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Maternal left ventricular mass and diastolic function during pregnancy

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ABSTRACT

Objective *To evaluate changes in left ventricular mass and diastolic function during normal pregnancy.*

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 maternal left ventricle and left atrium was performed.*

Results *During pregnancy left ventricular mass increased by 52%. There was an increase in left ventricular end-diastolic and end-systolic diameters (12% and 20%, respectively), left ventricular posterior wall diameter during diastole and systole (22% and 13%, respectively) and left intraventricular septum during diastole and systole (15% and 19%, respectively). Mitral valve A-wave maximum velocity increased during pregnancy by 19%, while mitral valve E-wave maximum velocity and the ratio of E-wave/A-wave velocities increased early in pregnancy by about 14% and 6%, respectively, with a subsequent decline to 4% and 10%, respectively, below non-pregnant levels.*

Conclusion *Left ventricular mass increases during pregnancy, while left ventricular diastolic function, as demonstrated by the changes in mitral valve flow velocities, increases in the first two trimesters but declines in the third trimester.*

INTRODUCTION

Pregnancy exerts a major strain on the maternal cardiovascular system. A series of adaptational mechanisms are activated from as early as 5 weeks of gestation[1] in order to maximize oxygen delivery to maternal and fetal tissues.

Maternal cardiovascular maladaptation is strongly correlated to pregnancy outcome. It has, for example, been demonstrated that maternal systolic function is altered in pregnancies that are complicated with pre-eclampsia from as early as 12 weeks of gestation. These pregnancies are characterized by a hyperdynamic circulation before the symptomatic phase of the disease and a subsequent depletion of the intravascular space coinciding with the onset of the clinical syndrome[2–4]. Furthermore, there is evidence that pregnancies complicated by intrauterine growth restriction are associated with impaired expansion of the maternal intravascular space and a lack of increase in cardiac output from 4 to 5 weeks of gestation[5]. It is thus evident that the study of maternal cardiovascular adaptation during pregnancy provides an insight into the interaction between maternal and fetal homeostasis and may prove a useful screening tool for pregnancy complications.

Although impairment of diastolic function of the left ventricle (LV) precedes systolic dysfunction in the evolution of most cardiac diseases[6,7] there is a scarcity of reports on diastolic function during pregnancy.

The aim of this study was to investigate the changes of LV diastolic function in singleton uncomplicated pregnancies.

METHODS

Patient selection

This was a cross-sectional study. One hundred and twenty-five pregnant women with singleton pregnancies at 9–42 weeks were examined once during their pregnancy and compared with 19 non-pregnant women in the first phase of their menstrual cycle. Gestational age was calculated from the maternal last menstrual period and was confirmed by first-trimester ultrasound. All subjects were healthy with a medical and family history free of cardiovascular disease. None of the non-pregnant controls was taking hormonal contraception and none of the pregnancies was complicated by pre-eclampsia, pregnancy-induced hypertension or gestational diabetes. There were no statistically significant differences in the demographic characteristics between the pregnant and control groups (Table 1). All women gave written informed consent. The study was approved by the research and ethics committee of King's College Hospital.

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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.

Study protocol

The patients were studied after a rest period of 15 min in the left lateral decubitus position in order to avoid the hemodynamic effects of the gravid uterus. Measurements were obtained when three consecutive electrocardiographic measurements of the heart rate demonstrated a variation of < 10%. A single examiner (N.K.) performed all measurements and for all parameters three cardiac cycles were averaged.

Blood pressure measurements were performed using an automated device (Spacelabs Medical 90207, WA, USA) validated in pregnancy and calibrated according to the recommendations of the British Hypertension Society[8]. Mean arterial pressure (MAP) was calculated from the equation:

$$MAP = (BP\ syst + (2 \times BP\ dias))/3,$$

where BP syst is systolic blood pressure and BP dias is diastolic blood pressure.

Two-dimensional and M-mode echocardiography were performed with a Powervision 7000 – SSA 380 (Toshiba Corporation, Tokyo, Japan) using a 3.5-MHz transducer.

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. Ejection time was measured from the opening to the closing artifact of the continuous-wave aortic signal.

Left ventricular and atrial dimensions were calculated according to the recommendations of the American Society of Echocardiography [9] 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 (ESV) and end-diastolic (EDV) volumes were estimated by the Teichholz formula[10] and the ejection fraction (EF) was calculated from the equation:

$$EF = 100 \times (EDV - ESV)/EDV.$$

This was a subsidiary measurement of systolic function for the purposes of comparison with the literature.

