**Risk factors for coarctation of the aorta on prenatal ultrasound:**

**a systematic review and meta-analysis**

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**Short title:** Risk factors for coarctation of aorta

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**ABSTRACT**

**Background:** Prenatal diagnosis of 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-effect and HSROC model meta-analyses were used to analyse the data.

**Results:** 794 articles were identified and 12 (922 fetuses at risk for CoA) 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 compared to those without CoA (p=0.01). Mean Aortic valve diameter z-score was lower in fetuses with CoA compared to normal fetuses (p= <0.001), but the ascending aorta diameter, expressed as z-score or mm, 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 three-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 compared to controls, while aortic isthmus/arterial duct diameter ratio was lower in fetuses with CoA compared to those without CoA (p<0.001). The presence of coarctation shelf and aortic arch hypoplasia were more common in fetuses with CoA compared to controls (OR: 26.0, 95% CI 4.42-153, p<0.001 and OR: 38.2, 95% CI 3.01-486, p=0.005), while 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. Multi-parametric 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 multicentre studies sharing the same imaging protocols are needed in order to develop objective models for risk assessment in these fetuses.

**CLINICAL PERSPECTIVES**

**What is new?**

Fetuses affected by CoA show differences in the left inflow (MV diameter z-score) and outflow tracts (AoV and AoI diameter z-scores, RV/LV and PA/AAo AoI/Ad ratios) cardiac parameters. The presence of a coarctation shelf or hypoplastic arch was 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). Multi-parametric 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 in order to ascertain the diagnostic performance of ultrasound in detecting CoA prenatally.

**INTRODUCTION**

Coarctation of the aorta (CoA) is one of the most common congenital heart defects (CHD) in the paediatric population accounting for 5 to 8% of children with CHD (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 centre with paediatric cardiology service, starting prostaglandin infusion immediately after birth in order 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 re-intervention later in life (4).

Prenatal detection of CoA has been reported to be generally poor and this anomaly is usually not suspected until the third trimester of pregnancy when ventricular and/or vascular disproportion is detected (5,6). However, as 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, in order 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 05.02.2016 utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for “coarctation of aorta”, “prenatal diagnosis” and “ultrasound” (Supplemental Table 1). The search and selection criteria were restricted to 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 (AF, MM) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus; full text copies of those articles were obtained and the same two reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. If more than one study was published for the same cohort with identical endpoints, 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 Supplemental Table 2 .

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS). According to NOS, each study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment outcome of interest (10). According to NOS a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two 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 with as compared to those without CoA that had their diagnosis confirmed or refuted at post-natal imaging and/or surgery. The analysed 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 ultrasound parameters assessed were:

* 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/aortic isthmus angle (DAo/AoI), MPA/AoI, AoI/AD, AD/AoI diameter.
* Doppler signs: AoI pulsatility index (PI), AoI peak systolic velocity (PSV), 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 (VSD), bicuspid aortic valve (BAV), coarctation shelf, arch hypoplasia, left common carotid to left subclavian artery distance (LCSA), carotid subclavian index (CSI), AAo/DAo angle, transverse aortic arch/descending aorta angle (TAo–DAo angle), AoI-AD angle.

Either z-scores, computed upon gestational age (GA) and femur length (FL), 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 compared to those without.

Studies excluded were :

* 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 of published before 2000 as we considered that advances in prenatal imaging techniques, improvements in the diagnosis and definition of fetal cardiac anomalies make these less relevant.
* Studies not providing a clear classification of the anomaly
* case reports, conference abstracts and case series with fewer than 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-effect model and computed a summary mean difference, its 95% confidence interval (CI) and the relative intra-study heterogeneity (which was quantified using the I2 metric). Then we used random-effect meta-analysis to compute a summary odd 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 (HSROC) model to compute summary estimates of sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR-) and diagnostic odds ratio (DOR) (11,12). Rutter and Gatsonis HSROC parameterization was used because its hierarchical modelling 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 less than four study estimates could be pooled, the DerSimonian-Laird random-effect model was used.

