Predictive Models for Normal Fetal Cardiac Structures

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Background: Clinicians rely on age- and size-specific measures of cardiac structures to diagnose cardiac disease. No universally accepted normative data exist for fetal cardiac structures, and most fetal cardiac centers do not use the same standards. The aim of this study was to derive predictive models for *Z* scores for 13 commonly evaluated fetal cardiac structures using a large heterogeneous population of fetuses without structural cardiac defects.

Methods: The study used archived normal fetal echocardiograms in representative fetuses aged 12 to 39 weeks. Thirteen cardiac dimensions were remeasured by a blinded echocardiographer from digitally stored clips. Studies with inadequate imaging views were excluded. Regression models were developed to relate each dimension to estimated gestational age (EGA) by dates, biparietal diameter, femur length, and estimated fetal weight by the Hadlock formula. Dimension outcomes were transformed (e.g., using the logarithm or square root) as necessary to meet the normality assumption. Higher order terms, quadratic or cubic, were added as needed to improve model fit. Information criteria and adjusted R^2 values were used to guide final model selection.

Results: Each *Z*-score equation is based on measurements derived from 296 to 414 unique fetuses. EGA yielded the best predictive model for the majority of dimensions; adjusted R^2 values ranged from 0.72 to 0.893. However, each of the other highly correlated ($r > 0.94$) biometric parameters was an acceptable surrogate for EGA. In most cases, the best fitting model included squared and cubic terms to introduce curvilinearity.

Conclusions: For each dimension, models based on EGA provided the best fit for determining normal measurements of fetal cardiac structures. Nevertheless, other biometric parameters, including femur length, biparietal diameter, and estimated fetal weight provided results that were nearly as good. Comprehensive *Z*-score results are available on the basis of highly predictive models derived from gestational age or other biometrics as preferable for clinical reasons. These results supplant current equations and will provide a foundation for future multicenter collaborations. (J Am Soc Echocardiogr 2016;29:1197-206.)

Keywords: Fetal echocardiography, *Z* score, Cardiac parameters in the fetus

High-quality normative data for two-dimensional measures of cardiac structures is useful in the accurate diagnosis of congenital heart disease in the fetus. This is particularly true in early gestation, when signs of valve and outflow tract abnormalities may be very subtle. In addition to diagnosing abnormalities, fetal cardiologists must predict and counsel about the most likely postnatal clinical course, including surgical repair and long-term outcomes. As part of clinical care and decision making, pediatric cardiologists and surgeons use "*Z*-score" calculations of two-dimensional measurements of structures to make decisions about the type of surgery to perform. Universally accepted predictive models do not yet exist for fetuses, although a small body of literature suggests that they may be useful.[1]

Calculation of *Z* scores normalizes cardiac structures to body size.[2,3] This technique has become the standard method of assessing normality in pediatrics and obstetrics.[4-6] Yet no comprehensive set of normative *Z*-score equations exist to express the size of fetal cardiac structures in the literature. Existing studies have been based on modest patient numbers, used M-mode measurements, studied only small numbers of parameters, or focused on parameters that would be more useful for obstetric purposes.[7-14] The largest body of literature available examined absolute values of normal structures across gestation.[15-19] Using our growing experience with fetal echocardiography, we sought to determine the best predictive models for normal cardiac structures across a broad range of fetal development.

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In memory of Dr. Jodi Ilyse Pike whose energy and optimism have left a lasting contribution to the field of fetal cardiology.

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Abbreviations

AoVA = aortic valve annulus

AoI = aortic isthmus

Asc Ao = ascending aorta

Dsc Ao = descending aorta

BPD = Biparietal diameter

EGA = Estimated gestational age

FL = Femur length

FW = Fetal weight

LPA = left pulmonary artery

LVL = left ventricular length

MPA = Main pulmonary artery

MSE = Mean squared error

MVA = mitral valve annulus

PDA = patent ductus arteriosus

PVA = pulmonary valve annulus

RPA = right pulmonary artery

RVL = right ventricular length

TVA = tricuspid valve annulus

We derived predictive models for *Z* scores for 13 commonly evaluated fetal cardiac structures using a large heterogeneous population of fetuses without significant structural cardiac disease.

METHODS

This study was approved by the institutional review board at our institution.

Patient Selection

The echocardiography database at our hospital was queried to collect normal fetal echocardiographic reports from a representative population over a 1-year period (2009–2010) in subjects ranging from 12 to 39 weeks' gestation, as determined by early obstetric ultrasound dating. Both singleton and twin fetuses were included. Excluded were fetuses with structural cardiac disease. Selection was performed using a search engine with finding codes for "normal fetal echocardiogram" and "no structural fetal cardiac disease." These terms would exclude any fetus with a definitive diagnosis of congenital heart defect. If a fetus in the cohort had multiple measurements, only the first study was used.

