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Reference values for variables of fetal cardiocirculatory dynamics at 11–14 weeks of gestation

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KEYWORDS: echocardiography; fetal cardiac function; first trimester; reference ranges; Tei index

ABSTRACT

Objective *Despite the increasing popularity of first-trimester fetal echocardiography, the evaluation of fetal heart function during this period remains challenging. The parameters of normal cardiac function at 11–14 weeks' gestation are not well defined and appropriate reference values have not yet been established. The purpose of this study was to evaluate the fetal cardiocirculatory dynamics during routine first-trimester screening and establish cross-sectional reference ranges for 11–14 weeks' gestation.*

Methods *Fetal echocardiography was performed on 202 women with singleton pregnancies at $11 + 0$ to $13 + 6$ weeks' gestation. Global cardiac function was evaluated using the heart : chest area ratio and Tei index of the left (LV) and right (RV) ventricles. The proportion of isovolumic contraction (ICT%) and ejection (ET%) times of the cardiac cycle, and the outflow velocities described the systolic function. Diastolic function was evaluated by the proportion of relaxation (IRT%) and filling (FT%) times, the ratio of the blood velocity through the atrioventricular valves during early filling (E) and atrial contraction (A) phases of the cardiac cycle, and ductus venosus pulsatility index for veins (DV-PIV). All participants had additional fetal echocardiography in the second trimester and neonatal clinical examination after birth to confirm normality.*

Results *The mean heart : chest area ratio (0.203 ± 0.04) and the Tei indices of both ventricles did not vary significantly during weeks 11–14, but the mean Tei index of the LV (0.375 ± 0.092) was significantly higher than that of the RV (0.332 ± 0.079) ($P = 0.001$). The fetal heart rate (FHR) decreased with increasing crown–rump length (CRL) ($P < 0.00001$). The LV-ICT% did not vary significantly ($P = 0.27$), LV-IRT% ($P = 0.03$) and LV-ET% decreased ($P = 0.01$), whereas the LV-FT% increased ($P = 0.02$) with CRL. The RV-ET% ($P = 0.84$) and RV-FT% ($P = 0.60$) remained relatively stable. The LV-ET% was lower than the RV-ET% ($P = 0.0001$). The LV ($P = 0.004$) and RV ($P < 0.00001$) outflow velocities and E : A ratios of both ventricles ($P < 0.0001$) increased with advancing gestation. The E-velocity of the LV ($P = 0.003$) and RV ($P = 0.002$) increased significantly but the increase in A-velocity was not significant. The outflow velocity ($P = 0.008$) and E-velocity ($P = 0.005$) of the RV were higher than that of the LV but the A-velocities were similar ($P = 0.066$). The mean DV-PIV was 0.97 ± 0.23 and did not change significantly ($P = 0.95$) during weeks 11–14. The FHR and DV-PIV did not correlate with the Tei index of either ventricle.*

Conclusion *We have established reference ranges for the noninvasive evaluation of fetal cardiocirculatory dynamics at 11–14 weeks' gestation. Copyright © 2010 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

A policy of first-trimester screening for chromosomal defects using maternal age and fetal nuchal translucency (NT) measurement has been firmly established in many countries. In many centers it is further supplemented with maternal serum biochemistry and a detailed ultrasonographic scan looking for additional markers. This presents an opportunity for early diagnosis of structural fetal malformations[1] including heart defects[2–7]. Although a comprehensive assessment of the fetal

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heart function may be difficult in the first trimester, use of certain simple parameters of cardiocirculatory dynamics, such as the fetal heart rate (FHR) and rhythm, time intervals of the different phases of the cardiac cycle, cardiac inflow and outflow blood velocities, and the presence or absence of valve regurgitation, cardiomegaly, effusions etc., may provide useful supplemental information that may help in the prognosis and management. So far, only a few studies have been published on the embryonic[8–10] and fetal[11–15] cardiac function in the first trimester of human pregnancy, and appropriate reference values are still lacking. Furthermore, most previous studies have focused on single parameters rather than providing reference values for a set of parameters that allows evaluation of their inter-relationship and fetal cardiocirculatory dynamics as a whole. Therefore, establishing reference ranges for such parameters has obvious clinical value. Our objective was to evaluate the fetal cardiocirculatory condition using two-dimensional echocardiography and Doppler ultrasonography during routine first-trimester screening and construct cross-sectional reference ranges for 11–14 weeks' gestation.

METHODS

This was part of a larger prospective study investigating cardiovascular physiology in early human pregnancy using Doppler ultrasonography. The study protocol was reviewed and approved by the bioethics board of the Silesian Medical Academy, Katowice, Poland. All participants gave informed written consent to the study.

Healthy pregnant women who had a singleton pregnancy and a live fetus with a crown–rump length (CRL) of between 45 and 84 mm were included in the absence of any significant fetal anomaly, if the measured NT thickness put them at low risk for having a baby with a chromosomal defect. Exclusion criteria were: multiple pregnancy; previous history of any significant obstetric complication; and medical illness that may have an adverse effect on the course and outcome of pregnancy.

