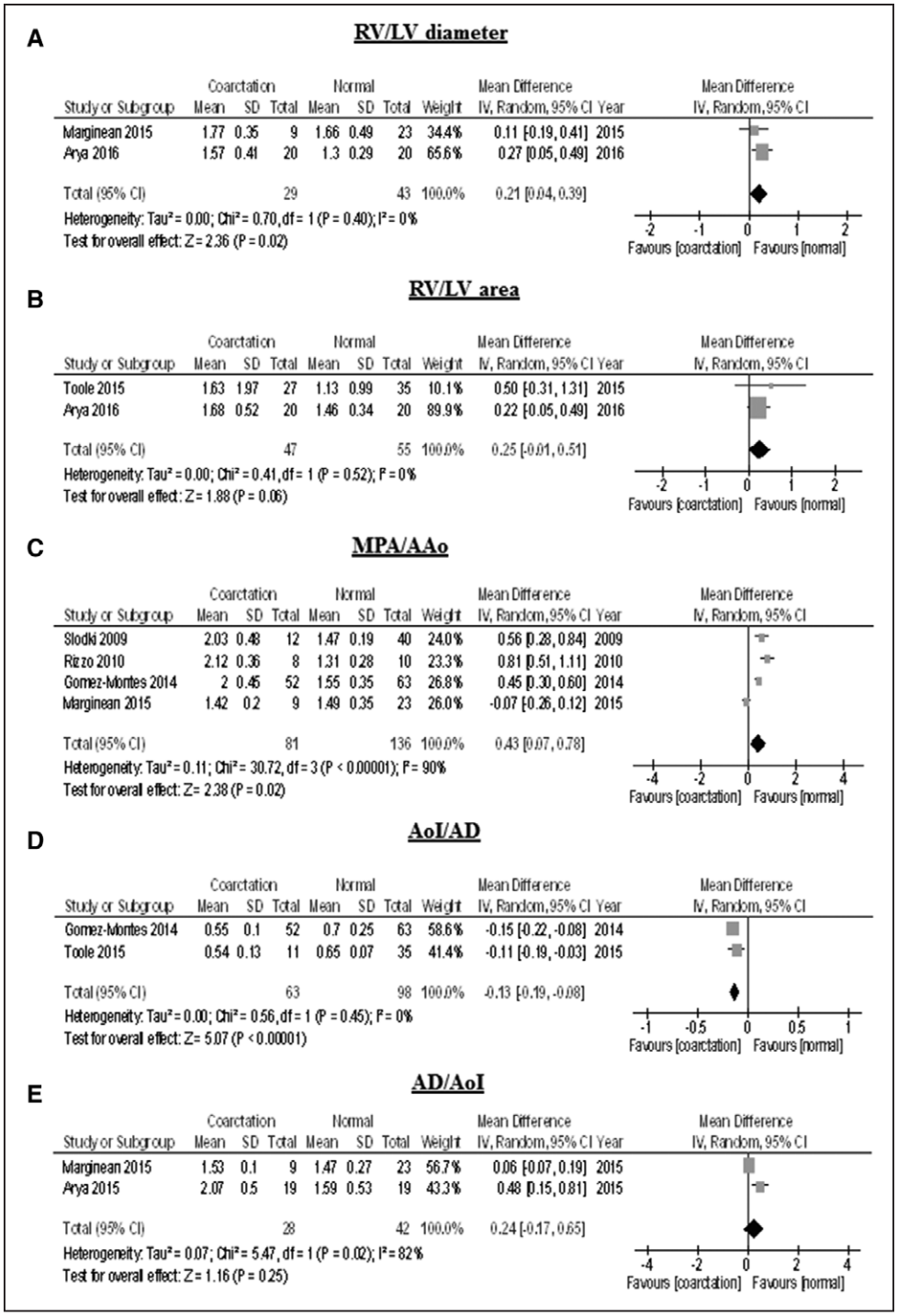

Figure 4. MD ratios.
Results of the meta-analysis comparing the mean ratios of RV/LV diameter (**A**), RV/LV area (**B**), MPA/AAo (**C**), AoI/AD (**D**), and AD/AoI (**E**) of fetuses with CoA in comparison with those without CoA. AAo indicates ascending aorta; AD, arterial duct; AoI, aortic isthmus; CI, confidence limit; CoA, coarctation of the aorta; IV, inverse-variance approach; MD, mean difference; MPA, main pulmonary artery; RV/LV, right ventricular/left ventricular; and SD, standard deviation.

