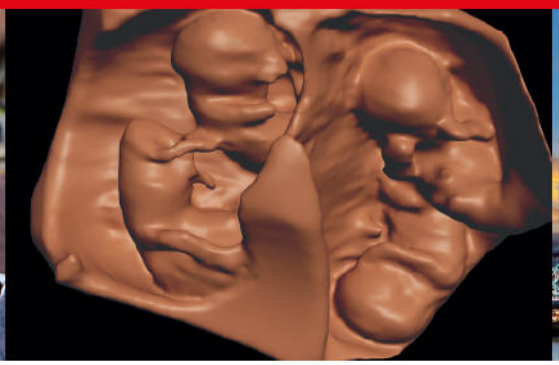
ISUOG Education 2019


Delivering up-to-date knowledge and clinical guidance for a range of topics in ultrasound in obstetrics and gynecology.

view upcoming courses

Ultrasound Obstet Gynecol 2007; **29**: 628–633
Published online 3 May 2007 in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.4021

Z-scores of the fetal aortic isthmus and duct: an aid to assessing arch hypoplasia

L. PASQUINI*, M. MELLANDER†, A. SEALE†, H. MATSUI*†, M. ROUGHTON‡, S. Y. HO† and H. M. GARDINER*†

**Institute of Reproductive and Developmental Biology, Faculty of Medicine, Imperial College at Queen Charlotte's and Chelsea Hospital, †Brompton Fetal Cardiology, Royal Brompton Hospital and the National Heart and Lung Institute and ‡Royal Brompton and Harefield NHS Trust, London, UK*

KEYWORDS: aortic isthmus; coarctation of the aorta; fetus; *Z*-scores

ABSTRACT

Objective *Prenatal diagnosis of isolated coarctation of the aorta suffers from high false positive and false negative rates. The aim of our study was to develop Z-scores for the aortic isthmus in normal fetuses as a reference for fetuses with suspected coarctation.*

Methods *The aortic isthmal diameter, immediately proximal to the insertion of the arterial duct, was measured prospectively in the transverse (three vessel and trachea) and sagittal views in 221 normal fetuses at 18 to 37 weeks' gestation. The ductal diameter was measured immediately before it entered the descending aorta in the same view. All measurements were repeated three times by a single investigator and averaged. A second investigator re-measured the images of 50 cases to assess interobserver variability. Z-scores were created relating isthmal and ductal diameters to femur length and gestational age. The ratio between the isthmal and ductal diameters was calculated.*

Results *The formula used to calculate Z-scores for the three diameters was: [ln(measured isthmal diameter) − (m ln(femur length or gestational age) + c)]/root MSE, where c is the intercept, m is a multiplier and MSE is the mean squared error. The ratio between isthmal and ductal diameters was close to a constant value of 1 (95% CI 0.97–1.01), regardless of the value of femur length or gestational age.*

Conclusion *We have defined Z-scores for the fetal aortic isthmus and arterial duct measured in the three vessels and trachea view and for the isthmus in the sagittal plane. In suspected coarctation, these Z-scores and the isthmal to ductal ratio may help in longitudinal assessment of the aortic arch and aid in the prenatal diagnosis of coarctation. Copyright © 2007 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Coarctation of the aorta (CoA) remains one of the most difficult cardiac defects to diagnose before birth. Although suspicion is raised when there is ventricular disproportion (with a smaller left than right ventricle) the sensitivity of ventricular disproportion is only moderate and the specificity is poor, especially after 34 weeks' gestation[1,2].

Morphological examination of the arch confirms that arch hypoplasia is more common in fetal CoA than it is in CoA presenting in infancy or in childhood. The narrowest area is at the aortic isthmus just before the region where the arterial duct enters the descending aorta (Figure 1).

The three vessel and trachea view (imaged from a transverse plane, high in the fetal chest) (Figure 2) allows comparison of the aortic and ductal arches and assessment of the fetal aortic isthmus without measurement artifact due to overlay of the larger ductal arch that may occur in the sagittal view. Widespread incorporation of this view into antenatal screening programs has resulted in an increase in referrals of fetuses with disproportion at arch level that may have CoA, but no normal reference data exist to assess the sensitivity and specificity of this view in the diagnosis of CoA in early gestation.