All examinations were performed by two investigators (W.R-W. and A.W.) using a Voluson 730 Expert (GE Medical Systems, Kretz Ultrasound, Zipf, Austria) ultrasound system equipped with RIC 5-9H vaginal and RAB 4-8L abdominal transducers. Ultrasonography was performed strictly adhering to the ALARA (as low as reasonably achievable) principle, and the total time of ultrasound exposure was restricted to a maximum of 20 min. After confirming fetal viability and excluding the presence of any obvious fetal anomaly, the CRL and NT were measured. Echocardiography was performed transabdominally in all cases, and additional transvaginal examination was performed when the transabdominal image was suboptimal. A systematic assessment of fetal heart structure was performed, obtaining standard two-dimensional views[16]. In a cross-sectional view of the thorax, the circumferences of the chest and the heart in a four-chamber view were measured and the heart : chest area ratio was calculated. Color Doppler was used to visualize the direction of blood flow. The right ventricular (RV) inflow and outflow blood velocity waveforms were obtained by insonating the tricuspid and pulmonary valves separately with pulsed-wave Doppler and the maximum velocities, RV time *a* (time interval between the closure and the opening of the tricuspid valve), time *b* (time interval between the opening and the closure of the pulmonary valve, i.e. RV ejection time), filling time (RV-FT) and the total period of the cardiac cycle were measured. The RV Tei index was calculated as: (Time a − Time b)/Time b[17] (Figure 1). Valve clicks were used to identify the closure and opening of the atrioventricular and semilunar valves while measuring the time intervals[18]. The left ventricular (LV) inflow and outflow blood velocity waveforms were obtained simultaneously[19] and the following parameters were measured: isovolumic contraction time (ICT) (time interval between the closure of the mitral valve and the opening of the aortic valve); isovolumic relaxation time (IRT) (time interval between the closure of the aortic valve and the opening of the mitral valve); ejection time (LV-ET) (time interval between the opening and the closure of the aortic valve); LV-FT (time interval between the opening and the closure of the mitral valve); and the total length of the cardiac cycle.

The modified LV Tei index was calculated as: (ICT + IRT)/LV-ET[18,20] (Figure 2). The blood velocity waveforms were also obtained separately from the mitral and aortic valve, keeping the insonation angle < 15° and maximum velocities were measured.

The systolic variables studied included the outflow velocities and the proportions of isovolumic contraction (ICT%) and ejection (ET%) times of the cardiac cycle. In diastole the proportions of relaxation (IRT%) and filling (FT%) times, and the ratio of the blood velocity through the atrioventricular valves during early filling (E) and atrial contraction (A) phases of the cardiac cycle

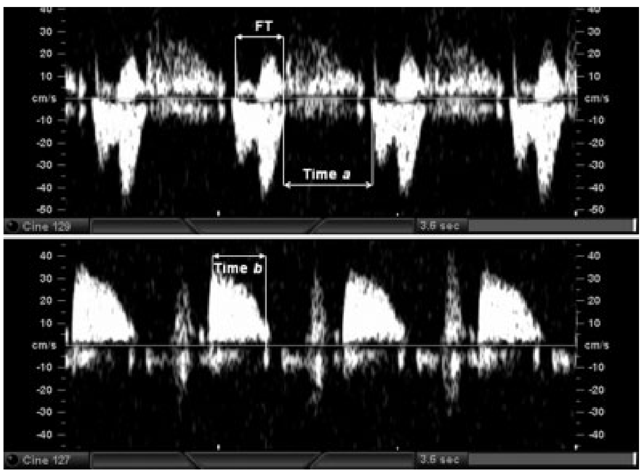

Figure 1 Measurement of cardiac cycle time intervals and the right ventricular (RV) Tei index using blood flow velocity waveforms obtained from the pulmonary and tricuspid valves in a series (RV Tei index = $(a - b)/b$). *a*, time interval between closure and opening of the tricuspid valve; *b*, time interval between opening and closure of the pulmonary valve (ejection time); FT, filling time.

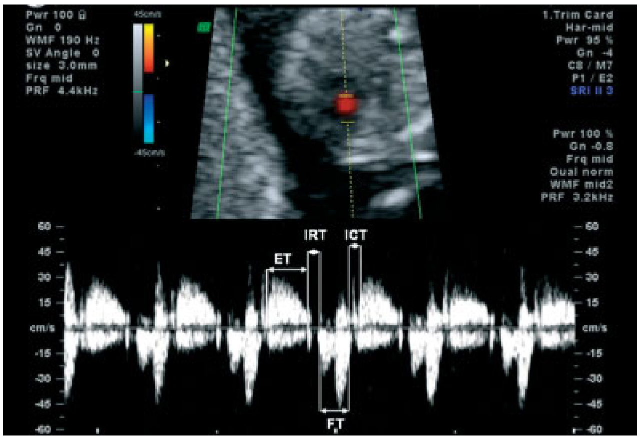

Figure 2 Measurement of cardiac cycle time intervals and the left ventricular (LV) Tei index using blood flow velocity waveforms obtained simultaneously from the mitral and aortic valves (LV Tei index = (ICT + IRT)/ET). ET, ejection time; FT, filling time; ICT, isovolumic contraction time; IRT, isovolumic relaxation time.

were evaluated. Additionally, ductus venosus (DV) blood velocity waveforms were recorded and the pulsatility index for veins (PIV) was calculated as: PIV = (peak systolic velocity − velocity during atrial contaction)/time-averaged maximum velocity.

