Assessment of fetal cardiac function in early fetal life: feasibility, reproducibility, and early fetal nomograms

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BACKGROUND: Fetal cardiology has shown a rapid development in the past decades. Fetal echocardiography is not only used for the detection of structural anomalies but also to assess fetal cardiac function. Assessment of the fetal cardiac function is performed mostly in the second and third trimesters. The study of fetal cardiac function at the end of first trimester has not been investigated properly, and there is a lack of reference values at early gestational weeks.

OBJECTIVE: This study aimed to assess if the measurement of time-related parameters of cardiac function in the left ventricle of the fetal heart is feasible and reproducible at the end of the first trimester. If possible, we provide nomograms of these parameters from 11 to 13+6 gestational weeks.

STUDY DESIGN: We conducted a prospective observational study from March to September 2022. The study was carried out in 2 hospitals (Hospital Universitari Dexeus, Barcelona, and Hospital VITAHS 9 Octubre, Valencia, Spain). The scans were performed by 3 specialists in fetal medicine. The exclusion criteria were fetal cardiac rhythm abnormalities, abnormal nuchal translucency, abnormal ductus venosus, fetal malformations, stillbirth, estimated fetal weight <10 percentile, diabetes, and gestational hypertensive disorders. The cardiac function parameters studied in the left ventricle were isovolumetric contraction time, isovolumetric relaxation time, ejection time, filling time, cycle time, myocardial performance index, ejection time fraction, and filling time fraction. We study the feasibility and intra- and interobserver reproducibility of these parameters using the interclass correlation coefficient. Nomograms were created and the percentiles of the values of the different parameters were calculated.

RESULTS: A total of 409 cases were recruited but only 296 could be included in the statistical analysis once the exclusion criteria were applied. The intraobserver reproducibility study was excellent (interclass correlation coefficient >0.900), and the interobserver reproducibility study was good (interclass correlation coefficient >0.700). The data regression analysis showed that cycle time, filling time, isovolumetric contraction time, and filling time fraction increased with gestational age, whereas ejection time fraction decreased with gestational age and myocardial performance index (mean, 0.43±0.08), isovolumetric relaxation time (mean, 0.04±0.01), and ejection time (mean, 0.16±0.01) remained constant from 11 to 13 weeks.

CONCLUSION: The study of fetal cardiac function is feasible and reproducible at 11 to 13+6 gestational weeks. Nomograms of the studied parameters are provided.

Key words: fetal cardiac function, fetal echocardiogram, first trimester, heart

Introduction

Fetal cardiology has shown a rapid development in the last decades. Fetal echocardiography is not only used for the detection of structural anomalies but also to assess fetal cardiac function.[1–5] The new technologies allow physicians to identify subtle changes in cardiac function during a long subclinical period of cardiac dysfunction before end-stage heart failure.[6] Most of the evaluations done to understand these changes in cardiac function are conducted in the second and third trimesters. So far, only a few studies have

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The authors report no conflict of interest.

This study did not receive any funding.

Patient consent was not required because no personal information or details were included.

The findings of this study were presented at the 33rd world congress of the International Society of Ultrasound in Obstetrics and Gynecology, Seoul, South Korea, October 16–19, 2023.

Cite this article as: Prats P, Izquierdo MT, Rodríquez MA, et al. Assessment of fetal cardiac function in early fetal life. Feasibility, reproducibility, and early fetal nomograms. Am J Obstet Gynecol Glob Rep 2024;4:100325.

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2666-5778/$36.00

http://dx.doi.org/10.1016/j.xagr.2024.100325

AJOG Global Reports at a Glance

Why was this study conducted?

This study aimed to investigate the fetal cardiac function at early gestational weeks.

Key findings

Measurement of fetal cardiac cycle time, left ventricle myocardial performance index, left ventricle filling time fraction, left ventricle ejection time fraction, left ventricle ejection time, left ventricle filling time, left ventricle isovolumetric contraction time, and left ventricle isovolumetric relaxation time at 11 to 13.6 gestational weeks is feasible and reproducible. Nomograms are provided.

What does this add to what is known?

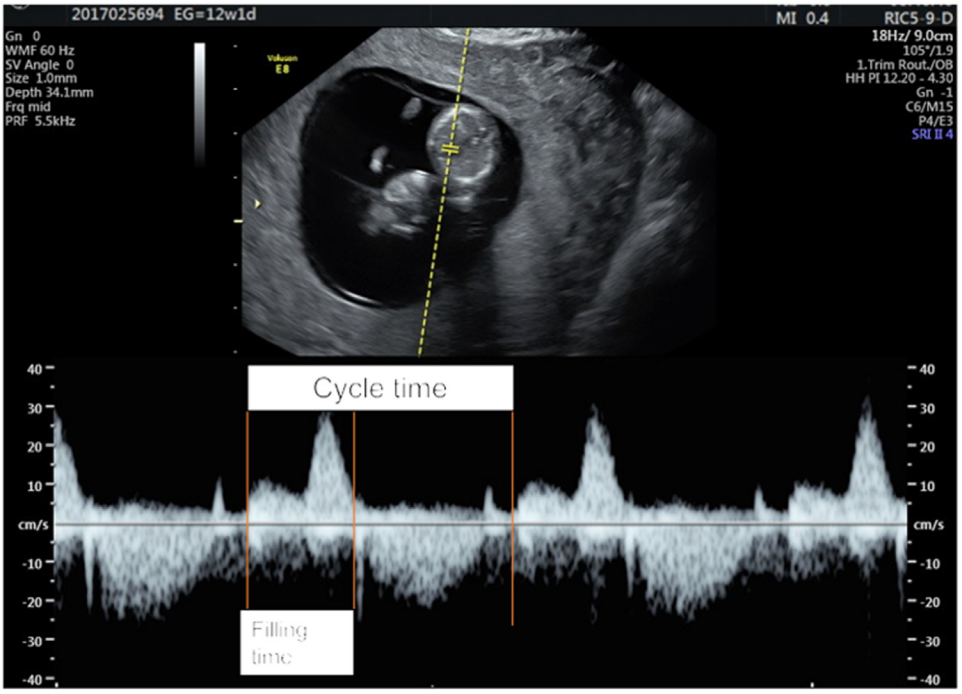
Our nomograms can be used to assess normality or pathologic deviation in early stages of pregnancy. High-risk pregnancies could benefit from early assessment, and proper management protocols should be applied from early gestational weeks.