Echocardiography

Echocardiography was performed using a curvilinear C4-7 MHz probe on either a Vivid 7 (GE Healthcare, Milwaukee, WI) or a Philips iE33 (Philips Medical Systems, Best, The Netherlands) echocardiographic machine with fetal preset. A standard fetal echocardiographic imaging protocol is used at our institution on the basis of the guidelines of the American Society of Echocardiography.[20] Measurements were performed by a cardiologist with specialized training in fetal echocardiography (J.I.P.), who was blinded to demographics and to the prior measurements. Studies with substandard imaging planes were not included (5%–32%). Measurements were performed on a stand-alone digital workstation (Philips Medical Systems, Andover, MA). All fetal echocardiograms coded as normal or as depicting no structural cardiac defects were considered for inclusion in the study. Estimated gestational age (EGA) at our institution is taken from the determination of the referring maternal fetal medicine specialist or in some cases obstetrician and is calculated by early ultrasound dating or last menstrual period. The most appropriate measurement is determined by the referring physician, and in this case an assumption was made that they use national standards for dating. Femur length (FL), biparietal diameter (BPD), and abdominal circumference (incorporated into fetal weight [FW]) were measured using standard methods, and a calculated gestational age if performed at the time of the study was also recorded from these measurements. FW was calculated using the Hadlock formula. Although postnatal follow-up could not be obtained, diagnostic accuracy of fetal diagnosis for major cardiac defects is 97%.[21]

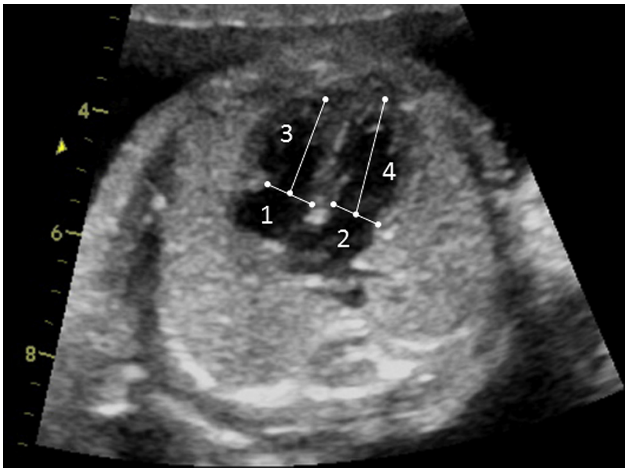

Figure 1 Apical four-chamber view of the fetal heart showing measurement of the (1) tricuspid valve annulus, (2) mitral valve annulus, (3) right ventricular length, and (4) left ventricular length.

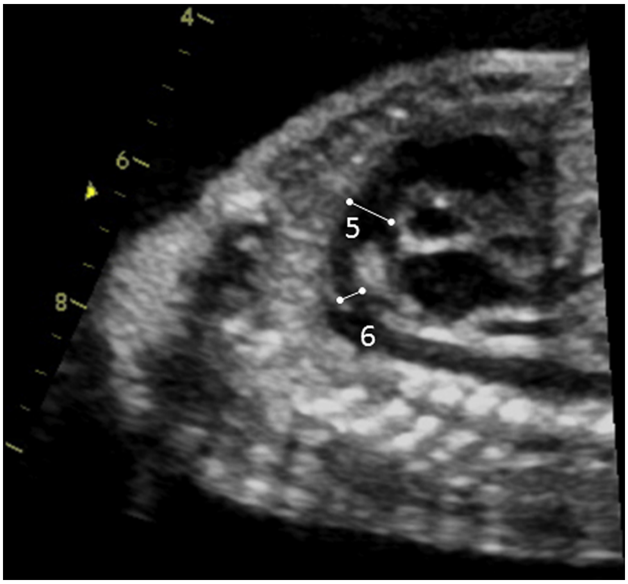

Figure 2 Ductal arch view of the fetal heart showing measurement of the (5) MPA and (6) patent ductus arteriosus.

Structures Assessed

A total of 13 cardiac dimensions were evaluated: aortic valve annulus (AoVA), pulmonary valve annulus (PVA), tricuspid valve annulus (TVA), mitral valve annulus (MVA), main pulmonary artery (MPA), ascending aorta (Asc Ao), descending aorta (Dsc Ao), aortic isthmus (AoI), patent ductus arteriosus (PDA), left pulmonary artery (LPA), right pulmonary artery (RPA), left ventricular length (LVL), and right ventricular length (RVL). Examples of echocardiographic images illustrating the measured structures can be found in Figures 1–6. Measurements of the AoVA, PVA, MVA, TVA, LVL, and RVL were performed in the four-chamber transverse view. Measurements for the Asc Ao diameter, Dsc Ao diameter, and AoI were performed in the sagittal view. Measurements for the MPA,