Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

Reference Ranges for the Size of the Fetal Cardiac Outflow Tracts From 13 to 36 Weeks Gestation

A Single-Center Study of Over 7000 Cases

See Editorial by Moon-Grady and Peyvandi

Trisha V. Vigneswaran, MBBS
Ranjit Akolekar, MD
Argyro Syngelaki, PhD
Marietta Charakida, MD, PhD
Lindsey D. Allan, MD
Kypros H. Nicolaides, MD
Vita Zidere, MD
John M. Simpson, MD

BACKGROUND: Assessment of the outflow tract views is an integral part of routine fetal cardiac scanning. For some congenital heart defects, notably coarctation of the aorta, pulmonary valve stenosis, and aortic valve stenosis, the size of vessels is important both for diagnosis and prognosis. Existing reference ranges of fetal outflow tracts are derived from a small number of cases.

METHODS AND RESULTS: The study population comprised 7945 fetuses at 13 to 36 weeks' gestation with no detectable abnormalities from pregnancies resulting in normal live births. Prospective measurements were taken of (1) the aortic and pulmonary valves in diastole at the largest diameter with the valve closed, (2) the distal transverse aortic arch on the 3 vessel and trachea view beyond the trachea at the distal point at its widest systolic diameter, and (3) the arterial duct on the 3 vessel and trachea view at its widest systolic diameter. Regression analysis, with polynomial terms to assess for linear and nonlinear contributors, was used to establish the relationship between each measurement and gestational age. The measurement for each cardiac diameter was expressed as a z score (difference between observed and expected value divided by the fitted SD corrected for gestational age) and percentile. Analysis included calculation of gestation-specific SDs. Regression equations are provided for the cardiac outflow tracts and for the distal transverse aortic arch:arterial duct ratio.

CONCLUSIONS: The study established reference ranges for fetal outflow tract measurements at 13 to 36 weeks' gestation that are useful in clinical practice.

Key Words: aortic valve ■ arterial duct ■ fetus ■ gestational age ■ pulmonary valve

http://circimaging.ahajournals.org

CLINICAL PERSPECTIVE

Before birth, congenital heart disease is typically suspected by recognition of abnormal cardiac anatomy during screening or specialist ultrasound examination. However, for lesions such as coarctation of the aorta, pulmonary stenosis, or aortic stenosis, the size of the outflow tracts relative to that expected at a particular gestational age is an important consideration both for diagnosis and prognosis.

We report gestation-specific reference ranges and z scores for the cardiac outflow tracts from a phenotypically normal population of >7000 fetuses between 13 and 36 weeks' gestation. The pulmonary and aortic valves were measured in diastole at maximal diameter when closed thus enabling visualization of the valve. Previously, measurement of the aortic isthmus was described, but technically this structure is not identifiable on standard transverse views and thus, we describe the measurement of the distal transverse aortic arch at its widest systolic diameter made on the 3 vessel and tracheal view beyond the trachea. Regression analysis, with polynomial terms to assess for linear and nonlinear contributors, was used to establish the relationship between each measurement and gestational age. Gestation-specific SDs were calculated.

We have established reference ranges for fetal outflow tract measurements which should prove useful in clinical practice. They may provide further insight into the natural history of valve lesions in fetal life and provide increased confidence of normal ranges in size across a wide gestational age range.

During fetal life, congenital heart disease is typically suspected either by obstetric ultrasound examination or specialist fetal echocardiography. Over recent years, the outflow tract views have been integrated into routine fetal screening.[1,2] For many forms of congenital heart disease, the primary diagnosis is not based on the size of heart structures but by recognition of abnormal cardiac connections. However, for some cardiac lesions, notably coarctation of the aorta, pulmonary valve stenosis, and aortic valve stenosis, the size of vessels is an important consideration both for diagnosis and prognosis.[3–6] It can be extremely important to compare an observed size of a valve or vessel to a size expected at a particular gestational age (GA).[7] One method of assessing potential deviation from normality is by the use of z scores which describe the number of gestation-specific SDs a given measurement lies from the gestation-specific mean.[8] The impact of this method of assessment is well described in fetal cardiology particularly with respect to prediction of postnatal development of coarctation of the aorta, early neonatal intervention in tetralogy of Fallot and of single versus biventricular repair in cases of critical left or right ventricular outflow tract obstruction,[5,6,9–15] and identification of suitable cases for fetal cardiac intervention.[16–18] Reference ranges of fetal outflow tracts have been published previously, but the number of cases examined was small ranging from 130 to 390.[19–21] Lee at al[22] published a series of 2735 cases, but measurements of the aortic and ductal arches were not reported.

The objective of this study is to report reference ranges for the diameter of fetal aortic valve, pulmonary valve, arterial duct, and distal transverse aortic arch (DTAA) and the ratio of DTAA: arterial duct from the study of 7945 fetuses who had measurements made prospectively at a single tertiary fetal cardiology center.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure but can be available on request. All fetal echocardiograms performed or reported by a fetal cardiologist between 2002 and 2015 were identified from the departmental database (Viewpoint version 5.6, General Electric Healthcare) at Harris Birthright Center for Fetal Medicine at King's College Hospital, London, United Kingdom. The center serves the local population and also receives tertiary referrals for fetal medicine, including fetal cardiology, predominantly from the South East of England. Fetal echocardiography is performed for a wide variety of predefined indications, including family history of congenital heart disease, elevated nuchal translucency, or suspected congenital heart disease. Measurement of the size of the aorta, pulmonary artery, ductal arch, and aortic arch was part of the cardiac protocol throughout the study period, and all measurements were made prospectively. In all cases, pregnancy dating was based on an ultrasound measurement of the fetal crown-rump length at 11 to 13 weeks' gestation. This was a cross-sectional study and measurements of the outflow tracts from each fetus were taken only once. Pregnancy outcome was obtained from the hospital records, general practitioners, or the parents.

Inclusion Criteria

The inclusion criteria were singleton pregnancies with fetal echocardiography at 13 to 36 weeks' gestation, resulting in the live birth of phenotypically normal babies.

Exclusion Criteria

The exclusion criteria were GA <13 and >36 weeks' gestation, prenatal, or postnatal diagnosis of any form of congenital heart disease or variant of normal cardiac anatomy (persistent left superior vena cava, aberrant right subclavian artery, interrupted inferior vena cava, left atrial isomerism, malposition of the heart), major extracardiac defect, chromosomal abnormality, genetic syndrome, termination of pregnancy, and intrauterine or neonatal death.

