

Development of Z-scores for fetal cardiac dimensions from echocardiography

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ABSTRACT

Objectives Z-scores for cardiac dimensions are well established in postnatal life, but have yet to be developed for fetal cardiac dimensions. These would be of real advantage to the clinician in accurately quantifying size and growth of cardiac dimensions and to the researcher by allowing mathematical comparison of growth in differing subgroups of a disease. The purpose of this observational study, conducted at tertiary fetal medicine and cardiology units, was to produce formulae and nomograms allowing computation of Z-scores for fetal cardiac dimensions from knowledge of femur length (FL), biparietal diameter (BPD) or gestational age (GA) using fetal echocardiography.

Methods Seventeen fetal cardiac dimensions were measured in 130 pregnant women with singleton fetuses of gestational age 15–39 weeks. Regression equations were derived relating all dimensions to FL, BPD and GA. From the calculations, formulae were then developed allowing fetal cardiac Z-score computation.

Results The relationships between cardiac dimensions and FL, BPD or GA were described following natural log transformation. From this analysis, FL (taken as an expression of fetal size) had the highest correlation to fetal cardiac dimensions. From the developed nomograms, Z-scores of specific fetal cardiac structures could be estimated from knowledge of the FL, BPD or GA and echocardiographically derived measurements.

Conclusions This study allowed computation of Z-scores in fetal life for 17 cardiac dimensions from FL, BPD or GA. Previous studies of normal data allowed qualitative assessment of where abnormal cardiac dimensions lay with regard to the normal range. Z-scores

from this study allow quantitative analysis of where such dimensions lie relative to the mean. This permits exact assessment of growth of fetal cardiac structures in normal hearts and particularly in congenitally abnormal hearts where quantitative assessment of the growth of cardiac structures is important in analyzing and planning treatment strategies. Copyright © 2005 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

The use of centiles to determine size and growth of cardiac structures is well recognized in prenatal as well as postnatal life and allows accurate placement of measurements within the normal range thus allowing semiquantification of data. However, for values that fall outside the extreme centile range, interpretation of measurements is usually qualitative. In fetal life, centiles are usually normalized to gestational age^{1–4}. However, as the size of the fetus can vary hugely with a several-fold difference by late pregnancy, interpretation of the size of the various cardiac structures requires normalization against some parameter of fetal size. Although normalization of centiles that account for fetal size has been reported^{5,6}, much of the information is M-mode-based and limited to a small number of cardiac structures.

An alternative method to centiles is the use of Z-scores. These are expressed as the number of SDs a measurement departs from the population mean and were originally suggested by Rimoldi and Lev⁷. The use of Z-scores is well established in postnatal life, allowing relatively simple quantification to normalize growth of cardiac structures relative to body size rather than age⁸. It would be useful to quantify growth of cardiac structures compared to

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overall somatic growth in prenatal life. In addition, the use of a 'number' (SD) to express a measured value is a further advantage over centiles as Z-scores always offer the exact quantification of data. Therefore, the use of Z-scores is particularly useful in research analysis by allowing subgroup comparison, which is not possible using centiles.

The management of *in-utero* congenital heart disease depends in part on knowledge of size and growth of various fetal cardiac structures. In prenatal life, however, Z-score data are limited to two reports^{2,9} where they are generated from formulae relating cardiac structures to gestational age rather than measurement of any direct parameter of fetal size^{3,10}. To date, formulae and nomograms allowing Z-scores to be calculated directly from parameters of fetal size have not been published. The aim of this study was to produce formulae and nomograms allowing the direct computation of Z-scores for fetal cardiac dimensions from knowledge of femur length (FL), biparietal diameter (BPD) and gestational age (GA) using cross-sectional fetal echocardiography.

