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Maternal left ventricular transverse and long-axis systolic function during pregnancy

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ABSTRACT

Objectives *Circumferential fiber shortening has been the dominant basis for conventional analysis by echocardiography of left ventricular systolic function during pregnancy. Results in the literature have been conflicting due mainly to the fact that geometric assumptions for the calculation of these indices are made that may not be valid due to changes in left ventricular shape during pregnancy. Left ventricular long-axis displacement is expected to be a useful index of systolic function, independent of the changes in left ventricular geometry. The aim of this study was to compare circumferential to long-axis shortening during left ventricular contraction in pregnant women.*

Methods *This was a cross-sectional study of 125 pregnant women at 9–42 weeks of gestation and 19 non-pregnant female controls. Two-dimensional and M-mode echocardiography of the left ventricle was performed including measurement of left ventricular long-axis displacement and activation time on the lateral, septal, anterior and inferior sides of the mitral annulus. Activation time was assessed as the time from the start of the Q-wave of the electrocardiogram to the onset of left ventricular long-axis shortening.*

Results *Mean arterial pressure and activation time decreased during pregnancy, reaching a nadir at about 19 weeks' gestational age of 4% and 13%, respectively, below non-pregnant values; they subsequently increased towards term. Left ventricular long-axis displacement mirrored the changes in mean arterial pressure and activation time and increased with gestational age at all four sites of the atrioventricular plane reaching a peak at about 23 weeks (+ 12% compared to non-pregnant levels). The ejection fraction and fractional shortening remained stable until 30 and 32 weeks, respectively, and then decreased towards term.*

Conclusion *Changes in left ventricular long-axis performance during pregnancy occur earlier than do measures of transverse function.*

INTRODUCTION

Normal pregnancy is known to be associated with profound alterations in the maternal cardiovascular system. There is an initial decrease in peripheral resistance causing an increase in maternal heart rate from as early as 5 weeks' gestational age[1]. There is a rise in stroke volume reaching a peak early in the third trimester[2,3] achieved mainly through an increase in blood volume[4]. After mid-pregnancy, there is a progressive increase in systemic blood pressure, which together with the increase in blood volume leads to left ventricular (LV) hypertrophy[3,5].

However, the effects of these changes in preload and afterload on LV systolic function during pregnancy are uncertain. Some studies have suggested that there is no change in fractional shortening or the ejection fraction with gestation[6–9] and others that there is a decline towards term[3,10]. These discrepancies may be partly due to the fact that the ejection fraction was calculated by the Teichholz formula, which makes geometric assumptions that may not be valid due to changes in LV shape during pregnancy[11]. These problems could possibly be avoided with the assessment of long-axis LV systolic function.

Long-axis shortening of the LV is the result of the contraction of the longitudinally orientated subendocardial myocardial fibers and can be assessed by the measurement of long-axis displacement during LV contraction. The subendocardial fibers are more vulnerable to ischemia than are the transverse layers, so that longitudinal function is a potentially more sensitive marker of LV dysfunction[12–19] and has prognostic importance after coronary angioplasty[20]. It is also a quick and easily mastered technique, with small intra- and interobserver variability[21]. The aim of this study was to describe the changes of long-axis function during normal pregnancy and to make a comparison with other indices of LV systolic function.

METHODS

This was a cross-sectional study of 125 pregnant women with singleton pregnancies at 9–42 weeks' gestation and 19

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Table 1 Demographic characteristics of the study populations

Characteristic	*Pregnant*	*Non-pregnant*
Age (years, mean (SD))	31.3 (5.03)	32.3 (3.0)
Height (cm, mean (SD))	164.9 (6.46)	167.8 (4.42)
Weight (kg, mean (SD))	61.1 (11.12)	58.9 (8.75)
Nulliparous (%)	50	63
Ethnicity		
Caucasian (%)	85	79
Afro-Caribbean (%)	13	16

There were no statistical differences between pregnant women and non-pregnant controls. SD, standard deviation.

non-pregnant women in the first phase of their menstrual cycle, with no statistically significant differences in their demographic characteristics (Table 1). Two-dimensional and M-mode echocardiography was performed with a Powervision 7000 – SSA 380 (Toshiba Corporation, Tokyo, Japan) using a 3.5-MHz transducer. Patient selection, methods and statistical analysis have been described elsewhere in this issue of the Journal[22].

Two-dimensional echocardiography

Stroke volume was the product of the cross-sectional area of the LV outflow tract and the velocity time integral of the pulsed Doppler subaortic waveform measured in the five-chamber view. Cardiac output was calculated as the product of heart rate and stroke volume. The ejection time was measured from the opening to the closing artifact of the continuous-wave aortic signal.

