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Full title: **Nomograms of fetal cardiac dimensions at 18 to 41 weeks of gestation.**

Running head: **Fetal heart nomograms.**

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ABSTRACT

Objective: There is need of 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: 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 (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.

Keywords: nomograms, fetal heart.

MANUSCRIPT

Introduction

Fetal echocardiography was initially used to identify congenital heart defects (CHD) and arrhythmias [1–3]. Since then, technical advances have allowed to notably improve the assessment of cardiac structure and function.

Recently, 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 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 prevention of cardiovascular consequences [11].

However, there is a lack of standardised 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 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 (in different moments of the diastole in case of ventricular dimensions and without considering the closure of the AV valve as a landmark to define 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 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 to undergo comprehensive fetal echocardiography.

Methods

Study population and protocol

The study design was a prospective cohort including low-risk singleton pregnancies from the Maternal-Fetal Medicine Department at BCNatal (Hospitals Clínic and Sant Joan de Déu, Barcelona, Spain) from 2014 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 collection of baseline and perinatal characteristics and the performance of a single fetal ultrasound including assessment of estimated fetal weight (EFW) [18], conventional feto-placental Doppler and echocardiography for each pregnancy from 18 to 41 weeks of gestation. Gestational age (GA) was calculated according to first trimester crown-rump length [19]. All participants were informed and signed written consent approved by the local Ethical Committee.

<u>Fetal echocardiography</u>

Fetal echocardiography was performed using 6-4 MHz linear curved-array and 2-10 MHz phased-array probes with a Siemens Sonoline Antares machine (Siemens Medical Systems, Malvern, PA, USA) by four maternal-fetal specialists with at least 3 years' 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 four-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 -Figure 1A-. Atrial diameters and areas were measured on 2D images at atrial maximum distension from a four-chamber view at end-systole, defined by the frame preceding the atrioventricular valves opening. The atrial measurements did not include the pulmonary veins/arteries neither the AV valve annulus -Figure 1B-[21,22]. Ventricular dimensions and areas were measured on 2D images from an apical or basal four-chamber view at end-diastole [22]. The ventricular basal, midventricular and longitudinal dimensions were measured at the level of the atrioventricular valves; below the atrioventricular valves leaflets and from atrioventricular valves (including the atrioventricular valves annulus) to inner myocardium apex, respectively -Figure 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 four-chamber view at end-diastole -Figure 1D- as well as using M-mode (supplementary).

Statistical analysis

Statistical analysis was performed using Stata IC version 14 (StataCorp. LP, College Station,TX). The statistical model described by Royston and Wright was used to construct normal ranges [23]. 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 gestational age. 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 <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 mean and 5th and 95th centiles for each GA (centile = estimated mean ±1.645SD). A similar analysis was also performed to construct nomograms by EFW (supplementary data). Intraclass correlation coefficient (ICC) and its 95% confidence interval (CI) were used to determine interobserver and intraobserver variability (supplementary data).

Results

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 estimated fetal weight and no signs of placental insufficiency in the fetuses finally included in the study. The mean EFW was 1867 g ± 988 and the EFW centile was 57.95 ± 23.54. Median Z-scores for pulsatility index of uterine arteries, umbilical artery and middle cerebral artery were -0.27 [range -0.97-0.47]; -0.32 [-0.75-0.10] and 0.01 [-0.58-0.79] respectively.

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 reproductibility was estimated in 45 cases (15 cases per gestational age in the following intervals: 18-25; 26-33 and 34-41 weeks of gestational age). Intraobserver reproductibility 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 cardiac parameters evaluated (ICC >0.811 and ICC >0.957 respectively –see supplementary data A-).

Fetal cardiac morphometric nomograms

Regression equations for cardiac (transverse and longitudinal diameters and area), atrial (transverse and longitudinal diameters and areas) and ventricular (transverse and longitudinal diameters and areas) dimensions and wall thicknesses using 2D according to GA are shown in Table 3. The best model for most parameters was a second-degree linear polynomial. Scatterplots by GA with mean, 5th and 95th centile lines for these parameters are shown in Figures 2, 3, 4 and 5 respectively. Supplementary material includes values for the mean, 5^{th} and 95^{th} centiles for all cardiac measurements at each GA (Suppl. B) and results of myocardial wall thicknesses by M-mode (Suppl. C). Supplementary material includes, as well, curves estimating the relationship between the studied variables and EFW and values for the median, 5^{th} and 95^{th} centiles for all cardiac measurements by EFW (Suppl. 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 gestational age. We also demonstrate high feasibility and reproducibility for these measurements by 2D and M-mode 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 increased quadratically with gestational age 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 dissimilar methodology for transverse diameter. 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 provide 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 atrioventricular valve annulus in their measurements- [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 its absence of muscular fibers and its inability to hypertrophy-.

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 comparison of data [12,13,29,31] even though they are mostly consistent. The only exception comes from Shapiro *et al.* that reported [12] 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 describe and monitor ventricular remodeling.

Myocardial wall thicknesses

Finally, normal values for septal and lateral myocardial wall thicknesses are also reported both in 2D (main document) and M-mode (supplementary data) showing a progressive increase throughout gestation with excellent feasibility and consistency with previous studies, although methodological heterogeneity used in previous studies [16,29,32–34] hampers 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 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 absence of CHD or major comorbidities was postnatally confirmed in all cases.

Conclusions

In conclusion, we provide 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 [35,36], maternal diabetes [9], twin-to-twin transfusion syndrome [37], FGR [38], conception by ART [7], fetal anemia [39], congenital diaphragmatic hernia [40] or exposure to antiretroviral drugs [8]. A better understanding and follow-up of fetal cardiac adaptations could enable early interventions and minimize long-term cardiovascular consequences [41].

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FIGURE LEGENDS

Figure 1: Fetal echocardiographic images illustrating the measurement of (A) cardiac diameters and area, (B) atrial diameters and areas, (C) ventricular diameters and areas and (D) myocardial wall thicknesses.

Figure 2: Scatterplots of the cardiac transverse (a) and longitudinal diameters (b) and cardiac area (c) plotted against gestational age in the study population. Estimated 5th, 50th and 95th centile curves are shown.

Figure 3: Scatterplots of the left atrial transverse (a) and longitudinal diameters (b) left atria area (c) and the right atrial transverse (d) and longitudinal diameters (e) and right atria area (f) plotted against gestational age in the study population. Estimated 5th, 50th and 95th centile curves are shown.

Figure 4: Scatterplots of the left ventricular basal (a) midtransverse (b) and longitudinal (c) diameters and (d) area and the right ventricular basal (e) midtransverse (f) and longitudinal (g) diameters and (h) area plotted against gestational age in the study population. Estimated 5th, 50th and 95th centile curves are shown.

Figure 5: Scatterplots of the left (a) right (b) and septal (c) wall thicknesses plotted against gestational age in the study population. Estimated 5th, 50th and 95th centile curves are shown.