METHODS

Study population

The population studied comprised 130 fetuses from singleton pregnancies in women attending three centers: Hospital for Sick Children, Toronto, Canada; Chelsea and Westminster Hospital and St George's Hospital, London, UK. The women had been referred for a routine fetal echocardiogram for a variety of reasons comprising predominantly: suspected congenital heart disease on Level 1 scan (not confirmed), fetal premature contractions, family history of congenital heart disease and maternal drug ingestion. A strict definition of normality was adopted. The fetus was excluded if there was any structural abnormality, cardiac or non-cardiac. Other exclusion criteria comprised nuchal translucency greater than the 95th centile at 11–14 weeks, small-for-gestational age fetuses or diabetic mothers. Ascertainment was generally sequential, although earlier and later gestations were targeted to ensure as even a distribution as possible throughout pregnancy. Gestational age ranged from 15 to 39 (mean, 26.3; SD 6.3) weeks. To exclude potential bias from serial measurements in a single fetus, each subject was studied only once.

Echocardiography

Recordings of routine cross-sectional fetal echocardiography studies were performed using standard views and the same methodology by two fetal cardiologists (P.E.F.D. and J.S.C.) as in a previous study by one of the authors⁸. The cardiologists were assisted by two fetal echocardiography technicians using Ultramark (ATL/Philips, Amsterdam, Netherlands), Acuson (Siemens, Munich, Germany) and Aloka (Tokyo, Japan) equipment with appropriately sized transducers (3.5–7.5-MHz). In each case, during the same hospital visit, fetal FL and BPD were measured. The

GA was calculated from the date of the last menstrual period. If appropriate, this was amended at the second-trimester ultrasound scan, when there was a discrepancy between size and dates.

All scans were recorded on S-VHS videotape. To minimize interobserver error, all fetal cardiac measurements were performed offline after review of each study by two fetal cardiologists (P.E.F.D. and C.S.) who oversaw the routine echocardiography scans in each hospital. One of the cardiologists (P.E.F.D.) participated in both Toronto and London phases of the study. Measurements were obtained using electronic calipers and post-processing capabilities of the Sonos 5500 echocardiographic machine (Philips, Amsterdam, Netherlands). Cardiac dimensions were measured at their maximal size. The great vessels and the arterial valves were measured in systole, the atrioventricular valves and ventricular chambers in diastole. Measurements were taken from inner-edge to inner-edge. At least three estimates of each dimension were taken from separate frames and the mean used.

Seventeen cardiac dimensions were measured using two-dimensional transabdominal echocardiography (Figure 1). The following measurements were made on the right side of the heart: inferior vena cava, tricuspid valve, right ventricular inlet length, right ventricular end-diastolic dimension, right ventricular area, pulmonary valve, main pulmonary artery, right and left pulmonary arteries and arterial duct; and left side of the heart: mitral valve, left ventricular inlet length, left ventricular end-diastolic dimension, left ventricular area, aortic valve, ascending and descending aorta.

The echocardiographic views of the aortic valve, ascending aorta, descending aorta and inferior vena cava were measured using only longitudinal views. The main pulmonary artery and branches were measured in either the oblique short-axis view or an oblique transverse plane of the fetal thorax giving a longitudinal view of the pulmonary artery and its bifurcation. The duct was measured in an oblique short-axis view, halfway between its emergence from the pulmonary artery and its entrance into the descending aorta. For the ventricular areas in the four-chamber view, the areas of the papillary muscles were included, by tracing the endocardial contour parallel to that of the epicardium, and straight lines were traced across the atrioventricular valvar orifices.

For any given cardiac dimension, measurements were made only if excellent views of the cardiac structure had been obtained and recorded. Consequently, not all structures were measured in every subject. However, no structure was measured in fewer than 80 subjects and measurements were made on greater than 110 subjects for 13 of the 17 structures and dimensions.

Statistical analysis

The Z-score regression equations were developed for each structure by relating the natural logarithm of the measured structure to the natural logarithm of the normalizing variable. Measurements from 130 fetuses were available