The purpose of this study was to produce *Z*-scores for the diameter of the distal end of the fetal aortic isthmus in normal singleton pregnancies.

METHODS

The study group was recruited over a 3-month period from a non-consecutive population of healthy pregnant women with singleton pregnancies undergoing ultrasound screening to exclude fetal anomalies, or during routine follow-up for reasons unrelated to fetal well-being. They were non-consecutive in order to achieve sufficient

Correspondence to: Dr H. M. Gardiner, Institute of Reproductive and Developmental Biology, Faculty of Medicine, Imperial College, Queen Charlotte's and Chelsea Hospital, Du Cane Road, London, W12 0HS, UK (e-mail: helena.gardiner@imperial.ac.uk)

Accepted: 19 January 2007

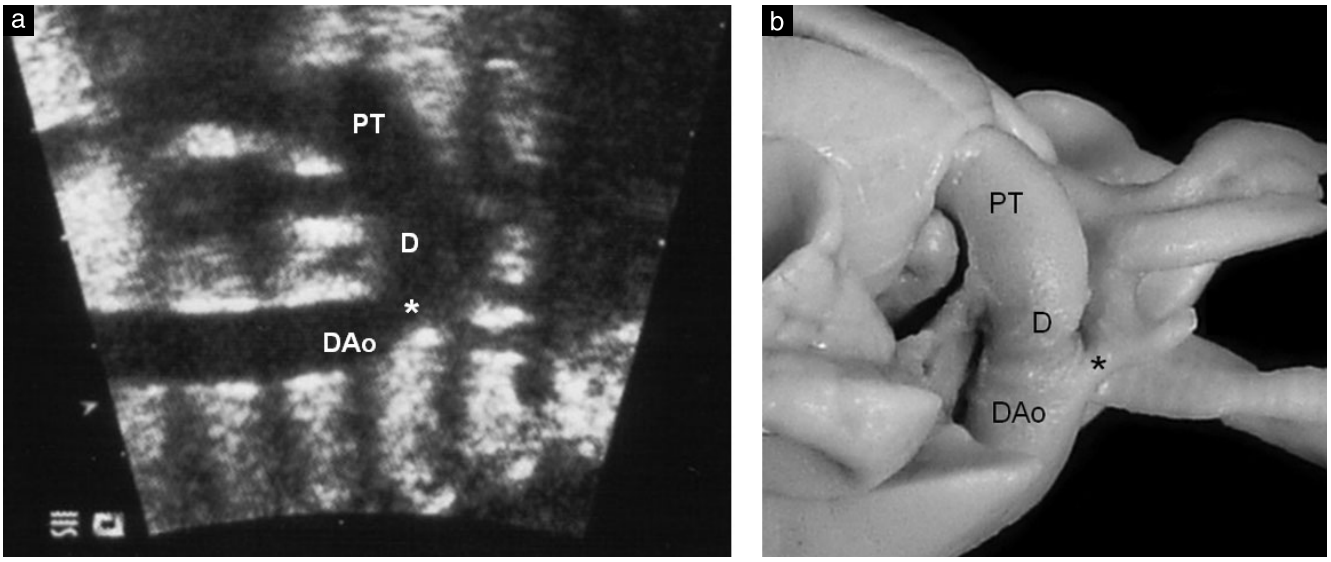


Figure 1 (a) Sagittal ultrasound image of an abnormal aortic arch at 22 weeks' gestation. (b) Fetal heart specimen simulating the sagittal view of the ultrasound image and orientated in the same way. The distal isthmus (*) is partially overlapped by the arterial duct (D) before it enters the descending aorta (DAo). PT, pulmonary trunk.