M-mode and long-axis measurements

Left ventricular and atrial dimensions were calculated according to the recommendations of the American Society of Echocardiography[23] from the parasternal long-axis view and fractional shortening (FS) was calculated from the equation:

$$FS = 100 \times (LVDD - LVSD)/LVDD,$$

where LVDD is left ventricular diastolic diameter and LVSD is left ventricular systolic diameter.

Left ventricular end-systolic and end-diastolic volumes were estimated by the Teichholz formula[24]. This was a subsidiary measure of systolic function for the purposes of comparison with the literature.

Long-axis function was evaluated by two-dimensionally guided M-mode recordings through the mitral annulus, using the apical four-chamber view for the lateral and septal sides and the two-chamber view for the anterior and inferior sides, respectively. Care was taken to equalize the angle between the ultrasound beam and the atrioventricular plane at both the lateral and septal sides and the anterior and posterior sides[12,20,25]. Results were expressed for each side and in addition, a global measure was calculated from the mean of all four sides. The time from the onset of the Q-wave on the electrocardiogram to the onset of the LV long-axis displacement was also measured (i.e. the activation time).

Statistical analysis

Statistical analysis was performed as previously described[22]. In addition, multiple regression analysis was used to assess the effect on global LV long-axis displacement of gestational age, maternal age, height, weight, parity, stroke volume, fractional shortening, mean arterial pressure, heart rate and ejection time. The hemodynamic variables used in the multiple regression analysis were selected by univariate regression analysis between the individual variable and global long-axis values. Multiple regression was performed in the pregnant population as a whole and after division into two groups by a cut-off of 25 weeks' gestational age. This cut-off was taken because this was the point at which stroke volume reached its peak and hematocrit its nadir, indicating the maximum increase in blood volume.

The coefficients of variation for the LV outflow tract and aortic velocity time integral were 2.1% and 1.4%, respectively. The coefficients of variation for long-axis displacement on the lateral, septal, anterior and inferior sides were 2.6%, 2.1%, 3.4% and 5.1%, respectively, and for activation time were 2.8%, 1.5%, 2.0% and 2.2%, respectively.

Using the standard deviation of the non-pregnant controls, recruitment of 18 non-pregnant women and 109 women with singleton pregnancies was calculated to allow detection of a difference of 1 L in cardiac output, 1.5 mm in long-axis displacement and 10 ms in activation time with 90% power at the 5% level.

The statistical package SPSS 8.0 (SPSS for Windows, Rel. 8.0.0. 1997, Chicago, IL, USA) was used.

RESULTS

Two-dimensional echocardiography and heart rate

Cardiac output increased with gestation ($y = -0.0053x^2 + 0.291x + 2.55$; $P < 0.0001$; $r^2 = 0.14$; Figure 1) to a maximum at about 30 weeks of 52% above non-pregnant controls and then fell towards term to 32% above non-pregnant levels. The hematocrit, mirroring the changes of cardiac output, decreased with gestation ($y = 42.5 - 0.62 \times ga + 0.01 \times ga^2$; $P = 0.006$; $r^2 = 0.10$; Figure 1) to a nadir at about 25 weeks of 10% below non-pregnant controls and thereafter increased towards term to levels 5% below non-pregnant controls.

The change in cardiac output was as a result of an increase in both stroke volume and heart rate. Stroke volume reached a maximum at about 30 weeks ($y = -0.066x^2 + 3.59x + 45.41$; $P < 0.0001$; $r^2 = 0.15$; Figure 1) to a level 31% above non-pregnant controls and then fell towards term to a level 12% above non-pregnant controls. Heart rate increased early, between 10 and 14 weeks, to reach a level 16% above non-pregnant controls (78 beats/min vs. 67 beats/min, $t = -3.82$; $P < 0.0001$). Thereafter there was a small but not statistically significant increase ($y = 0.165x + 76.47$; $P = 0.13$; $r^2 = 0.018$; Figure 1).

M-mode echocardiography

Detailed results of the changes during pregnancy of left atrial and LV dimensions are described elsewhere in this issue[22].