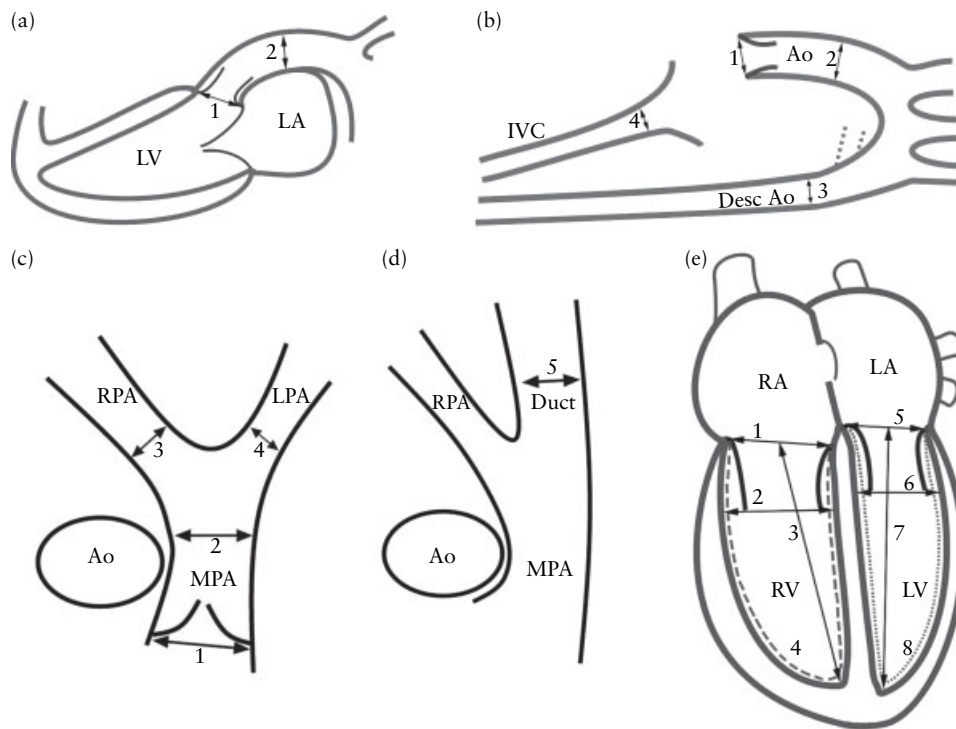


Figure 1 Fetal echocardiographic views from which the cardiac structures and dimensions were measured. (a) Long-axis view of the left ventricle showing the aortic valve (1) and ascending aorta (2). (b) Aortic arch view showing the aortic valve (1), ascending aorta (2), descending aorta (3) and inferior vena cava (4). (c) Short-axis view, showing the pulmonary valve (1), main (2), right (3) and left (4) pulmonary arteries. (d) Oblique short-axis view, showing the pulmonary trunk and the arterial duct (5). (e) Four-chamber view, showing the tricuspid valve (1), right ventricular end-diastolic dimension (2), right ventricular inlet length (3), right ventricular area (dashed line) (4), mitral valve (5), left ventricular end-diastolic dimension (6), left ventricular inlet length (7) and left ventricular area (dotted line) (8). Ao, aorta; Desc Ao, descending aorta; IVC, inferior vena cava; LA, left atrium; LPA, left pulmonary artery; LV, left ventricle; MPA, main pulmonary artery; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle.

for regression analysis. While the measurements spanned an appreciable range of body size and gestation, fewer measurements were available at the more extreme ends at which fetal echocardiography is performed. While statistical methods are not available to judge the adequacy of the number of study subjects formally, plots of the actual data superimposed on the derived regression lines and CIs showed excellent fit over the entire range. Nonetheless, caution might be exercised when using regression results in interpreting measurements made at the more extreme ends of body size and gestation.

In this study, the GA, FL and BPD were highly correlated and separate regressions were developed for each. The data were not entered into multivariable models. Plots of the regressions were made, together with 95% CIs, and the original data were then superimposed. In addition, practical nomograms were created to allow derivation of Z-scores without having to solve the regression equations. All analyses were performed using SAS Statistical Software version 8 (SAS Institute, Inc., Cary, NC, USA) using default settings.

RESULTS

The relationship between the various fetal cardiac dimensions and three fetal parameters describing fetal size (as represented by FL, BPD or GA) were best described

following natural log transformation, according to the formula:

$$\ln(\text{predicted cardiac dimension}) = m \cdot \ln(\text{FL, GA or BPD}) + c, \quad (\text{Equation 1})$$

where \ln represents the natural logarithm of the fetal parameter; FL, femur length in centimeters; GA, gestational age in completed weeks; BPD, biparietal diameter in centimeters; m , multiplier and c , intercept. The cardiac dimension for the fetal parameters is expressed in centimeters or centimeters squared. The multiplier (m) and intercept (c) values for each cardiac dimension are shown in Tables 1–3 for the parameters FL, BPD and GA, respectively.

