Nomograms of Fetal Cardiac Dimensions at 18–41 Weeks of Gestation

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Keywords
Nomograms · Fetal heart · Congenital heart defects

Abstract

Objective: There is a need for standardized reference values for cardiac dimensions in prenatal life. The objective of the present study was to construct nomograms for fetal cardiac dimensions using a well-defined echocardiographic methodology in a low-risk population. Methods: This is a prospective cohort study including 602 low-risk singleton pregnancies undergoing a standardized fetal echocardiography to accurately assess fetal cardiac, ventricular, and atrial dimensions. Parametric regressions were tested to model each measurement against gestational age from 18 to 41 weeks of gestation. Results: Nomograms were constructed for fetal cardiac dimensions (transverse and longitudinal diameters and areas) of the whole heart, atria, and ventricles, as well as myocardial wall thicknesses. All dimensions showed a progressive increase with gestational age. The best model for most parameters was a second-degree linear polynomial. Fetal cardiac, ventricular, and atrial diameters and areas were successfully obtained in 98.6% of the fetuses, while myocardial wall thicknesses could be obtained in 96.5% of the population. The results showed excellent interobserver and intraobserver reproducibility (intraclass correlation coefficient, ICC > 0.811 and ICC > 0.957, respectively). Conclusions: We provide standardized and comprehensively evaluated reference values for fetal cardiac morphometric parameters across gestation in a low-risk population. These nomograms would enable the early identification of different patterns of fetal cardiac remodeling.