Left ventricular mass was calculated using the M-mode measurements by the formula of Devereux and Reichek and LV end-systolic meridian wall stress (ESSmerid) by the formula[11]:

$$ESSmerid = (1.35 \times BPsyst \times LVSD)/(4 \times LVPWS \times (1 + LVPWS)/LVSD),$$

where BPsyst is systolic blood pressure, LVSD is left ventricular end-systolic diameter and LVPWS is left ventricular posterior wall during systole.

Transmitral flow was assessed with pulsed wave Doppler from the apical four-chamber view. The sample volume was placed just above the mitral valve leaflets during diastole, and the peak flow velocities during early diastole (E-wave) and during atrial contraction (A-wave) were measured.

Statistical analysis

The Kolmogorov–Smirnov test was used to assess normality of the distribution of the data and univariate regression analysis was used to investigate the changes of each parameter with gestational age. Non-linear effects of the gestational age were investigated by including a quadratic term in the regression equation.

Unpaired *t*-tests were performed to examine the differences in the demographic and clinical characteristics between non-pregnant controls and pregnant women. The comparison between pregnant women and non-pregnant controls included only values obtained in the first two trimesters of pregnancy because this was the stage at which most of the indices of systolic function reached their maximum values and mean arterial pressure its nadir. The test for comparison of two proportions from independent groups was also used to examine the differences in the demographic characteristics between the two populations for the categorical data.

The coefficients of variation for the mitral valve E-wave and A-wave maximum velocities were 3.7% and 2.8%, respectively. The coefficients of variation for the left intraventricular septum during systole and diastole were 4.2% and 3.9%, respectively; for the LV posterior wall during systole and diastole they were 1.9% and 3.34%, respectively, and for the LV end-systolic and end-diastolic diameters they were 3.7% and 3.7%, 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 20 g in LV mass, 5 ms in mitral valve A-wave maximum velocity and 7 mm in left atrial diameter 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

The changes of the measured parameters with gestational age and the comparison of the values in the first two trimesters of pregnancy with non-pregnant controls are presented in Tables 2 and 3.

Changes during pregnancy

Changes with gestational age in the parameters from two-dimensional echocardiography have been described elsewhere in this issue of the Journal[12].

Table 2 Results of the multiple regression between pregnant women and non-pregnant controls

Parameter	*Regression Equation*	r^2	*P*
Left atrial diameter	$y = 26.2 + 0.76 \times ga - 0.009 \times ga^2$	0.37	< 0.0001
LV end-diastolic diameter	$y = 41.7 + 0.56 \times ga - 0.0087 \times ga^2$	0.11	0.001
LV end-systolic diameter	$y = 27.4 + 0.16 \times ga$	0.17	< 0.0001
Left intraventricular septum diameter during systole	$y = 8.95 + 0.05 \times ga$	0.11	< 0.0001
Left intraventricular septum diameter during diastole	$y = 5.9 + 0.03 \times ga$	0.12	< 0.0001
LV posterior wall diameter during systole	$y = 11.8 + 0.04 \times ga$	0.07	0.003
LV posterior wall diameter during diastole	$y = 6.3 + 0.02 \times ga$	0.07	0.003
LV mass	$y = 104.6 + 1.36 \times ga$	0.17	< 0.0001
LV end-systolic meridian wall stress	$y = 62.67 + 0.33 \times ga$	0.032	0.04
Mean arterial pressure	$y = 90.96 - 0.894 \times ga + 0.023 \times ga^2$	0.17	< 0.0001
Mitral valve E-wave maximum velocity	$y = 83.6 - 0.3 \times ga$	0.06	0.005
Mitral valve A-wave maximum velocity	$y = 42.55 + 0.32 \times ga$	0.03	0.08
Mitral valve E/A ratio	$y = 1.83 - 0.01 \times ga$	0.08	0.002

LV, left ventricular; ga, gestational age.