been published on the embryonic[7–10] and fetal cardiac[7,9–15] function in the first trimester. The most common parameters used to assess fetal function are ventricular inflow and outflow peak velocities by spectral Doppler, myocardial velocities by tissue Doppler imaging, and annular displacement and shortening of ejection fraction by M mode.[6] Nowadays, cardiac cycle time–related parameters are currently being considered.[16] Changes in the duration of diastole (isovolumetric relaxation [IRT] and filling times [FT]) and systole (isovolumetric contraction time [ICT] and ejection times [ET]) can reflect impaired ventricular contractility or relaxation.[17–19] Because the duration of the different cardiac events is dependent on the heart rate, some authors have proposed new parameters that adjust timing intervals for cardiac cycle duration.[20]

To our knowledge, there is a lack of reference values in fetal cardiac cycle time–related parameters at 11 to 13+6 weeks of pregnancy. This scan is one of the biggest hits in prenatal diagnosis and screening campaigns. It presents an opportunity for early diagnosis of structural and functional heart defects that may have clinical implications. Therefore, we aim to evaluate[1] the feasibility and reproducibility of cardiac cycle time–related parameters (cycle time [CT], left ventricle myocardial performance index [LV-MPI], left ventricle filling time fraction [LV-FTF], left ventricle ejection time fraction [LV- ETF], left ventricle ET [LV-ET], left ventricle FT [LV-FT], left ventricle ICT [LV-ICT], and left ventricle IRT [LV-IRT])

FIGURE 1

Spectral Doppler tracing of ventricular inflow and outflow waves illustrating the measurement of time intervals needed for the calculation of filling time fraction



The filling time was measured from E-wave onset to A-wave termination and cycle time measured between the onset of 2 consecutive E-waves.

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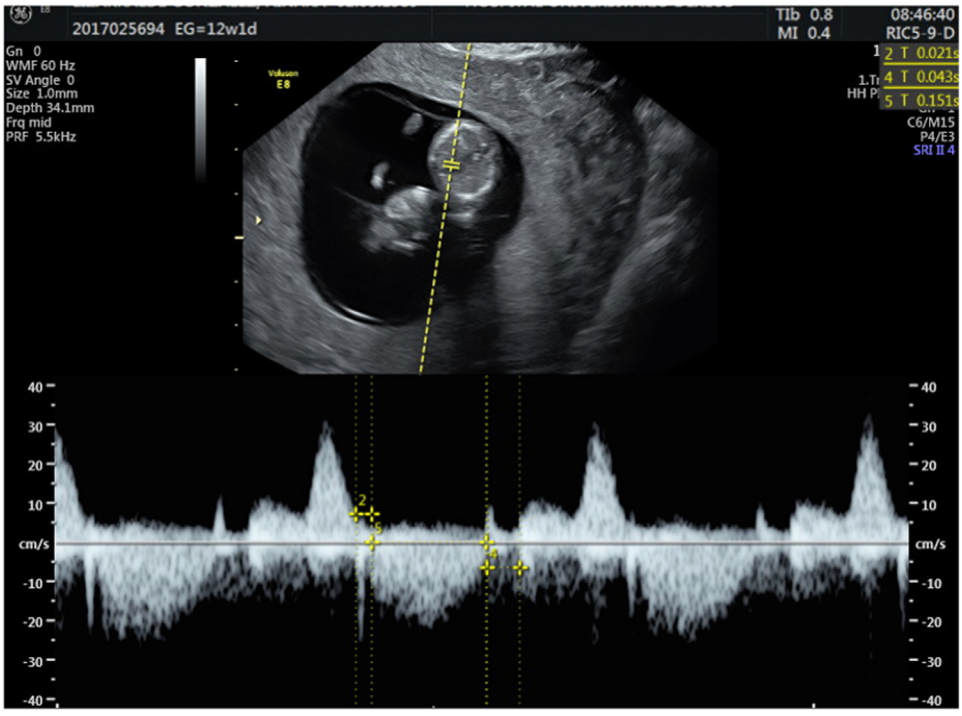
FIGURES 2
Myocardial performance index (MPI) measured by valve clicks in the Doppler trace



MPI = (ICT + IRT)/ET. Caliper placement is indicated by the *dotted lines*.

ET, ventricular ejection time; *ICT*, isovolumetric contraction time; *IRT*, isovolumetric relaxation time.

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by spectral Doppler from 11 to 13+6 gestational weeks and[2] to provide nomograms for these parameters.