Using these parameters in Equation 1, Z-scores for new measurements of specific cardiac dimensions could then be calculated from the following formula:

$$\text{Z-score} = (\ln(\text{actual}) - \ln(\text{predicted cardiac dimension})) / \text{root MSE}, \quad (\text{Equation 2})$$

where 'actual' represents the cardiac dimension actually measured and 'predicted' the predicted cardiac dimension for a given FL, GA or BPD derived from Equation 1. \ln represents the natural logarithm. The 'root mean

Table 1 Regression equations relating cardiac dimensions and femur length are shown in addition to the regression coefficient and root mean square error

Structure	n	Intercept (c)	Multiplier (m)	Root MSE	r*
Aortic valve	119	-2.274	0.8972	0.1103	0.95
Pulmonary valve	115	-2.148	0.9437	0.1110	0.95
Ascending aorta	118	-2.141	0.8968	0.1225	0.94
Main pulmonary artery	114	-2.072	0.9465	0.1645	0.90
Tricuspid valve	118	-1.735	0.9937	0.1386	0.93
Mitral valve	117	-1.550	0.8473	0.1202	0.93
RV EDD	118	-1.485	0.9625	0.1435	0.92
LV EDD	117	-1.516	0.9554	0.1403	0.92
RV inlet	118	-0.8249	0.9305	0.1520	0.91
LV inlet	117	-0.6751	0.8772	0.1216	0.93
RV area	118	-2.488	1.905	0.2651	0.93
LV area	115	-2.283	1.823	0.2145	0.94
Descending aorta	110	-2.368	0.9415	0.1224	0.94
Inferior vena cava	108	-2.502	0.8365	0.1885	0.85
Right pulmonary artery	103	-2.623	0.8685	0.1780	0.87
Left pulmonary artery	83	-2.785	0.9219	0.1935	0.84
Arterial duct	86	-2.251	0.7370	0.1830	0.83

* $P < 0.0001$. n represents the number of cases in which the cardiac dimension was measured and r the correlation coefficient. EDD, end-diastolic dimension; LV, left ventricle; MSE, mean square error; RV, right ventricle.

Table 2 Regression equations relating cardiac dimensions and biparietal diameter are shown in addition to the regression coefficient and root mean square error

Structure	n	Intercept (c)	Multiplier (m)	Root MSE	r*
Aortic valve	119	-2.848	1.039	0.1307	0.92
Pulmonary valve	116	-2.813	1.126	0.1171	0.94
Ascending aorta	118	-2.758	1.060	0.1227	0.93
Main pulmonary artery	114	-2.774	1.144	0.1455	0.92
Tricuspid valve	118	-2.439	1.188	0.1456	0.92
Mitral valve	117	-2.118	0.9921	0.1296	0.91
RV EDD	118	-2.145	1.138	0.1525	0.91
LV EDD	117	-2.087	1.080	0.1652	0.88
RV inlet	118	-1.403	1.064	0.1661	0.87
LV inlet	117	-1.262	1.024	0.1313	0.91
RV area	118	-3.643	2.165	0.3193	0.88
LV area	115	-3.335	2.042	0.2691	0.90
Descending aorta	111	-2.998	1.101	0.1332	0.92
Inferior vena cava	105	-3.159	1.031	0.1892	0.85
Right pulmonary artery	103	-3.223	1.025	0.1813	0.85
Left pulmonary artery	82	-3.383	1.062	0.2001	0.82
Arterial duct	85	-2.694	0.8236	0.2042	0.78

* $P < 0.0001$. n represents the number of cases in which the cardiac dimension was measured and r the correlation coefficient. EDD, end-diastolic dimension; LV, left ventricle; MSE, mean square error; RV, right ventricle.

square error (MSE) for each cardiac dimension (from the regression equation) is shown in Tables 1–3 for FL, BPD and GA, respectively.