Measurements

All fetal echocardiograms were reviewed contemporaneously by a fetal cardiologist and measurements were made prospectively at the time of the scan (Drs Vigneswaran, Zidere, Charakida and Professors Allan, Simpson). Our scanning protocol uses a series of transverse views to assess the 4 chamber view and outflow tracts consistent with published recommendations.[1] The left and right ventricular outflow tracts were assessed using this approach, and the aortic arch and ductal arch were assessed in the 3 vessel and tracheal view as shown in Figure 1. Measurements were made with the ultrasound beam orthogonal to the plane of the vessel where possible, but other projections were used if fetal lie was less favorable. Online measurements were made of the aortic valve, pulmonary valve, DTAA, and arterial duct diameters using electronic calipers. Our policy was to measure the semilunar valves at their largest diameter in diastole with the valve closed so that the exact position of the valve was clear. Measurements were made from inner edge to inner edge on 2-dimensional (2D) echocardiography. The aortic arch was measured at its most distal point beyond the trachea at the widest systolic diameter (DTAA). This region is often referred to as the aortic isthmus in fetal life, but as the relationship to the left subclavian artery and arterial duct cannot be determined on this view, we have referred to it as the DTAA. The arterial duct was measured on the same view at its widest systolic diameter (Figure 1). Measurements were made only where the relevant structure could be visualized adequately at the time of the scan so not all measurements could be made in every patient. 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 appropriate to the GA.

Statistical Analysis

A reference range for fetal echocardiographic measurements was established from the study population of pregnancies with live births that fulfilled the inclusion criteria. The distributions for each fetal cardiac measurement were assessed for Gaussian normality by inspecting histograms and probability plots. Transformation of data were considered if the distribution of the variable was non-Gaussian. In case of each measurement, the mean and SD of the normally distributed data were estimated. The study population for development of reference range was selected for each cardiac measurement by excluding outliers outside the mean±3 SD. The selected population after exclusion of outliers was reassessed to ensure Gaussian normality as described above. Regression analysis was used to examine the association of each cardiac measurement with GA at measurement. Before the regression analysis, the GA was centered by subtracting the arithmetic mean from the GA in weeks to minimize effects of multicollinearity

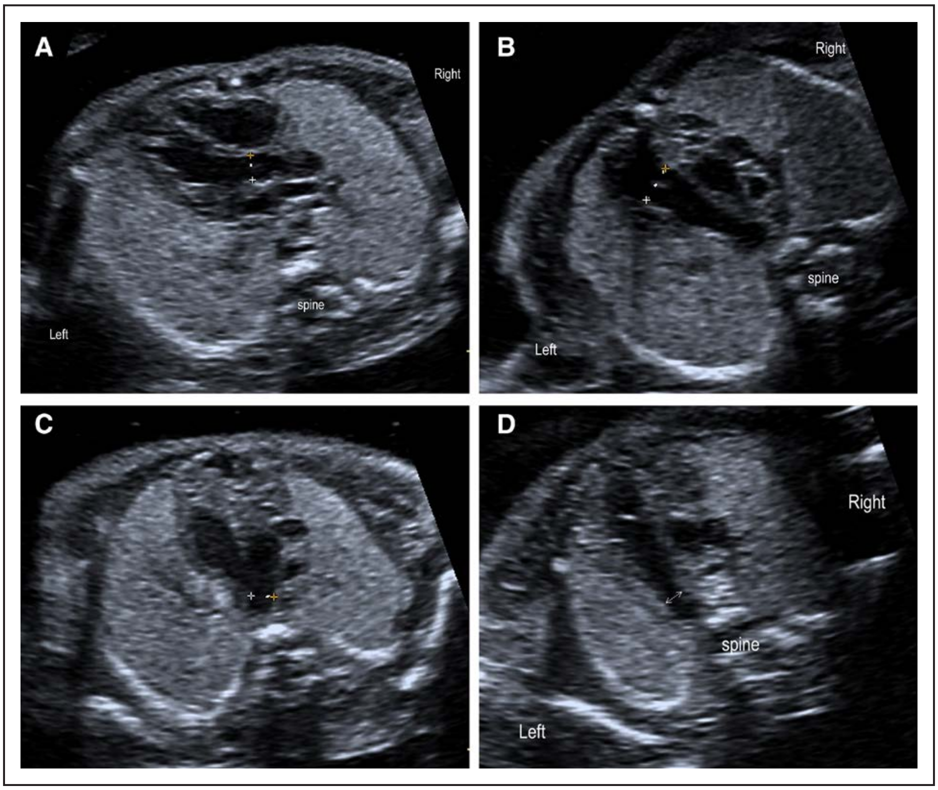

Figure 1. Measurement of cardiac structures.
A, Aortic valve is measured in diastole at the largest diameter with the valve closed. **B**, Pulmonary valve is measured in diastole at the largest diameter with the valve closed. **C**, Distal transverse aortic arch is measured on the 3 vessel and tracheal view beyond the trachea at the distal point at its widest systolic diameter. **D**, Arterial duct is measured on the 3 vessel and tracheal view at its widest systolic diameter. All measurements are made inner edge to inner edge.

associated with introduction of polynomial terms in the regression analysis.[23] The relationship between the dependent variable for each cardiac measurement and the independent variable of GA was assessed for linear and nonlinear trends by introducing polynomial terms in the regression analysis to determine the best fit. The significance of contribution of variables was assessed by examination of *P* values and effect size. The effect size of the coefficients was assessed by calculating Cohen's d (coefficient/SD) and partial η^2 from the multivariate regression analysis. Effect size of Cohen's d ≤0.2 and partial η^2 ≤0.01 was considered small. The final model was selected based on the terms that provided a significant contribution in prediction of the cardiac measurement. To determine the parametric reference centiles, we estimated whether the SD was constant or was dependant on the GA at measurement by regression analysis of the residuals on estimated mean value of the cardiac measurement using linear and nonlinear terms. The fitted SD was then estimated by multiplying the expected absolute residuals derived from the regression analysis by $\sqrt{\pi/2}$, where π=3.14159. The observed measurement for each cardiac measurement was then expressed as a z score (difference between observed and expected value divided by the fitted SD corrected for GA) and percentile. The reference range for each measurement were constructed using the fifth, 10th, 50th, 90th, and 95th percentiles. The statistical software package SPSS 24.0 (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp, 2016) and Medcalc, version 15.0 (Medcalc Software, Ostend, Belgium) were used for the data analyses. Institutional review board approval was not required as all data were collected for clinical purposes according to a defined clinical protocol and consent was not required.

RESULTS

During the study period 17 292 fetal echocardiograms were performed and 7945 of these fulfilled the inclusion criteria. The indications for fetal echocardiography are shown in Table 1. The ethnicity of the mother was recorded as: white (n=6139), Afro-Caribbean (n=1102), South Asian (n=343), East Asian (n=191), and mixed race (n=170). The number of cases analyzed for each variable were aortic valve: 7544, pulmonary valve: 7535, arterial duct: 6176, DTAA: 6176, and DTAA: arterial duct ratio 6176. All variables showed Gaussian distribution (Figure 2) and therefore transformation was not required. A polynomial regression equation using GA provided the best fit for all the data. Increasing the order beyond a squared analysis showed no significant improvement in the fit of the model for the aortic valve, pulmonary valve, DTAA, and arterial duct measures. The coefficients for the regression equations are provided in Table 2 and further data are available in Tables I through V in the Data Supplement and Figure 3. The z score for each parameter can be calculated as follows:

$$Z-score=\begin{pmatrix}Observed\ measurement\\ -Expected\ measurement\end{pmatrix}/\ fitted\ SD$$

where Expected=Intercept+a(GA–20)+b(GA–20)^2+c(GA–20)^3;

SD=Intercept+d(expected value)+e(expected value)^2; and fitted SD=1.253314×SD.