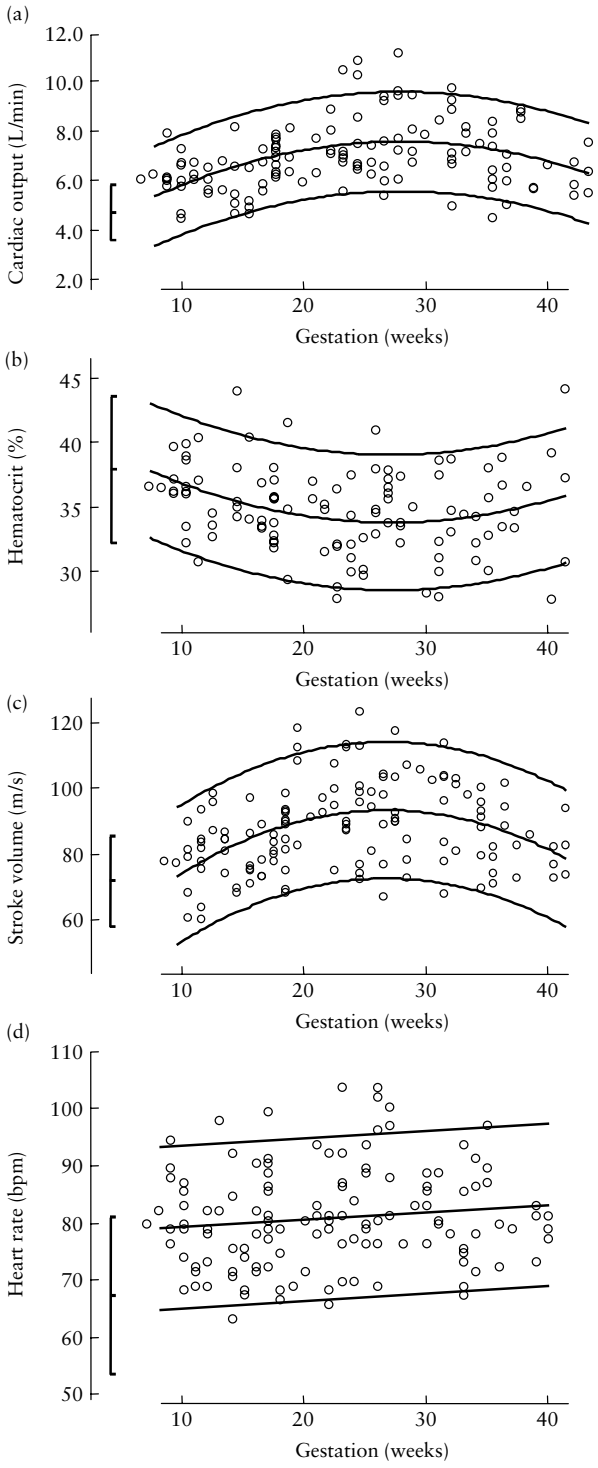

Figure 1 Changes in cardiac output (a), hematocrit (b), stroke volume (c) and heart rate (d) with advancing gestation. Each graph illustrates individual values and the regression lines of the 5th, 50th and 95th centiles. The vertical line on the left of each graph illustrates the 5th, 50th and 95th centiles of the non-pregnant controls.