Figure 2 shows a sample scatterplot of the individual data points for the relation of the size of the pulmonary valve to FL, superimposed on which are solid lines representing the regression equation that best described

Table 3 Regression equations relating cardiac dimensions and gestational age are shown in addition to the regression coefficient and root mean square error

Structure	n	Intercept (c)	Multiplier (m)	Root MSE	r*
Aortic valve	128	-5.019	1.263	0.1282	0.93
Pulmonary valve	124	-5.114	1.352	0.1208	0.94
Ascending aorta	127	-4.886	1.261	0.1330	0.92
Main pulmonary artery	123	-5.025	1.347	0.1570	0.91
Tricuspid valve	127	-4.766	1.395	0.1394	0.93
Mitral valve	126	-4.084	1.173	0.1315	0.91
RV EDD	127	-4.455	1.363	0.1442	0.92
LV EDD	126	-4.292	1.298	0.1560	0.90
RV inlet	127	-3.566	1.277	0.1658	0.88
LV inlet	126	-3.231	1.193	0.1376	0.91
RV area	127	-8.133	2.625	0.2957	0.91
LV area	124	-7.430	2.432	0.2564	0.92
Descending aorta	119	-5.365	1.360	0.1216	0.94
Inferior vena cava	114	-5.140	1.201	0.1893	0.85
Right pulmonary artery	109	-5.307	1.230	0.1802	0.87
Left pulmonary artery	87	-5.390	1.231	0.1966	0.84
Arterial duct	90	-4.440	1.013	0.1913	0.81

* $P < 0.0001$. n represents the number of cases in which the cardiac dimension was measured and r the correlation coefficient. EDD, end-diastolic dimension; LV, left ventricle; MSE, mean square error; RV, right ventricle.

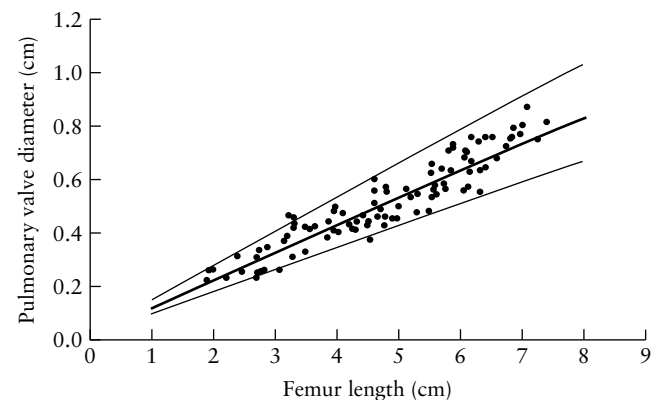


Figure 2 Sample scatterplot showing the relationship between the size of the pulmonary valve and femur length, superimposed on which are solid lines representing the regression equation and 95% CIs. For other scatterplots see Figure E1.

that relation and 95% CIs. Additional scatterplots are available online as Supplementary Material. FL was the parameter that gave the highest correlation coefficients in relation to most fetal cardiac dimensions, followed by GA and BPD. For example, for the aortic valve, the strongest relationship was with FL ($r = 0.95$), using the natural log – natural log model (Table 1).

A sample nomogram for determining the Z-score for a new measurement of aortic valve for a given FL is shown in Figure 3. Additional nomograms are available online as Supplementary Material. To derive the Z-score for an individual cardiac dimension using the appropriate Z-score nomogram, it is first necessary to locate the curved nomogram line with the correct measurement

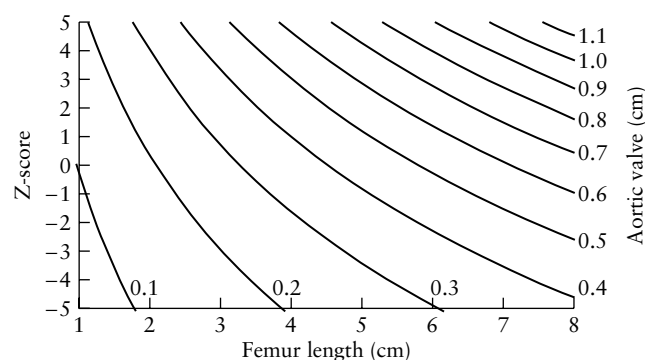


Figure 3 Sample Z-score nomogram relating aortic valve to femur length (FL). This allows determination of the Z-score from knowledge of the size of the aortic valve and the FL. For further nomograms of other cardiac dimensions relating to FL, biparietal diameter and gestational age either use Equations 1 and 2 and Tables 1–3 or see Figure E2.

of that dimension. Second, the appropriate FL (BPD or GA) should be located on the *x*-axis and a vertical line should be drawn to the appropriate curved nomogram line. This point should then be connected to the *y*-axis with a horizontal line, where the Z-score can be read off. Z-scores can also be precisely determined using Equations 1 and 2 and the data presented in Tables 1–3.