Table 1. Indications for Fetal Echocardiography

Referral Reason	No. of Cases
Increased nuchal translucency	4220
High risk for trisomies	19
Family history of congenital heart disease	705
Maternal diabetes mellitus	454
Maternal anti-Ro antibodies	40
Suspected congenital heart disease	1014
Maternal exposure to teratogenic drug	170
Advanced maternal age	44
Potential rhythm disturbance	90
Heart difficult to image	514
Tricuspid regurgitation at first-trimester scan	675

DISCUSSION

This study has established reference ranges for fetal outflow tract measurements from 13 to 36 weeks' gestation. The strengths of the study include first, examination of a large number of fetuses in all 3 trimesters of pregnancy; second, accurate pregnancy dating based on the measurement of fetal crown-rump length in the first trimester; and third, inclusion of fetuses with known normal outcome and exclusion of those with abnormalities which were only apparent after birth and furthermore, prospective recording of measurements according to a defined protocol under the supervision of a team of fetal cardiologists. In previous studies the number of fetuses examined was very small and in the case of z score for the aortic arch the number was <400;[19–21] second, in one study pregnancy dating was based on menstrual age,[22] which can be inaccurate; and third, in some studies postnatal outcome was not ascertained.[19,22]

The prospective approach used in our study avoided the potential selection bias of retrospective studies which can result in inclusion of only the best images. This approach, however, may carry its own confirmation bias because each study is performed by the individual operators for a known specific indication; the mindset of the operator might be different if he or she were simply performing the measurements to collect data. In the development of reference ranges there is a balance between accurate sampling with one observer using very strict methodology and of multiple observers that accounts for the variability in quantification among observers.

We included measurements from fetuses of diabetic mothers and those with an isolated increased nuchal translucency thickness, provided there were no cardiac

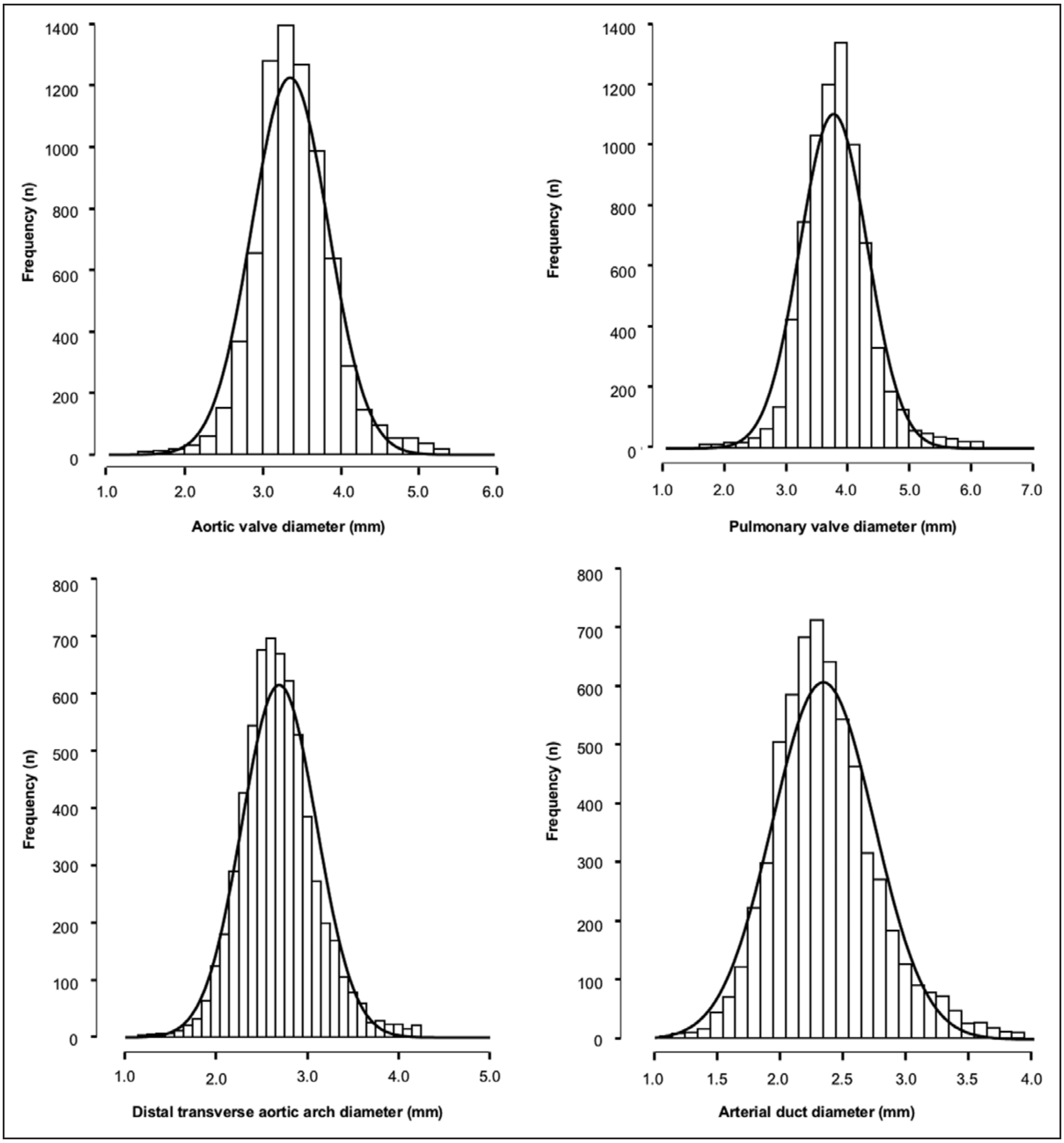

Figure 2. **A–D, Histograms demonstrating Gaussian distribution for all variables.**

or extracardiac defects, and the pregnancies resulted in live births with no abnormalities. We deliberately included such fetuses because they constitute a high proportion of referrals for specialist fetal echocardiography and their exclusion may skew the reference ranges or make them nonapplicable. Previous studies have

Table 2. **Coefficients for Calculation of Estimated Population Mean and SD**

	Expected Mean				SD		
Parameter	Intercept	a	b	c	Intercept	d	e
Aortic valve diameter	3.21642	0.23062	0.00612	…	−0.07740	0.17950	−0.01889
Pulmonary valve diameter	3.62029	0.27517	0.00586	…	0.06882	0.06978	…
Arterial duct diameter	2.25683	0.15999	0.00485	…	0.08028	0.08233	…
DTAA diameter	2.57163	0.18126	0.00513	…	0.07811	0.06885	…
Ratio of DTAA: arterial duct	1.1583	0.0070	0.0015	−0.0001	−0.4876	0.5306	…

Where a, b, c, d, and e are multipliers. The estimated population mean is to be calculated as intercept+a(GA−20)+b$(GA-20)^2$+c$(GA-20)^3$ and SD as intercept+d(estimated mean)+e$(\text{estimated mean})^2$. DTAA indicates distal transverse aortic arch.