All the Doppler recordings were performed during fetal quiescence over 4–6 cardiac cycles. For all the parameters assessed, an average of three separate measurements was used for statistical analysis.

All the participants had additional fetal echocardiography in the second trimester and neonatal clinical examination after birth to confirm normality. The information on the course of pregnancy and perinatal outcome was obtained from the hospital records.

Reproducibility (repeatability and reliability) of the measurements was evaluated in 15 additional fetuses (five examined at the start of the study, five approximately halfway through the study and five at its conclusion). These fetuses were evaluated by two operators (W.R-W. and A.W.), one of them making two measurements in succession to evaluate intraobserver reproducibility and the other performing the same measurements once again for interobserver reproducibility. The repeatability and reliability of measurements were assessed using intra- and interobserver variability and intraclass correlation coefficients (ICC) for intra- and interobserver agreement, with their respective 95% confidence intervals.

Statistical analysis

Data analysis was performed using Microsoft Excel for Windows XP and Statistical Software for Social Sciences for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± SD or median (range) as appropriate. The assumption of normality was checked using the Shapiro–Wilk test, and non-parametric tests were applied when the distribution was not normal. The associations between measured parameters of fetal cardiac function and CRL were evaluated by regression analysis. The accuracy of adjustment of the polynomial regression was determined with the use of a regression factor. The curves obtained were used to estimate the mean and the standard deviation (SD) of the residuals (i.e. difference between the measurements and the estimated mean curve). The CRL-specific reference intervals were calculated according to the method described by Royston and Wright[21]. The 95th and 5th percentiles were calculated as mean ± 1.645 SD. Correlations between variables were assessed using the Pearson correlation coefficient or Spearman rank correlation test as appropriate. $P \leq 0.05$ was considered to be statistically significant.

RESULTS

Of a total of 202 fetuses examined, four had structural abnormalities – aortic stenosis, megacystis, nonimmune hydrops and gastroschisis – and were excluded from analysis, leaving 198 observations for the statistical analysis. The mean maternal age was 30 ± 5 years, and 46% of the participants were nulliparous. Outcome data were available for 166 neonates. The median gestational age at delivery was 40 (range, 33–42) weeks and 48 (28.9%) babies were delivered by Cesarean section for the following reasons: fetal distress, $n = 15$; previous Cesarean section, $n = 9$; lack of satisfactory progress in labor, $n = 7$; antepartum hemorrhage, $n = 3$; pre-eclampsia, $n = 3$; fetal macrosomia, $n = 2$; and various maternal diseases and conditions (genital herpes, orthopedic conditions, previous third degree perineal tear, maternal anxiety and fear of labor), $n = 9$. In 98.8% ($n = 164$) of the neonates, the 5-min Apgar score was > 7, and there were no perinatal deaths.

Results of the reproducibility study for the parameters of fetal cardiocirculatory dynamics are presented in Tables 1 and 2. Regression equations for the calculation of the 5th percentile, mean and 95th percentile for each parameter in relation to CRL are presented in Table 3.

The mean heart : chest area ratio was 0.203 ± 0.04 (Figure 3) and did not change significantly ($P = 0.16$) during weeks 11–14. The FHR ranged between 144 and 176 beats/min and decreased significantly ($P < 0.00001$) with increasing CRL (Figure 4). The reference values for the LV cardiac cycle time intervals are presented in Figure 5 and the RV cardiac cycle time intervals and DV-PIV are presented in Figure 6. The LV-ICT% did not vary significantly ($P = 0.27$) but the IRT% decreased ($P = 0.03$) with increasing CRL. The LV-ET% was lower than the RV-ET% ($P = 0.0001$). The LV-ET% decreased ($P = 0.01$) and the FT% increased ($P = 0.02$) with CRL, whereas the RV-ET% ($P = 0.84$) and RV-FT% ($P = 0.60$) remained relatively stable during weeks 11–14. The mean DV-PIV was 0.97 ± 0.23 and did not change significantly ($P = 0.95$) during weeks 11–14.

The mean Tei index of the LV was 0.375 ± 0.092 and that of the RV was 0.332 ± 0.079. The Tei indices of both the ventricles did not vary significantly with CRL (Figure 7). However, the Tei index of the LV was significantly higher than that of the RV ($P = 0.001$). The

Table 1 Intra- and interobserver coefficients of variation (CV) with their 95% CIs