Worked example to calculate the Z-score for the aortic valve based on FL

For a fetus with a FL of 4 cm, the aortic valve is measured at 0.3 cm. The first step is to calculate the predicted size of the aortic valve for a fetus with this size FL using Equation 1 and obtaining the appropriate *m* and *c* values for the aortic valve from Table 1.

$$\begin{aligned} \ln(\text{predicted cardiac dimension}) &= m \cdot \ln(\text{FL}) + c \\ &= 0.8972(\ln(4 \text{ cm})) + (-2.274) \\ &= 0.8972(1.386) - 2.274 \\ &= -1.030. \end{aligned}$$

From this figure the predicted aortic valve diameter can also be calculated and would be the inverse natural log, which is 0.36 cm. To calculate the Z-score Equation 2 is used obtaining root MSE, also from Table 1.

$$\begin{aligned} \text{Z-score} &= (\ln(\text{actual}) - \ln(\text{predicted}))/\text{root MSE} \\ &= (\ln(0.3 \text{ cm}) - (-1.030))/0.1103 \\ &= (-1.204 + 1.030)/0.1103 \\ &= -1.578. \end{aligned}$$

Therefore, the Z-score is -1.578 . In practice this could also be derived, albeit with less accuracy, from Figure 3.

DISCUSSION

This study presents formulae and nomograms allowing Z-scores to be calculated for 17 cardiac structures in fetal

life from knowledge of the FL, BPD or GA using cross-sectional transabdominal echocardiography. FL was the independent variable that provided the highest correlation coefficient with most fetal cardiac dimensions. A natural logarithmic – natural logarithmic model best described the relationship between cardiac dimensions and FL, BPD or GA. Similar to centiles, Z-scores are used to measure growth in comparison to the normal range. In cases that are very far away from the norm it is difficult to determine very small structures precisely. However, Z-scores provide accurate measurements and interpretation of growth. This would be particularly relevant to the clinician in determining the treatment strategy of patients with a congenital heart disease. In the research setting, Z-scores can allow statistical comparisons between subgroups of fetuses. For example, in fetal pulmonary atresia with intact ventricular septum, Z-scores could be used to assess whether fetal catheter intervention results in increased growth of right heart structures by comparing the Z-scores of treated and untreated groups. Such mathematical manipulation is extremely difficult and problematic using centiles.

Knowledge of the size of cardiac dimensions *in utero* is an important part of the evaluation of a fetus with congenital heart disease. It is well established that cardiac lesions can progress prenatally^{11,12}. Therefore, it is important to ascertain whether a cardiac structure is maintaining its growth relative to somatic growth. With the advent of fetal cardiac interventions, the decision to intervene may be taken if the cardiac chamber or outflow is thought to be growing at a much smaller rate than somatic growth. Since there is such huge growth in prenatal life, particularly during the third trimester, it is essential that the measured size of a cardiac structure be compared (or normalized) to some parameter reflecting fetal size.

Frequently, cardiac dimensions are compared to GA as a surrogate of fetal size^{1–4,10,13–21}. Whilst it may be reasonable to normalize to GA in the second trimester, in the third trimester there is significant variability between GA and size of the fetus²², and by term there can be a several-fold difference in the size of the fetus. Serial plotting of cardiac dimensions on ‘centile’ charts based on GA can provide some qualitative information about growth of a cardiac structure^{1,2}; however, it is extremely difficult to derive quantitative information.