synthesis could not be performed. Despite all these limitations, this review represents the most up-to-date overall assessment of fetal echocardiography in detecting CoA prenatally, potentially being the basis for prenatal counseling.

Implications for Clinical Practice

Accurate prenatal diagnosis of CoA allows a preplanned management of the condition, thus reducing the burden of short- and long-term morbidities associated with this anomaly.[3] Despite this, prenatal diagnosis of CoA is chal-

Table 4. Likelihood of Presenting Each Cardiovascular Anomaly in Fetuses With a Diagnosis of Coarctation of the Aorta Versus Normal Fetuses

Categorical Parameters	No. Studies	References	Total Sample	OR (95% CI)	*P* Value	I^2, %	Sensitivity % (95% CI)	Specificity % (95% CI)	DOR (95% CI)	LR+ (95% CI)	LR– (95% CI)
PLSVC	8* Ω	14–17,19,22-24	662	1.08 (0.48–2.42)	0.85	51	11.7 (7.39–18.0)	89.6 (79.4–95.1)	1.14 (0.57–2.30)	1.12 (0.60–2.10)	0.98 (0.92–1.06)
VSD	8* Ω	14,16–18,22-25	554	2.33 (0.80–6.80)	0.12	73	26.9 (16.5–40.6)	87.2 (77.9–91.7)	2.30 (0.83–6.34)	1.95 (0.87–4.36)	0.85 (0.68–1.05)
Shelf	2† Ψ	18,23	75	26.0 (4.42–153)	<0.001‡	0	48.4 (30.2–66.9)	97.7 (88.0–99.9)	26.0 (4.42–153)	13.9 (2.76–69.6)	0.54 (0.39–0.76)
Hypoplastic aortic arch	5* Ω	14,17,19,23,24	506	38.2 (3.01–486)	0.005‡	90	90.0 (48.6–98.8)	87.1 (59.4–96.9)	60.8 (3.16–1169)	6.99 (1.73–28.2)	0.12 (0.014–0.91)
Bicuspid aortic valve	6* Ω	14,16–18,23,25	360	4.79 (0.45–51.2)	0.20	84	24.8 (14.9–38.4)	95.7 (75.4–99.4)	7.35 (0.90–59.9)	5.78 (0.81–41.4)	0.78 (0.66–0.94)

For each parameter, summary estimates of sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR–), and diagnostic odds ratio (DOR) to predict coarctation of the aorta were also computed. Depending on the number of studies, computations were based on the DerSimonian-Laird random-effects or hierarchical summary receiver operating characteristic (HSROC) model. CI indicates confidence interval; OR, odds ratio; PLSVC indicates persistent left superior vena cava; and VSD, ventricular septal defect

*HSROC model.

†DerSimonian-Laird random-effects model.

‡Statistically significant value.

lenging. The overall detection rate of prenatal ultrasound in identifying this anomaly has been reported to be poor at the time of the routine anomaly scan.[5] The overall diagnostic performance of cardiovascular disproportion during a third trimester scan is poor and is associated with a high false-positive rate. Moreover, routine third-trimester scan is not universally performed, unless fetal or maternal complications are suspected, and it is usually performed almost exclusively to assess fetal growth. In this scenario, the presence of cardiovascular disproportion may be easily overlooked, thus explaining the reported low detection rate for CoA. The definition of cardiovascular disproportion is usually subjective, and structurally normal fetal hearts in the third trimester of pregnancies exhibit a slight degree of physiological disproportion.[25] Conversely, disproportion detected in the late second or early third trimester of pregnancies carries an increased risk for the occurrence of CoA. In the current review, a disproportion of PV/AoV ratio >1.6 was significantly associated with CoA with an OR of 15.11 (95% CI, 6.80–33.6). However, when translated into a predictive model, it had a good sensitivity (86.2%; 95% CI, 77.5–92.4), but a low specificity (51.8%; 95% CI, 46.1–57.4).