Materials and Methods

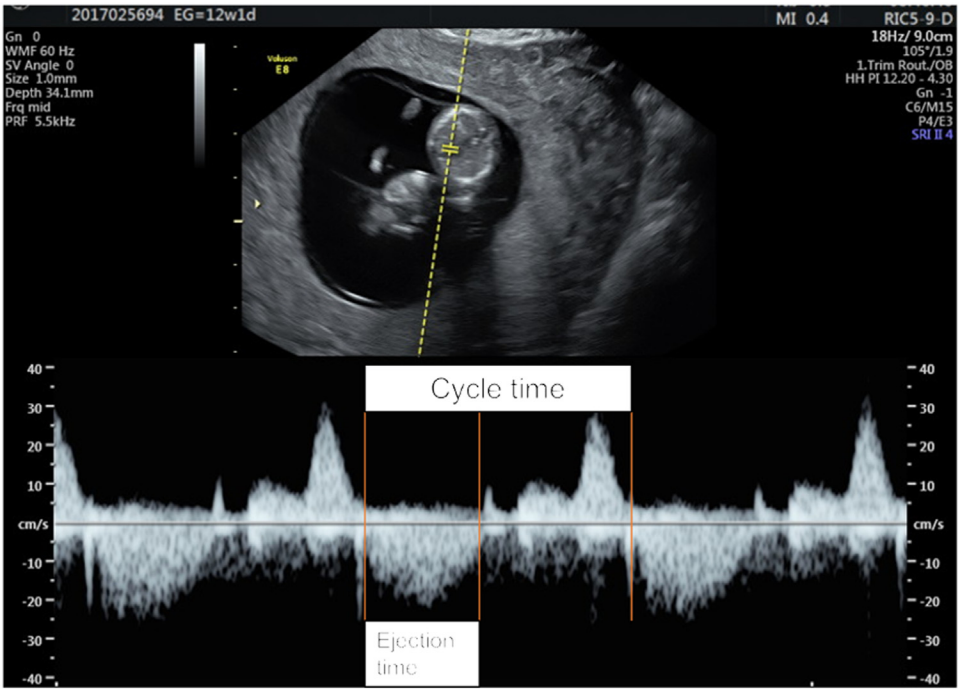
This was a prospective, clinically collected data study. It was performed from March 2022 to September 2022 in 2 clinical settings, namely the Fetal Medicine Unit, Obstetrics Department, Dexeus University Hospital, Barcelona, Spain, and the Gynecologic and Obstetric Ultrasound Unit, Hospital VITHAS 9 Octubre, Valencia, Spain.

We included all patients who attended routine pregnancy care at 11+0 to 13+6 weeks' gestation at 1 of the 2 clinical settings and who fulfilled the inclusion criteria, namely singleton pregnancies, women >18 years old, accurate gestational age (GA) calculated by first trimester (8−10 weeks' gestation) crown-rump length (CRL), and written consent signature. Exclusion criteria were fetal cardiac rhythm abnormalities. In addition, to compile the study parameters nomograms, we also excluded all cases from the statistical analysis that included any of the following: abnormal nuchal translucency (NT), abnormal ductus venosus (DV), fetal malformations, stillbirth, estimated fetal weight <10 percentile, diabetes, and gestational hypertensive disorders.

All examinations were performed by 3 investigators (P.P., M.A.R., M.T.I.) using a Voluson E8 or E10 (GE medical Systems, Zipf, Austria) or a WS80A ultrasound system (Samsung Medison, Seoul, Korea). Ultrasonography was performed in strict adherence with the as low as reasonably achievable (ALARA) principle, and the total time of ultrasound exposure was restricted to a maximum of 20 minutes. The scan was performed transvaginally or/and transabdominally. After confirming fetal viability and excluding the presence of any obvious fetal anomaly, the CRL, NT, DV, mean uterine arteries pulsatility index (PI), and fetal heart rate were measured.

Echocardiography was also performed transabdominally or/and transvaginally. A systematic assessment of fetal heart structure was performed using standard 2-dimensional views.[1] Color Doppler was used to visualize the direction of blood flow. The fetal heart function parameters in the LV included in this study were ICT, IRT, ET, FT, CT, MPI, ETF, and FTF. The 3 physicians who participated in the study were given practical training in the accurate assessment of fetal cardiac parameters by fulfilling the following: pulsed Doppler measurements performed in fetal quiescence with an insonation angle as close to 0° as possible, magnification of the image so that the fetal thorax occupied at least two-thirds of the screen, Doppler sampling volume set at an axial length of 1 mm, pulse Doppler gain adjusted to enhance visualization of the valve opening and

FIGURE 3
Spectral Doppler tracing of ventricular inflow and outflow waves illustrating the measurement of time intervals needed for the calculation of ejection time fraction



The ejection time was measured from opening to closure of the aortic valve and cycle time between 2 consecutive valve opening clicks.

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closure click, time cursors placed at the beginning of each valve click, sweep speed high (2−3 cm/s) and at least 3 consecutive uniform Doppler velocity waveforms obtained.

LV-FT was obtained from a basal or apical 4-chamber view, placing the pulsed Doppler volume at the tips of the mitral valve (MV) leaflets when open. FT was defined as the interval between E-wave onset to A-wave termination. Cardiac CT, of the same cardiac cycle, was defined as the interval between the onset of 2 consecutive E-waves. LV-FTF was calculated as follows: LV-FTF = (LV-FT/CT) × 100 (Figure 1). LV-MPI was calculated on the same wave form from a 4-chamber view of the heart with an apical/basal projection and an angle of insonation <20°. The transducer was slightly displaced in the cranial direction where the MV and aortic valve (AV) are visible. The Doppler sampling was conducted at the cross between the inflow and outflow of the LV and included the leaflets of the MV and AV with a 1 to 3 mm gate size. We chose the beginning of the valve clicks as the landmark for the measurement period of MPI. The calipers were placed just before each valve click. The LV-ICT was measured from closure of the MV to opening of the AV, LV-IRT was measured from closure of the AV to opening of the MV, and LV-ET was measured from the opening to closure of the AV. LV-MPI was calculated as follows: LV-MPI = (LV-ICT + LV-IRT) / LV-ET

TABLE 1
Maternal baseline characteristics

Characteristic	Values for entire cohort
Age (mean ± SD)	34.78±4.62
BMI (mean ± SD)	23.53±4.11
Mode of conception, n	
ART	86
Spontaneous conception	323
Pregestational diabetes, n	10
Pregestational HTA, n	9

The data for N=409 individuals are presented.