Various surrogates of fetal size have been used as the basis of normalization including fetal weight²³, BPD^{5,6,16,17,20}, abdominal circumference⁶ and FL⁶. We found that FL gave the better correlation coefficient with fetal cardiac dimensions (following natural logarithmic transformation) although good correlations were also found for BPD and GA. In childhood, Schneider *et al.* found that height was the best means of normalizing cardiac dimensions²⁴. As it is difficult to measure height prenatally, FL provides a satisfactory substitute. It is important to bear in mind, however, that where there are abnormalities of FL (dwarfism) or head

size (microcephaly, dolichocephaly) then an alternate parameter may be preferable.

Several groups found a linear model best described the relationship between fetal cardiac dimension and somatic size, others a quadratic polynomial or cubic relation. We found the relationship to be nonlinear and the highest correlation coefficients were achieved following natural log transformation. This was also found in a previous study postnatally⁸.

Comparison of the present data with other published fetal echocardiographic studies is limited by differing mathematical descriptions of the relationship as well as a lack of consistency in the definitions of cardiac dimensions (measurements made in systole vs. diastole). Which definition used is probably less important than ensuring consistency in measurement and normalization method. A choice of parameter is presented here: FL, BPD and GA, the latter in case direct measurement of the first two parameters is not possible. We believe we have used the methods of measurement that are most commonly used in clinical practice to allow the relative size and growth of fetal cardiac structures to be quantified, which may lead to earlier prediction of *in-utero* progression of disease. This, in turn, may clarify the indications for *in-utero* intervention

CONCLUSIONS

Whereas previous studies of normal fetal cardiac dimensions have allowed qualitative assessment of fetal cardiac growth (using centiles), the present study allows quantitative assessment, using Z-scores. This will permit mathematical assessment of serial growth of fetal cardiac structures, allow subgroup comparison and improve the challenging task of assessing growth and charting development in hearts with a congenital abnormality. This demonstration of Z-scores in fetal life should serve as significant reference data in predicting outcomes.

