Ultrasound Obstet Gynecol 2012; **39**: 430–437
Published online 12 March 2012 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.10089

Left ventricular midwall mechanics at 24 weeks' gestation in high-risk normotensive pregnant women: relationship to placenta-related complications of pregnancy

G. P. NOVELLI*, B. VASAPOLLO†‡, G. GAGLIARDI†, G. M. TIRALONGO†, I. PISANI†, D. MANFELLOTTO‡, L. GIANNINI§ and H. VALENSISE†

**Department of Cardiology, San Sebastiano Martire Hospital Frascati, Rome, Italy; †Department of Obstetrics and Gynecology, Tor Vergata University, Rome, Italy; ‡AFaR, Associazione Fatebenefratelli per la Ricerca, Fatebenefratelli Hospital Isola Tiberina, Rome, Italy; §Neonatal Intensive Care Unit, Policlinico Umberto I, La Sapienza University, Rome, Italy*

KEYWORDS: echocardiography; fetal growth restriction; hemodynamics; midwall mechanics; pre-eclampsia; pregnancy

ABSTRACT

Objectives *Most studies during pregnancy have assessed maternal left ventricular (LV) function by load-dependent indices, assessing only chamber function. The aim of this study was to assess afterload-adjusted LV myocardial and chamber systolic function at 24 weeks' gestation and 6 months postpartum in high-risk normotensive pregnant women.*

Methods *A group of 118 high-risk women with bilateral notching of the uterine arteries underwent an echocardiographic examination to evaluate midwall mechanics (midwall shortening (mFS%) and stress-corrected midwall shortening (SCmFS%)) of the LV at 24 weeks' gestation and 6 months postpartum. Patients were followed until delivery and pregnancies were classified retrospectively as uneventful (uncomplicated outcome) or complicated. A control group of 54 low-risk women with uneventful pregnancies without bilateral notching was also enrolled.*

Results *The pregnancy was uneventful in 74 (62.7%) women, whereas 44 (37.3%) developed complications. At 24 weeks' gestation, mFS% and SCmFS% were greater in the uncomplicated-outcome compared with the complicated-outcome group (25.9 ± 4.8 vs $18.8 \pm 5.0\%$, $P < 0.001$ and 107.9 ± 18.4 vs $77.9 \pm 20.7\%$, $P < 0.001$, respectively). At 6 months postpartum, SCmFS% remained greater in the uncomplicated-outcome compared with the complicated-outcome group (100.4 ± 21.6 vs 87.8 ± 19.1, $P < 0.05$). In the uncomplicated-outcome group, SCmFS% was higher during pregnancy than it was postpartum, whereas in the complicated-outcome group, it was lower during pregnancy than it was postpartum ($P < 0.05$).*

Conclusions *Maternal cardiac midwall mechanics appear to be enhanced (SCmFS% increased compared with controls) during pregnancy compared with postpartum in high-risk patients with uncomplicated pregnancy, whereas midwall mechanics are depressed both during pregnancy and postpartum in patients with pregnancy complications.*

INTRODUCTION

Bilateral notching of the uterine arteries has been used extensively as a screening tool to identify patients at risk for complications in pregnancy and to predict the later development of pre-eclampsia, fetal growth restriction (FGR), placental abruption and stillbirth[1–5]. Nevertheless, this screening test has high negative (97–99%) and low positive (25–30%) predictive values[1–12]. Recently, echocardiography in patients with notching of the uterine arteries has been used to determine maternal left ventricular (LV) morphological parameters and systemic vascular resistance (SVR), an index of LV afterload, which have been found reliable in the identification of pregnancies subsequently developing severe complications[13–15]. In fact, patients with bilateral notching of the uterine arteries and subsequent complications might show altered LV geometry and a hypertrophied heart, even in the presence of normal blood pressure (BP) levels, whereas patients with subsequently uncomplicated pregnancies mainly show normal geometry of the LV[13–15]. Since hypertrophy and geometric alterations of the LV might influence myocardial function[14–17], it seems reasonable to speculate that midwall mechanics might differ in these two types of patients. Moreover, it is not known if

Correspondence to: Dr G. P. Novelli, Department of Cardiology, San Sebastiano Martire Hospital, Via Tuscolana 2, 00044-Frascati, Rome, Italy (e-mail: bgp.novelli@tiscali.it)

Accepted: 15 August 2011

normotensive women with uncomplicated pregnancies have different myocardial performance according to the presence or absence of bilateral notching of the uterine arteries.