The findings of this systematic review show that, in fetuses at risk, detailed assessment of several cardiac parameters might help in stratifying the risk for CoA.

These results are mainly applicable to fetuses with cardiovascular disproportion on the third-trimester ultrasound, and, therefore, the actual performance of prenatal ultrasound when applied on an unselected population needs further evaluation.[26]

Coarctation shelf refers to a prominent posterior infolding in the vessels media, which may extend around the entire circumference of the aorta. It is more commonly detected after birth when ductal tissue believed to encircle the aorta constricts during ductal closure. On the basis of the concept that abnormal insertion of the ductus arteriosus into the descending aorta during development might not only play an important role in the development of CoA, but also affect the shape of the aortic arch, evaluation angle between segments of the aortic arch, and the ductus arteriosus has been suggested to be useful for diagnosing CoA.[14,15] The presence of the shelf had a high specificity but a low sensitivity for CoA, which is explained in part by difficulties in the visualization at prenatal echocardiography. In the present review, hypoplastic aortic arch, mainly assessed in fetuses with ventricular disproportion, showed the best combination of sensitivity and specificity for CoA. Specific cutoffs for defining the arch as hypoplastic have not been reported yet, and the diagnosis is mostly subjective.

PLSVC has been associated with the occurrence of CoA in other prenatal series.[27,28] In our study, PLSVC did not significantly increase the risk for CoA but this finding might be influenced by the nature of the population reported in the included studies, and PLSVC may represent an independent risk factors in for CoA in fetuses not showing any suspicious sign of CoA.

BAV is commonly associated with CoA in the postnatal series.[29] Although its occurrence was higher in fetuses with CoA in the current review, BAV was not associated with a significantly increased risk for this anomaly and was affected by an overall poor diagnostic performance (Table 4).

Spectral and color Doppler ultrasound are commonly used in clinical practice to confirm CoA, but our review