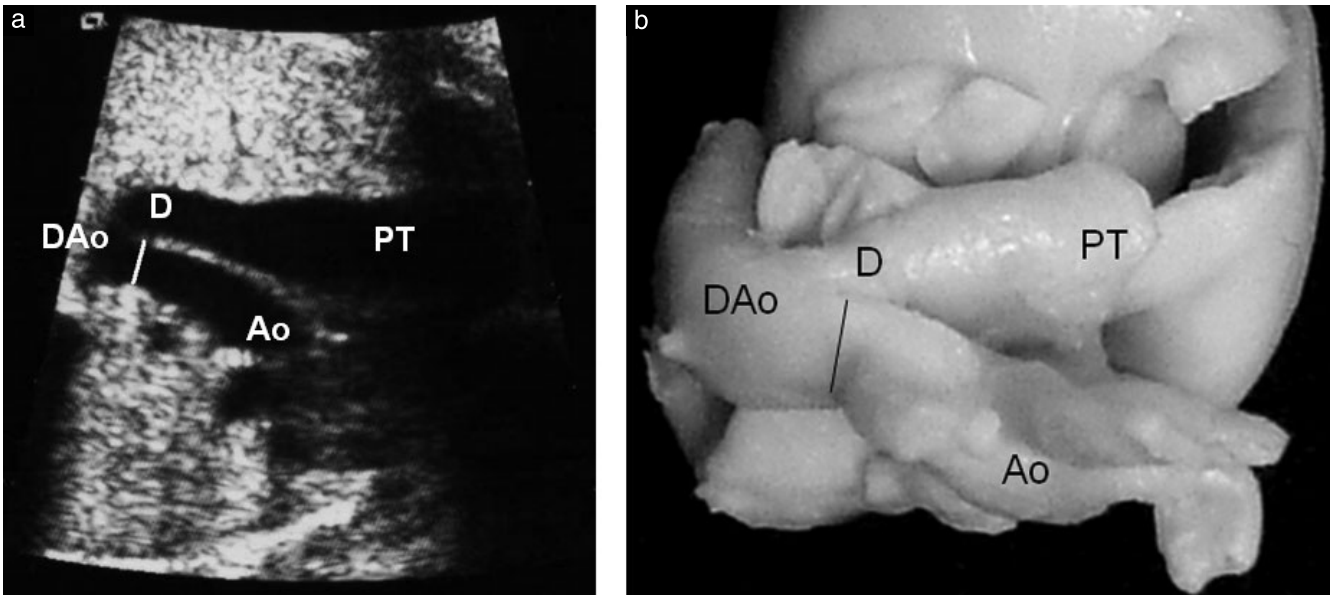


Figure 2 (a) Three vessel and trachea ultrasound image of an abnormal aortic arch showing the pulmonary trunk (PT) leading into the arterial duct (D). The isthmus is measured as shown by the line just before it enters the descending aorta (DAo) and the duct is measured directly above it. (b) Fetal heart specimen simulating the three vessels and trachea view of the ultrasound image and orientated in the same way. Ao, aortic arch.

numbers in each gestational week to create reference ranges. Fetuses with suspicion of a cardiac or extracardiac malformation, chromosomal abnormality or growth restriction were excluded from the study. In all cases gestational age had been verified by sonographic measurement of the crown–rump length in early pregnancy, and gestational age varied between 18 + 4 and 37 + 3 weeks.

Transabdominal fetal echocardiography was performed in five transverse views and femur length measured. All scans were performed by one of three trained operators (L.P., C.M. and E.D.-J.) using an Acuson Sequoia S12 ultrasound machine interfaced to a curvilinear 6C2 transducer (Siemens Medical Solutions, Acuson Division, Mountain View, CA, USA). Data were stored digitally and measured off-line. The internal diameter of the aortic isthmus was measured immediately proximal to the insertion of the arterial duct in the three vessels and trachea and sagittal views using trailing edge to leading edge (Figures 1 and 2). The ductal diameter was measured in the three vessels and trachea view only (Figure 2). Orientation of image acquisition was manipulated to ensure axial rather than lateral resolution of the image by moving on the maternal abdomen. Measurements were

repeated three times on the same digital clip by a single investigator and averaged.

Measurements were attempted in 221 patients. Images were of sufficient quality in 204 (92%) for the three vessels and trachea view and in 190 (86%) for the sagittal view. We created *Z*-scores relating isthmal and ductal diameters to femur length and to gestational age and calculated the ratio of the isthmal to ductal diameters. A second investigator re-measured the stored images of 50 randomly selected cases for calculation of interobserver variability.

Ethical considerations

Institutional review board approval was not necessary since the sonographic measurements were performed as an integral part of routine clinical visits to the ultrasound department and the fetal medicine unit and scans were anonymized. Outcome of the neonates was tracked by postcode and verified from the neonatal records and admissions for investigation or repair of coarctation of the aorta during the year following birth from the local pediatric cardiology unit at the Royal Brompton Hospital and from the other two London surgical units using a centrally held database.

