# Impact of prospective measurement of outflow tracts in the prediction of coarctation of the aorta

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**CONTRIBUTION**

**What are the novel findings of this work?**

1. Risk equations for prediction of coarctation of the aorta are derived. They can be used to aatribute a risk of coarctation of the aorta (COA) according to specific measurements in a fetus.

2. There is a higher than expected prevalence of bicuspid aortic valve in patients who were suspected, but not proven to have COA.

**What are the clinical implications of this work?**

Measurement of the distal transverse aortic arch and the arterial duct should be routinely included in assessment of fetuses with COA and may improve accuracy of prenatal diagnosis

Parents should be counselled regarding the possibility of a bicusid aortic valve and the implications of this even in the absence of aortic stenosis in the fetus

**ABSTRACT**

**Background:** Prenatal diagnosis of coarctation of the aorta (COA) is associated with reduced mortality and morbidity, however, accurate prenatal prediction remains challenging. To date, studies have measured the outflow tracts retrospectively to gauge the potential to predict COA. Our primary objective was to evaluate prospectively acquired measurements of the outflow tracts in prenatally suspected COA. A secondary aim was to report the postnatal prevalence of bicuspid aortic valve in this cohort.

**Methods:** Measurement of the aortic valve, pulmonary valve, distal transverse aortic arch (DTAA) and arterial duct (AD) diameters were undertaken routinely in fetuses with suspected COA between 2002–2017. Using published reference ranges based on >7000 fetuses from our own unit, z scores were computed.

**Results:** COA was confirmed after birth in 77/149 (52%) cases. DTAA z score and the z score of DTAA:AD were smaller in cases with confirmed COA compared to false positive (FP) (-2.8 vs -1.9, p=0.039; -3.13 vs -2.61, p=0.005, respectively). Multiple regression analysis demonstrated that z scores of DTAA and AD were the only significant predictors (p=0.001). Bicuspid aortic valve was identified in 30% of the FP group.

**Conclusion:** Measurement of the DTAA and AD z scores can be used to attribute risk for postnatal COA in a selected cohort. The significance of the high incidence of bicuspid aortic valve in FP cases merits further study both with respect to aetiology and longer- term significance.

## INTRODUCTION

Prenatal diagnosis of coarctation of the aorta (COA) is associated with reduced morbidity,[1] but it continues to be a difficult form of major congenital heart disease to diagnose with accuracy before birth.[2] Unlike other forms of congenital heart disease, it is associated with a significant false positive diagnosis rate of up to 69%.[3-6] The prenatal diagnosis of COA is suspected when there is asymmetry of the ventricles and/or great arteries with hypoplasia of the aortic arch (figure 1). Studies investigating the impact of measurement of left heart structures to improve the diagnostic accuracy of COA have all been retrospective [6-9] apart from a single prospective study which included less than 40 cases;[10] thus a recent meta-analysis emphasised the need for larger prospective studies.[6]

At our unit, measurement of the relevant cardiac structures have been made routinely by experienced fetal cardiologists permitting evaluation of measurements made at the time of clinical assessment. Furthermore, z scores of the size of the great arteries and aortic arch using data from over 7000 cases have been published recently. This provided an opportunity to investigate the value of measurements made prospectively as part of standard clinical care to predict COA using suitable z scores.[11] A further objective of the study was to document the incidence of bicuspid aortic valve in this cohort.