Introduction

Fetal echocardiography was initially used to identify congenital heart defects (CHD) and arrhythmias [1–3]. Since then, technical advances have enabled a notable improvement in the assessment of cardiac structure and function.
| Authors                  | Year of publication | Design                        | n  | Population                           | GA at scan, weeks | Parameters studied                                         | Methods                                | Timing                      | Limitations                                                                 |
|-------------------------|---------------------|-------------------------------|----|--------------------------------------|-------------------|-----------------------------------------------------------|----------------------------------------|-----------------------------|----------------------------------------------------------------------------|
| **2D ultrasound**       |                     |                               |    |                                      |                   |                                                           |                                        |                             |                                                                            |
| Tan et al. [29]         | 1992                | Retrospective                 | 100| Volunteer healthcare professionals | 18–40             | Basal and longitudinal ventricular diameters              | Different cardiac views depending on the measurement | End-diastole               |                                                                            |
|                         |                     |                               |    |                                      |                   | Myocardial wall thicknesses                               |                                        |                             |                                                                            |
|                         |                     |                               |    |                                      |                   | Atria width and length                                   |                                        |                             |                                                                            |
|                         |                     |                               |    |                                      |                   |                                                           |                                        |                             |                                                                            |
|                         |                     |                               |    |                                      |                   |                                                           |                                        |                             |                                                                            |
| Shauald et al. [31]     | 1992                | Retrospective                 | 100–337| High-risk pregnancies (referred for fetal echocardiogram) | 16–40             | Ventricular width (n = 337)                               | Measurement below coapted atrioventricular valves | End-diastole               |                                                                            |
|                         |                     |                               |    |                                      |                   | Longitudinal ventricular diameters (n = 100)              |                                        |                             |                                                                            |
|                         |                     |                               |    |                                      |                   |                                                           |                                        |                             |                                                                            |
| Shapiro et al. [12]     | 1998                |                               | 637| Women at routine sonographic examination | 14–40             | Basal ventricular diameters                               | Measurement below the atrioventricular valve | End-diastole               | Maximal dilatation                                                        |
|                         |                     |                               |    |                                      |                   | Atrial transverse diameters                               |                                        |                             |                                                                            |
|                         |                     |                               |    |                                      |                   |                                                           |                                        |                             |                                                                            |
| Firpo et al. [14]       | 2001                | Longitudinal and cross-sectional data | 124| Volunteer healthcare professionals | 12–32 | Ventricular width | Ventricular length | Ventricular wall and ventricular septum | Ventricular width below coapted atrioventricular valves | End-diastole | Maximal dilatation                                                        |
|                         |                     |                               |    | Women referred for family history of congenital heart disease | | | | | Variety of views depending on the parameter studied (4-chamber view, long-axis view and short-axis view) | | | Irregular volume of data depending on GA |
|                         |                     |                               |    |                                      |                   | Atria width and length                                   |                                        |                             |                                                                            |
|                         |                     |                               |    |                                      |                   |                                                           |                                        |                             |                                                                            |
| Schneider et al. [13]   | 2005                | Retrospective                 | 130| High-risk pregnancies (referred for fetal echocardiogram) | 15–39             | Tricuspid and mitral valve                               | Diastole                              | Ventricular measurements not performed at end-diastole (atrioventricular valves opened) |                                                                            |
|                         |                     |                               |    |                                      |                   | Ventricular inlet length                                  |                                        |                             |                                                                            |
|                         |                     |                               |    |                                      |                   | Ventricular basal diameters                               |                                        |                             |                                                                            |
|                         |                     |                               |    |                                      |                   | Ventricular area                                         |                                        |                             |                                                                            |
| Chanthasenanont et al. [34] | 2008               |                               | 480| Pregnant women who routinely attended the antenatal clinic | 16–39             | Left ventricular dimensions                               | Diastole                              |                                                                            |
|                         |                     |                               |    |                                      |                   | Left and septal myocardial wall thicknesses              |                                        |                             |                                                                            |
| Lee et al. [32]         | 2010                | Retrospective cross-sectional | 2,735| Database of routine scans           | 17–41            | Ventricular basal diameters                               | End-diastole                           | Study population initially derived from a database |                                                                            |
|                         |                     |                               |    |                                      |                   | Z-scores using menstrual age, BPD, and FL as independent variables |                                        |                             |                                                                            |
| Li et al. [17]          | 2015                | Cross-sectional               | 809|                                      | 11–40            | Transverse heart diameter                                | End-diastole                           | Exclusively Chinese population |                                                                            |
|                         |                     |                               |    |                                      |                   | Heart length                                             |                                        |                             |                                                                            |
|                         |                     |                               |    |                                      |                   | Heart circumference                                       |                                        |                             |                                                                            |
|                         |                     |                               |    |                                      |                   | Heart area                                               |                                        |                             |                                                                            |
| Gu et al. [15]          | 2016                | Cross-sectional               | 4,596|                                      | 20–34            | Transverse cardiac diameter                               | End-diastole and end-systole           | Exclusively Chinese population |                                                                            |
|                         |                     |                               |    |                                      |                   | Ventricular basal diameter                               |                                        |                             |                                                                            |
|                         |                     |                               |    |                                      |                   | Atrial transverse diameter                               |                                        |                             |                                                                            |
| **M-mode ultrasound**   |                     |                               |    |                                      |                   |                                                           |                                        |                             |                                                                            |
| Allan et al. [3]        | 1981                | Retrospective                 | 178|                                      | 18–40            | Left and septal myocardial wall thicknesses              | Short-axis view                        | Not specified               |                                                                            |
| Patchakapat et al. [35] | 2006                |                               | 410| Pregnant women who routinely attended the clinic | 32–35.6         | Interventricular septal thickness                        | Diastole and systole                   | Exclusively Thai population |                                                                            |
| Gagnon et al. [16]      | 2016                | Retrospective                 | 104| High-risk pregnancies (referred for a fetal echocardiogram) | 18–39            | Basal ventricular diameters                               | Short-axis or 4-chamber view           | End-diastole and end-systole |                                                                            |

GA, gestational age; BPD, biparietal diameter; FL, femur length.
The concept of cardiac remodeling – defined as changes in size, shape, structure, and function of the heart in order to adapt to an insult [4] – is now being applied in fetal life not only in CHD cases [5] but also in other prenatal conditions, such as fetal growth restriction (FGR) [6], the use of assisted reproductive techniques (ART) [7], exposure to toxics [8], and pregestational diabetes [9]. An adverse prenatal environment during the crucial period of in utero development might have a direct impact on fetal cardiac structure and long-lasting consequences on health [10]. The use of echocardiography during fetal life enables the early identification of subtle or minor changes in cardiac morphometry potentially useful for fetal monitoring and the prevention of cardiovascular consequences [11].