Table 3 Results of 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
Left atrial diameter (mm)	29.9 (4.2)	37.5 (4.26)	–7.0	< 0.0001
LV end-diastolic diameter (mm)	44.7 (3.1)	49.1 (3.9)	–5.2	< 0.0001
LV end-systolic diameter (mm)	28.5 (2.9)	30.3 (3.0)	–2.2	0.03
Left intraventricular septum during systole (mm)	9.22 (1.3)	9.91 (1.2)	–2.0	0.04
Left intraventricular septum during diastole (mm)	6.3 (0.7)	6.64 (0.8)	–1.5	0.1
LV posterior wall during systole (mm)	12.2 (1.2)	12.7 (1.3)	–1.6	0.1
LV posterior wall during diastole (mm)	7.1 (1.1)	6.6 (0.7)	1.7	0.09
LV mass (g)	106.5 (19.9)	131.1 (28.4)	–4.4	< 0.0001
LV end-systolic meridian wall stress (dyne/cm^2)	65.7 (11.8)	68.0 (15.7)	–0.7	0.47
Mitral valve E-wave maximum velocity (cm/s)	67.9 (14.2)	77.4 (10.5)	–2.6	0.01
Mitral valve A-wave maximum velocity (cm/s)	42.2 (5.7)	48.9 (8.9)	–3.9	< 0.0001
Mitral valve E/A ratio	1.61 (0.2)	1.62 (0.3)	–0.1	0.8

SD, standard deviation; LV, left ventricular.

The left atrial diameter (Table 2, Figure 1) and LV end-diastolic diameter (Table 2, Figure 1) increased with gestational age, reaching a peak at about 34 and 32 weeks, to levels of 40% and 12%, respectively, above non-pregnant controls.

The LV end-systolic diameter increased linearly with gestational age (Table 2, Figure 2) to levels 20% above non-pregnant controls, LV intraventricular septum diameter during systole (Table 2, Figure 2) and diastole (Table 2, Figure 1) to levels 19% and 15%, respectively, above non-pregnant controls, and LV posterior wall diameter during systole (Table 2, Figure 2) and diastole (Table 2, Figure 1) to levels 13% and 22%, respectively, above non-pregnant controls. The LV mass increased with gestational age (Table 2, Figure 3) to levels 52% above non-pregnant controls. The LV end-systolic meridian wall stress increased with gestational age (Table 2, Figure 3) to levels 17% above non-pregnant controls.

The mean arterial pressure decreased with gestational age (Table 2, Figure 3) to a nadir at about 20 weeks of 5% below non-pregnant controls and thereafter increased towards term to levels 8% above non-pregnant controls.

The mitral valve E-wave maximum velocity increased and subsequently decreased with gestational age (Table 2, Figure 4) to levels 3% above non-pregnant controls at term. The mitral valve A-wave maximum velocity did not change with gestational age (Table 2, Figure 4) but the values in pregnant women were higher than in non-pregnant controls (50.4 vs. 42.2; $t = -3.8$; $P < 0.0001$). The ratio of the E-wave and A-wave maximum velocities (E/A ratio) decreased with gestational age (Table 2, Figure 4).

Comparison with non-pregnant controls

In the first two trimesters (10–28 weeks) LV mass, LV end-diastolic and end-systolic diameters, LV intraventricular septum during systole and LV atrial diameter were higher in pregnant women than in non-pregnant controls by 23%, 9%, 6%, 7.5% and 25%, respectively (Table 3). Similarly, mitral valve E-wave and A-wave maximum velocities were higher in pregnant women than in non-pregnant controls by 14% and 15%, respectively (Table 3).

DISCUSSION

The results of this study demonstrate that LV mass increases during pregnancy by about 50%. Mitral valve A-wave maximum velocity increased with pregnancy, while mitral valve