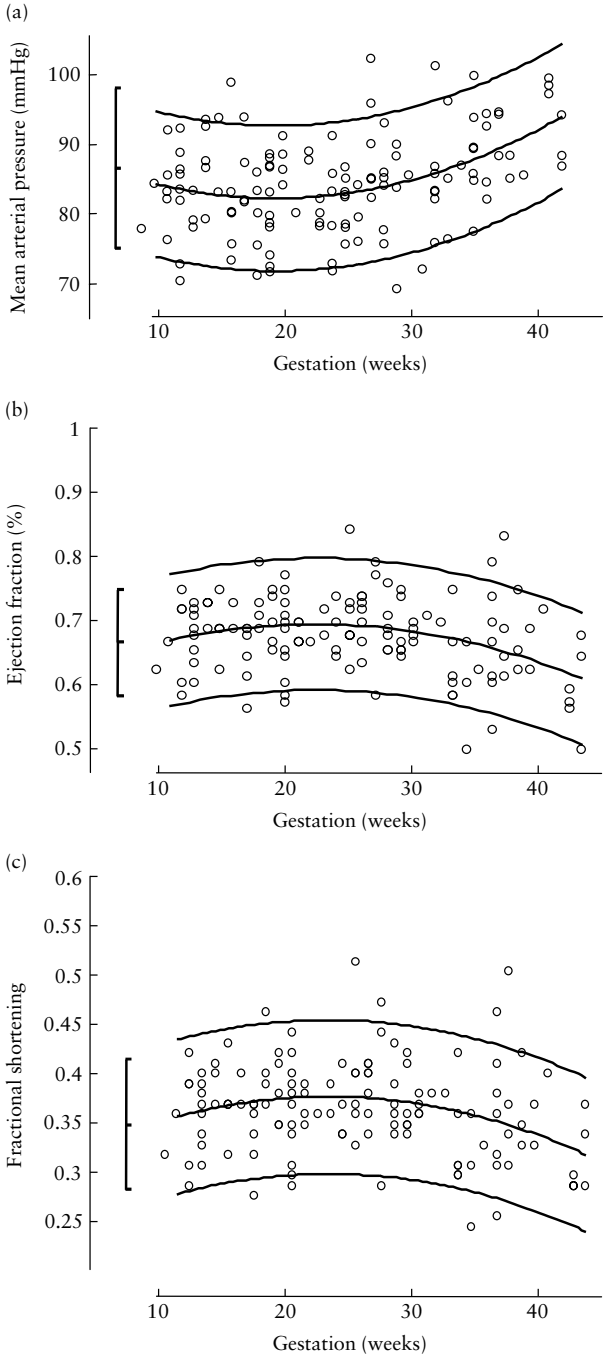

Figure 2 Changes in mean arterial pressure (a), the ejection fraction (b) and fractional shortening (c) with advancing gestation. Each graph illustrates individual values and the regression lines of the 5th, 50th and 95th centiles. The vertical line on the left of each graph illustrates the 5th, 50th and 95th centiles of the non-pregnant controls.

Fractional shortening and the ejection fraction did not change up to about 32 and 30 weeks, respectively, and subsequently fell below prepregnancy levels (fractional shortening: $y = -0.00014x^2 + 0.0061x + 0.321$; $P = 0.005$; $r^2 = 0.1$; ejection fraction: $y = -0.00019x^2 + 0.008x + 0.601$; $P = 0.001$; $r^2 = 0.11$; Figure 2).

The LV long-axis displacement increased with gestation at all four sites to reach a peak at about 23 weeks. The maximum was 13%, 8%, 13% and 10% above non-pregnant control values for the lateral, septal, anterior and inferior regions, respectively (Figure 3, Table 2). Subsequently, the LV long-axis