However, there is a lack of standardized reference values for many cardiac morphometric parameters in fetal life. Most nomogram studies were performed in the 80s using relatively low-resolution equipment and usually based on a selected high-risk population undergoing clinically prescribed echocardiography [12–14] (Table 1). Furthermore, the proposed methodology to assess fetal cardiac dimensions frequently varied within and across studies, from 2D [15] to M-mode [16] with dissimilar cardiac views (transverse [17] vs. apical/basal [13]) and moment of the cardiac cycle (at different points of the diastole in case of ventricular dimensions and without considering the closure of the AV valve as a landmark to define the end-diastole [13, 15]), highlighting the need for a well-defined methodology using stringent criteria.

The objective of the present study was to provide high-quality fetal cardiac dimension nomograms using a stringent methodology on a low-risk population of fetuses throughout pregnancy. For that purpose, we specifically created a prospective cohort of low-risk singleton pregnancies from the 18th to the 41st weeks of gestational age (GA) to undergo comprehensive fetal echocardiography.
Table 2. Maternal baseline characteristics and perinatal outcome (n = 602)

| Maternal characteristics |   |
|--------------------------|---|
| Age, years               | 32.5±5.0 |
| Body mass index          | 23.7±3.9 |
| Ethnicity                |   |
| Caucasian                | 411 (68.3) |
| Latin American           | 107 (17.1) |
| Maghreb                  | 20 (3.3) |
| South Asian              | 21 (3.5) |
| Black                    | 2 (0.3) |
| Nulliparity              | 323 (50.3) |
| Low socioeconomic status | 142 (23.6) |
| Smoking during pregnancy | 39 (6.48) |

Pregnancy and perinatal outcome

|                          |   |
|--------------------------|---|
| Gestational diabetes     | 27 (4.5) |
| Preeclampsia             | 11 (1.8) |
| Cesarean section         | 94 (15.6) |
| GA at delivery, weeks    | 39.6±1.4 |
| Preterm delivery         | 14 (2.3) |
| Birth weight, g          | 3,333 (442) |
| Birth weight centile     | 53.7 (30.2) |
| Small-for-GA             | 46 (7.64) |
| 5-min Apgar score        | 9 (7–10) |
| Admission at neonatal intensive care unit | 0 |
| Major neonatal morbidity | 0 |
| Perinatal mortality      | 0 |

Data are the mean ± SD, median (range), or n (%). Socioeconomic status was considered low when illiterate or with a primary educational level. Major neonatal morbidity was defined by the presence of bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage, periventricular leukomalacia, retinopathy, persistent ductus arteriosus, or sepsis. Perinatal mortality was defined as intrauterine fetal death after 22 weeks of pregnancy or neonatal death within the first 28 days of life. GA, gestational age.

Methods

Study Population and Protocol

The study involved a prospective cohort including low-risk singleton pregnancies from the Maternal-Fetal Medicine Department at BCNatal (Hospitals Clinic and Sant Joan de Déu, Barcelona, Spain) from 2015 to 2017. Conditions that might affect cardiovascular remodeling, such as conception by ART, maternal pregestational diabetes, chronic hypertension, HIV infection, preeclampsia or FGR at the time of scan, fetal malformations, as well as chromosomal abnormalities, were considered exclusion criteria. The study protocol included the collection of baseline and perinatal characteristics and the performance of a single fetal ultrasound including the assessment of estimated fetal weight (EFW) [18], conventional feto-placental Doppler, and echocardiography for each pregnancy from 18 to 41 weeks of gestation. GA was calculated according to the first trimester crown-rump length [19]. All participants were informed of the study and signed written consent was approved by the local ethics committee.