Variable	*Intraobserver CV (% (95% CI))*	*Interobserver CV (% (95% CI))*
FHR	1.3 (0.7–1.7)	1.8 (1.0–2.3)
HA : CA ratio	4.1 (0.0–5.8)	9.4 (5.5–12.1)
LV-ICT	12.7 (3.4–17.6)	20.1 (15.8–23.6)
LV-IRT	10.7 (5.1–14.2)	14.9 (11.1–18.0)
LV-ET	2.3 (1.3–2.9)	3.1 (2.5–3.7)
MV E-wave velocity	4.4 (2.6–5.7)	3.9 (3.1–4.5)
MV A-wave velocity	2.2 (1.4–2.7)	2.5 (1.6–3.1)
Ao-PSV	2.5 (2.0–3.0)	4.6 (1.8–6.3)
LV Tei index	7.3 (0.0–11.1)	7.1 (4.6–8.9)
TV E-wave velocity	3.1 (2.1–3.8)	4.5 (2.6–5.9)
TV A-wave velocity	2.0 (1.8–2.3)	3.7 (0.0–5.4)
RV time *a*	3.2 (2.3–3.8)	4.8 (2.6–6.3)
PA-PSV	4.7 (2.3–6.2)	3.3 (2.0–4.2)
RV Tei index	5.7 (3.0–7.4)	6.3 (0.0–9.0)
RV-ET	4.1 (2.8–5.0)	5.1 (3.5–6.3)
DV-PIV	8.8 (6.2–10.9)	4.3 (2.5–5.5)
LV-FT	4.2 (3.0–5.2)	4.4 (2.7–5.6)
RV-FT	5.2 (3.8–6.2)	3.3 (2.0–4.3)
LV E : A ratio	7.5 (3.6–10.1)	4.6 (2.8–6.0)
RV E : A ratio	5.7 (3.0–7.5)	6.3 (4.0–8.0)

Ao, aorta; DV, ductus venosus; E : A ratio, ratio between early ventricular filling (E-wave) and filling during atrial contraction (A-wave) velocities; ET, ejection time; FHR, fetal heart rate; FT, filling time; HA : CA, heart area : chest area ratio; ICT, isovolumic contraction time; IRT, isovolumic relaxation time; LV, left ventricle; MV, mitral valve; PA, pulmonary artery; PIV, pulsatility index for veins; PSV, peak systolic velocity; RV, right ventricle; TV, tricuspid valve.

Table 2 Intraclass correlation coefficients (ICC) for intraobserver and interobserver agreement with their 95% CIs

Variable	*Intraobserver ICC (95% CI)*	*Interobserver ICC (95% CI)*
FHR	0.84 (0.64–0.93)	0.68 (0.36–0.86)
HA : CA ratio	0.96 (0.87–0.99)	0.87 (0.62–0.96)
LV-ICT	0.69 (0.32–0.88)	0.13 (0.00–0.57)
LV-IRT	0.65 (0.25–0.86)	0.16 (0.00–0.59)
LV-ET	0.90 (0.77–0.96)	0.77 (0.52–0.90)
MV E-wave velocity	0.95 (0.88–0.98)	0.96 (0.90–0.98)
MV A-wave velocity	0.98 (0.95–0.99)	0.98 (0.95–0.99)
Ao-PSV	0.97 (0.92–0.99)	0.94 (0.85–0.98)
LV Tei index	0.93 (0.84–0.97)	0.91 (0.79–0.96)
TV E-wave velocity	0.97 (0.93–0.99)	0.94 (0.85–0.98)
TV A-wave velocity	0.98 (0.95–0.99)	0.97 (0.93–0.99)
RV time *a*	0.63 (0.30–0.83)	0.18 (0.00–0.55)
PA-PSV	0.92 (0.81–0.97)	0.96 (0.90–0.98)
RV Tei index	0.94 (0.86–0.98)	0.90 (0.77–0.96)
RV-ET	0.71 (0.41–0.87)	0.60 (0.23–0.82)
DV-PIV	0.71 (0.34–0.89)	0.94 (0.83–0.98)
LV-FT	0.96 (0.91–0.98)	0.93 (0.84–0.97)
RV-FT	0.93 (0.84–0.97)	0.96 (0.91–0.98)
LV E : A ratio	0.83 (0.62–0.93)	0.89 (0.75–0.95)
RV E : A ratio	0.86 (0.68–0.94)	0.75 (0.47–0.89)

Ao, aorta; DV, ductus venosus; E : A ratio, ratio between early ventricular filling (E-wave) and filling during atrial contraction (A-wave) velocities; ET, ejection time; FHR, fetal heart rate; FT, filling time; HA : CA, heart area : chest area ratio; ICT, isovolumic contraction time; IRT, isovolumic relaxation time; LV, left ventricle; MV, mitral valve; PA, pulmonary artery; PIV, pulsatility index for veins; PSV, peak systolic velocity; RV, right ventricle; TV, tricuspid valve.

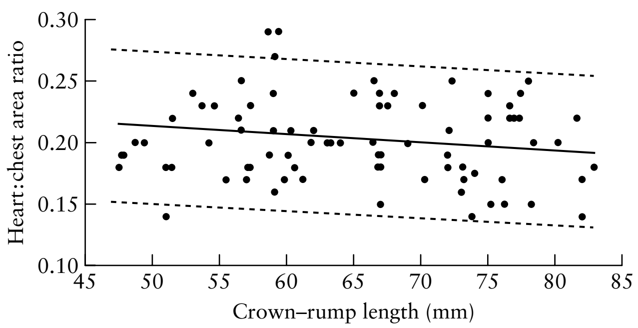

Figure 3 Reference ranges for fetal heart : chest area ratio in relation to crown–rump length at 11–14 weeks' gestation ($n = 83$). Lines represent the 5th, 50th and 95th percentiles.