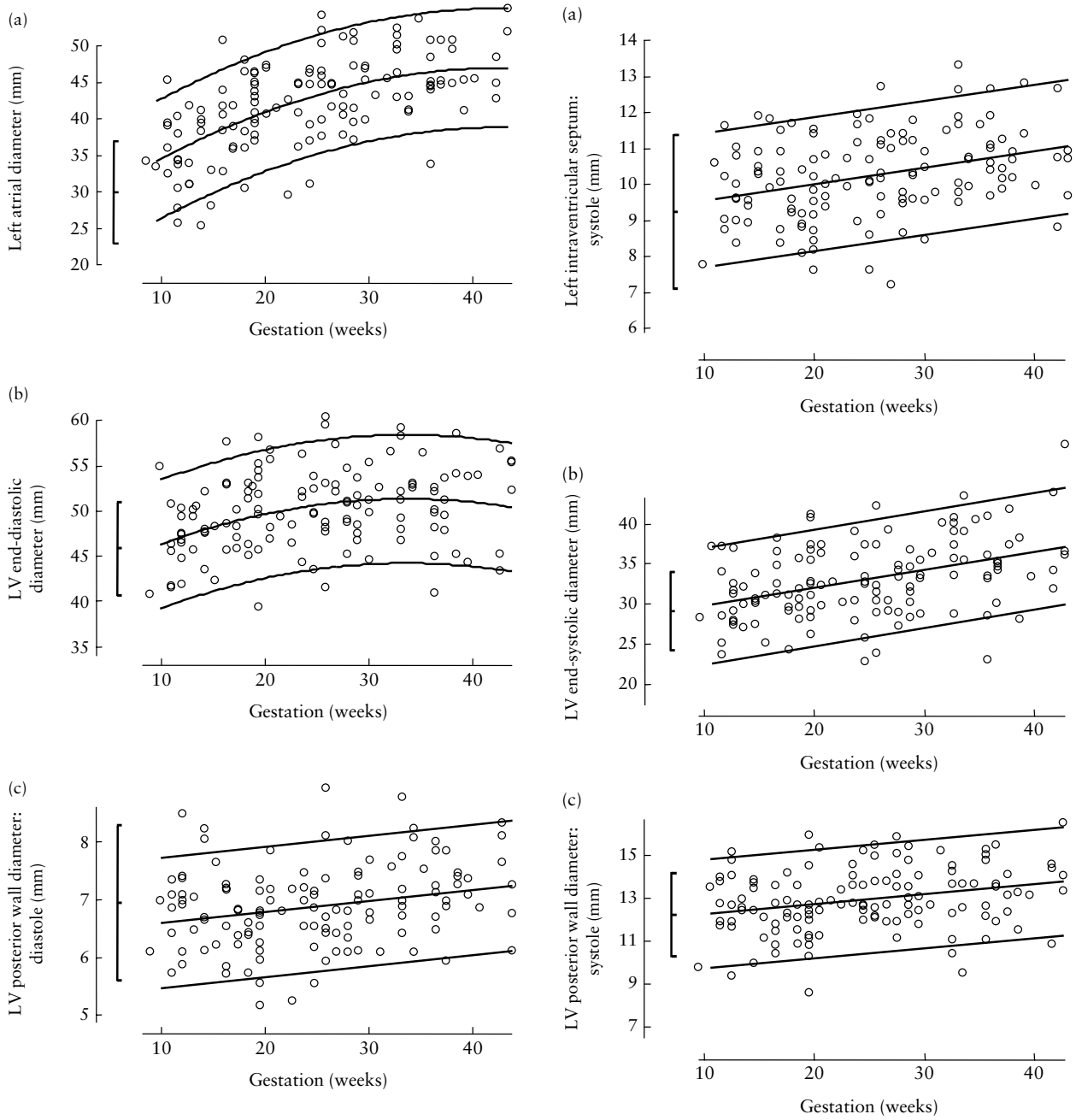

Figure 2 Changes in left intraventricular septum diameter during systole (a), left ventricular end-systolic diameter (b) and left ventricular posterior wall diameter during systole (c) with advancing gestation. Each graph illustrates the individual values of the pregnant women and the regression lines 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. LV, left ventricular.

Figure 1 Changes in left atrial diameter (a), left ventricular end-diastolic diameter (b), left ventricular posterior wall diameter during diastole (c) and left intraventricular septum diameter during diastole (d) with advancing gestation. Each graph illustrates the individual values of the pregnant women 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. LV, left ventricular.