ART, assisted reproductive techniques; *BMI*, body mass index; *HTA*, arterial hypertension; *SD*, standard deviation.

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TABLE 2
Obstetrical and perinatal outcomes of the study population

Obstetrical and perinatal outcomes	No. of cases (%)
Gestational diabetes	28 (6.8)
Pregnancy hypertension disorders	22 (5.3)
Pregnancy hypertension	11 (2.6)
Preeclampsia	10 (2.4)
HELLP syndrome	1 (0.2)
Fetal malformations	11 (2.7)
SGA	18 (4.4)
IUGR	11 (2.7)
Birth	391 (95.5)
Vaginal birth	266 (63.8)
Cesarean delivery	125 (30.6)
TOP	18 (4.5)
NIC admissions	5 (1.2)
Stillbirth	1 (0.2)

The data for N=409 individuals are presented.

IUGR, intrauterine growth retardation; *NIC*, neonatal intensive care; *SGA*, small gestational age; *TOP*, termination of pregnancy.

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(Figure 2). LV-ET was measured from aortic pulsed Doppler systolic flow. The Doppler cursor was placed just downstream of the semilunar valve in the center of the vessel. AV velocity was measured from a basal or apical 5-chamber view. From the 4-chamber view, the operator angled cephalad with slight rotation to see the left ventricular outflow tract and aorta in the same view. The Doppler spike of valve opening and closure was observed to confirm correct positioning across the semilunar valve. ET was measured from the opening to closure of the AV. Cardiac CT was defined as the time between 2 consecutive opening clicks. LV-ETF was calculated as follows: LV-ETF = (LV-ET/CT) × 100 (Figure 3).

All the participants had additional fetal echocardiography in the second trimester and neonatal clinical examination after birth to confirm normality.

A specific electronic case report form (eCRF) for the collection of the study data was provided to the investigators who were responsible for ensuring that all required data were captured. All study data, baseline patient characteristics, and perinatal outcomes were entered in the eCRF. Baseline characteristics included maternal age, maternal body mass index (BMI), mode of conception (spontaneous vs assisted artificial techniques), pregestational maternal diabetes, and pregestational maternal hypertension. Perinatal outcomes included gestational diabetes, pregnancy hypertensive disorders (hemolysis, elevated liver enzymes, and low platelet count syndrome, preeclampsia, gestational hypertension), fetal malformations, fetal weight, GA at delivery, stillbirth, mode of delivery (cesarean delivery, vaginal delivery, termination of pregnancy [TOP]), and neonatal intensive care unit admission. The same extraction form (eCRF) used for the baseline characteristics and perinatal data was used to record efficacy and safety endpoints.

TABLE 3
Sonographic findings and biochemical maternal markers in the 409 cases included

Measurements (n=409)	Mean ± SD (n=409)
CRL (mm)	63.21±7.08
NT (mm)	1.72±0.79
HR (bpm)	159.45±13.62
PI uterine arteries	1.55±0.48
PAPP-A (mUI/L)	343.09±819.54
MoM PAPP-A	1.18±0.93
BHCG (ng/mL)	71.02±47.94
MoM BHCG	1.20±0.79
PIGF (pg/mL)	28.85±19.86
MoM PIGF	1.06±1.58

BHCG, beta human chorionic gonadotrophin; *bpm*, beats per minute; *CRL*, crump-rump length; *HR*, heart rate; *MoM*, Median multiples; *NT*, nuchal translucency; *PAPP-A*, pregnancy associated plasma protein-A; *PI*, pulsatility index; *PIGF*, placental growth factor; *SD*, standard deviation.

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Statistical analysis

Feasibility and reproducibility. For the feasibility and reproducibility study, a sample of 90 examinations distributed at weeks 11, 12, and 13 was used based on a recent publication by Soveral et al.[16] These fetuses were evaluated by 2 operators (P.P. and M.A.R.). Operator P.P. performed the measurements as previously described and stored the images. The same image was re-

TABLE 4
Intraclass correlation coefficient for inter- and intraobserver reproducibility for LV-ICT, LV-IRT, LV-ET, CT, LV-FT LV-MPI, LV-FTF, and LV-ETF

	Intraobserver reproducibility		Interobserver reproducibility	
Measurement	ICC	Confidence interval	ICC	Confidence interval
LV-ICT	0.99	0.98–0.99	0.7	(0.55–0.80)
LV-IRT	0.98	0.97–0.99	0.71	0.57–0.81)
LV-ET	0.97	0.95–0.99	0.79	(0.69–0.87)
LV-MPI	0.97	0.95–0.99	0.74	(0.60–0.83)
LV-FT	0.98	0.96–0.99	0.91	(0.86–0.94)
CT	0.99	0.98–0.99	0.82	(0.73–0.88)
LV-FTF	0.98	0.96–0.99	0.79	(0.68–0.86)
LV-ETF	0.98	0.96–0.99)	0.73	(0.59–0.82)

CT, cycle time; *ICC*, interclass correlation coefficient; *LV-ET*, left ventricle ejection time; *LV-ETF*, left ventricle ejection time fraction; *LV-FT*, left ventricle filling time; *LV-FTF*, left ventricle filling time fraction; *LV-ICT*, left ventricle isometric contraction time; *LV-IRT*, left ventricle isometric relaxation time; *LV-MPI*, left ventricle myocardial performance index.

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evaluated after 2 weeks by P.P. to assess the intraobserver reproducibility. Interobserver reproducibility was assessed by P.P. and M.A.R., each one re-evaluating the stored images and performing the same measurements as the first operator did.