Statistical analysis

The data were analyzed using STATA (version 9.2, 2006). Linear regression analysis was used to determine the relationship between vessel size and femur length and between vessel size and gestational age (Table 1). The normality assumptions underpinning the linear regression analysis were checked graphically. Bland–Altman analysis was used to assess interobserver reproducibility[3].

Z-scores for the diameter of the isthmus and arterial duct as related to femur length and to gestational age were created using natural logarithms (ln) as described by our group previously[4]. The *Z*-scores were calculated in a two-stage process: (1) predicted isthmal diameter: ln(predicted isthmal diameter) = m ln(femur length or gestational age) + c; (2) *Z*-score: [ln(measured isthmal diameter) − ln(predicted isthmal diameter)]/root MSE, where c is the intercept, m is a multiplier and MSE is mean squared error. This process was repeated for the arterial duct, substituting the ductal diameter measurements for the isthmal diameter in the equations.

RESULTS

The interobserver mean difference for the measurement of the isthmal diameter in the three vessels and trachea view was −0.04 mm (95% limits of agreement (LOA) −0.8 to 0.71 mm). In the sagittal view the results were 0.02 (LOA −0.39 to 0.43) mm for isthmal diameter and −0.03 (LOA −0.59 to 0.52) mm for ductal diameter. Bland–Altman plots for the three measurements are shown in Figure 3. The logged values of isthmal and ductal diameters were plotted against logged values of femur length and gestational age and confirmed normal after graphical inspection of the regression residuals. Graphical displays of the *Z*-scores for the aortic isthmus in three vessels and trachea and sagittal views and the ductal diameter are shown in Figure 4, and a simple calculator to use this in clinical practice is available to download online (Supplementary Material S1).

Table 1 Regression equations relating cardiac dimensions to femur length and gestational age, showing the root mean-squared error (RMSE) and the R^2 values for the regression equations

	n	*Intercept*	*Slope*	*RMSE*	R^2
Femur length					
Three vessels and trachea isthmus	204	−2.560	0.967	0.163	0.69
Arterial duct	204	−3.009	1.090	0.179	0.70
Sagittal isthmus	190	−2.261	0.879	0.181	0.61
Gestational age					
Three vessels and trachea isthmus	204	−2.822	1.224	0.164	0.69
Arterial duct	204	−3.359	1.396	0.176	0.71
Sagittal isthmus	190	−2.489	1.109	0.182	0.60

Regression analysis of the ratio between isthmal and ductal diameters in the normal fetus (from the three vessels and trachea view) against femur length (ratio 1.11, slope −0.003 (LOA −0.004 to −0.001)) and gestational age (ratio 1.15, slope −0.006 (LOA −0.009 to −0.003)) showed that it was very close to a constant value of 1, regardless of the value of femur length or gestational age (as shown previously)[5]. The mean (± SD) of the ratio was 0.99 (± 0.13) with a 95% CI of 0.97–1.01. Based on these results, 95% of all ratio values would be expected to lie between 0.74 and 1.23. The further away from a value of 1, the more likely the presence of arch hypoplasia or coarctation.

DISCUSSION

We have generated *Z*-scores for the aortic isthmus and ductal arch from the three vessels and trachea view in normal fetuses. Reproducibility of the method was similar to that for obtaining views of the isthmus imaged from the traditional sagittal view. As the three vessels and trachea view is now standard in screening programs we would recommend its use in assessment of the fetal arch, and agree with others that aortic arch hypoplasia is best visualized in the three vessels and trachea view of the fetal heart, in which the diameter of the arch can be directly compared with the diameter of the ductal arch[1,6,7]. However, these measurements using *Z*-scores corrected for fetal size or gestation have not been quantified previously. Several investigators have reported absolute measurements of the fetal aortic arch in normal fetuses[8–10]. Hornberger *et al.* used long-axis images of the aortic arch in 92 normal fetuses between 16 and 38 weeks' gestation. Five diameters of the arch were measured including the isthmus immediately distal to