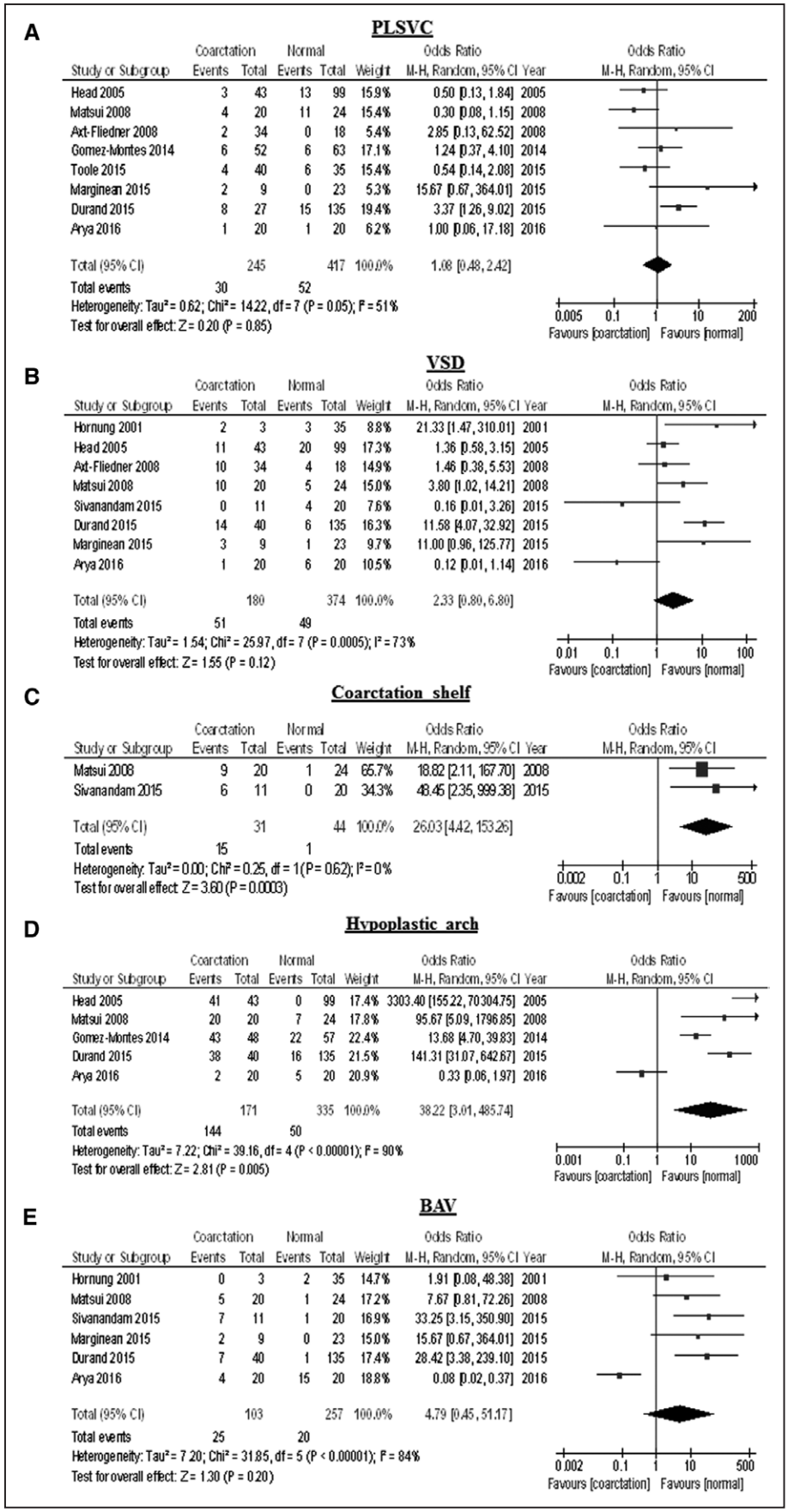

Figure 5. Odds ratios.
Results of the meta-analysis comparing the risk of PLSVC (**A**), VSD (**B**), coarctation shelf (**C**), hypoplastic arch (**D**) and BAV (**E**) in fetuses with CoA in comparison with those without CoA. BAV indicates bicuspid aortic valve; CI, confidence limit; CoA, coarctation of the aorta; M-H, Mantel-Haenszel test; PLSVC, persistent left superior vena cava; and VSD, ventricular septal defect.