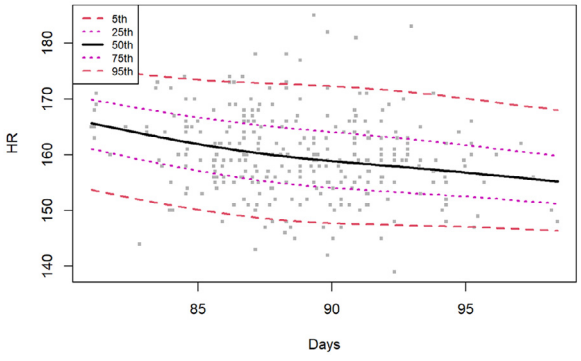
To evaluate the feasibility, we assessed the ratio of fetuses in which the image could be captured and all the parameters (CT, LV-FT, LV-ET, LV-ICT, LV-IRT, LV-MPI, LV-FTF and LV-ETF) could be calculated.

To assess the intra- and interobserver reproducibility, the intraclass correlation coefficient (ICC) was calculated, together with its corresponding 95% confidence interval (CI), for each of the measurements.

Normal distribution curve. For the reference curves, approximately 100 examinations per week were needed according to the methodology described by Royston and Altman. The rest of the analysis was exploratory, therefore there was no formal sample size calculation. The cases presenting the different characteristics were used.

To calculate the percentile curves, the Generalized Additive Model for Location, Scale and Shape (GAMLSS) framework developed by Rigby and Stasinopoulos[21,22] was used based on the methodology described by Cole and Green in 1992.[23]

FIGURE 4
Reference ranges for fetal heart rate in relation to gestational age at 11 to 13+6 weeks' gestation



Lines represent the 5th, 25th, 50th, 75th, and 95th percentiles.

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Ethical considerations

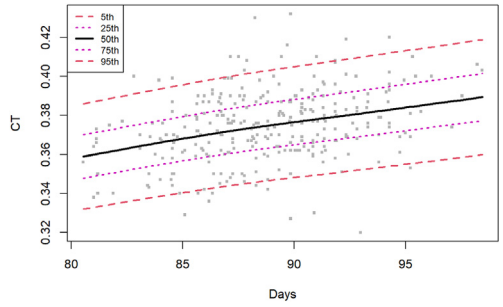
The study protocol was reviewed and approved by the ethical committee of Grupo Hospitalario QUIRON Barcelona, together with the information sheet for informed consent (22/02/2022 acta n° 04/2022). Written consent was obtained from all participants.

Results

A total of 409 fetuses were recruited in the study. Baseline maternal characteristics and obstetrical and perinatal outcomes of the study population are shown in Table 1 and 2.

All ultrasounds were performed at 11 to 13+6 gestational weeks. A summary of the ultrasound characteristics and biochemical maternal markers are shown in Table 3. The 409 cases were distributed as follows: 39 (9.5%) at 11 weeks, 257 (62.8%) at 12 gestational weeks, and 113 (27.6%) at 13 gestational weeks. Regarding chromosomal markers, DV A-wave form was abnormal in 16 cases (3.9%) (5 absent and 11 reverse), and in 33 cases (8.1%), NT was >99 percentile. In 8 cases (2%), we found abnormal fetal anatomy, and in 5 cases (1.2%), a cardiac defect was suspected. We performed an invasive procedure for 17 cases (4.1%). In 13 cases (3.1%), there was an abnormal karyotype. We had no cases of deletions or duplications detected by array comparative genomic hybridization screening. The mean GA at delivery was 37.85±5.45 weeks. In the study group, we had 207 male fetuses and 202 female

FIGURE 5
Reference ranges for cycle time in relation to gestational age at 11 to 13+6 weeks' gestation



Lines represent the 5th, 25th, 50th, 75th, and 95th percentiles.

CT, cycle time.

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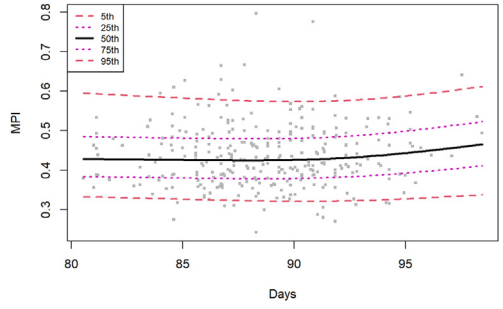
FIGURE 6
Reference ranges for the left ventricle myocardial performance index in relation to gestational age at 11 to 13+6 weeks' gestation



Lines represent the 5th, 25th, 50th, 75th, and 95th percentiles.

MPI, myocardial performance index.

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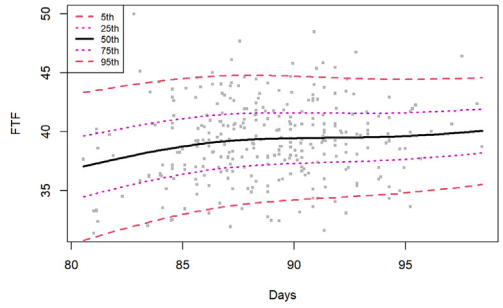
FIGURE 7
Reference ranges for the left ventricle filling time fraction in relation to gestational age at 11 to 13+6 weeks' gestation.



Lines represent the 5th, 25th, 50th, 75th, and 95th percentiles.

FTF, filling time fraction.

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fetuses with a mean weight at delivery of 3245±439.11 grams.

Feasibility and reproducibility

Adequate Doppler images for cardiac measurements could be obtained in >97% (90/92) of the fetuses studied. Interobserver reproducibility was estimated across 90 cases. Intraobserver reproducibility was estimated by analyzing 45 cases a second time by the same operator after 2 weeks. Global ICC and 95% CIs for all parameters included in the study are detailed in Table 4. The results show excellent intraobserver (ICC >0.900) and good interobserver reproducibility for all timing parameters assessed (ICC >0.700).