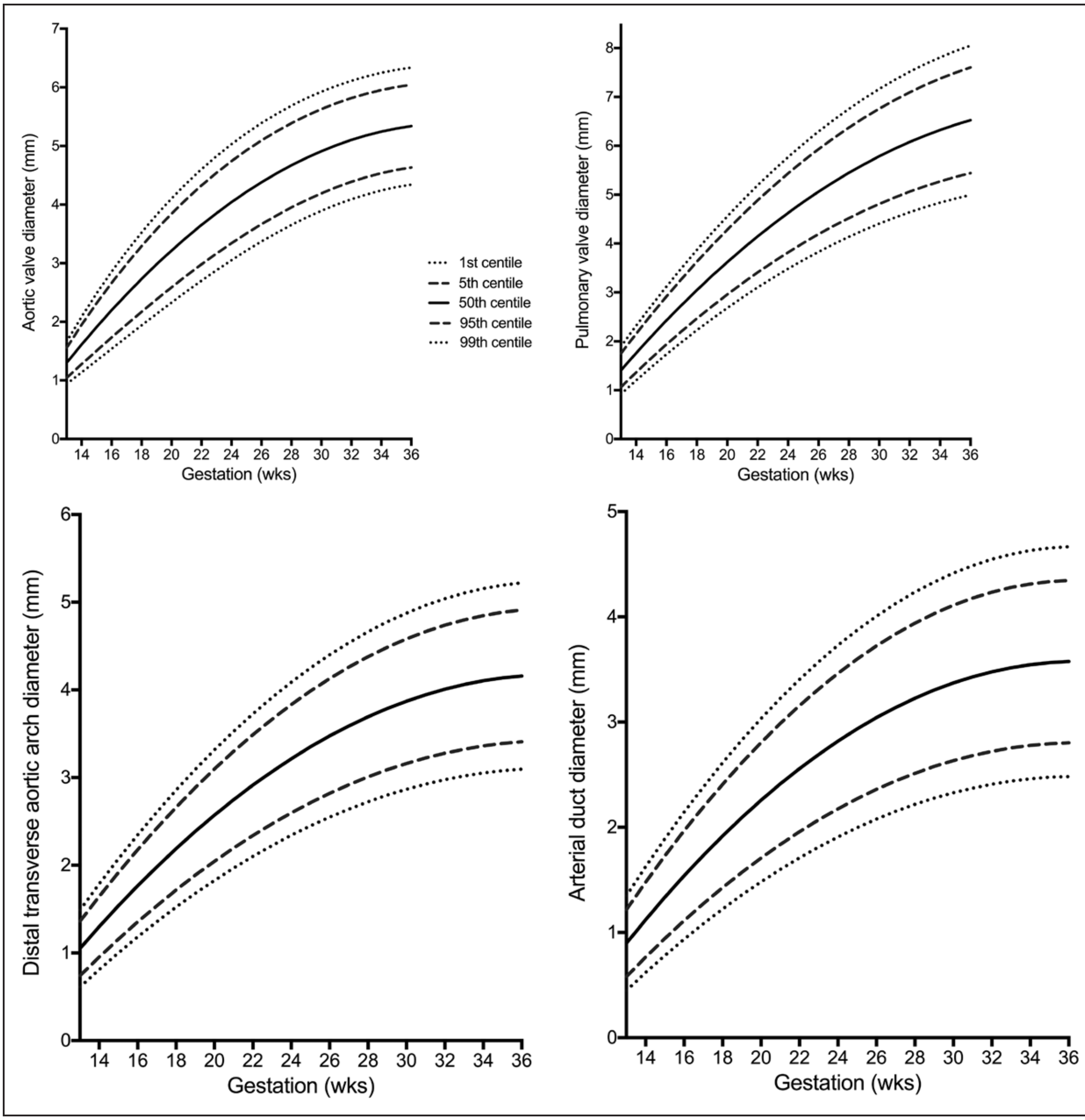

Figure 3. A–D, Graphical display of reference ranges for each variable with a demonstration of 1st, 5th, 50th, 95th, and 99th centiles.
The measurement of the aortic and pulmonary valves was made in diastole at the largest diameter with the valve closed. The distal transverse aortic arch was measured on the 3 vessel and tracheal view beyond the trachea at the distal point at its widest systolic diameter. The arterial duct was measured on the 3 vessel and tracheal view at its widest systolic diameter.

excluded fetuses of diabetic mothers[21,22] and those with increased nuchal translucency thickness.[20–22]

From a technical perspective, the measurement of the arterial valves was made with the valve closed and therefore the valve was visible making the measurement straightforward. This is in contrast to measurement during systole where the valve is not visible, but the exact approach and preference will vary by institution. Measurement of the distal aortic arch was performed on the 3 vessel and tracheal view and z scores are provided for this mode of measurement. Other studies have used sagittal measurements which have the advantage that the head and neck vessels may be visualized. However, sagittal views do not permit side by side comparison of the ductal and aortic arches and visualization is more dependent on the fetal lie than the 3 vessel and tracheal view which has been widely adopted during screening.[1] Finally, we used a standard statistical methodology which was used to create fetal reference measurements and z scores which vary with gestation.[23] To create accurate z scores and centiles we used linear and nonlinear trends in a large series of patients to derive not just the regressed means, but also to derive accurate estimates of variance by examining the relationship of residuals with GA using linear and polynomial trends.

The reference ranges for cardiac outflow tracts and z scores presented in this study can be applied in the assessment of patients with cardiac asymmetry, pulmonary stenosis, right ventricular outflow tract obstruction, or aortic stenosis[2,3,5,10,11,13,15,16,18,24–32]; in these cases knowledge of the accurate z score can aid in predicting the need for neonatal intervention and to plan perinatal management. Z scores may also be useful in forecasting the natural history of valve stenosis and in designing clinical trials on the value of in utero valvuloplasty, where patients can be stratified according to z scores.[5,10,33,34] A separate issue is whether measurement of the outflow tracts should constitute part of routine screening for prenatal diagnosis of outflow tract abnormalities. Published guidelines on fetal echocardiography[1,2,35] by several professional bodies recommend assessment of relative size of outflow tracts, but such assessment does not stipulate actual measurement. Our reference ranges could be used as part of future prospective studies that compare subjective versus objective measurements of size. Ideally, our z scores would need to be validated in an unselected population-based cohort before they are utilized within screening programs.