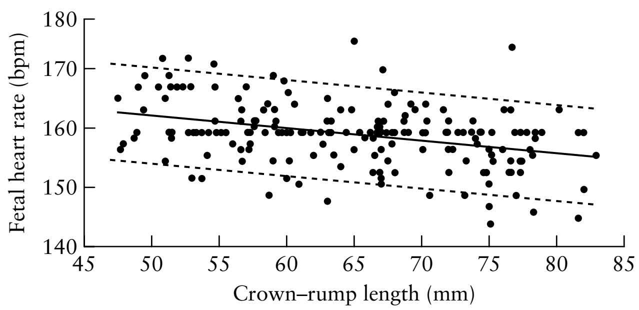

Figure 4 Reference ranges for fetal heart rate in relation to crown–rump length at 11–14 weeks' gestation ($n = 198$). Lines represent the 5th, 50th and 95th percentiles.

FHR and DV-PIV did not correlate with the Tei index of either ventricle.

The outflow velocities of the LV ($P = 0.004$) and RV ($P < 0.00001$) (Figure 8) and E : A velocity ratios (Figure 9) of both the ventricles ($P < 0.0001$) increased with advancing gestation. The early filling (E-wave) velocity of the LV ($P = 0.003$) and RV ($P = 0.002$) increased significantly but the gestational-age-dependent increase in A-wave velocity was not significant. The outflow velocity ($P = 0.008$) and E-wave velocity ($P = 0.005$) of the RV were higher than those of the LV, but the A-wave velocities were similar ($P = 0.066$).

DISCUSSION

Despite almost universal acceptance of NT screening at 11–14 weeks' gestation and the increasing popularity of first-trimester fetal echocardiography, the evaluation of fetal heart function during this period remains challenging. A number of pregnancies, especially those destined to miscarry or at risk of other adverse outcome, are likely to have cardiac dysfunction and may benefit from assessment during the first trimester. However, parameters of normal fetal cardiac function at 11–14 weeks are not well defined, and appropriate reference intervals have not yet been established. This study provides reference ranges for a number of

Table 3 Regression equations for calculation of the 5th percentile, mean and 95th percentile values for parameters of cardiocirculatory dynamics in relation to crown–rump length (CRL) at 11–14 weeks' gestation

Parameter	*5th Percentile*	*Mean*	*95th Percentile*
HA : CA ratio	−0.007CRL + 0.1851	−0.007CRL + 0.2466	−0.007CRL + 0.3081
FHR	−0.217CRL + 165.4	−0.217CRL + 173.8	−0.217CRL + 182.2
LV-ICT%	0.02CRL + 2.95	0.02CRL + 6.18	0.02CRL + 9.41
LV-IRT%	−0.05CRL + 9.11	−0.05CRL + 12.74	−0.05CRL + 16.37
LV-ET%	−0.083CRL + 43.83	−0.083CRL + 50.06	−0.083CRL + 56.29
LV-FT%	0.084CRL + 26.7	0.084CRL + 33.6	0.084CRL + 40.5
RV time *a*%	−0.026CRL + 56.9	−0.026CRL + 62.6	−0.026CRL + 68.3
RV-ET%	−0.007CRL + 40.74	−0.007CRL + 47.60	−0.007CRL + 54.46
RV-FT%	0.025CRL + 31.8	0.025CRL + 37.9	0.025CRL + 44.0
RV Tei index	0.00003CRL + 0.196	0.00003CRL + 0.327	0.00003CRL + 0.458
LV Tei index	0.0004CRL + 0.133	0.0004CRL + 0.353	0.0004CRL + 0.573
Ao-PSV	0.172CRL + 13.95	0.172CRL + 23.62	0.172CRL + 33.29
PA-PSV	0.324CRL + 4.73	0.324CRL + 15.15	0.324CRL + 25.57
TV E-wave velocity	0.158CRL + 6.99	0.158CRL + 14.13	0.158CRL + 21.27
MV E-wave velocity	0.159CRL + 5.94	0.159CRL + 12.79	0.159CRL + 19.64
LV E : A ratio	0.0024CRL + 0.278	0.0024CRL + 0.397	0.0024CRL + 0.516
RV E : A ratio	0.0032CRL + 0.249	0.0032CRL + 0.345	0.0032CRL + 0.441
DV-PIV	0.0001CRL + 0.574	0.0001CRL + 0.963	0.0001CRL + 1.352

Ao, aorta; DV, ductus venosus; E : A ratio, ratio between early ventricular filling (E-wave) and filling during atrial contraction (A-wave) velocities; ET, ejection time; FHR, fetal heart rate; FT, filling time; HA : CA, heart area : chest area ratio; ICT, isovolumic contraction time; IRT, isovolumic relaxation time; LV, left ventricle; MV, mitral valve; PA, pulmonary artery; PIV, pulsatility index for veins; PSV, peak systolic velocity; RV, right ventricle; TV, tricuspid valve.