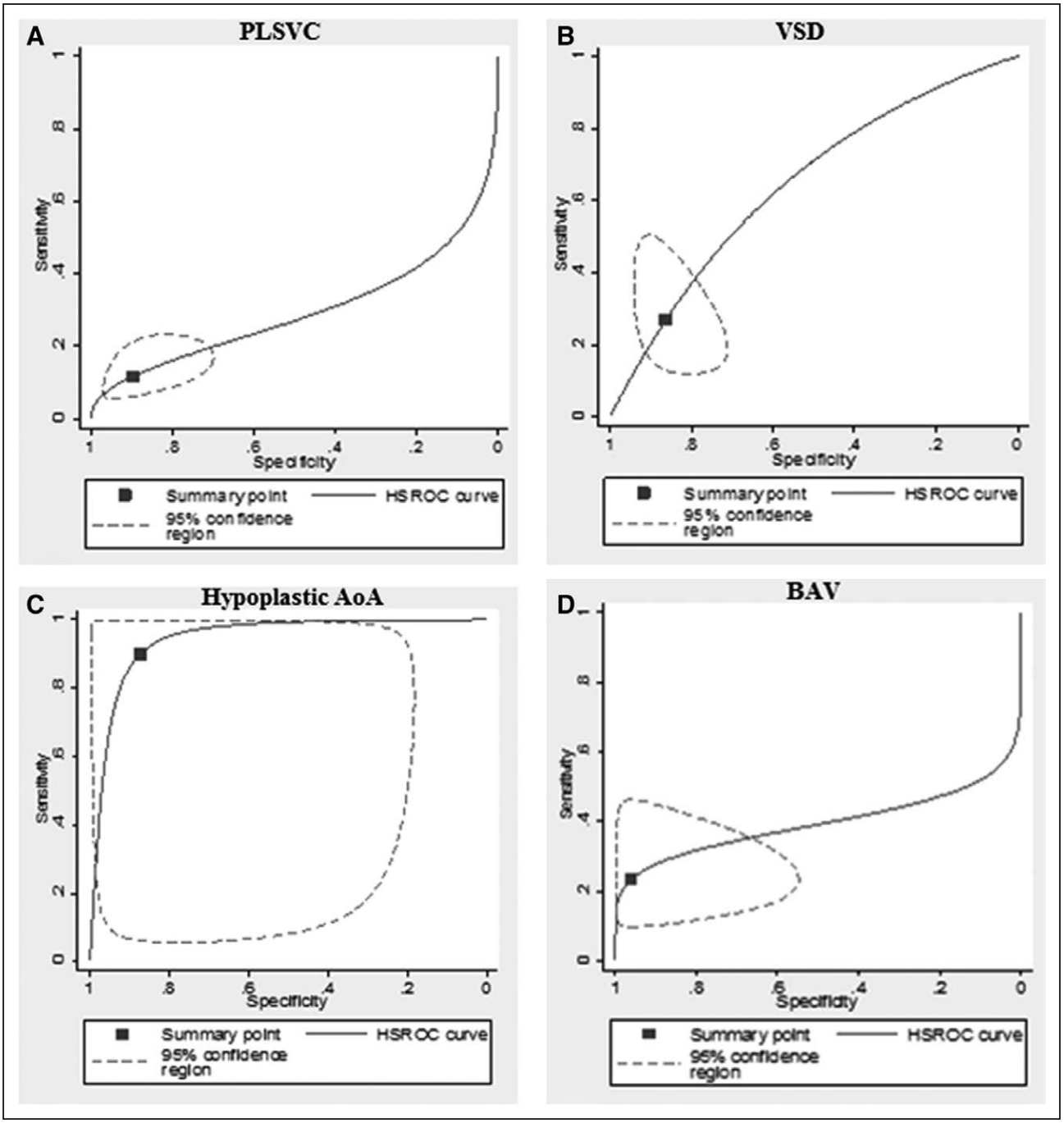

Figure 6. Hierarchical summary receiver operating characteristic.
Hierarchical summary receiver-operating characteristics (HSROC) curves of the diagnostic performance of persistent left superior vena cava (PLSVC) (A), ventricular septal defect (VSD) (**B**), hypoplastic aortic arch (AoA) (**C**), and bicuspid aortic valve (BAV) (**D**) detected on ultrasound for the detection of coarctation of the aorta. Curves from the HSROC model contain a summary operating point (■) representing summarized sensitivity and specificity point estimates for individual study estimates (dotted lines: 95% confidence interval).

could not quantify their role because only 1 study reported their use (online-only Data Supplement Table V).

GA at scan represents another relevant issue. It has been reported[19] that the diagnostic accuracy of ultrasound in detecting CoA prenatally may be improved by using different cutoffs according to the GA at scan but, in the present review, it was not possible to perform the analysis stratifying by GA. Further studies are needed to ascertain the contribution of GA at ultrasound in the prenatal diagnosis of CoA.