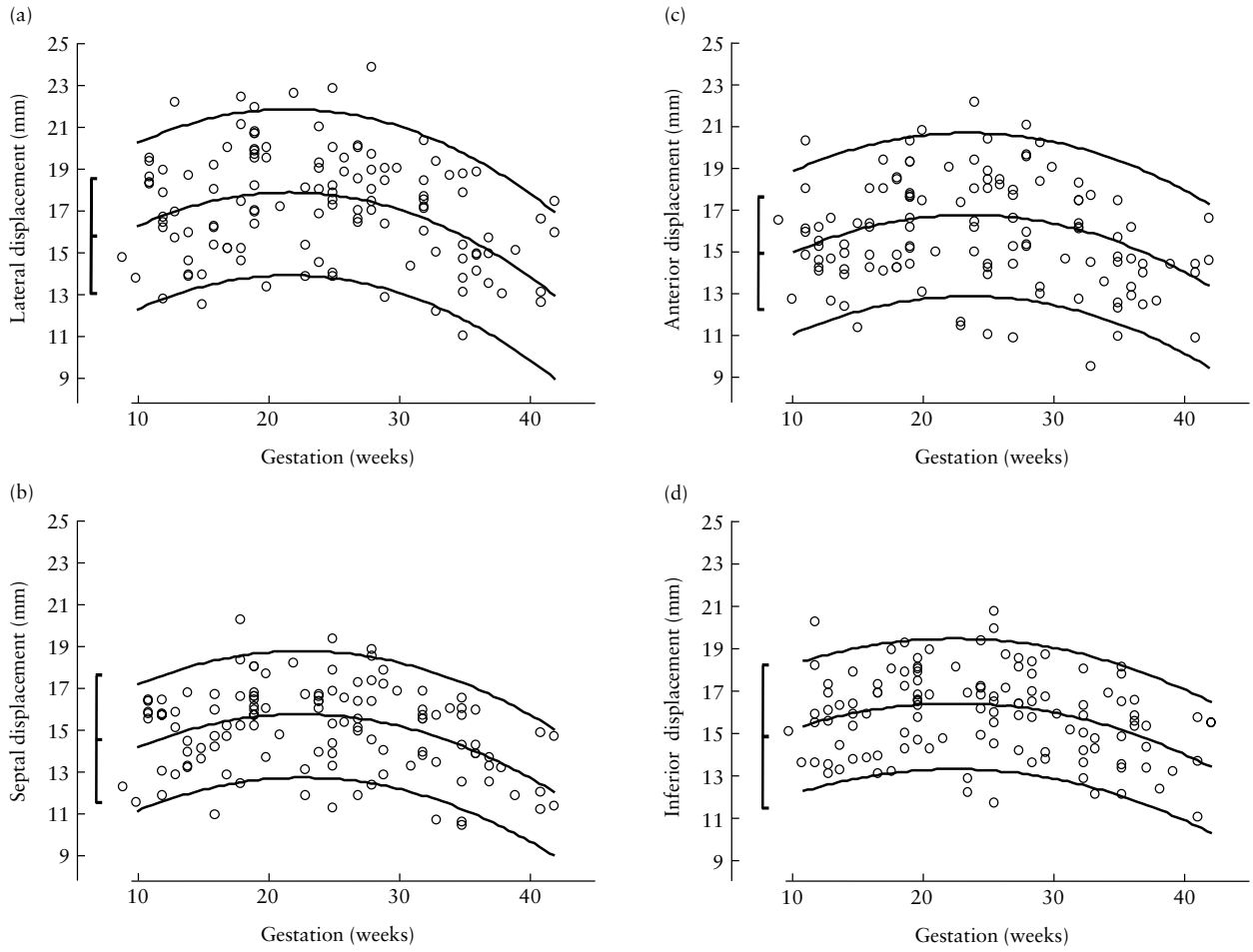

Figure 3 Changes in left ventricular long-axis displacement with advancing gestation on the lateral (a), septal (b), anterior (c) and inferior (d) planes. Each graph illustrates individual values and the regression lines of the 5th, 50th and 95th centiles. The vertical line on the left of each graph illustrates the 5th, 50th and 95th centiles of the non-pregnant controls.

Table 2 Left ventricular long-axis displacement and activation time: results of the multiple regression

	Regression		
Plane	*Equation*	r^2	P
Long-axis displacement			
Lateral	$y = -0.012x^2 + 0.52x + 12.22$	0.15	< 0.0001
Septal	$y = -0.01x^2 + 0.453x + 10.61$	0.17	< 0.0001
Anterior	$y = -0.01x^2 + 0.47x + 11.23$	0.12	0.001
Inferior	$y = -0.0075x^2 + 0.329x + 2.82$	0.12	0.001
Activation time			
Lateral	$y = 0.061x^2 - 2.1x + 90.165$	0.44	< 0.0001
Septal	$y = 0.06x^2 - 2.25x + 94.8$	0.36	< 0.0001
Anterior	$y = 0.044x^2 - 1.42x + 84.67$	0.29	< 0.0001
Inferior	$y = 0.059x^2 - 2.28x + 97.35$	0.39	< 0.0001

displacement decreased until, at term, levels were lower than those of the non-pregnant controls by 18%, 17%, 10% and 10% for the lateral, septal, anterior and inferior planes, respectively (Figure 3, Table 2). The LV long-axis displacement was higher at the lateral side of the ventricular wall compared to the septal side, both in non-pregnant controls (15.7 mm vs. 14.5 mm; $t = 2.10$; $P = 0.04$) and in pregnant subjects (17.1 mm vs. 14.9 mm; $t = 7.25$; $P < 0.0001$). The global LV long-axis displacement showed an initial increase of 11% above control levels to 23 weeks and then a decrease to 15% below control levels at term ($y = 11.72 + 0.444x - 0.01x^2$; $P < 0.0001$; $r^2 = 0.18$).

The activation time decreased with gestational age to reach a nadir at 18–19 weeks of 12%, 15%, 13%, and 15% below the level of the controls for the lateral, septal, anterior and inferior sides, respectively (Figure 4, Table 2). Subsequently, there was a significant increase by term to levels 34%, 25%, 20% and 20% higher than those of the non-pregnant controls for the lateral, septal, anterior and inferior sides, respectively (Figure 4, Table 2).

Mean arterial pressure and multiple regression

The mean arterial pressure initially decreased, reaching a nadir at about 19 weeks to levels 5% lower than non-pregnant controls. Thereafter it increased until term to levels 8% higher than non-pregnant controls ($y = 0.023x^2 - 0.894x + 90.96$; $P < 0.0001$; $r^2 = 0.17$; Figure 2).