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REFERENCES

- 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. *Circulation* 1992; **86**: 741–747.
- Hornberger LK, Sanders SP, Rein AJ, Spevak PJ, Parness IA, Colan SD. Left heart obstructive lesions and left ventricular growth in the midtrimester fetus. A longitudinal study. *Circulation* 1995; **92**: 1531–1538.
- Tan J, Silverman NH, Hoffman JI, Villegas M, Schmidt KG. Cardiac dimensions determined by cross-sectional echocardiography in the normal human fetus from 18 weeks to term. *Am J Cardiol* 1992; **70**: 1459–1467.
- Pineda LF, Moreno ATM, Azcárate MJM, Zea ML, Bullón MC, Gómez FR, Jiménez MQ. Cardiac growth in the normal human fetus. A two-dimensional echocardiographic study. *An Esp Pediatr* 1996; **44**: 475–481.
- DeVore GR, Siassi B, Platt LD. Fetal Echocardiography. IV. M-mode assessment of ventricular size and contractility during the second and third trimesters of pregnancy in the normal fetus. *Am J Obstet Gynecol* 1984; **150**: 981–988.
- DeVore GR, Siassi B, Platt LD. Fetal Echocardiography. V. M-mode measurements of the aortic root and aortic valve in second- and third-trimester normal human fetuses. *Am J Obstet Gynecol* 1985; **152**: 543–560.
- Rimoldi HJA, Lev M. A note on the concept of normality and abnormality in quantitation of pathologic findings in congenital heart disease. *Pediatr Clin North Am* 1963; **10**: 589–591.
- Daubeney PE, Blackstone EH, Weintraub RG, Slavik Z, Scanlon J, Webber SA. Relationship of the dimension of cardiac structures to body size: an echocardiographic study in normal infants and children. *Cardiol Young* 1999; **9**: 402–410.
- Hornberger LK, Lipshultz SE, Easley KA, Colan SD, Schwartz M, Kaplan S, Starc TJ, Ayres NA, Lai WW, Moodie DS, Kasten-Sportes C, Sanders SP. Cardiac structure and function in fetuses of mothers infected with HIV: the prospective P²C²HIV multicenter study. *Am Heart J* 2000; **140**: 575–584.
- Sharland GK, Allan LD. Normal fetal cardiac measurements derived by cross-sectional echocardiography. *Ultrasound Obstet Gynecol* 1992; **2**: 175–181.
- Allan LD, Cook A. Pulmonary atresia with intact ventricular septum in the fetus. *Cardiol Young* 1992; **2**: 367–376.
- Daubeney PE, Sharland GK, Cook AC, Keeton BR, Anderson RH, Webber SA. Pulmonary atresia with intact ventricular septum: impact of fetal echocardiography on incidence at birth and postnatal outcome. *Circulation* 1998; **98**: 562–566.
- Allan LD, Joseph MC, Boyd EG, Campbell S, Tynan M. M-mode echocardiography in the developing human fetus. *Br Heart J* 1982; **47**: 573–583.
- Wladimiroff JW, Vosters R, McGhie JS. Normal cardiac ventricular geometry and function during the last trimester of pregnancy and early neonatal period. *Br J Obstet Gynaecol* 1982; **89**: 839–844.
- St John Sutton MG, Gewitz MH, Shah B, Cohen A, Reichek N, Gabbe S, Huff DS. Quantitative assessment of growth and function of the cardiac chambers in the normal human fetus: a prospective longitudinal echocardiographic study. *Circulation* 1984; **69**: 645–654.
- Shime J, Gresser CD, Rakowski H. Quantitative two-dimensional echocardiographic assessment of fetal cardiac growth. *Am J Obstet Gynecol* 1986; **154**: 294–300.
- Cartier MS, Davidoff A, Warneke LA, Hirsh MP, Bannon S, Sutton MS, Doubilet PM. The normal diameter of the fetal aorta and pulmonary artery: echocardiographic evaluation *in utero*. *AJR Am J Roentgenol* 1987; **149**: 1003–1007.
- Shapiro I, Degani S, Leibovitz Z, Ohel G, Tal Y, Abinader EG. Fetal cardiac measurements derived by transvaginal and trans-abdominal cross-sectional echocardiography from 14 weeks of gestation to term. *Ultrasound Obstet Gynecol* 1998; **12**: 404–418.
- Mielke G, Benda N. Reference ranges for two-dimensional echocardiographic examination of the fetal ductus arteriosus. *Ultrasound Obstet Gynecol* 2000; **15**: 219–225.
- Gembruch U, Shi C, Smrcek JM. Biometry of the fetal heart between 10 and 17 weeks of gestation. *Fetal Diagn Ther* 2000; **15**: 20–31.
- Firpo C, Hoffman JIE, Silverman NH. Evaluation of fetal heart dimensions from 12 weeks to term. *Am J Cardiol* 2001; **87**: 594–600.
- Hadlock FP, Deter RL, Harrist RB, Park SK. Estimating fetal age: computer-assisted analysis of multiple fetal growth parameters. *Radiology* 1984; **152**: 497–501.
- Sahn DJ, Lange LW, Allen HD, Goldberg SJ, Anderson C, Giles H, Haber K. Quantitative real-time cross-sectional echocardiography in the developing normal human fetus and newborn. *Circulation* 1980; **62**: 588–597.

24. Schneider C, Cabizuca SV, Benchimol CB, Matsunaga LA, Ginefra P, Albanesi Filho FM, Gomes Filho JB. Normal echocardiographic patterns in children of the city of Rio de Janeiro. I. Relation between echocardiographic measurements and anthropometric standards [in Portuguese]. *Arq Bras Cardiol* 1986; 47: 189–192.

SUPPLEMENTARY MATERIAL ON THE INTERNET

The following material is available from the Journal homepage:

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

Figure E1 Scatterplots showing the relationship between the size of the respective cardiac dimension and (a) femur length, (b) biparietal diameter and (c) gestational age superimposed on which are solid lines representing the regression equation and 95% CIs.

Figure E2 Z-score nomograms relating tricuspid valve, right ventricular inlet length, right ventricular end-diastolic dimension, pulmonary valve, main pulmonary artery, mitral valve, left ventricular inlet length, left ventricular end-diastolic dimension, aortic valve, ascending aorta and descending aorta to (a) femur length (FL), (b) biparietal diameter (BPD) and (c) gestational age (GA) (selective nomograms only shown). This allows determination of the Z-score from knowledge of the size of the cardiac dimension and either FL, BPD or GA.