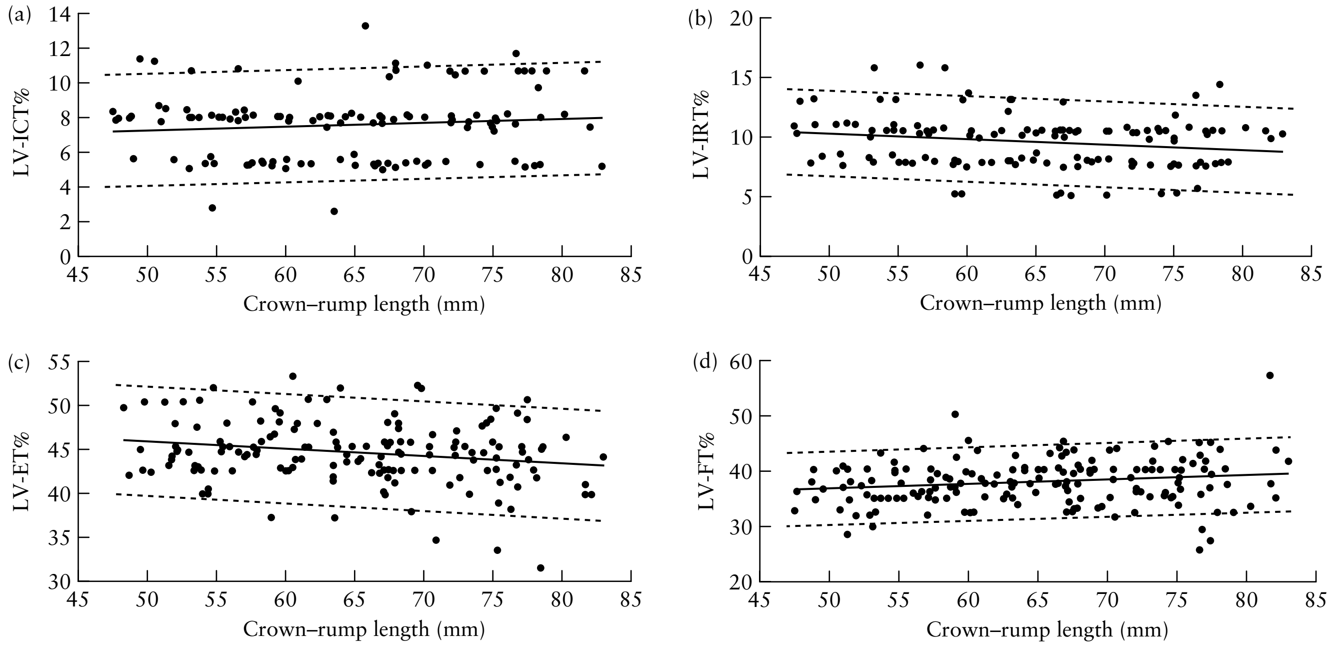

Figure 5 Reference ranges for the left ventricular (LV) cardiac cycle time intervals in relation to crown–rump length at 11–14 weeks' gestation ($n = 163$). Lines represent the 5th, 50th and 95th percentiles. (a) Proportion of the isovolumic contraction time of the cardiac cycle (ICT%); (b) proportion of the isovolumic relaxation time of the cardiac cycle (IRT%); (c) proportion of the ejection time of the cardiac cycle (LV-ET%); (d) proportion of the filling time of the cardiac cycle (LV-FT%).

noninvasive parameters of cardiocirculatory dynamics during the late first trimester of pregnancy.

Cardiac function is classically described using pressure, volume and time indices. However, all of these cannot be accurately measured using noninvasive methods. We assessed some of the most accepted noninvasive parameters used to describe the fetal cardiocirculatory condition during the first trimester. We used heart : chest area ratio and the myocardial performance index (Tei index) to describe the global cardiac function. Heart : chest area ratio > 0.35 has been used as a sign of cardiomegaly (a relatively consistent sign of congestive heart failure) in the second trimester[22] and has been shown to be useful in predicting fetal outcome in congenital heart disease and hydrops[23,24]. We found this ratio to be less than that reported in the second trimester, but