Fetal Echocardiography

Fetal echocardiography was performed using 6- to 4-MHz linear curved-array and 2- to 10-MHz phased-array probes with a Siemens Sonoline Antares machine (Siemens Medical Systems, Malvern, PA, USA) by 4 maternal-fetal specialists with at least 3 years of experience in fetal echocardiography. A comprehensive 2D, M-mode, and Doppler echocardiographic examination was performed to assess structural heart integrity and to evaluate cardiac morphometry following international guidelines [20]. Cardiac diameters and area were measured on 2D images at maximal distension from an apical or basal 4-chamber view at end-diastole. End-diastole was defined as the frame at which the atrioventricular valves closed and, thus, when the ventricles reached their largest size (Fig. 1a). Atrial diameters and areas were measured on 2D images at atrial maximum distension from a 4-chamber view at end-systole, defined by the frame preceding the atrioventricular valves opening. The atrial measurements did not include the pulmonary veins/arteries or the AV valve annulus (Fig. 1b) [21, 22]. Ventricular dimensions and areas were measured on 2D images from an apical or basal 4-chamber view at end-diastole [21]. The ventricular basal, midventricular, and longitudinal dimensions were measured at the level of the atrioventricular valves – below the atrioventricular valve leaflets and from the atrioventricular valves (including the atrioventricular valve annulus) to the inner myocardium apex, respectively (Fig. 1c). Both ventricular areas were measured by manual tracing along the true border of the inner myocardium, including the endocardium, the muscular trabeculations, and the moderator band. Myocardial wall thicknesses were measured on 2D images from a transverse 4-chamber view at end-diastole (Fig. 1d), as well as using M-mode (online suppl. material; for all online suppl. material, see www.karger.com/doi/10.1159/000494838).

Statistical Analysis

Statistical analysis was performed using Stata IC version 14 (StataCorp LP, College Station, TX, USA). The statistical model described by Royston and Wright [23] was used to construct normal ranges. Normal distribution of the fetal cardiac parameters was checked with the Shapiro–Francia W test. Original values or natural logarithm were used to model means and SD. Antilogs were applied to subsequently convert the results into the original scale. Linear, polynomial, or fractional polynomials regressions were used to construct the curves estimating the relationship between the studied variables and GA. Model fit was assessed using the Z-score distribution by GA and the count of the number of observations outside the range graph. Z-scores above or below 3 were considered as potential outliers. The subjective aspect of the fitted curve, R² statistics, and model simplicity were criteria for model selection. Equations of the polynomial regression curves were used to calculate the median and 5th and 95th centiles for each GA (centile = estimated mean ±1.645 SD). A similar analysis was also performed to construct nomograms by EFW (online suppl. material). Intraclass correlation coefficient (ICC) and its 95% confidence interval were used to determine interobserver and intraobserver variability (online suppl. material).
Fetal Heart Nomograms

Baseline, Standard Feto-Placental Ultrasound, and Perinatal Characteristics

Initially, 623 pregnancies were eligible, 21 of them were excluded (16 due to EFW below the 10th centile at fetal ultrasound, and 5 due to fetal cardiac abnormalities including ventricular septal defects and aberrant right subclavian artery). Finally, a total of 602 pregnancies were included for the nomograms’ construction. Baseline and perinatal characteristics of the study population are shown in Table 2.

The fetal standard ultrasound showed normal EFW and no signs of placental insufficiency in the fetuses finally included in the study. The mean EFW was 1,867 ± 988 g and the EFW centile was 57.95 ± 23.54 g. The median Z-scores for pulsatility index of the uterine arteries, umbilical artery, and middle cerebral artery were –0.27 (range –0.97 to 0.47), –0.32 (–0.75 to 0.10), and 0.01 (–0.58 to 0.79), respectively.

Results

Fetal Echocardiographic Feasibility and Reproducibility

Fetal cardiac, ventricular, and atrial diameters and areas were successfully obtained in 98.6% of the fetuses, while myocardial wall thicknesses could be obtained in 96.5% of the population. Interobserver reproducibility was estimated in 45 cases (15 cases per GA in the following intervals: 18–25, 26–33, and 34–41 weeks of GA). Intraobserver reproducibility was estimated analyzing the 45 cases a second time by the same operators after 2 months. The results showed excellent interobserver and intraobserver reproducibility for all of the cardiac parameters evaluated (ICC > 0.811 and ICC > 0.957, respectively; see online suppl. material A).