Limitations

The study population was not derived from routine screening in pregnancy but from fetuses examined in a fetal cardiology clinic. Although we excluded cases of fetal abnormalities and adverse pregnancy outcome, it is possible that the values obtained may not be truly representative of those in an unselected normal population. A further limitation is that in most patients normality was determined from a clinical examination in the neonatal period and it is possible that some genetic syndromes or chromosomal abnormalities may have not been diagnosed at this stage. In terms of major cardiac defects, we are confident that these would not have been missed as all babies with such defects are referred to our regional pediatric cardiac surgical center and thus feedback to the fetal medicine unit is provided.

Conclusions

The study has established reference ranges for fetal cardiac arterial measurements at 13 to 36 weeks' gestation that would assist both fetal medicine specialists and fetal cardiologists in clinical practice. The z scores can be used to assist in confirming normality, identifying deviation from normal dimensions, or providing prognostic information.

ARTICLE INFORMATION

Received January 16, 2018; accepted May 17, 2018.

The Data Supplement is available at http://circimaging.ahajournals.org/lookup/suppl/doi:10.1161/CIRCIMAGING.118.007575/-/DC1.

Correspondence

Trisha V. Vigneswaran, MBBS, MRCPCH, Department of Congenital Heart Disease, Evelina London Children's Hospital, Guy's and St Thomas' NHS Trust, Westminster Bridge Rd, London SE1 7EH, United Kingdom. E-mail trisha.vigneswaran@gmail.com

Affiliations

Harris Birthright Centre for Fetal Medicine, Fetal Medicine Research Institute, King's College Hospital NHS Foundation Trust, London, United Kingdom (T.V.V., R.A., A.S., M.C., L.D.A., K.H.N., V.Z., J.M.S.). Department of Congenital Heart Disease, Evelina London Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, United Kingdom (T.V.V., M.C., V.Z., J.M.S.).

Acknowledgments

We wish to acknowledge the input of the late Dr Ian Huggon who supervised and performed many of the echocardiograms and helped to drive the standards of fetal echocardiography within the unit. We also thank Dr Henry Chubb for his review of the paper.

Disclosures

None.

REFERENCES

1. Carvalho JS, Allan LD, Chaoui R, Copel JA, DeVore GR, Hecher K, Lee W, Munoz H, Paladini D, Tutschek B, Yagel S; International Society of Ultrasound in Obstetrics and Gynecology. ISUOG Practice Guidelines (updated): sonographic screening examination of the fetal heart. *Ultrasound Obstet Gynecol*. 2013;41:348–359. doi: 10.1002/uog.12403.
2. Donofrio MT, Moon-Grady AJ, Hornberger LK, Copel JA, Sklansky MS, Abuhamad A, Cuneo BF, Huhta JC, Jonas RA, Krishnan A, Lacey S, Lee W, Michelfelder EC Sr, Rempel GR, Silverman NH, Spray TL, Strasburger JF, Tworetzky W, Rychik J; American Heart Association Adults With Congenital Heart Disease Joint Committee of the Council on Cardiovascular Disease in the Young and Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Council on Cardiovascular and Stroke Nursing. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. *Circulation*. 2014;129:2183–2242. doi: 10.1161/01.cir.0000437597.44550.5d.
3. Hornberger LK, Weintraub RG, Pesonen E, Murillo-Olivas A, Simpson IA, Sahn C, Hagen-Ansert S, Sahn DJ. Echocardiographic study of the morphology and growth of the aortic arch in the human fetus. Observations related to the prenatal diagnosis of coarctation. *Circulation*. 1992;86:741–747.
4. Sharland GK, Chan KY, Allan LD. Coarctation of the aorta: difficulties in prenatal diagnosis. *Br Heart J*. 1994;71:70–75.
5. Simpson JM, Sharland GK. Natural history and outcome of aortic stenosis diagnosed prenatally. *Heart*. 1997;77:205–210.
6. Gardiner HM, Kovacevic A, Tulzer G, Sarkola T, Herberg U, Dangel J, Öhman A, Bartrons J, Carvalho JS, Jicinska H, Fesslova V, Averiss I, Mellander M; Fetal Working Group of the AEPC. Natural history of 107 cases of fetal aortic stenosis from a European multicenter retrospective study. *Ultrasound Obstet Gynecol*. 2016;48:373–381. doi: 10.1002/uog.15876.
7. Sharland GK, Allan LD. Normal fetal cardiac measurements derived by cross-sectional echocardiography. *Ultrasound Obstet Gynecol*. 1992;2:175–181. doi: 10.1046/j.1469-0705.1992.02030175.x.
8. Simpson JM, Chubb H. Do we finally have the A to Z of Z scores? *Circulation Cardiovascular Imaging*. 2017;10:e007191. doi: 10.1161/CIRCIMAGING.117.007191.
9. Quartermain MD, Glatz AC, Goldberg DJ, Cohen MS, Elias MD, Tian Z, Rychik J. Pulmonary outflow tract obstruction in fetuses with complex congenital heart disease: predicting the need for neonatal intervention. *Ultrasound Obstet Gynecol*. 2013;41:47–53. doi: 10.1002/uog.11196.
10. Mäkikallio K, McElhinney DB, Levine JC, Marx GR, Colan SD, Marshall AC, Lock JE, Marcus EN, Tworetzky W. Fetal aortic valve stenosis and the evolution of hypoplastic left heart syndrome: patient selection for fetal intervention. *Circulation*. 2006;113:1401–1405. doi: 10.1161/CIRCULATIONAHA.105.588194.
11. Roman KS, Fouron JC, Nii M, Smallhorn JF, Chaturvedi R, Jaeggi ET. Determinants of outcome in fetal pulmonary valve stenosis or atresia