Nomograms

Only 296 cases could be included in the statistical analysis to compose the nomograms once the exclusion criteria were applied.

The mean fetal heart rate was 159.45±13.62. It ranged between 140 and 185 beats/min and decreased significantly ($P<0.001$) with increasing GA (Figure 4).

The nomogram values for CT, LV-ET, LV-FT, LV-ICT, LV-IRT, LV-MPI, LV-FTF, and LV-ETF are presented in Figures 5 to 12.

The 5th, 10th, 50th, 90th, and 95th percentiles for the different values (CT, LV-ET, LV-FT, LV-ICT, LV-IRT, LV-MPI, LV-FTF and LV-ETF) are presented in Tables 5 to 12.

Regression analysis showed that CT, LV-ETF, LV-FTF, LV-ICT, and LV-FT are dependent on GA; CT, LV-FT, LV-ICT, and LV- FTF increased with the GA and LV- ETF decreased with GA.

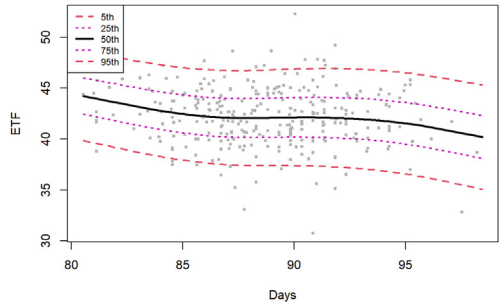
LV-MPI (mean 0.43±0.08), LV-IRT (mean 0.04±0.01), and LV-ET (mean 0.16±0.01) did not vary with increasing GA from 11 to 13 weeks.

Discussion

Principal findings

Our study demonstrated that the assessment of fetal cardiac function at 11 to 13.6 gestational weeks is feasible and reproducible with excellent intraobserver (ICC >0.900) and good interobserver reproducibility (ICC >0.700). In

FIGURE 8
Reference ranges for the left ventricle ejection time fraction in relation to gestational age at 11 to 13+6 weeks' gestation



Lines represent the 5th, 25th, 50th, 75th, and 95th percentiles.

ETF, ejection time fraction.

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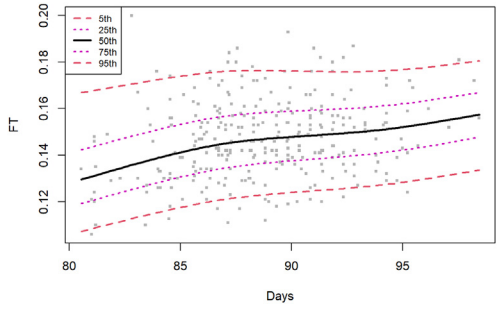
FIGURE 9
Reference ranges for the left ventricle filling time in relation to gestational age at 11 to 13+6 weeks' gestation



Lines represent the 5th, 25th, 50th, 75th, and 95th percentiles.

FT, filling time.

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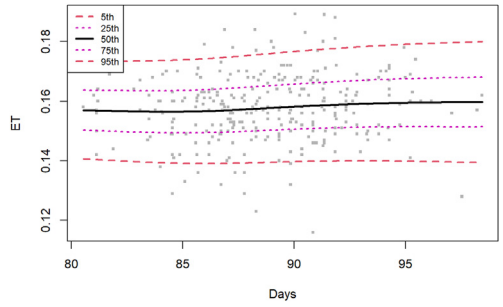
FIGURE 10
Reference ranges for the left ventricle ejection time in relation to gestational age at 11 to 13+6 weeks' gestation



Lines represent the 5th, 25th, 50th, 75th, and 95th percentiles.

ET, ejection time.

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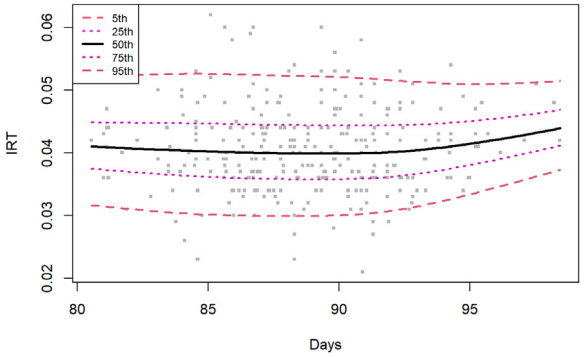
addition, we provided nomograms of all time-related cardiac function parameters assessed. Moreover, we could establish that CT and LV-FT, FTF, and IVC time increased with GA, and LV-ETF decreased with GA. In contrast, LV-MPI (mean, 0.43±0.08), IRT (mean, 0.04±0.01), and ET (mean, 0.16±0.01) did not vary with increasing GA from 11 to 13 weeks.

Results

To our knowledge, fetal cardiac function parameters at 11 to 13 weeks are not well studied, and appropriate nomograms have not been established yet. We did an exhaustive search in the literature to find all the studies that focused on fetal cardiac function assessment at 11 to 13+6 gestational weeks. We found 9 articles and most of them had very few cases included.[7,9–15,24] Four of these studies included <100 cases,[7,9,11,14] 2 of the studies included 150 cases,[13,24] and the studies reported by Rozmus-Warcholinska et al[15] and Gyenes et al[10] included >200 cases. Zidere et al[12] performed a wider study to provide reference ranges for fetal cardiac function parameters from 13 to 36 gestational weeks. However, the number of cases included at 13 to 15 gestational weeks were scarce (<80). Gyenes et al[10] studied the atrioventricular interval from 6 to 40 gestational weeks. They reported the largest series with the inclusion of 279 pregnancies (248 singleton, 28 twins, and 3 triplets).