**METHODS**

Cases of COA suspected by a fetal cardiologist were identified from the cardiac database at the Harris Birth Right Research Centre for Fetal Medicine, King's College Hospital, UK. This is a tertiary fetal cardiology centre in the United Kingdom. Fetuses were included if the main cardiac connections were normal and the attending fetal cardiologist had requested postnatal echocardiography to confirm or refute COA. Echocardiograms performed between 15-36 weeks gestational age were identified between January 2002 and December 2017. The study population comprised suspected cases of isolated COA with a minimum of six months postnatal follow-up to allow for later evolution/presentation of COA.[4] Cases of COA with a VSD and/or persistent left superior vena cava were also included. Exclusion criteria were: co-existent forms of major congenital heart disease (CHD) e.g. transposition of the great arteries, lesions causing abnormal cardiac loading e.g. direct connection of the umbilical vein to the right atrium and pregnancies which resulted in termination, miscarriage or stillbirth. Information about karyotype, nuchal translucency, extracardiac anomalies and outcome was recorded. The endpoint was surgery for COA within the first six months after birth. The decision to initiate prostaglandin E2 or not immediately after birth was made by the attending fetal cardiologist based on the findings at the last fetal echocardiogram. In all cases, the initial postnatal echocardiogram was reviewed and a decision made either to continue prostaglandin E2 if the findings supported a diagnosis of COA or else to observe the baby off prostaglandin E2 with serial clinical and echocardiographic assessment to look for signs of evolving coarctation. The monitoring included four limb blood pressure, clinical review of femoral pulses and measurement of serum lactate. The standard features of postnatal COA were applied including echocardiographic features of flow acceleration at the site of coarctation and loss of pulsatility of the descending aorta. Once clinical or echocardiographic signs of COA emerged then prostaglandin E2 was commenced, and surgery was scheduled. Data on pregnancy

outcome was ascertained from electronic records or patient contact in all women who underwent prenatal ultrasound. Children suspected to have heart disease at the postnatal assessment or community checks are referred to our paediatric cardiac service and therefore cases of congenital heart disease which were missed on routine prenatal screening or specialist fetal echocardiography in our unit would be identified.

**Echocardiographic Measurements**

All measurements were made on cart at the time of the fetal echocardiogram by one of a team of fetal cardiologists and these measurements were retrieved from the archived echocardiogram reports. Thus, the outcome was not known at the time of measurement. When several echocardiographic examinations were available for an individual patient, the dataset closest to 20 weeks gestation was used to compute z scores as the decision regarding site of delivery was made at this gestation. For assessment of the arterial duct, analysis was performed on echocardiograms <28 weeks gestation in view of the possible impact of an aneurysmal or tortuous arterial duct which can be present in the third trimester. Measurements were taken as previously described[11]: the aortic and pulmonary valve were measured in diastole at the maximal diameter with the valve closed and the distal transverse aortic arch diameter (DTAA) and arterial duct (AD) were measured in the 3 vessel and tracheal (3VT) view (figure 2). The outflow tract measurements were converted into gestational age-adjusted z scores using previously published departmental data based on prospectively collected measurements from a population of over 7000 fetuses with a normal outcome.[11] Echocardiograms were performed using the Acuson Aspen Advanced (Acuson, Mountain View, CA) with a 4 to 7 MHz curvilinear probe or a Voluson E8 (GE Medical Systems, Zipf, Austria) with a 4 to 8 MHz or 6 MHz curvilinear probe or a Toshiba Aplio 500 (Canon Medical Systems, Europe) with a 10MHz or 6

MHz appropriate to the gestational age. Postnatal echocardiograms undertaken after the year 2010 (availability of digital echocardiogram archive) were reviewed to ascertain aortic valve morphology.

**Statistical analysis**

Comparison of the two groups according to the outcome measure of operated COA within 6 months of birth was performed. Median values were calculated for all cardiac parameters and analysed using the Mann Whitney test. The performance of test variables was determined using receiver operating characteristic (ROC) curves analysis and logistic regression analysis to assess contribution of cardiac parameters (z scores of aortic valve, pulmonary valve, arterial duct, DTAA and AD:DTAA, aorta:pulmonary ratio) to prediction of postnatal COA. The statistical software package SPSS 24.0 for MAC (SPSS Inc.,Chicago, IL, USA) and Prism 7.0 for MAC (GraphPad software Inc.,CA, USA) was used for data analyses. Analysis of this data acquired for clinical reasons was approved by United Kingdom Health Research Authority (reference no:19/HRA/1096).