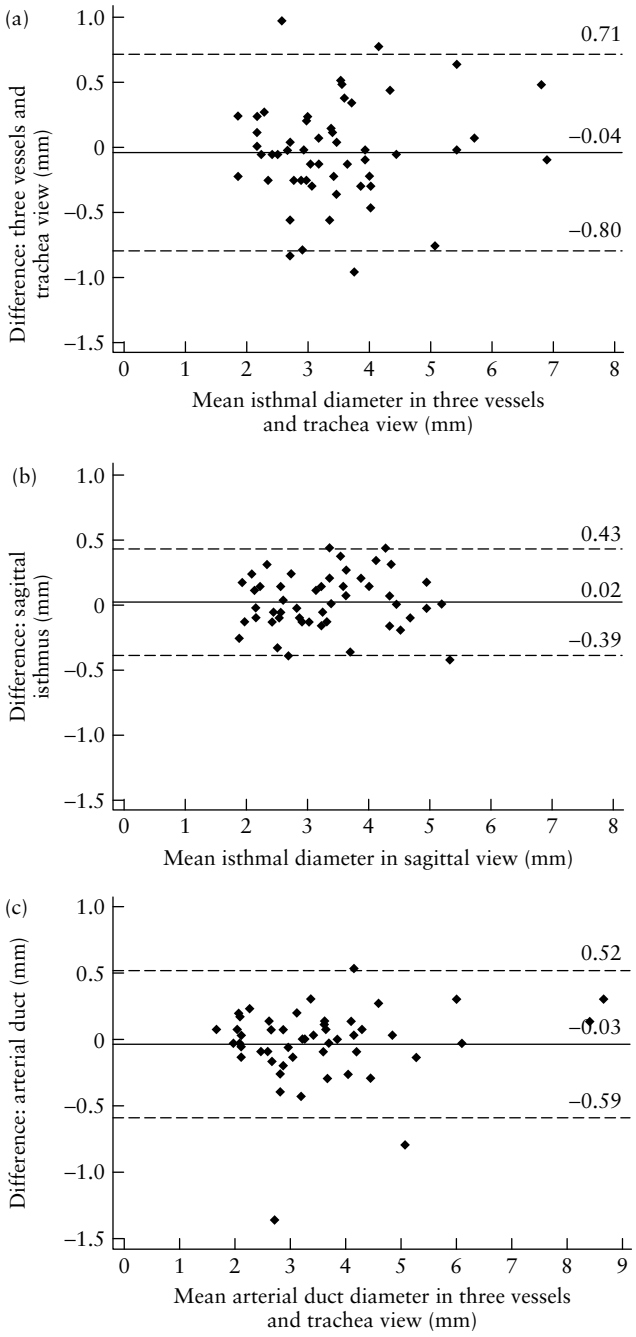


Figure 3 Bland–Altman plots of (a) isthmal diameter in the three vessels and trachea view, (b) isthmal diameter in the sagittal view and (c) arterial duct diameter in the three vessels and trachea view. Solid lines represent the means and dashed lines the limits of agreement.

the left subclavian artery. They observed that in most normal fetuses the smallest diameter was at the isthmus and that in five fetuses in which a prenatal diagnosis of aortic coarctation was confirmed postnatally, transverse aortic and isthmal measurements fell on or below the third percentile for gestational age[8]. Achiron *et al.* also measured the diameter of the arch in the long-axis view[9], using transvaginal or transabdominal images from 125 uncomplicated pregnancies between 14 and 38 weeks' gestation. Two diameters were measured – immediately distal to the origin of the left common carotid artery and 'at the end of the aortic cephalic curvature' at a 90° angle to the previous diameter. The distal diameter was found to be larger than the more proximal diameter and the authors speculated that the reason for this (unexpected) finding could be that 'the distal isthmic portion of the aorta is not necessarily the narrowest one *in utero* since it is perfused by the combined outflow', that is, it appears probable that the aorta was measured in its descending portion after the junction of the duct. Nomiyama *et al.* used a posterior coronal view of the fetus that imaged a longitudinal view of the connection between the aorta and the arterial duct in 110 uncomplicated pregnancies between 30 and 40 weeks' gestation[10]. Measurements included the middle of the isthmus and the isthmal end 'just proximal to the entry of the ductus arteriosus'. They constructed growth curves from these data to study 42 pregnancies at high risk for congenital heart defects. One of these pregnancies resulted in a newborn with a coarctation of the aorta. In this fetus the ratio of the isthmal end to the middle of the aortic isthmus was extremely low compared with normal.