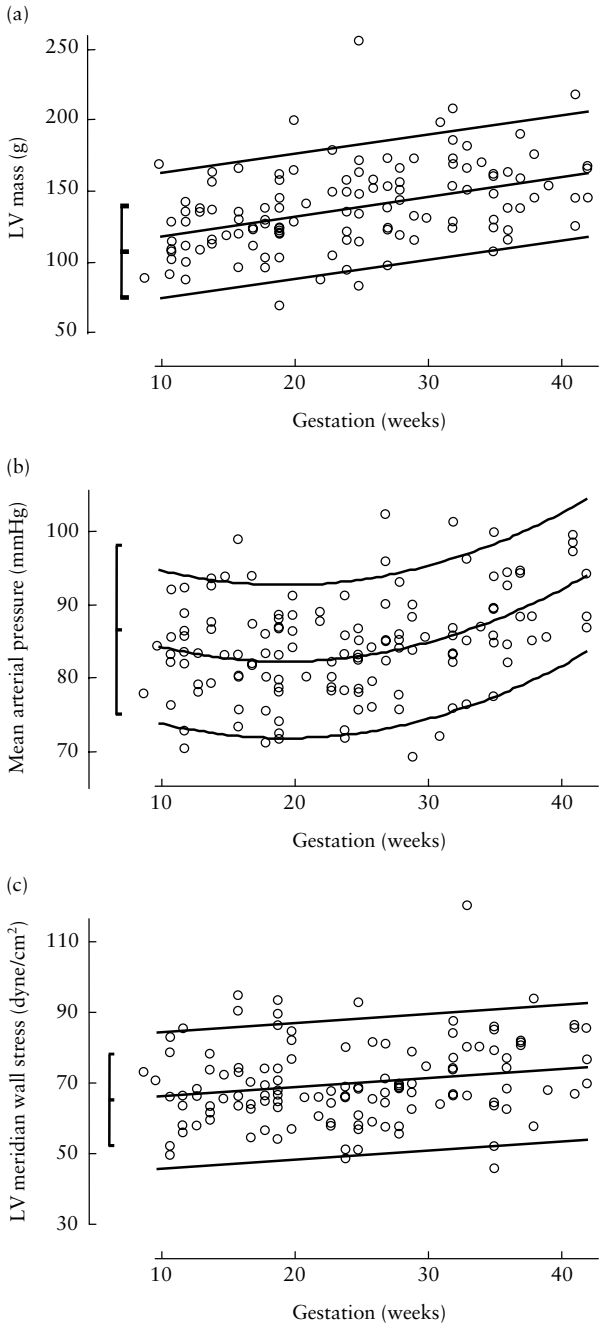

Figure 3 Changes in left ventricular mass (a), mean arterial pressure (b) and left ventricular meridian wall stress (c) with advancing gestation. Each graph illustrates the individual values of the pregnant women and the regression lines of the 5th, 50th and 95th centiles. The vertical line on the left of each graph illustrates the 5th, 50th and 95th centiles of the non-pregnant controls. LV, left ventricular.

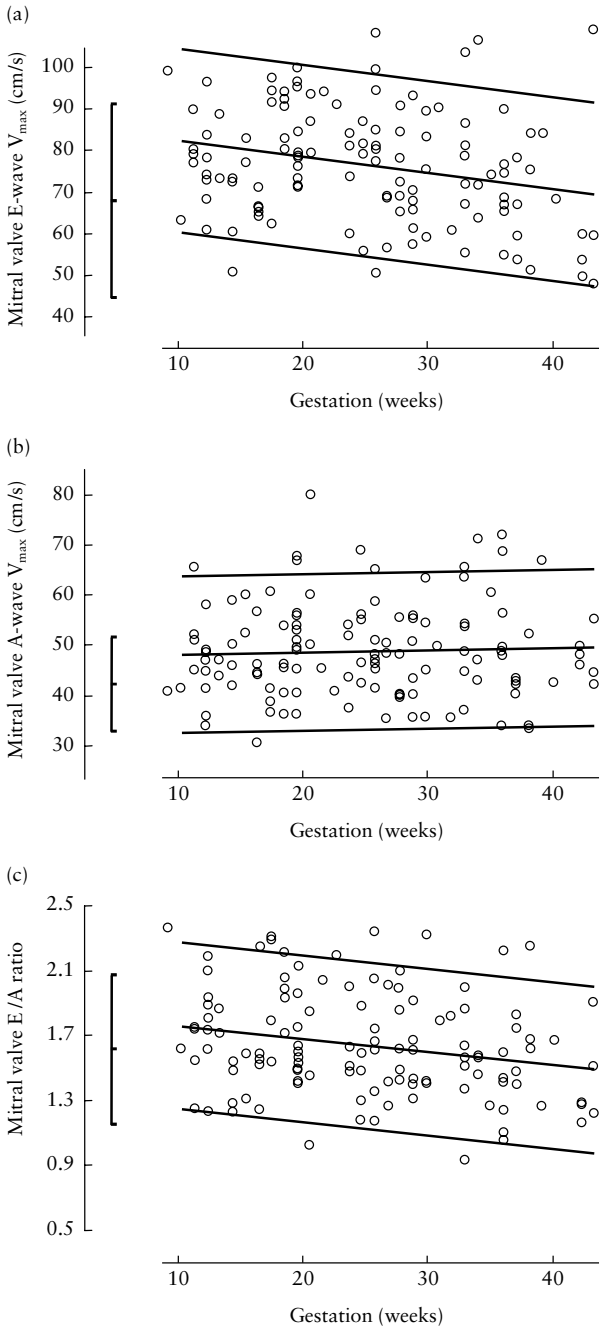

Figure 4 Changes in mitral valve E-wave (a) and A-wave (b) maximum velocities and mitral valve E/A ratio with advancing gestational age. Each graph illustrates the individual values of the pregnant women and the regression lines of the 5th, 50th and 95th centiles. The vertical line on the left of each graph illustrates the 5th, 50th and 95th centiles of the non-pregnant controls.