## RESULTS

There were 294 pregnancies with suspected COA, of which 171 continued, 93 cases were terminated due to major extracardiac abnormalities, chromosomal anomaly or for the potential for progression to single ventricle circulation. Thirty pregnancies ended in spontaneous intra-uterine death/stillbirth, 17 cases were born in other countries and 3 babies died in the neonatal period. In two cases measurement of the aortic and ductal arch measurements were not performed. Thus, 149 pregnancies were included in this study of whom 77 (52%) were confirmed to have COA within six months of age. The indications for fetal echocardiography were: suspected CHD (n=113), extracardiac anomalies (n=11), family history of CHD (n=5), nuchal translucency >95$^{th}$ centile (n= 20). Two of the fetuses with a family history had paternal history of COA repair. The karyotype was tested prenatally in 73/149 patients and chromosomal/genetic syndromes were identified in 20/149 (15%) patients with: 45XO (n=5), trisomy 21 (n=3), mosaic 45 X0/XY (n=1), microdeletion chromosome 22q11 (n=1), balanced duplications (n=2), 47-XXY (n=1), Coffin-Siris syndrome (n=1), Kabuki syndrome (n=1), Cornelia De Lange (n=1), 13q deletion (n=1), VACTERL (n=1), CHARGE (n=1) and Russell Silver (n=1). The morphology of the aortic valve was identified as bicuspid after birth in 34/60 (57%) of the true COA group and 18/59 (30%) of the false positive group (p=0.04).

### Outcome

The true positive rate of diagnosis of COA was 77/149 (52%) of which 74/149 (49.7%) were diagnosed in the neonatal period and 3/149 (2%) beyond the neonatal period at 5 weeks, 9 weeks and 6 months after birth. There were no known cases of COA which were overlooked on specialized fetal echocardiography or with routine ultrasonography from Kings College Hospital during the study period. True and false positive cases did not differ with respect to gestational age at echocardiogram nor the presence of a

persistent left superior vena cava. A ventricular septal defect (VSD) was present in both true and false positive cases, but was seen more commonly in those with confirmed COA (table 1). The ratio of the aortic:pulmonary valve diameter, DTAA diameter, second trimester ratio of DTAA:AD were significantly smaller in fetuses with confirmed COA (supplementary table 1, supplementary figure 1). With reference to the computed z scores, the aortic valve z score, DTAA z score and second trimester z score of the ratio of DTAA:AD were significantly different between the two groups. No abnormal cardiac, genetic or extracardiac findings were identified after birth in 31/72 (43.1%) cases in the false positive cohort.

Logistic regression analysis demonstrated that DTAA z-score and arterial duct z-score were the only predictive variables. The model explained 18% (Nagelkerke $R^2$) of the variance of outcome and correctly classified 63% of cases. The calculated equation was as follows:

y=-1.54+(-0.559*DTAA z score) + (0.303*AD z score). Other echocardiographic parameters, gestational age at scan, presence of left SVC, aortic valve morphology, presence of VSD were not predictive. Thus, the patient-specific risk for COA can be calculated from the formula: Risk = odds / (1+ odds) where odds = $e^Y$.

**Predictive variables for COA**

Echocardiographic parameters were further assessed for their predictive value using area under the receiver operating characteristics (AUROC) curve (table 3). The sensitivity, specificity, positive predictive value and negative predictive values are provided for DTAA z scores in table 4.

## DISCUSSION

When COA is suspected prenatally, a series of observations and repeated investigations are needed postnatally to confirm or refute the diagnosis whilst the arterial duct constricts. A false diagnosis has a psychological impact on the parents[12] and creates mother-baby separation in the immediate newborn period. In addition to this unnecessary hospitalization, there is the financial impact of neonatal admission to monitor for evolution of a coarctation.[13]

In our assessment of fetuses seen in a fetal cardiology unit and suspected to have COA we have demonstrated that the DTAA z score and the ratio of DTAA:AD z score are smaller in fetuses with confirmed COA. The DTAA z score and the AD z score demonstrate predictive value for COA. Despite the introduction of biometric assessment at the time of prenatal diagnosis the background false positive rate is approximately 50%. Our data shows that computation of both the DTAA and AD z scores can lead to a better stratification of risk which may improve parental counselling and postnatal planning.