In neonatal coarctation the narrowest portion of the arch is usually the distal isthmus, just before the entry of the arterial duct (Figures 1 and 2). This measurement, therefore, should be the best indicator of fetal coarctation. Only one of the previous studies included this diameter and in this study all fetuses were over 30 weeks' gestation[10]. Our results are very similar for fetuses at > 30 gestational weeks, with almost identical age-related mean values and ranges. Importantly, however, our study includes measurements made at earlier gestational ages when anomaly screening is performed and the diagnosis of CoA first suspected.

We measured both the traditional sagittal and the newer three vessels and trachea views of the isthmus and calculated *Z*-scores for these diameters related to both femur length and gestational age. We consider femur length to be the preferred reference as it relates isthmal dimension to the size of the fetus, but if this measurement is not available gestational age can be used instead[4].

Although the interobserver variability was small it is likely that there will be some degree of overlap between normal cases, fetuses with arch hypoplasia and those with coarctation requiring neonatal surgery. For example, a 0.5-mm measurement difference in isthmal diameter may result in a *Z*-score of −2 instead of −1. We propose that the use of the ratio between the isthmal and ductal diameters may improve specificity. This ratio was almost constant over the gestational age interval studied, and the 95% confidence limits were narrow[10]. This is in accord with an earlier morphological study from our group[5]. Moreover in fetal coarctation one might expect the ductal diameter to be larger than normal because of diminished intracardiac right to left shunting and increased right ventricular output and ductal flow. This would result in a further decrease of this ratio, but this hypothesis should be tested in a prospective study of fetuses with suspected coarctation in early gestation.

In conclusion prenatal diagnosis of coarctation suffers from low sensitivity and specificity. As the three vessels