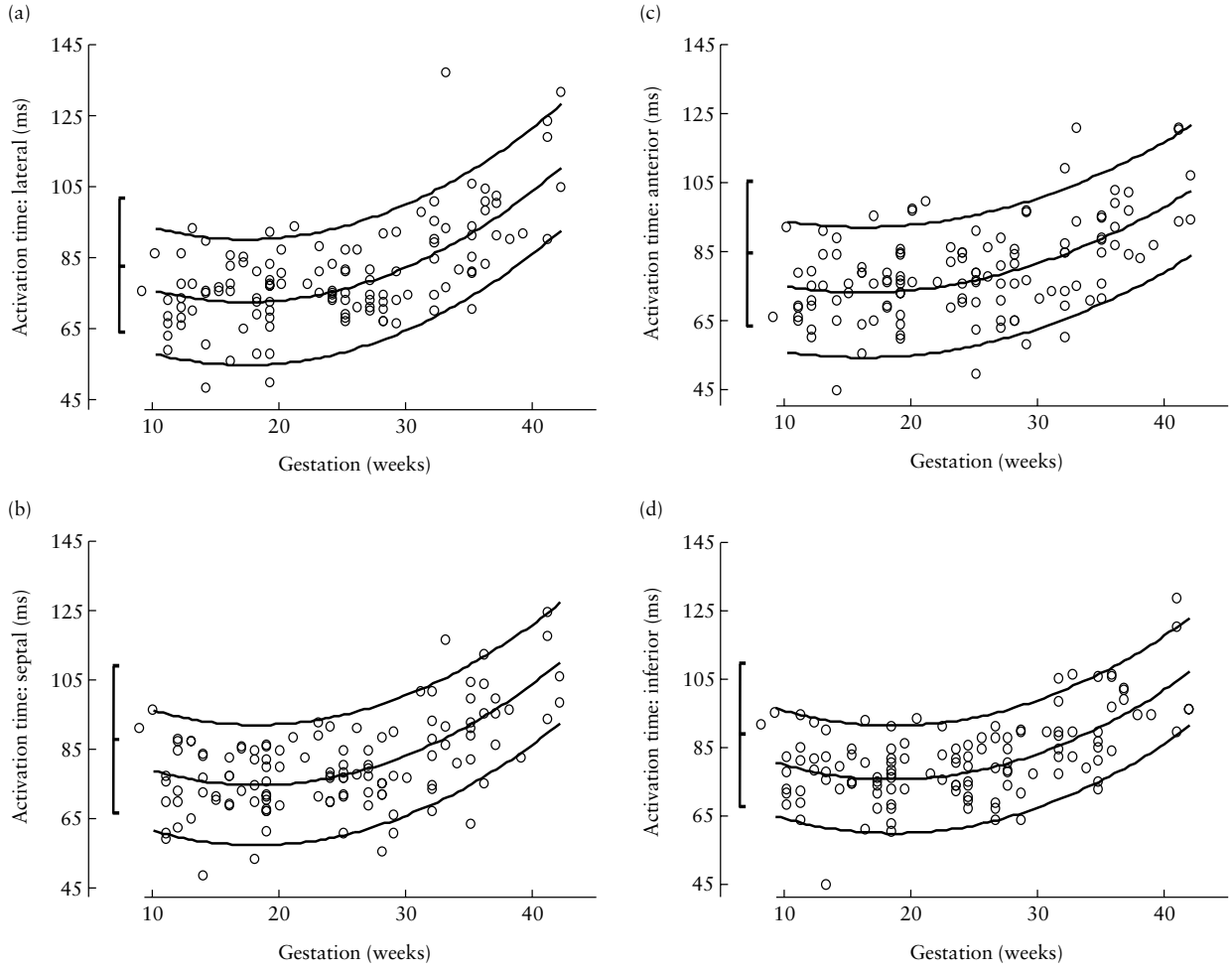

Figure 4 Changes in activation time with advancing gestation on the lateral (a), septal (b), anterior (c) and inferior (d) planes. Each graph illustrates individual values and the regression lines of the 5th, 50th and 95th centiles. The vertical line on the left of each graph illustrates the 5th, 50th and 95th centiles of the non-pregnant controls.

Backward stepwise regression analysis demonstrated that global LV long-axis displacement during pregnancy was significantly and independently related to gestational age (ga), fractional shortening (FS) and stroke volume (SV):

global displacement = $8.96 + 0.14 \times ga - 0.00396 \times ga^2 + 9.31 \times FS + 0.032 \times SV$; $P < 0.0001$; $r^2 = 0.24$).

The global LV long-axis displacement before 25 weeks' gestational age was significantly related only to stroke volume:

global displacement (at < 25 weeks) = $12.79 + 0.041SV$ ($P = 0.014$, $r^2 = 0.10$).