### Comparison to published data

Even in expert hands, COA remains a challenging diagnosis to correctly ascertain prenatally as evidenced by the high false positive rate reported in the literature.[6] The single prospective study assessing the impact of prenatal aortic arch measurements in the prediction of COA[10] reviewed 32 cases in the third trimester and confirmed COA in 9. Prediction for COA was improved if ratio of the AD:aortic isthmus and an absolute measurement of the aortic isthmus<4.2mm were used.[10] This threshold value for the aortic isthmus of 4.2mm is above the 50$^{th}$ centile at 32-36weeks gestation and in our cohort gives low specificity for the diagnosis (table 4). That study[10] was one of seven studies included in a recent meta-analysis to identify risk factors for the prenatal diagnosis of COA.[6] Six studies were conducted retrospectively and each

included 31-85 fetuses with suspected COA. The results we present are consistent with the meta-analysis to the extent that a there is a smaller aortic valve and aortic isthmus in fetuses with confirmed COA compared to false positives. In our study, we have provided an additional risk assessment according to DTAA z score and AD z score which can be applied to each case to provide further information for parental counselling. It may also aid in planning postnatal assessment according to risk and potentially reducing neonatal length of stay, mother-baby separation and health care costs.[13]

Other studies[8, 14-16] recommend integration of the isthmus:AD ratio to reduce the false positive rate and our data using the z score of DTAA:AD ratio supports this, but demonstrates an overlap of measurements such that any cut-off would require compromise between diagnostic rate and diagnostic accuracy. This lack of clear cut-off is conceivable given that the initial criteria for diagnosis is subjective appearance of disproportion of the great arteries.

**New findings from this study**

The high incidence of bicuspid aortic valve (BAV) in COA is well recognised,[17] however, the prevalence of BAV in the false positive cohort is reportedly low or not reported.[5, 7, 10, 18-21] Our study provides novel data regarding the unexpectedly high prevalence of BAV (30%) in false positive cases, exceeding the expected population prevalence and that from other studies. The determination of aortic valve morphology was based on postnatal echocardiography due to the difficulty in visualisation before birth. The higher prevalence of BAV in our cohort may be explained by the use of arterial disproportion compared to other studies which only used ventricular asymmetry, a marker for non-cardiac pathology. Only two patients in the false positive group underwent fetal echocardiography for family history of COA/BAV and therefore,

is not a confounder. BAV is associated with development of dilatation of the ascending aorta with advancing age. In paediatric cohorts where there is no aortic valve stenosis/regurgitation or coarctation gradient, the ascending aorta can remain normal.[22] Common gene mutations to bicuspid valve aortopathy and COA such as NOTCH1, MATR3, GATA5 have been reported.[23-25] However, the high incidence of BAV in association with hypoplasia of the aortic arch in utero without postnatal development of COA has not been described previously. We suggest that the potential association with BAV morphology should be included in prenatal counselling and that postnatal surveillance should also assess the aortic valve morphology given the potential consequences of aortic valve stenosis, regurgitation or aortopathy.[26-29]

**Methodological strengths of this study**

These include measurement of the outflow tracts using protocolised criteria, taken on cart at the time of the echocardiogram by specialist fetal cardiologists. Retrospective studies can result in a bias toward inclusion of cases with better image quality, and true blinding to postnatal outcome may be difficult. Secondly, the DTAA was measured on the 3VT view and not used interchangeably with the aortic isthmus measurements on sagittal views of the arch. Thirdly, calculation of z scores used our own published departmental data[11] from >7000 prospectively assessed fetuses whereas previous studies have used z scores from a smaller cohort(<204) of retrospectively assessed fetuses.[15] Furthermore, we have taken a consistent approach to assessment and our conclusions are not constrained by limitations of a meta-analysis combining studies using various methodologies of measurement and small caseloads.