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

**RESULTS**

***Study selection and characteristics***

794 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). 922 fetuses undergoing echocardiography for the suspicion of CoA were included; out of these, 283 (30.69%, 95% CI 27.7-33.8) were confirmed to have a CoA post-natally.

Ventricular disproportion was defined as a ratio between the right and left ventricles >1.5, 1.6 and 1 in three studies, respectively, while the majority did not report any specific cut-off (16, 21, 25). Three studies (17,19,21) reported a cut-off 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= <0.001, I2: 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; DOR: 15.1, 95% CI 6.80-33.5).

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

***Synthesis of the results***

The mean MV diameter z-score was significantly lower in fetuses with CoA compared to those without CoA (mean difference, MD: -0.97, 95% CI -1.43; -0.51, p<0.001), while the mean TV diameter z-score was significantly higher in fetuses with CoA compared to controls (MD: 0.40, 95% CI 0.09; 0.71; p=0.01) (Figure 2).

The mean AoV diameter z-score computed upon GA was significantly lower in fetuses with CoA compared to normal fetuses (MD: -1.19, 95% CI -1.56; -0.82, p= <0.001), while 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 two studies. The mean AoI diameter z-scores measured either in sagittal view (MD: -1.24, 95% CI -2.27; -0.22, p= 0.02) or in 3VTV (MD: 1.47, 95% CI -2.27; -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 compared to 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 and thus could not be plotted in a quantitative synthesis are reported in Supplemental Table 3.

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

The majority of the signs detected at fetal echocardiography was reported by single studies and thus could not be integrated in the quantitative synthesis (Supplemental Table 4).

Quantitative data synthesis was possible for five categorical variables: PLSVC, VSD, coarctation shelf, hypoplastic aortic arch and BAV. PLSVC (p= 0.85), VSD (p= 0.12) and BAV (p= 0.20) were not associated with an increased risk of CoA, while the presence of coarctation shelf was significantly more common in fetuses with CoA compared to controls (OR: 26.0, 95% CI 4.42-153, p<0.001) (Table 4, Figure 5). Finally, 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+ and LR- and DOR to predict CoA that were computed using the HSROC model for all categorical variables included in the data synthesis are presented in Table 4 (Figure 6). The presence of an 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 48.6-98.8, a specificity of 87.1%, 95% CI 59.4-96.9, a LR+ of 6.99, 95% CI 1.73-28.2, a LR- of 0.12, 95% CI 0.014-0.91 and a DOR of 60.8, 95% CI 3.16-1169. Coarctation shelf had a high specificity (97.7%, 95% CI 88.0-99.9), but was affected by a low sensitivity (Table 4). All other parameters in isolation had an overall poor diagnostic accuracy in detecting CoA prenatally.

Multi-parametric diagnostic models integrating different ultrasound signs for the detection of CoA were reported only by four studies (14-16,19) (Table 5); because all these models integrate different variables with different cut-offs, it was not possible to perform a quantitative data synthesis. In the study by Toole et al. a multiple risk factors model incorporating MV diameter, MV/TV ratio, isthmus/ductal diameter ratio and isthmus–ductal angle had an AUC of 0.92 (95% CI 0.80–1.00) with a sensitivity of 85% and a specificity of 60% (15), while in the study by Gomez-Montes *et al.* the best predictive accuracy was accomplished by AAo z-score + AoI z-score (3VT view) before 28 weeks of gestations with an area under the curve (AUC) of 0.98 (95% CI 0.94-1.0) (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, while in the study by Mărginean et al. 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) (16).

**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, RV/LV and PA/AAo AoI/Ad ratios). The presence of a coarctation shelf or hypoplastic arch was 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 multicentre prospective studies including fetuses with different risk factors for CoA are needed in order 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 cut-off for many 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. Finally, the majority of the ultrasound signs associated with CoA were reported only by single studies and thus a comprehensive quantitative data 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 counselling.

***Implications for clinical practice***

Accurate prenatal diagnosis of CoA allows a pre-planned 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 challenging. 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 carried out 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 (27). 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 ratio was significantly associated with CoA with an OR of 15.11 (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.