Fetal Cardiac Morphometric Nomograms

Regression equations for cardiac, atrial, and ventricular (transverse and longitudinal diameters and areas) dimensions and wall thicknesses using 2D images according to GA are shown in Table 3. The best model for

| Parameter | Mean | SD |
|-----------|------|----|
| Cardiac transverse diameter, mm | \(-29.6753+2.84667\times GA–0.02696\times GA^2\) | \(-0.39781+0.10449\times GA\) |
| Cardiac longitudinal diameter, mm | \(-1.06572+0.07778\times GA^2–0.00117\times GA^3\) | \(-0.34589+0.11718\times GA\) |
| ln(cardiac area), cm² | \(-10.2607+3.80207\times ln(GA)–0.000016\times GA^3\) | 0.141 |
| Atria Left atrial transverse diameter, mm | \(-7.38672+0.80863\times GA–0.00561\times GA^2\) | \(-0.25816+0.06081\times GA\) |
| Left atrial longitudinal diameter, mm | \(-10.1159+0.99838\times GA–0.00859\times GA^2\) | \(-0.45664+0.07486\times GA\) |
| Left atrial area, cm² | \(-1.68184+0.10351\times GA\) | \(-0.35074+0.02298\times GA\) |
| Right atrial transverse diameter, mm | \(-13.823+1.29517\times GA–0.01303\times GA^2\) | \(-0.05374+0.05455\times GA\) |
| Right atrial longitudinal diameter, mm | \(-10.692+1.04367\times GA–0.00962\times GA^2\) | \(-0.5316+0.07057\times GA\) |
| Right atrial area, cm² | \(-1.7789+0.10843\times GA\) | \(-0.40217+0.02549\times GA\) |
| Ventrices Left ventricular basal transverse diameter, mm | \(1.46269+0.00228\times GA^3–0.00056\times GA^3\times ln(GA)\) | \(-0.27006+0.063138\times GA\) |
| Left ventricular midtransverse diameter, mm | \(-13.8461+1.26043\times GA–0.01397\times GA^2\) | \(-0.146+0.06328\times GA\) |
| Left ventricular longitudinal diameter, mm | \(-57.2942+23.16726\times ln(GA)\) | 0.03780+0.09427\times GA |
| ln(left ventricle area), cm² | \(-5.29535+0.32352\times GA–0.00399\times GA^2\) | 0.252 |
| Right ventricular basal transverse diameter, mm | \(1.5692+0.002193\times GA^3–0.00053\times GA^3\times ln(GA)\) | \(-0.66837+0.08084\times GA\) |
| Right ventricular midtransverse diameter, mm | \(-14.4111+1.279293\times GA–0.01366\times GA^2\) | 0.00208+0.0575\times GA |
| Right ventricular longitudinal diameter, mm | \(-17.2023+1.71982\times GA–0.01682\times GA^2\) | \(-0.10+0.10836\times GA\) |
| ln(right ventricle area), cm² | \(-5.5167+0.3338\times GA–0.00415\times GA\) | 0.254 |
| Myocardial wall thicknesses ln(left ventricle wall thickness), mm | \(-0.97057+0.09367\times GA–0.00091\times GA^2\) | 0.190 |
| Right ventricle wall thickness, mm | \(-0.44595+0.10877\times GA\) | \(-0.05049+0.01796\times GA\) |
| Septal wall thickness, mm | \(-0.46813+0.11716\times GA\) | \(0.04945+0.01449\times GA\) |

GA, gestational age; ln, (natural) logarithm.

Table 3. Regression equations for fetal cardiac morphometric nomograms according to GA at scan
most parameters was a second-degree linear polynomial. Scatterplots by GA with the median, 5th and 95th centile lines for these parameters are shown in Figures 2–5, respectively. The online supplementary material includes values for the median, 5th and 95th centiles for all cardiac measurements at each GA (online suppl. material B), and results of myocardial wall thicknesses by M-mode (online suppl. material C). The online supplementary material also includes curves estimating the relationship between the studied variables and EFW and values for the median and 5th and 95th centiles for all cardiac measurements by EFW (online suppl. material D).

**Discussion**

The present study provides reference values for fetal cardiac, atrial, and ventricular dimensions and myocardial wall thicknesses in a large prospective cohort of low-risk pregnancies from 18 to 41 weeks of GA. We also demonstrated high feasibility and reproducibility for these measurements by 2D and M-mode ultrasound following stringent criteria and standardized landmarks.