**Future directions**

Although biometry of the great arteries is important, with transition to the neonatal circulation, an increase in left ventricular preload may alter the dimensions of the aortic arch. This may explain why despite a very small DTAA z score, the risk assessment does not reach 100%. Further refinement of prenatal diagnosis may be achieved with complementary physiological methods.[30-36] The association of aortic arch hypoplasia in utero and BAV merits further study.

**Limitations**

Whilst measurements were taken prospectively during the fetal echocardiogram, the measurements were not taken with the *a priori* goal to test our hypothesis. Measurements were made by multiple observers and therefore interobserver variability may occur. Our protocol did not include routine assessment of ventricular size, but focused on the outflow tracts to enhance diagnosis and understanding in this region as it was perceived that these were the crucial areas rather than ventricular sizes.

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**Figure legends**

*Figure 1: Four chamber view and great artery views of two fetuses at 22 weeks gestation with suspected coarctation of the aorta. Both fetuses demonstrate ventricular asymmetry and disproportion of the great arteries. The fetus in panels a-c was proven to have coarctation of the aorta, whereas the fetus in panels d-f did not require surgery for coarctation of the aorta. [Abbreviations: Ao – aorta, PA – pulmonary artery, *: superior vena cava]*

*Figure 2a: The distal transverse aortic arch diameter was measured on the 3 vessel and tracheal view beyond the trachea at the distal point of its widest systolic diameter. 2b: The arterial duct was measured on the 3 vessel view at its widest systolic diameter. Both measurements are made from inner edge to inner edge.*

*Supplementary figure 1. A: Aortic valve z score; B: Distal transverse aortic arch z score; C: Ratio of Distal transverse aortic arch:arterial duct z-score. [Abbreviations: COA coarctation of the aorta]*

*Table 1: Comparison of fetal outflow tract z scores in fetuses with neonatal coarctation of the aorta and false positive cases. Variables are reported as median with range or counts. Mann Whitney test to assess for differences between groups. * indicates there was a significant difference between the false positive and true COA groups. [Abbreviations: DTAA: distal transverse aortic arch, AD: arterial duct, VSD: ventricular septa defect]*

| | **False positive (n=72)** | **True coarctation (n=77)** | **P value** |
|---|---|---|---|
| Median gestational age (range) in weeks | 23 (19-35) | 23 (15-37) | *0.76* |
| Nuchal translucency >95$^{th}$ centile | 12/47 | 13/41 | *0.52* |
| Persistent left SVC | 20/72 (28%) | 16/77 (21%) | *0.32* |
| No. of patients with VSD | 20/72 (28%) | 34/77 (44%) | *0.038** |
| No. of confirmed cases of bicuspid aortic valve | 18/59 (30%) | 34/60 (57%) | *0.004** |
| Aortic valve z score | -1.3 (-4.6 to 3.8) | -1.7 (-4.8 to 2.9) | *0.036** |
| Pulmonary valve z score | 1.1 (-4.3 to 5.2) | 1.8 (-1.3 to 5.4) | *0.058* |
| DTAA z score | -1.9 (-4.0 to 3.8) | -2.8 (-5.5 to 0.4) | *0.039** |
| Arterial duct z score (2$^{nd}$ trimester) | 0.42 (-1.5 to 5.2) | 0.87 (-3.8 to 5.8) | *0.53* |
| Arterial duct z score (all cases) | 0.4 (-1.5 to 11.8) | 0.9 (-3.8 to 7.9) | *0.344* |
| Z score of ratio DTAA:AD z score (2$^{nd}$ trimester) | -2.61 (-4.33 to 2.01) | -3.13 (-5.45 to -0.26) | *0.005* |

| | | | |
|---|---|---|---|
| Z score of ratio DTAA:AD z score (all cases) | -2.61<br>(-4.33 to 2.01) | -3.2<br>(-5.45 to 8.4) | *<0.001** |