Assessment of fetal hemodynamics using prenatal cardiac MRI has been recently suggested to add useful information in fetuses affected by left-sided congenital

Table 5. Predictive Models for Coarctation of the Aorta Integrating Multiple Risk Factors

Author	Year	Predictive model	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Arya [14]	2016	AAo-DAo angle+TAo-DAo angle	NS	95 (75–100)	100 (83–100)
Toole[15]	2015	MV d+MV/TV ratio+ IDD+IDA+IDD	0.92 (0.80–1.00)	85 (66–96)	60 (42–76)
Mărginean[16]	2015	RV/LV<1.5+AoI <4.2 mm + AD/AoI >1.4	NS	56 (21–86)	87 (66–97)
Gomez-Montes[19]	2014	*z* score AAo + *z* score AoI (sagittal view) (≤28 wk)	0.88 (0.72–1.00)	60 (41–77)*	78 (45–94)†
Gomez-Montes[19]	2014	*z* score AAo + *z* score AoI (3VT view) (≤28 wk)	0.98 (0.94–1.00)	91 (76–97)*	91 (62–98)†
Gomez-Montes[19]	2014	*z* score AAo + TV/MV ratio (≤28 wk)	0.85 (0.71–0.99)	44 (29–59)*	69 (42–87)†
Gomez-Montes [19]	2014	*z* score AAo + MPA/AAo ratio (≤28 wk)	0.87 (0.76–0.99)	78 (63–88)*	62 (36–82)†
Gomez-Montes[19]	2014	*z* score AoI (sagittal view) + *z* score AoI (3VT view) (≤28 wk)	0.97 (0.91–1.00)	86 (65–95)*	89 (57–98)†
Gomez-Montes[19]	2014	*z* score AoI (sagittal view) + TV/MV ratio (≤28 wk)	0.82 (0.63–1.00)	23 (11–42)*	70 (40–89)†
Gomez-Montes [19]	2014	*z* score AoI (sagittal view) + MPA/AAo ratio (≤28 wk)	0.85 (0.72–0.98)	68 (48–83)*	44 (19–73)†
Gomez-Montes[19]	2014	*z* score AoI (3VT view) + TV/MV ratio (≤28 wk)	0.94 (0.84–1.00)	87 (71–95)*	83 (55–95)†
Gomez-Montes[19]	2014	*z* score AoI (3VT view) + MPA/AAo ratio (≤28 wk)	0.89 (0.75–1.00)	48 (32–65)*	82 (52–95)†
Gomez-Montes[19]	2014	TV/MV ratio + MPA/AAo ratio (≤28 wk)	0.82 (0.67–0.96)	44 (29–59)*	54 (29–77)†
Gomez-Montes[19]	2014	GA+ *z* score AAo + *z* score isthmus (3VT view) + PV/AV (≤28 wk)	0.85 (0.73–0.98)	40 (26–54)*	64 (39–84)†
Gomez-Montes[19]	2014	TV/MV ratio +MPA/AAo ratio (>28 wk)	0.84 (0.67–1.00)	63 (31–86)*	43 (30–58)†
Gomez-Montes[19]	2014	GA+ *z* score AAo + *z* score AoI (3VT view) + PV/AV (>28 wk)	0.90 (0.83–0.98)	44 (19–73)*	82 (69–90)†

AAo indicates ascending aorta; AD, arterial duct; AoI, aortic isthmus; AUC, area under the curve; AV, aortic valve; CHD, congenital heart defect; CI, confidence interval; d, diameter; DAo, descending aorta; GA, gestational age; IDA, isthmus-ductal angle; IDD, isthmus:ductal diameter; LV, left ventricle; MPA, main pulmonary artery; MV, mitral valve; PV, pulmonary valve; RV, right ventricle; TAoA, transverse aortic arch; TV, tricuspid valve; and 3VT, 3 vessels and trachea.

*For 10% false-positive rate.

†For 10% false-negative rate.

heart defects and to correlate with lung and brain development.[30] Ascertaining the role of fetal cardiac MRI as a potential diagnostic tool for CoA is challenging, but it might help to confirm or refute the diagnosis in some cases of ventricular or great vessel disproportion.

CONCLUSION

Detailed fetal echocardiography can stratify the risk for CoA in fetuses with a suspected diagnosis. Prenatal detection rate of CoA may improve when a multiple-criteria prediction model is adopted. Further large multicenter studies sharing the same imaging protocols are needed to develop objective models for risk assessment in these fetuses, and to ascertain the actual diagnostic performance of prenatal ultrasound in detecting this anomaly.

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FOOTNOTES

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