MPI describes global cardiac function. Several investigators have published reference values for the MPI during the second half of pregnancy.[19,25–32] Literature on first-trimester values is scarce, and so far, only 3 studies reported MPI values in the first trimester at 11 to 14 weeks' gestation.[13–15] One of these studies[14] had only 32 observations and another included a reasonable number of normal fetuses (n=159) with the primary goal of investigating the cardiac function among fetuses with increased NT.[13] The study of Rozmus-Warcholinska[15] was the biggest and included 202 cases. Our reference value for MPI (0.43±0.08) is in between the reference

FIGURE 11
Reference ranges for the left ventricle isovolumetric relaxation time in relation to gestational age at 11 to 13+6 weeks' gestation



Lines represent the 5th, 25th, 50th, 75th, and 95th percentiles.

IRT, isovolumetric relaxation time.

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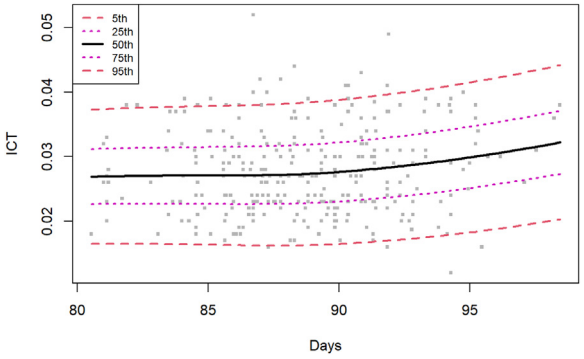
FIGURE 12
Reference ranges for the left ventricle isovolumetric contraction time in relation to gestational age at 11 to 13+6 weeks' gestation



Lines represent the 5th, 25th, 50th, 75th, and 95th percentiles.

ICT, isovolumetric contraction time.

Prats. Early fetal cardiac function assessment. Am J Obstet Gynecol Glob Rep 2024.

values published by the previous studies.[13–15] Huggon et al[13] and Rozmus-Warcholinska et al[15] published very similar values, namely 0.378 and 0.375, respectively. The mean MPI was a little bit higher in the study of Russel et al[14] with a mean value of 0.5. Despite the differences in the mean values, the trend was reported to be similar, and the MPI did not change with GA. Interestingly, the MPI mean values reported in the late second and third trimesters are also quite similar.[19,26,28,31] However, if we compare the 5th to 95th percentiles in the reference values of MPI, IRT, ICT, and ET reported by Herandez-Andrade et al,[19] we observed that our 95th percentiles for all parameters at 11 to 13+6 gestational is slightly higher.

Other cardiac CT-related parameters have received considerably less attention, despite being easy to measure by spectral Doppler and being clinically useful.[16,33] The cardiac cycle can be divided into diastolic (IRT and filling time) and systolic (ICT and ET) periods. Changes in the duration of these intervals can reflect impaired ventricular contractility or relaxation in relation to adverse loading caused by various mechanisms, including myocardial rigidity or hypertrophy.[16] To date, some timing-based parameters, such as inflow and outflow absolute times[17,18] have been evaluated in the fetus. However, because the absolute duration of cardiac events is dependent on heart rate, some authors have proposed adjusting timing intervals for cardiac cycle duration.[16,20] FTF and ETF have been used in the early diagnosis of cardiac dysfunction in twin-to-twin transfusion syndrome,[20] in evaluating response to fetal aortic

TABLE 5
Percentiles (5th, 10th, 50th, 90th, and 95th) for cycle time according to gestational age

GA	5th	10th	50th	90th	95th
11	0.304	0.337	0.358	0.379	0.385
12	0.316	0.350	0.372	0.394	0.400
13	0.325	0.360	0.382	0.405	0.411

GA, gestational age.

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TABLE 6
Percentiles (5th, 10th, 50th, 90th, and 95th) for left ventricle myocardial performance index according to gestational age

GA	5th	10th	50th	90th	95th
11	0.27	0.35	0.43	0.55	0.60
12	0.25	0.34	0.43	0.54	0.58
13	0.24	0.35	0.44	0.55	0.58

GA, gestational age.

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TABLE 7
Percentiles (5th, 10th, 50th, 90th, and 95th) for left ventricle filling time fraction according to gestational age

GA	5th	10th	50th	90th	95th
11	24.08	31.85	36.81	41.77	43.17
12	28.08	34.87	39.20	43.53	44.75
13	29.74	35.73	39.55	43.37	44.46

GA, gestational age.

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TABLE 8
Percentiles (5th, 10th, 50th, 90th, and 95th) for left ventricle ejection time fraction according to gestational age

GA	5th	10th	50th	90th	95th
11	35.75	41.07	44.46	47.85	48.82
12	32.84	38.49	42.09	45.69	46.71
13	31.95	37.96	41.79	45.62	46.71

GA, gestational age.

Prats. Early fetal cardiac function assessment. Am J Obstet Gynecol Glob Rep 2024.

valvuloplasty,[34] and in predicting the outcome of several fetal pathologies.[35–38] A recent study published in 2021 that included a cohort of 602 low-risk fetuses, demonstrated that measuring ETF and FTF are feasible and reproducible, and they provided FTF and ETF nomograms for 18 to 41 gestational weeks.[16] To our knowledge, 2 studies studied ETF and FTF at 11 to 13+6 weeks pregnancy.[11,15] In accordance with our results, in both studies, FTF and CT increased and ETF decreased with GA. The 5th to 95th percentile ranges for ETF and FTF values

TABLE 9
Percentiles (5th, 10th, 50th, 90th, and 95th) for left ventricle filling time according to gestational age

GA	5th	10th	50th	90th	95th
11	0.091	0.110	0.128	0.156	0.166
12	0.102	0.126	0.145	0.168	0.176
13	0.105	0.132	0.151	0.170	0.176

GA, gestational age.