The global LV long-axis displacement after 25 weeks gestational age was significantly and independently related to gestational age and mean arterial pressure (MAP) but not to stroke volume:

global displacement at (> 25 weeks) = $28.48 - 0.2ga + 0.075MAP$ ($P < 0.0001$; $r^2 = 0.38$).

Comparison with non-pregnant controls

In the first two trimesters (10–28 weeks) cardiac output, stroke volume, heart rate, ejection fraction, fractional shortening and global mitral annulus displacement were higher in pregnant women than in non-pregnant controls by 45%, 22.5%, 19%, 4.5%, 5.5% and 8%, respectively. On the contrary, hematocrit, mean arterial pressure and global activation time were lower in pregnant women than in non-pregnant controls by 7%, 4% and 13.3%, respectively (Table 3).

DISCUSSION

This study demonstrated that long-axis function, as assessed by LV long-axis displacement and activation time, was more sensitive than traditional systolic indices in detecting changes in LV systolic function during pregnancy. In the first 25 weeks of pregnancy LV long-axis displacement correlated well with stroke volume and thereafter with mean arterial pressure.

The LV systolic function, as assessed by cardiac output, fractional shortening, ejection fraction and mitral annulus

Table 3 Results of the *t*-test on examined parameters in pregnant women in the first two trimesters (10–28 weeks) and non-pregnant controls

Parameter	*Non-pregnant (mean (SD))*	*Pregnant (mean (SD))*	*t-test results*	
			t-*statistic*	P
Cardiac output (L/min)	4.8 (0.7)	6.95 (1.3)	−9.9	< 0.0001
Stroke volume (mL)	71.5 (8.4)	87.6 (14.3)	−6.5	< 0.0001
Heart rate (bpm)	67.2 (8.3)	79.8 (11.4)	−5.5	< 0.0001
Hematocrit (%)	37.8 (3.4)	35.1 (3.2)	2.74	0.01
Ejection fraction (%)	0.65 (0.05)	0.68 (0.05)	−2.06	0.04
Fractional shortening	0.36 (0.04)	0.38 (0.04)	−2.4	0.02
Mean arterial pressure (mmHg)	86.5 (6.9)	83.1 (6.2)	1.9	0.06
Global activation time (ms)	85.67 (11.8)	75.6 (8.2)	3.5	0.002
Global mitral annulus excursion (mm)	15.0 (1.6)	16.3 (1.9)	−3.18	0.003

displacement appeared enhanced in the first two trimesters, with a decline towards term. The cardiac output remained about 30% above non-pregnant levels and fractional shortening and ejection fraction dropped to non-pregnant levels, while mitral annulus displacement declined to below prepregnancy levels in the third trimester. The results of this study confirm previous reports on LV systolic function that demonstrated an increase in cardiac output (as a result of an increase in heart rate and stroke volume) reaching a peak early in the third trimester[3,26–28]. Thereafter, there was a decline to about 30% above non-pregnant levels towards term. There is discrepancy in the literature regarding the changes in cardiac output in the third trimester. Our results confirm previous studies that demonstrated a decline in cardiac output in the third trimester[1,28–32] and contradict others that demonstrated either no further changes with gestational age[3,33] or even an increase towards term[34–36]. These differences have been attributed to variations in methodology or population characteristics[5,37]. However, the largest longitudinal study of cardiac output in 400 pregnant women reported a decline in cardiac output after 34 weeks[26]. The increase in stroke volume is largely attributed to an increase in blood volume and preload, as demonstrated by the increase in left atrial and LV end-diastolic dimensions.

Anatomical and physiological considerations

The myocardium of the LV is comprised of three layers of fibers. The middle layer is circumferentially arranged and is responsible for the contraction of the short axis of the LV[38] while the other two layers are arranged mainly longitudinally[39] and are responsible for long-axis shortening[38].

The subendocardial fibers are at greater risk from ischemia and are more sensitive to blood pressure changes than the circumferential layers so that a decrease in the amplitude of long-axis displacement precedes transverse dysfunction in patients with coronary artery disease[20] hypertension, mitral valve disease and cardiomyopathies[17,40,41]. The agreement of LV long-axis displacement with 'gold standard' techniques such as radionuclide ventriculography has already been established[42].