with intact ventricular septum. *Am J Cardiol*. 2007;99:699–703. doi: 10.1016/j.amjcard.2006.09.120.
12. Arya B, Levasseur SM, Woldu K, Glickstein JS, Andrews HF, Williams IA. Fetal echocardiographic measurements and the need for neonatal surgical intervention in Tetralogy of Fallot. *Pediatr Cardiol*. 2014;35:810–816. doi: 10.1007/s00246-013-0857-3.
13. Beattie M, Peyvandi S, Ganesan S, Moon-Grady A. Toward improving the fetal diagnosis of coarctation of the aorta. *Pediatr Cardiol*. 2017;38:344–352. doi: 10.1007/s00246-016-1520-6.
14. Gómez-Montes E, Herraiz I, Gómez-Arriaga PI, Escribano D, Mendoza A, Galindo A. Gestational age-specific scoring systems for the prediction of coarctation of the aorta. *Prenat Diagn*. 2014;34:1198–1206. doi: 10.1002/pd.4452.
15. Gardiner HM, Belmar C, Tulzer G, Barlow A, Pasquini L, Carvalho JS, Daubeney PE, Rigby ML, Gordon F, Kulinskaya E, Franklin RC. Morphologic and functional predictors of eventual circulation in the fetus with pulmonary atresia or critical pulmonary stenosis with intact septum. *J Am Coll Cardiol*. 2008;51:1299–1308. doi: 10.1016/j.jacc.2007.08.073.
16. Gómez Montes E, Herraiz I, Mendoza A, Galindo A. Fetal intervention in right outflow tract obstructive disease: selection of candidates and results. *Cardiol Res Pract*. 2012;2012:592403. doi: 10.1155/2012/592403.
17. Freud LR, McElhinney DB, Marshall AC, Marx GR, Friedman KG, del Nido PJ, Emani SM, Lafranchi T, Silva V, Wilkins-Haug LE, Benson CB, Lock JE, Tworetzky W. Fetal aortic valvuloplasty for evolving hypoplastic left heart syndrome: postnatal outcomes of the first 100 patients. *Circulation*. 2014;130:638–645. doi: 10.1161/CIRCULATIONAHA.114.009032.
18. Moon-Grady AJ, Morris SA, Belfort M, Chmait R, Dangel J, Devlieger R, Emery S, Frommelt M, Galindo A, Gelehrter S, Gembruch U, Grinenco S, Habli M, Herberg U, Jaeggi E, Kilby M, Kontopoulos E, Marantz P, Miller O, Otaño L, Pedra C, Pedra S, Pruetz J, Quintero R, Ryan G, Sharland G, Simpson J, Vlastos E, Tworetzky W, Wilkins-Haug L, Oepkes D; International Fetal Cardiac Intervention Registry. International Fetal Cardiac Intervention Registry: a worldwide collaborative description and preliminary outcomes. *J Am Coll Cardiol*. 2015;66:388–399. doi: 10.1016/j.jacc.2015.05.037.
19. Krishnan A, Pike JI, McCarter R, Fulgium AL, Wilson E, Donofrio MT, Sable CA. Predictive models for normal fetal cardiac structures. *J Am Soc Echocardiogr*. 2016;29:1197–1206. doi: 10.1016/j.echo.2016.08.019.
20. Pasquini L, Mellander M, Seale A, Matsui H, Roughton M, Ho SY, Gardiner HM. Z-scores of the fetal aortic isthmus and duct: an aid to assessing arch hypoplasia. *Ultrasound Obstet Gynecol*. 2007;29:628–633. doi: 10.1002/uog.4021.
21. Schneider C, McCrindle BW, Carvalho JS, Hornberger LK, McCarthy KP, Daubeney PE. Development of Z-scores for fetal cardiac dimensions from echocardiography. *Ultrasound Obstet Gynecol*. 2005;26:599–605. doi: 10.1002/uog.2597.
22. Lee W, Riggs T, Amula V, Tsimis M, Cutler N, Bronsteen R, Comstock CH. Fetal echocardiography: z-score reference ranges for a large patient population. *Ultrasound Obstet Gynecol*. 2010;35:28–34. doi: 10.1002/uog.7483.
23. Silverwood RJ, Cole TJ. Statistical methods for constructing gestational age-related reference intervals and centile charts for fetal size. *Ultrasound Obstet Gynecol*. 2007;29:6–13. doi: 10.1002/uog.3911.
24. Nomiyama M, Ueda Y, Toyota Y, Kawano H. Fetal aortic isthmus growth and morphology in late gestation. *Ultrasound Obstet Gynecol*. 2002;19:153–157. doi: 10.1046/j.0960-7692.2001.00609.x.
25. Jowett V, Aparicio P, Santhakumaran S, Seale A, Jicinska H, Gardiner HM. Sonographic predictors of surgery in fetal coarctation of the aorta. *Ultrasound Obstet Gynecol*. 2012;40:47–54. doi: 10.1002/uog.11161.
26. Familiari A, Morlando M, Khalil A, Sonesson SE, Scala C, Rizzo G, Del Sordo G, Vassallo C, Elena Flacco M, Manzoli L, Lanzone A, Scambia G, Acharya G, D'Antonio F. Risk factors for coarctation of the aorta on prenatal ultrasound: a systematic review and meta-analysis. *Circulation*. 2017;135:772–785. doi: 10.1161/CIRCULATIONAHA.116.024068.
27. Godfrey ME, Tworetzky W, Morash D, Friedman KG. Cardiac findings in the fetus with cerebral arteriovenous malformation are associated with adverse outcome. *Fetal Diagn Ther*. 2017;41:108–114. doi: 10.1159/000446432.
28. Arzt W, Tulzer G, Aigner M, Mair R, Hafner E. Invasive intrauterine treatment of pulmonary atresia/intact ventricular septum with heart failure. *Ultrasound Obstet Gynecol*. 2003;21:186–188. doi: 10.1002/uog.48.
29. Tulzer G, Arzt W, Franklin RC, Loughna PV, Mair R, Gardiner HM. Fetal pulmonary valvuloplasty for critical pulmonary stenosis or atresia with intact septum. *Lancet*. 2002;360:1567–1568. doi: 10.1016/S0140-6736(02)11531-5.
30. Tworetzky W, McElhinney DB, Marx GR, Benson CB, Brusseau R, Morash D, Wilkins-Haug LE, Lock JE, Marshall AC. In utero valvuloplasty for pulmonary atresia with hypoplastic right ventricle: techniques and outcomes. *Pediatrics*. 2009;124:e510–e518. doi: 10.1542/peds.2008-2014.
31. Galindo A, Gutiérrez-Larraya F, Velasco JM, de la Fuente P. Pulmonary balloon valvuloplasty in a fetus with critical pulmonary stenosis/atresia with intact ventricular septum and heart failure. *Fetal Diagn Ther*. 2006;21:100–104. doi: 10.1159/000089058.
32. Hunter LE, Chubb H, Miller O, Sharland G, Simpson JM. Fetal aortic valve stenosis: a critique of case selection criteria for fetal intervention. *Prenat Diagn*. 2015;35:1176–1181. doi: 10.1002/pd.4661.
33. McElhinney DB, Marshall AC, Wilkins-Haug LE, Brown DW, Benson CB, Silva V, Marx GR, Mizrahi-Arnaud A, Lock JE, Tworetzky W. Predictors of technical success and postnatal biventricular outcome after in utero aortic valvuloplasty for aortic stenosis with evolving hypoplastic left heart syndrome. *Circulation*. 2009;120:1482–1490. doi: 10.1161/CIRCULATIONAHA.109.848994.
34. Freud LR, Tworetzky W. Fetal interventions for congenital heart disease. *Curr Opin Pediatr*. 2016;28:156–162. doi: 10.1097/MOP.0000000000000331.
35. American Institute of Ultrasound in Medicine. AIUM practice guideline for the performance of fetal echocardiography. *J Ultrasound Med*. 2013;32:1067–1082. doi: 10.7863/ultra.32.6.1067.