Prats. Early fetal cardiac function assessment. Am J Obstet Gynecol Glob Rep 2024.

TABLE 10
Percentiles (5th, 10th, 50th, 90th, and 95th) for left ventricle ejection time (LV-ET) according to gestational age.

GA	5th	10th	50th	90th	95th
11	0.125	0.144	0.157	0.170	0.173
12	0.121	0.143	0.157	0.171	0.175
13	0.121	0.144	0.159	0.174	0.179

GA, gestational age.

Prats. Early fetal cardiac function assessment. Am J Obstet Gynecol Glob Rep 2024.

TABLE 11
Percentiles (5th, 10th, 50th, 90th, and 95th) for left ventricle isometric contraction time according to gestational age

GA	5th	10th	50th	90th	95th
11	0.006	0.019	0.027	0.035	0.037
12	0.005	0.019	0.027	0.036	0.038
13	0.006	0.020	0.029	0.038	0.041

GA, gestational age.

Prats. Early fetal cardiac function assessment. Am J Obstet Gynecol Glob Rep 2024.

described in the second and third trimester[16] were comparable with ours.

A recently published review article by Rocha et al[39] highlighted the need for the Z score of functional measurements of the fetal heart in a larger sample population. Consequently, Zidere et al[12] reported the largest study in fetal cardiac function from 13 to 36 weeks' gestation. They included 7885 cases and provided reference ranges for fetal heart inflow Dopplers (mitral and tricuspid E-wave, A-wave and E/A ratio), outflow tract Dopplers (AV and pulmonary valve peak velocity) and heart rate. The authors also believed that the reference ranges, starting as early as the 13 weeks' gestation, are important as first-trimester diagnosis of fetal cardiac defects is increasing.

We aimed to add more data to the reference values previously reported. Our goal was to study different parameters (cardiac CT-related parameters) that have been assessed less commonly during early pregnancy. Prenatal diagnosis is developing an increasing urge for early diagnosis and the new high-level technology facilitates the early diagnosis of different fetal conditions and/or heart malformations at 11 to 13.6 gestational weeks.

Clinical implications

Our reference parameters may be useful for research studies that investigate the association of abnormal cardiac function in high-risk pregnancies (maternal diabetes, fetal growth restriction cardiomyopathy, myocarditis, fetal anemia, absent ductus venosus, twin-to-twin transfusion syndrome, arteriovenous malformations, and fetal tumors).

Research implications

Early fetal cardiac function assessment could be used to identify subtle abnormalities in ventricular function and future research should include other techniques such as speckle tracking. However, new studies are warranted to evaluate the potential use of these techniques and to define the best combination of parameters. New cardiovascular

TABLE 12
Percentiles (5th, 10th, 50th, 90th, and 95th) for left ventricle isometric relaxation time (LV-IRT) according to gestational age

GA	5th	10th	50th	90th	95th
11	0.015	0.034	0.041	0.049	0.052
12	0.018	0.032	0.040	0.049	0.052
13	0.024	0.034	0.041	0.049	0.051

GA, gestational age.

Prats. Early fetal cardiac function assessment. Am J Obstet Gynecol Glob Rep 2024.

parameters should be incorporated with caution, and all of the potential limitations of fetal echocardiography should be taken into account. More research is needed to define specific protocols for each fetal condition that may affect cardiac function.

Strengths and limitations

One of the main strengths of our study is the examination of a large number of fetuses with prospective recording of measurements according to a defined protocol. Furthermore, there was accurate pregnancy dating based on the measurement of fetal CRL in the first trimester. The prospective approach used in our study avoided the potential selection bias of retrospective analysis. Our reference ranges from as early as 11 weeks' gestation are likely to be useful in clinical practice, because first-trimester diagnosis of fetal cardiac defects is increasingly used for prenatal diagnosis. These reference ranges of fetal cardiac Doppler parameters may be useful for research studies that investigate the association of abnormal cardiac function in high-risk pregnancies with maternal diabetes or fetal growth restriction.

A limitation of this study is that postnatally, normality is determined based on normal findings during the neonatal clinical examination. Hence, this may be seen as a limitation, because some genetic abnormalities may not be diagnosed in this period. However, we are confident that major cardiac defects will not be missed, because all babies with cardiac concerns are referred to our regional pediatric cardiac surgical center, and regular feedback is provided to the fetal medicine unit. Another limitation of the study is that different machines were used over the study period. However, all measurements were obtained using standard protocols on machines optimized for fetal cardiac scanning, which have not changed over the study period. So although there may be some variations because of machine differences, these are unlikely to be of major significance. A comparison of the MPI, FTF, and ETF values with values obtained using other tools to evaluate fetal cardiac function was not performed. This comparison in larger studies, including different pathologies, will help to define the clinical role of the cycle-time parameters.

Conclusion

This study has established nomograms for fetal cardiac time−related parameters in the LV measured using spectral Doppler at 11 to 13+6 gestational weeks. They can be used to confirm normality or to identify deviation from normal Doppler flow patterns in clinical practice. ■

CRediT authorship contribution statement

Pilar Prats: Writing − review & editing, Writing − original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. **M. Teresa Izquierdo:** Validation, Supervision, Investigation, Data curation. **M. Ángeles Rodríguez:** Writing − review & editing, Visualization, Validation, Investigation, Data curation, Conceptualization. **Ignacio Rodríguez:** Writing − review & editing, Validation, Supervision, Software, Methodology, Formal analysis, Data curation. **Alberto Rodríguez-Melcón:** Writing − review & editing. **Bernat Serra:** Writing − review & editing. **Gerard Albaiges:** Writing − review & editing. ■

ACKNOWLEDGMENTS

This study was conducted with the auspices of the Càtedra d'Investigació en Obstetrícia i Ginecologia de la Universitat Autònoma de Barcelona.

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