Previous work

Circumferential fiber shortening has been the dominant basis for conventional analysis of LV systolic function during pregnancy by echocardiography with measurement of ventricular dimensions and hence the fractional shortening, ejection fraction and, mainly for research purposes, mean velocity of circumferential fiber shortening[43]. Robson *et al.*[3] reported a decline in LV systolic performance after 30 weeks' gestational age as demonstrated by a reduction in fractional shortening and the ejection fraction. Similarly Mone *et al.*[10] found a reduction at term in fractional shortening and mean velocity of circumferential fiber shortening. Furthermore, when they examined the changes with gestation of an afterload-adjusted and preload-independent index of contractility (the relationship between mean velocity of circumferential fiber shortening and end-systolic meridian wall stress), they found a reduction at term. Similar results were shown by Geva *et al.*[44]. Conversely, others have reported no changes during pregnancy in fractional shortening[6,7,9,34,44,45], mean velocity of circumferential fiber shortening[6,7,9,44] or the ejection fraction estimated by the Teichholz formula[6,8,31,46]. Gilson *et al.*[9] also observed no changes in fractional shortening and the ejection fraction (estimated by Simpson's rule) during the course of pregnancy but concluded that there was increased myocardial contractility, as demonstrated by the reduction in indices of wall stress.

These conflicting data demonstrate the known weaknesses of the traditional systolic indices. In these studies the ejection fraction was mainly measured by the Teichholz formula, which makes unwarranted geometrical assumptions. The calculation of end-diastolic and end-systolic volumes assumes that the LV is an ellipsoid with its length double its width[24]. This is not valid in cases of ventricular dilatation[47] such as in pregnancy when there is a 40% increase in blood volume. Another shortcoming of the traditional indices is that the cursor-derived systolic and diastolic dimensions of the LV from the parasternal view are not from the same part of the LV because of the movement of the heart along the long axis during the cardiac cycle. In pregnancy, calculation of the ejection fraction by two-dimensional echocardiography might also be limited because for the estimation of the ventricular systolic and diastolic dimensions good image quality is required for adequate tracing of the endocardial borders. This might be compromised, especially towards term, because the soft tissue edema and the change in position of the heart due to the pressure from the gravid uterus make adequate visualization of endocardial borders difficult.

Left ventricular long-axis displacement is expected to be a useful index of systolic function, independent of the changes in LV geometry. Studies in healthy subjects have revealed a

LV long-axis displacement of 14–17 mm[12,48–50] and this range is in agreement with our results. Similarly, the changes of the activation time in healthy subjects, reflecting the time of isovolumic contraction, are in agreement with previous publications that examined the changes in systolic time intervals during pregnancy[51–54]. An initial decrease in the pre-ejection period has been reported in the first two trimesters and a subsequent increase in the third trimester. This increase appears to be sustained even in the postpartum period, suggesting residual suppression of myocardial function[52,54].

Pregnancy is an excellent model of physiological hypertrophy that coincides with a number of factors affecting oxygen supply or demands of the myocardium. Blood flow through the arteries that supply the subendocardial part of the myocardium occurs mainly during diastole[55,56]. Since diastole is of shorter duration when the heart rate is increased, blood flow is compromised when the heart rate is fast, as it is during pregnancy[55]. Heart rate increments during pregnancy range in the literature from 10 to 30%[3,5,9] and stroke volume increments range between 10 and 50%[1,3,9,46]. Furthermore, oxygen consumption of the subendocardial part of the myocardium is higher than that of the subepicardial part in animals[57] and this consumption is increased with increasing stroke volume and/or increasing peripheral blood pressure[55], both of which occur during pregnancy. Mean arterial blood pressure appears to drop to a nadir at mid-pregnancy and then increases to pre-pregnancy levels towards term[1,3,9]. It is therefore conceivable that although the progressive rise in preload, afterload and heart rate during the course of pregnancy is within normal limits, the coexistence of these three factors towards term might inflict excessive strain to the subendocardial part of the myocardium and impair the long-axis function of the LV (and thus demonstrate changes in the LV long-axis displacement and activation time) before any signs of deterioration of the circumferential shortening become apparent.

Study limitations

This was a cross-sectional study and thus the observed changes in the long-axis function during pregnancy are not based on serial observations. However, the number of patients examined is one of the largest in the literature and complies with the requirements of the sample size calculation. Furthermore, the changes observed in the systolic function of the LV were consistent in both two-dimensional and M-mode measurements, indicating an increase in cardiac performance up to the beginning of the third trimester and a decline towards term.

CONCLUSIONS

Left ventricular long-axis displacement reflects changes in preload and afterload earlier in pregnancy than do traditional indices of LV systolic function such as fractional shortening. In the first half of pregnancy it is influenced by changes in stroke volume and in the second half by changes in mean arterial pressure. Left ventricular long-axis displacement may prove to be a sensitive prognostic tool in pregnancies complicated by pre-eclampsia but further longitudinal studies are necessary.

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