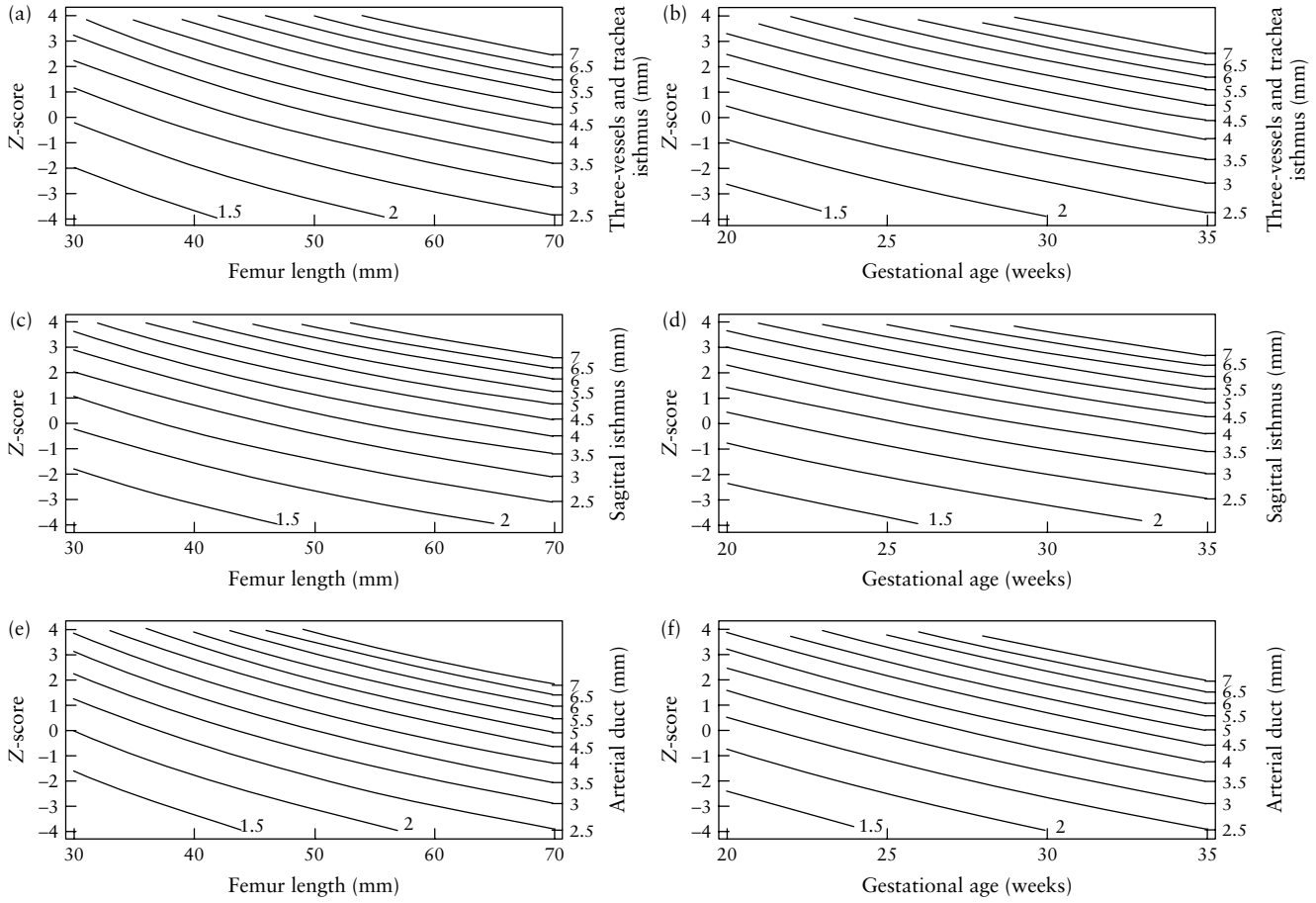


Figure 4 Graphical display of *Z*-scores for isthmal diameter in the three vessels and trachea view based on femur length (a) and on gestational age (b), for isthmal diameter in the sagittal view based on femur length (c) and on gestational age (d), and for ductal diameter in the three vessels and trachea view based on femur length (e) and on gestational age (f).

and trachea view is now used by many in routine screening of the fetal heart a visual appreciation of disproportion at the transverse aortic and ductal arches may be important in reducing false negative cases. Our hope is that the subsequent management of these cases by fetal cardiologists may be aided by the availability of the *Z*-scores presented in this paper and may help decrease the number of false positive diagnoses of fetal coarctation.

ACKNOWLEDGMENTS

Our thanks go to sonographers Ciara Mckenna and Elizabeth Daly-Jones, Obstetric Ultrasound Department, Queen Charlotte's and Chelsea Hospital, London for their technical expertise.

REFERENCES

1. Sharland GK, Chan KY, Allan LD. Coarctation of the aorta: difficulties in prenatal diagnosis. *Br Heart J* 1994; **71**: 70–75.
2. Brown DL, Durfee SM, Hornberger LK. Ventricular discrepancy as a sonographic sign of coarctation of the fetal aorta: how reliable is it? *J Ultrasound Med* 1997; **16**: 95–99.
3. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **1**: 307–310.
4. 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.
5. Angelini A, Allan LD, Anderson RH, Crawford D, Chita SK, Ho SY. Measurements of the dimensions of the aortic and pulmonary pathways in the human fetus: a correlative echocardiographic and morphometric study. *Br Heart J* 1988; **60**: 221–226.
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**: 417–423.
7. 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**: 1070–1074.
8. 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.
9. Achiron R, Zimand S, Hegesh J, Lipitz S, Zalel Y, Rotstein Z. Fetal aortic arch measurements between 14 and 38 weeks' gestation: *in-utero* ultrasonographic study. *Ultrasound Obstet Gynecol* 2000; **15**: 226–230.
10. Nomiyama M, Ueda Y, Toyota Y, Kawano H. Fetal aortic isthmal growth and morphology in late gestation. *Ultrasound Obstet Gynecol* 2002; **19**: 153–157.

SUPPLEMENTARY MATERIAL ON THE INTERNET

The following material is available from the Journal homepage:

http://www.interscience.wiley.com/jpages/0960-7692/suppmat (restricted access)

S1 Calculator to obtain *Z*-scores of the isthmus from three vessels and trachea and sagittal views and the arterial duct on three vessels and trachea views based on gestational age and femur length.