E-wave maximum velocity and the E/A ratio increased early in pregnancy, with a subsequent decline to below non-pregnant levels.

One of the most consistent findings in the literature is physiological myocardial hypertrophy during pregnancy[1,13–15]. The term physiological hypertrophy characterizes the reversible increase in LV mass as a compensatory mechanism to repetitive physical exertion. Physiological hypertrophy is a mechanism that aims to maintain cardiac output despite the chronically increased load on the LV. This could be due to increased blood volume (preload) or increased peripheral resistance (afterload) or both. In the first phase of increased load, the heart needs to generate more force and tension during systole, and there is therefore increased myocardial work and oxygen consumption. This increase in energy demand is

met initially by the increased utilization of fatty acids[16]. In later stages, the increased load on the LV augments further myocardial wall tension and stress. According to the law of Laplace the tension exerted on the myocardial wall is the product of the distending pressure and the radius of the curvature (Tension = pressure × radius/2)[17] and the myocardial wall stress is proportionate to the tension and inversely proportionate to the thickness of the myocardial wall[11]. Therefore, the second line of defence for the myocardium is to aim to reduce wall stress (and hence oxygen needs) by increasing wall thickness and reducing the radius of the curvature. This is achieved by the hypertrophy of the myocardium, i.e. the increase in myocardial cell size. The most important stimulus for myocardial hypertrophy is the stretching of the myocardial fibers, although other factors such as adrenaline, nor-adrenaline[16] thyroid hormones[16] angiotensin II[18] and the induction of immediate early genes (*c-fos*, *c-myc*)[19,20] can stimulate hypertrophic growth of the myocardium, irrespective of loading conditions or peripheral resistance. Unfortunately, LV hypertrophy is not concentrated only in myocytes but also in fibroblasts, which produce increased amounts of collagen that leads to structural remodeling of the cardiac interstitium and decreased myocardial compliance[15]. Thus, in long-term loading conditions there is an increase in LV myocardial rigidity and impaired diastolic function, which usually precedes systolic dysfunction. The former is progressively manifested as decreased LV compliance, increased end-diastolic pressure relative to diastolic volume, decreased rate of early diastolic filling and prolonged late filling phase and delayed relaxation[6]. Hence, impaired diastolic function leads to progressively shorter diastole and longer systole, which in turn causes less time for ventricular filling and coronary artery perfusion and a greater chance of the development of subendocardial ischemia.

Diastolic function, and hence resistance to filling of the LV, was assessed by the maximum velocity of the E-wave and A-wave of the transmitral flow. These reflect the pressure gradient between the left atrium and ventricle during diastole. An increase in venous return in the left atrium (preload) increases the maximum velocity of the E-wave[21] and the A-wave[6] while an increase in peripheral resistance (afterload) decreases the maximum velocity of the E-wave and increases the maximum velocity of the A-wave[21]. Therefore, the increase in E-wave maximum velocity early in the first two trimesters is consistent with the increased venous return in the left atrium (preload) and normal LV compliance. With advancing gestation, the decline in E-wave maximum velocity indicates a reduction in LV compliance due to the hypertrophied myocardium and an increase in peripheral resistance. The increase in A-wave maximum velocity during pregnancy is likely to be the result of the interplay between the increased mean arterial pressure and the increased heart rate and preload in the left atrium, and reflects the increase in work of the left atrium in order to maintain a sufficient pressure gradient for adequate LV filling[6]. Our results agree with those previously published by Valensise *et al.*[22]. They examined serially 43 pregnant women and demonstrated a reduction in E-wave maximum velocity, and in the E/A ratio during pregnancy and an increase in A-wave maximum velocity in the second trimester which remained stable thereafter. Similarly, Mesa *et al.*[15] examined 37 pregnant women and reported an increase in E-wave maximum velocity and in the E/A ratio during the first trimester, with the E/A ratio decreasing towards term. The A-wave maximum velocity also increased with pregnancy and, although values were higher in the third trimester, the differences between the three trimesters did not reach statistical significance. Mabie *et al.*[23] also concluded that diastolic function in pregnancy was affected by the increased preload and LV hypertrophy as demonstrated by the increase in A-wave maximum velocity and decline in the E/A ratio with advancing gestation.