Circulation
Cardiovascular Imaging

Reference Ranges for the Size of the Fetal Cardiac Outflow Tracts From 13 to 36 Weeks Gestation: A Single-Center Study of Over 7000 Cases

Trisha V. Vigneswaran, Ranjit Akolekar, Argyro Syngelaki, Marietta Charakida, Lindsey D. Allan, Kypros H. Nicolaides, Vita Zidere and John M. Simpson

Circ Cardiovasc Imaging. 2018;11:
doi: 10.1161/CIRCIMAGING.118.007575
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-9651. Online ISSN: 1942-0080

SUPPLEMENTAL MATERIAL

Parameter	Expected mean				Standard deviation			
		β (95% confidence interval)	SE	p		β (95% confidence interval)	SE	p
Aortic valve	Intercept	3.21642 (3.20681 to 3.22604)	0.00490	<0.0001	Intercept	-0.07740 (-0.29354 to 0.13874)	0.11026	0.483
	(GA in weeks – 20)	0.23062 (0.22236 to 0.23887)	0.00421	<0.0001	(Estimated aortic valve diameter)	0.17950 (0.05793 to 0.30107)	0.06202	0.004
	(GA in weeks – 20)^2	-0.00612 (-0.00729 to -0.00496)	0.00059	<0.0001	(Estimated aortic valve diameter)^2	-0.01889 (-0.03614 to -0.00165)	0.00880	0.032
Pulmonary valve	Intercept	3.62029 (3.60992 to 3.63066)	0.00529	<0.0001	Intercept	0.06882 (0.00708 to 0.13057)	0.03150	0.028
	(GA in weeks – 20)	0.27517 (0.26612 to 0.28421)	0.00462	<0.0001	(Estimated pulmonary valve diameter)	0.06978 (0.05351 to 0.08605)	0.00830	<0.0001
	(GA in weeks – 20)^2	-0.00586 (-0.00729 to -0.00444)	0.00073	<0.0001	-	-	-	-
Arterial duct	Intercept	2.25683 (2.24684 to 2.26683)	0.00510	<0.0001	Intercept	0.08028 (0.01797 to 0.14260)	0.03179	0.011
	(GA in weeks – 20)	0.15999 (0.15050 to 0.16948)	0.00484	<0.0001	(Estimated arterial duct diameter)	0.08233 (0.05605 to 0.10861)	0.01341	<0.0001
	(GA in weeks – 20)^2	-0.00485 (-0.00602 to -0.00369)	0.00059	<0.0001	-	-	-	-
DTAA	Intercept	2.57163 (2.56230 to 2.58096)	0.00476	<0.0001	Intercept	0.07811 (0.01869 to 0.13753)	0.03031	0.009
	(GA in weeks – 20)	0.18126 (0.17281 to 0.18971)	0.00431	<0.0001	(Estimated DTAA diameter)	0.06885 (0.04682 to 0.09087)	0.01123	<0.0001
	(GA in weeks – 20)^2	-0.00513 (-0.00624 to -0.00401)	0.00057	<0.0001	-	-	-	-
DTAA: arterial duct ratio	Intercept	1.1583 (1.1533 to 1.1633)	0.0026	<0.0001	Intercept	-0.4876 (-0.8976 to -0.0597)	0.2137	0.025
	(GA in weeks – 20)	-0.0070 (-0.0115 to -0.0025)	0.0023	0.002	(Estimated DTAA: arterial duct ratio)	0.5306 (0.1683 to 0.8930)	0.1848	0.004
	(GA in weeks – 20)^2	0.0015 (0.0005 to 0.0015)	0.0005	0.003	-	-	-	-
	(GA in weeks – 20)^3	-0.0001 (-0.0001 to 1.9e^{-05})	3.2 e^{-05}	0.010	-	-	-	-

Supplementary table 1: *Regression analysis intercept and multipliers for calculation of the estimated mean and the SD with 95% confidence interval and statistical significance of associations. [abbreviations: DTAA – distal transverse aortic arch]*

Supplementary table 2*: Values for aortic valve diameter based on 1st, 5th, 10th, 50th, 90th, 95th and 99th centiles according to gestational age. [abbreviations: GA – gestational age]*

		Aortic valve diameter						
GA	**No. cases**	**1st centile**	**5th centile**	**10th centile**	**50th centile**	**90th centile**	**95th centile**	**99th centile**
13	21	0.940	1.046	1.103	1.302	1.502	1.558	1.665
14	28	1.137	1.277	1.351	1.612	1.874	1.948	2.087
15	25	1.337	1.505	1.595	1.910	2.226	2.316	2.483
16	38	1.538	1.731	1.834	2.196	2.559	2.661	2.854
17	21	1.739	1.953	2.067	2.469	2.872	2.986	3.200
18	69	1.938	2.170	2.294	2.731	3.167	3.291	3.523
19	764	2.135	2.382	2.514	2.980	3.445	3.577	3.824
20	4989	2.329	2.589	2.727	3.216	3.706	3.844	4.104
21	751	2.518	2.788	2.932	3.441	3.949	4.094	4.364
22	452	2.702	2.981	3.129	3.653	4.177	4.326	4.604
23	210	2.880	3.165	3.317	3.853	4.389	4.541	4.826
24	62	3.051	3.341	3.496	4.041	4.586	4.741	5.031
25	33	3.215	3.508	3.665	4.217	4.768	4.925	5.218
26	20	3.370	3.666	3.823	4.380	4.936	5.094	5.390
27	32	3.516	3.813	3.972	4.531	5.090	5.248	5.546
28	64	3.653	3.951	4.109	4.670	5.230	5.389	5.687
29	23	3.779	4.077	4.236	4.796	5.357	5.516	5.814
30	11	3.895	4.192	4.351	4.911	5.470	5.629	5.927
31	18	3.999	4.296	4.454	5.013	5.571	5.729	6.026
32	22	4.092	4.388	4.546	5.103	5.659	5.817	6.113
33	16	4.173	4.468	4.625	5.180	5.735	5.892	6.188
34	17	4.242	4.536	4.692	5.246	5.799	5.955	6.250
35	6	4.298	4.591	4.747	5.299	5.850	6.006	6.300
36	10	4.341	4.634	4.790	5.340	5.890	6.046	6.338

Supplementary table 3*: Values for pulmonary valve diameter based on 1st, 5th, 10th, 50th, 90th, 95th and 99th centiles according to gestational age. [abbreviations: GA – gestational age]*