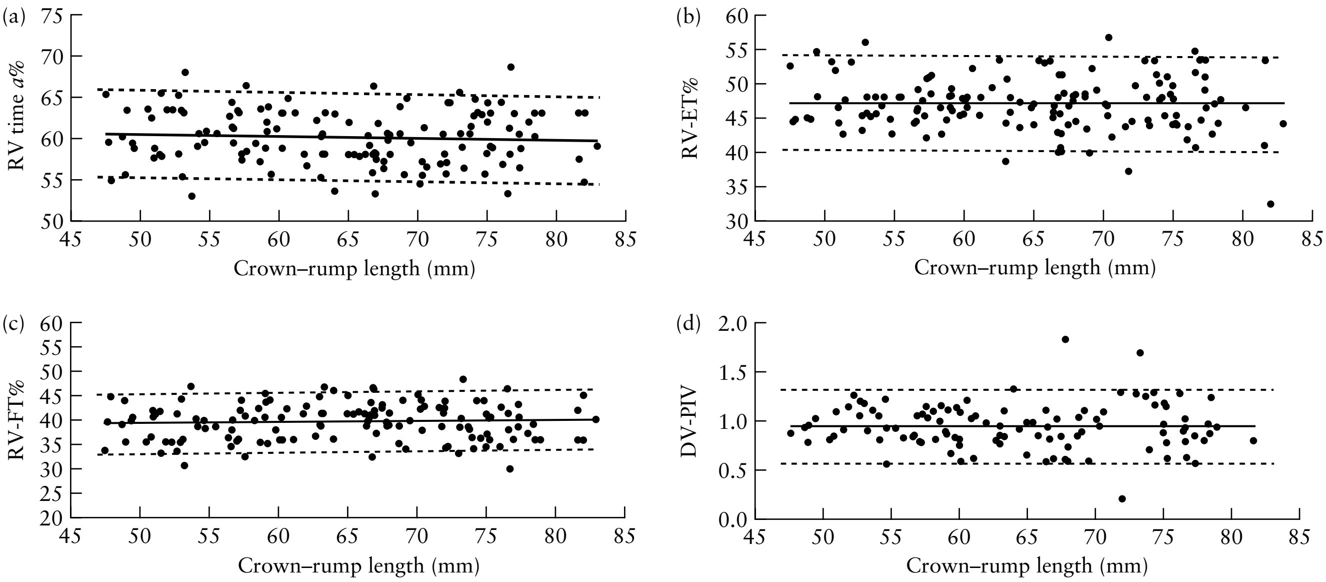

Figure 6 Reference ranges for the right ventricular (RV) cardiac cycle time intervals ($n = 130$) and ductus venosus pulsatility index for veins (DV-PIV) ($n = 160$) in relation to crown–rump length at 11–14 weeks' gestation. Lines represent the 5th, 50th and 95th percentiles. (a) Proportion of the time interval of the cardiac cycle between closure and opening of the tricuspid valve (RV time *a*%); (b) proportion of ejection time of the cardiac cycle (RV-ET%); (c) proportion of the filling time of the cardiac cycle (RV-FT%); (d) DV-PIV.

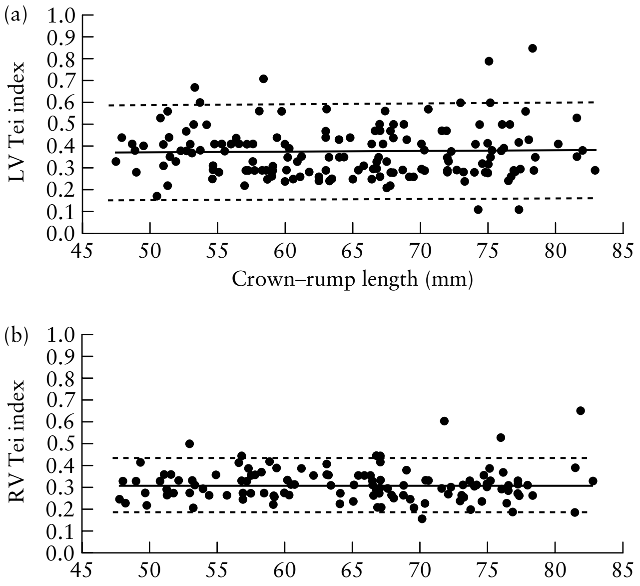

Figure 7 Reference ranges for the left (LV) ($n = 163$) (a) and right (RV) ($n = 130$) (b) ventricular Tei indices in relation to crown–rump length at 11–14 weeks' gestation. Lines represent the 5th, 50th and 95th percentiles.

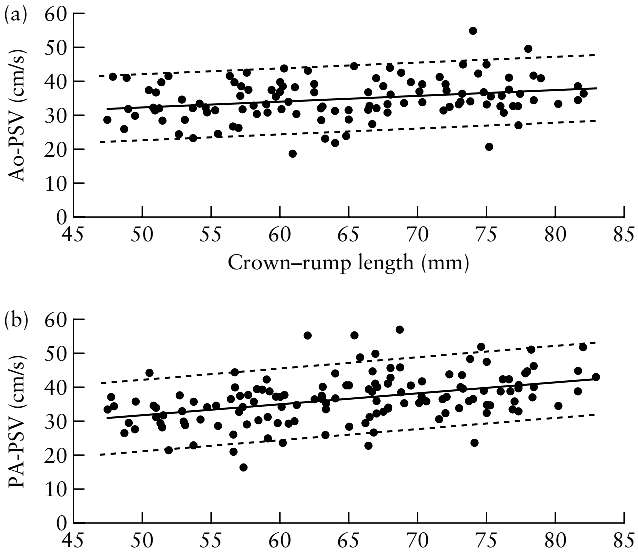

Figure 8 Reference ranges for the left (Ao-PSV) ($n = 116$) (a) and right (PA-PSV) ($n = 118$) (b) ventricular outflow peak systolic velocities in relation to crown–rump length at 11–14 weeks' gestation. Lines represent the 5th, 50th and 95th percentiles.

similar to what has been reported during the late first trimester[25]. Although our values differ slightly from some in previously published reports[26], the discrepancy may be related to methodological differences, e.g. measuring the thorax along the skin edge rather than the rib or using the ellipse rather than the diameter method to derive the circumference[27].