The changes in LV wall thickness seen during pregnancy mimic the changes observed in another population that is characterized by a physiological hypertrophy of the LV: endurance athletes (e.g. long distance runners). In professional athletes, increases of 10%, 15%, 14% and 45% have been reported for LV end-diastolic diameter, LV posterior wall diameter and LV intraventricular septum diameter during diastole and LV mass, respectively,[24] which are very similar to the reported values observed during pregnancy[1,13–15] and confirmed in this study. Myocardial hypertrophy in athletes is a common finding and is symmetrical, with small variation between segments[24] and regression after the cessation of training activity[25]. There are thus similarities but also important differences between LV conditioning during pregnancy and during systematic exercise. During maximum endurance exercise, cardiac output is increased mainly as a result of increased stroke volume, since heart rate in athletes is not different from that in untrained individuals[26]. However, the ejection fraction and fractional shortening during exercise are not different from those in control populations[27] and diastolic function in athletes is not impaired, since peak early (E) and late (A) flow velocities and their ratio (E/A) have been shown to be similar in athletes compared to controls[28,29]. Moreover, there is some evidence that LV diastolic function might actually be enhanced during exercise in endurance athletes[27].

One of the potential reasons for these differences between endurance athletes and pregnant women is that systolic and diastolic blood pressure is reduced in athletes[26] while in pregnant women there is an increase of mean arterial pressure towards the third trimester[30]. The heart of pregnant women therefore functions in the first half of the pregnancy under conditions of increased preload and in the second half both under conditions of increased preload and progressively increasing afterload. It is therefore obvious that the heart in pregnancy hypertrophies initially as a result of increased preload, with a further strain during the third trimester caused from the increased peripheral resistance. Furthermore, the increased heart rate that characterizes pregnancy (as opposed to the reduced heart rate of athletes during rest and submaximal exercise) is a contributing factor to the shorter diastole and may add a further impairment to the oxygenation of the myocardium. The myocardium compresses the transmural branches of the coronary artery during LV contraction; consequently blood flow through the arteries that supply the subendocardial part of the myocardium occurs mainly during diastole[31,32]. Since diastole is of shorter

duration when the heart rate is increased, coronary blood flow is compromised in tachycardia[31].

Whether the observed differences in LV mass and diastolic function between endurance athletes and pregnant women are due to the fact that cardiovascular adaptation during pregnancy has to occur in a much shorter time interval than in athletes, and thus does not allow sufficient time for the myocardium to adjust slowly to the altered preload, afterload and heart rate, or whether they are due to the fact that in pregnancy there are no relaxation intervals (i.e. training and non-training periods), causing an additional challenge to the strained myocardium, remains to be further investigated.

Diastolic function of the LV appears affected during the third trimester of pregnancy by the simultaneity in increase of preload, afterload and heart rate. Further studies are needed to determine the cause and extent of this dysfunction in normal and complicated pregnancies, such as in cases of pre-eclampsia and peripartum cardiomyopathy.