Coarctation shelf refers to a prominent posterior infolding in the vessels media, which may extend around the entire circumference of the aortaandit is more commonly detected after birth, when ductal tissue believed to encircle the aorta constricts during ductal closure. Based on 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 and this may be partially explained 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 cut-offs 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 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 colour Doppler ultrasound are commonly used in clinical practice to confirm CoA but our review could not quantify their role because all the investigated signs were reported only by single studies.

Gestational age (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 cut-off 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 in order to ascertain the contribution of GA at ultrasound in the prenatal diagnosis of CoA.

Assessment of fetal haemodynamics using prenatal cardiac magnetic resonance imaging (CMRI) has been recently suggested to add useful information in fetuses affected by left sided CHD and to correlate with lung and brain development (30). Ascertaining the role of fetal CMRI 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 vessels 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 multicentre studies sharing the same imaging protocols are needed in order 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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**Conflict of interest statement**

No conflict of interest to declare by any of the authors.

**References**

1. Rosenthal E. Coarctation of the aorta from fetus to adult: curable condition or life long disease process? Heart. 2005;91:1495–502.
2. Reifenstein GH, Levine SA, Gross RE. Coarctation of the aorta: a review of 104 autopsied cases of the “adult type,” 2 years of age or older. Am Heart J 1947;33:146–68.
3. Franklin O, Burch M, Manning N, Sleeman K, Gould S, Archer N. Prenatal diagnosis of coarctation of the aorta improves survival and reduces morbidity. Heart 2002;87:67-9.
4. Brown ML, Burkhart HM, Connolly HM, Dearani JA, Cetta F, Li Z, Oliver WC, Warnes CA, Schaff HV. Coarctation of the aorta: lifelong surveillance is mandatory following surgical repair. J Am Coll Cardiol 2013;62:1020-5.
5. Tegnander E, Williams W, Johansen OJ, Blaas HG, Eik-Nes SH. Prenatal detection of heart defects in a non-selected population of 30,149 fetuses detection rates and outcome. Ultrasound Obstet Gynecol 2006;27:252-65.
6. Hornberger LK, Sahn DJ, Kleinman CS, Copel J, Silverman NH. Antenatal diagnosis of coarctation of the aorta: a multicenter experience. J Am Coll Cardiol 1994;23:417-23.
7. Henderson LK, Craig JC, Willis NS, Tovey D, Webster AC How to write a Cochrane systematic review. Nephrology (Carlton) 2010;15:617-24.
8. NHS Centre for Reviews and Dissemination. Systematic reviews: CRD’s guidance for undertaking reviews in health care. University of York: York (UK), 2009.
9. Prisma statement. http://www.prisma-statement.org/ [accessed 20 November 2015]
10. GA Wells, B Shea, D O'Connell, J Peterson, V Welch, M Losos, P Tugwell,. Newcastle-Ottawa Scale for assessing the quality of nonrandomised studies in meta-analyses. <http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp>. [accessed 10 February 2016]
11. Cochrane Handobook for Systematic Reviews of Diagnostic Test Accuracy, Chapter 10; <http://srdta.cochrane.org/handbook-dta-reviews>. [accessed 15 January 2016]
12. Glas AS, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. J Clin Epidemiol 2003;56:1129-1135.
13. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. Stat Med 2001;20:2865-84.
14. Arya B, Bhat A, Vernon M, Conwell J, Lewin M. Utility of novel fetal echocardiographic morphometric measures of the aortic arch in the diagnosis of neonatal coarctation of the aorta. Prenat Diagn 2016;36:127-34.
15. Toole BJ, Schlosser B, McCracken CE, Stauffer N, Border WL, Sachdeva R. Importance of Relationship between Ductus and Isthmus in Fetal Diagnosis of Coarctation of Aorta. Echocardiography 2016;33:771-7