		Pulmonary valve diameter						
GA	**No. cases**	**1st centile**	**5th centile**	**10th centile**	**50th centile**	**90th centile**	**95th centile**	**99th centile**
13	23	0.920	1.063	1.139	1.407	1.675	1.751	1.894
14	25	1.200	1.363	1.451	1.758	2.066	2.153	2.317
15	23	1.470	1.654	1.752	2.098	2.444	2.542	2.725
16	38	1.732	1.935	2.043	2.426	2.808	2.917	3.120
17	22	1.984	2.206	2.324	2.742	3.160	3.278	3.501
18	71	2.226	2.466	2.595	3.047	3.499	3.627	3.867
19	764	2.459	2.717	2.854	3.339	3.824	3.961	4.219
20	4995	2.683	2.958	3.104	3.620	4.137	4.283	4.557
21	753	2.898	3.188	3.343	3.890	4.436	4.591	4.882
22	455	3.103	3.409	3.572	4.147	4.723	4.886	5.192
23	209	3.299	3.619	3.790	4.393	4.996	5.167	5.487
24	63	3.485	3.820	3.998	4.627	5.256	5.435	5.769
25	33	3.662	4.010	4.196	4.850	5.504	5.689	6.037
26	20	3.830	4.191	4.383	5.060	5.738	5.930	6.290
27	34	3.989	4.361	4.559	5.259	5.959	6.158	6.530
28	65	4.138	4.521	4.726	5.447	6.168	6.372	6.755
29	24	4.278	4.672	4.881	5.622	6.363	6.573	6.967
30	11	4.408	4.812	5.027	5.786	6.545	6.760	7.164
31	18	4.529	4.942	5.162	5.938	6.714	6.934	7.347
32	22	4.641	5.062	5.287	6.078	6.870	7.095	7.516
33	14	4.744	5.172	5.401	6.207	7.013	7.242	7.671
34	16	4.837	5.273	5.505	6.324	7.143	7.376	7.811
35	6	4.921	5.363	5.598	6.429	7.260	7.496	7.938
36	9	4.995	5.443	5.681	6.523	7.364	7.603	8.051

Supplementary table 4*: Values for arterial duct diameter based on 1^{st}, 5^{th}, 10^{th}, 50^{th}, 90^{th}, 95^{th} and 99^{th} centiles according to gestational age. [abbreviations: GA – gestational age]*

		Arterial Duct diameter						
GA	**No. cases**	**1st centile**	**5th centile**	**10th centile**	**50th centile**	**90th centile**	**95th centile**	**99th centile**
13	5	0.449	0.581	0.651	0.899	1.147	1.217	1.349
14	5	0.619	0.766	0.845	1.122	1.400	1.478	1.626
15	11	0.781	0.943	1.030	1.336	1.641	1.728	1.890
16	27	0.936	1.112	1.207	1.539	1.872	1.966	2.143
17	15	1.083	1.274	1.375	1.733	2.091	2.193	2.383
18	51	1.223	1.426	1.535	1.917	2.300	2.408	2.612
19	575	1.356	1.571	1.686	2.092	2.498	2.613	2.828
20	4039	1.481	1.708	1.829	2.257	2.684	2.805	3.033
21	637	1.599	1.837	1.964	2.412	2.860	2.987	3.225
22	433	1.709	1.958	2.090	2.557	3.025	3.157	3.405
23	201	1.813	2.071	2.208	2.693	3.178	3.316	3.574
24	53	1.908	2.175	2.317	2.819	3.321	3.463	3.730
25	29	1.997	2.272	2.418	2.936	3.453	3.599	3.874
26	18	2.078	2.360	2.511	3.042	3.573	3.724	4.006
27	30	2.152	2.441	2.595	3.139	3.683	3.837	4.127
28	58	2.218	2.513	2.671	3.226	3.782	3.939	4.235
29	22	2.277	2.578	2.738	3.304	3.870	4.030	4.331
30	11	2.328	2.634	2.797	3.372	3.947	4.110	4.415
31	17	2.372	2.682	2.847	3.430	4.012	4.178	4.487
32	20	2.409	2.722	2.889	3.478	4.067	4.234	4.547
33	14	2.439	2.755	2.923	3.517	4.111	4.280	4.595
34	15	2.461	2.779	2.948	3.546	4.144	4.313	4.631
35	5	2.476	2.795	2.965	3.565	4.166	4.336	4.655
36	10	2.483	2.803	2.973	3.575	4.177	4.347	4.667

Supplementary table 5*: Values for distal transverse aortic arch diameter based on 1st, 5th, 10th, 50th, 90th, 95th and 99th centiles according to gestational age. [abbreviations: GA – gestational age]*

		Distal transverse aortic arch diameter						
GA	**No. cases**	**1st centile**	**5th centile**	**10th centile**	**50th centile**	**90th centile**	**95th centile**	**99th centile**
13	6	0.613	0.741	0.810	1.052	1.293	1.362	1.490
14	11	0.811	0.954	1.030	1.300	1.569	1.645	1.788
15	12	1.001	1.158	1.242	1.537	1.833	1.916	2.073
16	26	1.183	1.353	1.444	1.765	2.085	2.176	2.346
17	15	1.356	1.539	1.637	1.982	2.326	2.424	2.607
18	52	1.522	1.717	1.821	2.189	2.556	2.660	2.856
19	600	1.679	1.886	1.996	2.385	2.774	2.885	3.092
20	4083	1.828	2.046	2.162	2.572	2.981	3.098	3.316
21	643	1.968	2.197	2.318	2.748	3.177	3.299	3.527
22	436	2.101	2.339	2.466	2.914	3.361	3.488	3.726
23	206	2.225	2.473	2.604	3.069	3.534	3.666	3.913
24	54	2.342	2.597	2.734	3.215	3.696	3.832	4.088
25	31	2.450	2.713	2.854	3.350	3.846	3.986	4.250
26	21	2.549	2.820	2.965	3.475	3.984	4.129	4.400
27	30	2.641	2.919	3.067	3.589	4.112	4.260	4.537
28	61	2.724	3.008	3.160	3.694	4.227	4.379	4.663
29	22	2.800	3.089	3.243	3.788	4.332	4.486	4.776
30	11	2.867	3.161	3.318	3.872	4.425	4.582	4.876
31	18	2.925	3.224	3.383	3.945	4.507	4.666	4.965
32	21	2.976	3.278	3.440	4.008	4.577	4.738	5.041
33	16	3.019	3.324	3.487	4.062	4.636	4.799	5.105
34	15	3.053	3.361	3.525	4.104	4.684	4.848	5.156
35	6	3.079	3.389	3.554	4.137	4.720	4.885	5.195
36	10	3.097	3.408	3.574	4.159	4.745	4.911	5.222

Supplementary table 6: *Assessment of significant of contribution of ethnicity in multivariate regression analysis by examination of significance value, Cohen's D and partial* η^2

Cardiac measurement	**P value**	**Cohen's D**	**Partial** η^2
Aortic valve diameter	<0.001	-0.17*	0.005
Pulmonary valve diameter	<0.001	-0.14*	0.003
Arterial duct diameter	0.410	0.048	0.0002
DTAA diameter	<0.001	0.12	0.003

* Cohen's d (coefficient/SD) estimated for the Afro-Caribbean group as this was the only group with a significant p value