**Cardiac Dimensions**

Nomograms for whole-heart dimensions throughout gestation are provided, confirming their high feasibility and reproducibility [24]. All cardiac dimensions in-
Fig. 3. Scatterplots of the left atrial transverse (a) and longitudinal diameters (b), left atrial area (c), right atrial transverse (d) and longitudinal diameters (e), and right atrial area (f) plotted against GA in the study population. Estimated 5th, 50th, and 95th centile curves are shown.
creased quadratically with GA, while their SD showed a linear progression. These nomograms are mostly concordant with previously published data [17, 25]. Most previous studies coincide on the methodology for measuring cardiac area and longitudinal diameter but with a dissimilar methodology for transverse diameters. While some authors measured the transverse cardiac diameter at the level of atrioventricular valves [17, 26–28], we and others propose to measure it below the atrioventricular valves [25] as it better corresponds to the mid-cardiac length reaching the maximal transverse diameter. These differences in methodology may justify our values to be slightly smaller than previously reported [17]. Assessment of whole-heart dimensions is relevant for describing cardiomegaly or cardiac compression.

**Atrial Dimensions**

We have provided nomograms for fetal atrial diameters and areas throughout pregnancy. Even though the accurate performance of this measurement could be challenging [14], we showed high feasibility and reproducibility. Our results are in agreement with most previous data [12, 14, 29], with slightly smaller longitudinal atrial diameters than previously reported [14, 29], most likely explained by the inclusion of the atrioventricular valve annulus in other studies [29]. This is the first report on fetal
atrial area normal values. Evaluation of atrial dimensions might be particularly relevant when studying cases with volume or pressure overload – as atrial dilatation readily occurs in response to these insults due to the absence of muscular fibers and its hypertrophy inability.

**Ventricular Dimensions**

Ventricular diameters and areas were rigorously measured demonstrating a high feasibility and reproducibility, as previously reported [30]. Methodological variability for measuring ventricular dimensions among previous studies, using different cardiac views and points of reference throughout the diastolic phase, limits the comparison of data [12, 13, 29, 31, 32] even though they are mostly consistent. The only exception comes from Shapiro et al. [12], who reported slightly smaller ventricular basal diameters, most likely due to the measurement being performed just below the atrioventricular valve instead of at the level of the annulus, as recommended [22]. An accurate evaluation of ventricular dimensions is the key to describing and monitoring ventricular remodeling.

**Myocardial Wall Thicknesses**

Finally, normal values for septal and lateral myocar
dial wall thicknesses are also reported both in 2D (main document) and M-mode (online suppl. material), showing a progressive increase throughout gestation with excellent feasibility and consistency with previous studies, although methodological heterogeneity used in previous studies [16, 29, 33–35] hampers the direct comparison of results. An accurate measurement of ventricular wall thicknesses is essential to assess myocardial hypertrophy as a common response to pressure/volume overload or toxicity.
Strengths and Limitations

This is a prospective study using a low-risk population scanned purposely for fetal cardiac morphometry. We used a well-defined and strict methodology for measuring dimensions in order to achieve the optimal accuracy and reproducibility. Also, to our knowledge, this is the first study to report fetal atrial areas. As limitations, we acknowledge that only a single type of ultrasound system was used, which may be both an advantage and disadvantage if the results are to be extrapolated to other centers. In addition, postnatal echocardiography was not systematically performed, although the absence of CHD or major comorbidities was postnatally confirmed in all cases.

Conclusions

We have provided standardized and comprehensive reference values for fetal cardiac morphometric parameters across gestation in a low-risk population. An accurate measurement of heart dimensions might be very useful to identify and monitor cardiac remodeling – change in shape, size, and structure – in response to pressure/volume overload or cardiac toxicity in many conditions, such as CHD [36, 37], maternal diabetes [9], twin-to-twin transfusion syndrome [38], FGR [39], conception by ART [7], fetal anemia [40], congenital diaphragmatic hernia [41], or exposure to antiretroviral drugs [8]. A better understanding and follow-up of fetal cardiac adaptations

Fig. 5. Scatterplots of the left (a), right (b), and septal (c) wall thicknesses plotted against GA in the study population. Estimated 5th, 50th, and 95th centile curves are shown.
could enable early interventions and minimize long-term cardiovascular consequences [42].

Statement of Ethics

Local ethical committee approval was obtained for this research.

Disclosure Statement

None of the authors have any financial, consultative, institutional, or other relationship that might lead to bias or a conflict of interest.

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