16. Mărginean C, Mărginean CO, Muntean I, Togănel R, Voidăzan S, Gozar L.. The role of ventricular disproportion, aortic, and ductal isthmus ultrasound measurements for the diagnosis of fetal aortic coarctation, in the third trimester of pregnancy. Med Ultrason 2015;17:475-81.
17. Durand I, Deverriere G, Thill C, Lety AS, Parrod C, David N, Barre E, Hazelzet T. Prenatal Detection of Coarctation of the Aorta in a Non-selected Population: A Prospective Analysis of 10 Years of Experience. Pediatr Cardiol 2015;36:1248-54.
18. Sivanandam S, Nyholm J, Wey A, Bass JL. Right Ventricular Enlargement In Utero: Is It Coarctation? Pediatr Cardiol 2015;36:1376-81.
19. Gómez-Montes E, Herraiz I, Gómez-Arriaga PI, Escribano D, Mendoza A, Galindo A. A Gestational age-specific scoring systems for the prediction of coarctation of the aorta. Prenat Diagn 2014;34:1198-206.
20. Rizzo G, Arduini D, Capponi A. Use of 4-dimensional sonography in the measurement of fetal great vessels in mediastinum to distinguish true-from false-positive coarctation of the aorta. J Ultrasound Med 2010;29:325-6.
21. Slodki M, Rychik J, Moszura T, Janiak K, Respondek-Liberska M. Measurement of the great vessels in the mediastinum could help distinguish true from false-positive coarctation of the aorta in the third trimester. J Ultrasound Med 2009;28:1313-7.
22. Axt-Fliedner R, Hartge D, Krapp M, Berg C, Geipel A, Koester S, Noack F, Germer U, Gembruch U. Course and outcome of fetuses suspected of having coarctation of the aorta during gestation. Ultraschall Med 2009;30:269-76.
23. Matsui H, Mellander M, Roughton M, Jicinska H, Gardiner HM. Morphological and physiological predictors of fetal aortic coarctation. Circulation 2008;118:1793-801.
24. Head CE, Jowett VC, Sharland GK, Simpson JM. Timing of presentation and postnatal outcome of infants suspected of having coarctation of the aorta during fetal life. Heart 2005;91:1070-4.
25. Hornung TS, Heads A, Hunter AS. Right ventricular dilatation in the fetus: a study of associated features and outcome. Pediatr Cardiol 2001;22:215-7.
26. Quarello E, Trabbia A. high-definition flow combined with spatiotemporal image correlation in the diagnosis of fetal coarctation of the aorta. Ultrasound Obstet Gynecol 2009;33:365-7.
27. Berg C, Knüppel M, Geipel A, Kohl T, Krapp M, Knöpfle G, Germer U, Hansmann M, Gembruch U. Prenatal diagnosis of persistent left superior vena cava and its associated congenital anomalies. Ultrasound Obstet Gynecol 2006;27:274-80.
28. Gustapane S, Leombroni M, Khalil A, Giacci F, Marrone L, Bascietto F, Rizzo G, Acharya G, Liberati M, D'Antonio F. Systematic review and meta-analysis on persistent left superior vena cava on prenatal ultrasound: associated anomalies, diagnostic accuracy and post-natal outcome. Ultrasound Obstet Gynecol 2016. [Epub ahead of print]
29. Siu SC, Silversides CK. Bicuspid aortic valve disease. J Am Coll Cardiol 2010;55:2789-800.
30. Sun L, Macgowan CK, Sled JG, Yoo SJ, Manlhiot C, Porayette P, Grosse-Wortmann L, Jaeggi E, McCrindle BW, Kingdom J, Hickey E, Miller S, Seed M. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. Circulation. 2015 Apr 14;131(15):1313-23.

**Figure Legend**

**Figure 1.** Systematic review flowchart.

**Figure 2.** Results of the meta-analysis comparing the mean tricuspid valve (TV) and mitral valve (MV) z-scores of fetuses with CoA compared to those without CoA.

**Figure 3.** Results of the meta-analysis comparing the mean aortic isthmus (AoI) 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 sagittal view and 3 vessels and trachea view, respectively (3VTV) (e,f) of fetuses with CoA compared to those without CoA.

**Figure 4.** 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 compared to those without CoA.

**Figure 5**. Results of the meta-analysis comparing the risk of PLSVC, VSD, coarctation shelf, hypoplastic arch and BAV in fetuses with CoA compared to those without CoA.

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