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REFERENCES

1 Duvekot JJ, Cheriex EC, Pieters FA, Menheere PP, Peeters LH. Early pregnancy changes in hemodynamics and volume homeostasis are consecutive adjustments triggered by a primary fall in systemic vascular tone. *Am J Obstet Gynecol* 1993; 169: 1382–92
2 Easterling TR, Benedetti TJ, Schmucker BC, Millard SP. Maternal hemodynamics in normal and preeclamptic pregnancies: a longitudinal study [see comments]. *Obstet Gynecol* 1990; 76: 1061–9
3 Easterling TR, Benedetti TJ, Schmucker BC, Carlson K, Millard SP. Maternal hemodynamics and aortic diameter in normal and hypertensive pregnancies. *Obstet Gynecol* 1991; 78: 1073–7
4 Bosio PM, McKenna PJ, Conroy R, O'Herlihy C. Maternal central hemodynamics in hypertensive disorders of pregnancy. *Obstet Gynecol* 1999; 94: 978–84
5 Duvekot JJ, Cheriex EC, Pieters FA, Peeters LL. Severely impaired fetal growth is preceded by maternal hemodynamic maladaptation in very early pregnancy. *Acta Obstet Gynecol Scand* 1995; 74: 693–7
6 Yamamoto K, Redfield MM, Nishimura RA. Analysis of left ventricular diastolic function. *Heart* 1996; 75: 27–35
7 Hirota Y. A clinical study of left ventricular relaxation. *Circulation* 1980; 62: 756–63
8 O'Brien E, Petrie J, Littler W, de Swiet M, Padfield PL, Altman DG, Bland M, Coats A, Atkins N. The British Hypertension Society protocol for the evaluation of blood pressure measuring devices. *J Hypertens* 1993; 11 (Suppl. 2): S43–S62
9 Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978; 58: 1072–83
10 Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence or absence of asynergy. *Am J Cardiol* 1976; 37: 7–11
11 Feigenbaum H. *Echocardiography*, 5th edn. Philadelphia: Lee & Febiger, 1994
12 Kametas N, McAuliffe F, Cook B, Nicolaides KH, Chambers J. Maternal left ventricular transverse and long-axis systolic function during pregnancy. *Ultrasound Obstet Gynecol* 2001; 18: 467–74
13 Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Physiol* 1989; 256: H1060–5
14 Katz R, Karliner JS, Resnik R. Effects of a natural volume overload state (pregnancy) on left ventricular performance in normal human subjects. *Circulation* 1978; 58: 434–41
15 Mesa A, Jessurun C, Hernandez A , Adam K, Brown D, Vaughn WK, Wilansky S. Left ventricular diastolic function in normal human pregnancy. *Circulation* 1999; 99: 511–7
16 Piano MR. Cellular and signaling mechanisms of cardiac hypertrophy. *J Cardiovasc Nurs* 1994; 8: 1–26
17 Ganong WF. *Review of Medical Physiology*, 16th edn. London: Lange Medical Publications, 1993
18 Malhotra R, Sadoshima J, Brosius FC, Izumo S. Mechanical stretch and angiotensin II differentially upregulate the renin-angiotensin system in cardiac myocytes In vitro. *Circ Res* 1999; 85: 137–46
19 Simpson PC. Proto-oncogenes and cardiac hypertrophy. *Ann Rev Physiol* 1989; 51: 189–202
20 Sadoshima J, Takahashi T, Jahn L, Izumo S. Roles of mechano-sensitive ion channels, cytoskeleton, and contractile activity in stretch-induced immediate-early gene expression and hypertrophy of cardiac myocytes. *Proc Natl Acad Sci USA* 1992; 89: 9905–9
21 Nishimura R. Diastolic function by Doppler echocardiography. In: Chambers J, Monaghan MJ, eds. *Echocardiography, an International Review*. Oxford: Oxford University Press 1993: 11–22
22 Valensise H, Novelli GP, Vasapollo B, Borzi M, Arduini D, Galante A, Romanini C. Maternal cardiac systolic and diastolic function: relationship with uteroplacental resistances. A Doppler and echocardiographic longitudinal study. *Ultrasound Obstet Gynecol* 2000; 15: 487–97
23 Mabie WC, DiSessa TG, Crocker LG, Sibai BM, Arheart KL. A longitudinal study of cardiac output in normal human pregnancy. *Am J Obstet Gynecol* 1994; 170: 849–56
24 Shapiro LM. The morphologic consequences of systemic training. *Cardiol Clin* 1997; 15: 373–9
25 Ehsani AA, Spina RJ. Loss of cardiovascular adaptations after physical inactivity. *Cardiol Clin* 1997; 15: 431–8
26 Charlton GA, Crawford MH. Physiologic consequences of training. *Cardiol Clin* 1997; 15: 345–54
27 Fagard RH. Effect of training on left ventricular structure and functioning of the normotensive and the hypertensive subject. *Blood Press Monit* 1997; 2: 241–5
28 Missault L, Duprez D, Jordaens L, de Buyzere M, Bonny K, Adang L, Clement D. Cardiac anatomy and diastolic filling in professional road cyclists. *Eur J Appl Physiol Occup Physiol* 1993; 66: 405–8
29 Cuspidi C, Sampieri L, Boselli L, Angioni L, Bragato R, Leonetti G, Zanchetti A. Left ventricular diastolic function in athletes and borderline hypertensives with mild cardiac hypertrophy. *Cardiology* 1991; 78: 278–81
30 Reiss RE, Tizzano TP, O'Shaughnessy RW. The blood pressure course in primiparous pregnancy. A prospective study of 383 women. *J Reprod Med* 1987; 32: 523–6
31 Ganong W. *Review of medical physiology*, 17th edn. London: Prentice Hall International Inc, 1995
32 Downey JM, Downey HF, Kirk ES. Effects of myocardial strains on coronary blood flow. *Circ Res* 1974; 34: 286–9