*Table 2: Risk assessment (%) for postnatal coarctation of the aorta in fetuses with suspected COA utilizing the DTAA z score and arterial duct z score*

| **Distal transverse aortic arch z score ↓** | **Arterial duct z score** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | -2.0 | -1.5 | -1.0 | -0.5 | 0 | 0.5 | 1.0 | 1.5 | 2.0 |
| DTAA z score -5.5 | 72 | 75 | 77 | 80 | 82 | 84 | 86 | 88 | 89 |
| DTAA z score -5.0 | 66 | 69 | 72 | 75 | 78 | 80 | 83 | 85 | 87 |
| DTAA z score -4.5 | 59 | 63 | 66 | 70 | 73 | 76 | 78 | 81 | 83 |
| DTAA z score -4.0 | 52 | 56 | 60 | 63 | 67 | 70 | 73 | 76 | 79 |
| DTAA z score -3.5 | 45 | 49 | 53 | 57 | 60 | 64 | 67 | 70 | 74 |
| DTAA z score -3.0 | 38 | 42 | 46 | 50 | 53 | 57 | 61 | 64 | 68 |
| DTAA z score -2.5 | 32 | 36 | 39 | 43 | 46 | 50 | 54 | 58 | 61 |
| DTAA z score -2.0 | 26 | 29 | 33 | 36 | 40 | 43 | 47 | 51 | 55 |
| DTAA z score -1.5 | 21 | 24 | 27 | 30 | 33 | 37 | 40 | 44 | 48 |

*Table 3: Comparison of the performance of prospectively acquired fetal echocardiographic measurements in prediction of coarctation of aorta by receiver-operating characteristics curve analysis. [Abbreviations ROC: receiver operating characteristics, DTAA: distal transverse aortic arch]*

| **Variables assessed** | **Area under ROC curve (95% CI)** | ***P value*** |
|---|---|---|
| Aortic valve z-score | 0.570 (0.465-0.675) | *0.19* |
| Ratio of aortic:pulmonary valve | 0.653 (0.563-0.743) | *0.002** |
| Arterial duct z-score (2nd trimester) | 0.541 (0.414-0.668) | *0.53* |
| DTAA z-score | 0.617 (0.515-0.719) | *0.03** |
| Ratio of DTAA:AD (2nd trimester) | 0.656 (0.539-0.773) | *0.06* |
| DTAA:AD ratio z-score (2nd trimester) | 0.656 (0.539-0.773) | *0.06* |

*Table 4: Sensitivity, specificity, positive predictive value and negative predictive value for distal transverse aortic arch z-score values. 95% confidence intervals are provided in parentheses. The false positive rate=1-positive predictive value.*

| | **Sensitivity** | **Specificity** | **Positive predictive value** | **Negative predictive value** | **Fishers exact p value** |
|---|---|---|---|---|---|
| DTAA z-score < -5 | 0.06 (0.02 - 0.14) | 0.99 (0.92 - 1) | 0. 8 (0.38 - 0.99) | 0.51 (0.43 - 0.6) | 0.37 |
| DTAA z-score < -4 | 0.16 (0.09 – 0.26) | 0.96 (0.88 – 0.99) | 0.79 (0.52 – 0.92) | 0.52 (0.44 – 0.61) | 0.05 |
| DTAA z-score < -3 | 0.36 (0.25 - 0.48) | 0.76 (0.65 - 0.85) | 0.6 (0.45 - 0.74) | 0.54 (0.44 - 0.64) | 0.19 |
| DTAA z-score < -2 | 0.66 (0.54 - 0.76) | 0.54 (0.42 - 0.65) | 0.59 (0.47 - 0.69) | 0.61 (0.48 - 0.72) | 0.04 |
| DTAA z-score < -1 | 0.75 (0.63 - 0.84) | 0.27 (0.18 - 0.39) | 0.51 (0.41 - 0.6) | 0.51 (0.36 - 0.67) | 0.99 |