Maturational changes are known to affect the FHR and its variability, resulting in a sequential decrease in rate and increase in variability with advancing gestation[28]. In line with this, the FHR in our study decreased with increasing CRL. The peak ventricular outflow velocities increased with CRL, which suggests an increase in stroke volume. Fetal cardiac output, the product of stroke volume and heart rate, is known to increase with advancing gestation during the first half of pregnancy[29]. Although in the lamb, variations in cardiac output are explained mainly by changes in heart rate[30], in the human fetus variations in heart rate (within the normal range) are not necessarily associated with a change in fetal cardiac output[31], and

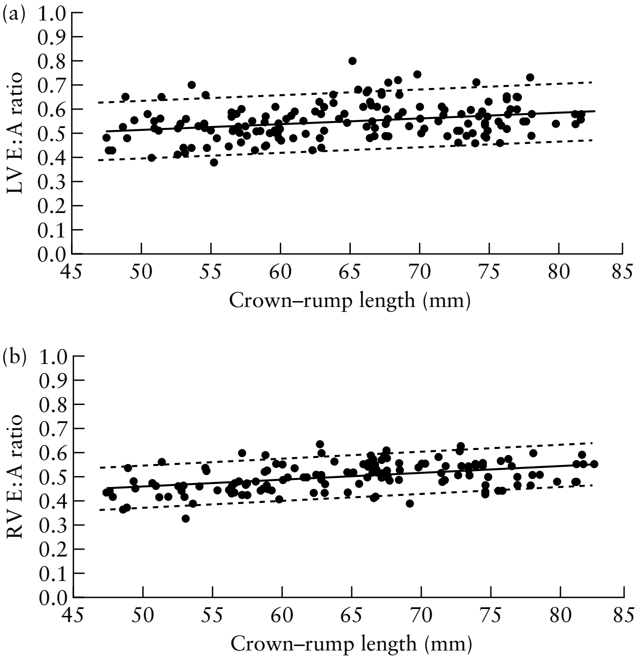

Figure 9 Reference ranges for the ratio of the left (LV) ($n = 142$) (a) and right (RV) ($n = 133$) (b) ventricular inflow peak velocities during the early filling (E) and atrial contraction (A) phases of the cardiac cycle (E : A ratio) in relation to crown–rump length at 11–14 weeks' gestation. Lines represent the 5th, 50th and 95th percentiles.

even fetuses with congestive heart failure may have normal heart rate[32].

Several investigators have published reference values for the Tei index during the second half of pregnancy[18,19,33–36,] but so far only two studies that report Tei index values in the first trimester, at 11–14 weeks' gestation, have been published in English[13,15]. One of these studies[15] had only 32 observations and although the other one included a reasonable number of normal fetuses ($n = 159$), its primary goal was to investigate the cardiac function in fetuses with increased NT[13]. Our reference values for the Tei indices are very similar to those reported by Huggon *et al.*[13] (0.375 vs. 0.378 for the LV and 0.332 vs. 0.352 for the RV) but differ from those of Russel and McAuliffe[15], who reported a value of 0.5 for both ventricles. Despite the differences regarding the normal values, the trend was reported to be similar, i.e. the Tei index did not change with gestational age. Interestingly, the values reported in the late second and third trimesters are also quite similar[19,20,34].

Tei index values obtained from simultaneous ventricular inflow and outflow Doppler recordings are more accurate and reproducible than those calculated from separate waveforms[18,19] as this method eliminates the potential error due to heart rate variations. Therefore, we utilized this technique for measuring the LV Tei index. However, as it is more difficult to obtain the inflow and outflow blood velocity waveforms simultaneously from the RV, we insonated the tricuspid and pulmonary valves separately. Russel and McAuliffe[15] reported that they were able to record the tricuspid and pulmonary valve Doppler velocity waveforms simultaneously at 11–14 weeks. However, it may not always be easy to differentiate the inflow–outflow waveforms of the RV and LV at this gestation, a supposition that is further supported by their finding of exactly the same Tei index value for both ventricles. In line with the findings of Huggon *et al.*[13], we found the RV Tei index to be lower than the LV Tei index; the lower RV Tei index arose owing to a relatively longer RV-ET, which may be explained by the higher afterload faced by the LV compared with the RV, as the low-resistance placental circulation is already established by 11–14 weeks' gestation.

Previous studies have demonstrated a gestational-age-dependent increase in E : A ratio in early pregnancy[8,11] as well as later in gestation[37]. Our study confirms that this occurs mainly owing to a gestational-age-related increase in E-wave velocity, as the A-wave velocity did not increase significantly during weeks 11–14 (as has been reported in the second half of pregnancy[37]). This, together with decreasing IRT%, is a sign of continuously improving diastolic function.

Several investigators have reported on the utility of DV Doppler to improve the sensitivity of first-trimester screening, and an abnormal DV Doppler waveform, especially in fetuses with increased NT, is frequently associated with fetal aneuploidy[38] or cardiac defects[39]. Furthermore, increased pulsatility in the fetal systemic veins is considered to be a sign of congestive heart failure[22]. However, the relationship between cardiac function and peripheral arterial and venous Doppler scans at 11–14 weeks has not been well explored. DV-PIV values in our study were similar to those reported by Prefumo *et al.*[40] and did not significantly correlate with other parameters of fetal cardiac function.

In conclusion, we have established reference ranges for the noninvasive evaluation of fetal cardiocirculatory dynamics at 11–14 weeks' gestation.

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