Most studies during pregnancy have assessed cardiac function by the most common echocardiographic parameters (including: LV cardiac output (CO, quantity of blood ejected per min); LV stroke volume (SV, quantity of blood ejected per beat); LV fractional shortening (FS%, at the endocardial level, an index of LV chamber function); and systolic long-axis function), using load-dependent indices and assessing only LV chamber function[14–20]. Very little is known about LV systolic functional indices adjusted for the afterload (end-systolic stress) and midwall mechanics during pregnancy[21], and no data are available on midwall mechanics before pregnancy complications or postpartum in normotensive primigravidae with bilateral notching of the uterine arteries. We therefore conducted a prospective study in asymptomatic normotensive high-risk (bilateral notching of the uterine arteries) nulliparous women to assess midwall mechanics at 24 weeks' gestation, and 6 months postpartum, comparing the data with those of a control group of normotensive nulliparous women with normal adaptation of the uteroplacental circulation (absence of notching of the uterine arteries) and a physiological pregnancy.

METHODS

Patient selection

Between 2004 and 2010 we recruited 118 consecutive white Caucasian asymptomatic nulliparous women with singleton pregnancies and bilateral notching of the uterine arteries at 24 weeks' gestation, referred to the outpatient clinic of Tor Vergata University. A control group of 54 normotensive nulliparous women with singleton pregnancies and with normal uterine artery Doppler parameters matched for age and gestational age was also enrolled during the same period (see supplementary Figure S1).

Inclusion criteria were: 1) normal BP values at enrolment and 6 months after delivery; 2) absence of proteinuria on routine urinalysis and normal renal and liver function test on blood chemistry panel (specifically, BUN (blood urea nitrogen), creatinine and liver enzymes); 3) estimated fetal weight > 10th percentile; 4) normal fetal Doppler parameters and amniotic fluid index. Exclusion criteria were: 1) undetermined gestational age; 2) tobacco use; 3) twin pregnancy; 4) maternal heart disease; 5) pre-existing maternal chronic medical problem; 6) chromosomal abnormalities and/or fetal abnormalities suspected on ultrasound; 7) use of medication other than iron supplements; 8) pregnancy achieved by assisted reproductive techniques. Approval of the local ethics committee was obtained, as was written informed consent from all patients.

Patients were followed until term. Gestational hypertension was diagnosed according to the definition of Davey and MacGillivray[22]. FGR was diagnosed when birth weight was < 10th centile for gestational age of the reference population[23] and a cessation or slowing of fetal growth was present, associated with Doppler indicators of fetal deterioration (abnormal ductus venosus and umbilical artery flow)[15].

Uterine artery ultrasound examination

Uterine artery Doppler examinations were performed using a Toshiba Xario (Toshiba Medical Systems Corp, Tochigi, Japan) or Technos Esaote (Esaote Biomedica, Genova, Italy) ultrasound machine equipped with a 3.5-MHz sector transducer, with the high pass filter set at 100 Hz. All patients underwent uterine artery color Doppler examination at 24 weeks' gestation as described previously[12,13,24,25]. Bilateral notching of the uterine arteries was noted.

Echocardiographic evaluation

Within 24 hours from the diagnosis of bilateral notching, M-mode, two-dimensional and Doppler echocardiographic investigation was performed by one of two different operators (G.P.N. and H.V.), to evaluate maternal hemodynamics including SVR and systolic and morphologic parameters of the LV. The echocardiographic examinations were performed, with the patient in a lateral position, using a commercially available echocardiographic machine (Toshiba Xario or Philips ie33 (Philips, Andover, MA, USA)), equipped with a 1.8–3.6-MHz transducer in harmonic imaging mode, according to the recommendation of the American Society of Echocardiography[26] as described previously[26–28] (see extended echocardiographic method in supplementary Appendix S1). Three consecutive cardiac cycles were measured, and average values were obtained.

Hemodynamic parameters

SV and CO were calculated as described previously[13–15,25]. At the end of the maternal echocardiographic examination, systolic and diastolic BP (SBP and DBP, respectively) were measured using a mercury sphygmomanometer with the woman in a seated position, with her arm at heart level and her feet supported or on the ground. Korotkoff phase V was used for the determination of DBP. SVR was calculated in dynes × s/cm^5 as described previously (Appendix S1).

Parameters of left ventricular (LV) systolic performance

FS% and circumferential end-systolic stress (cESS, an index of LV afterload) at the midwall were calculated from the M-mode measurements (Appendix S1).

Midwall mechanics were evaluated as described by Mayet *et al.*[29] and de Simone *et al.*[30–32], both as an absolute value of midwall shortening (mFS%, an index of LV afterload) and as a percentage (stress corrected, SCmFS%, an index of midwall mechanics adjusted for LV afterload) of the value predicted (expected mFS%) from the corresponding cESS (Appendix S1). To calculate the expected mFS%, a regression equation was developed from the data of the 54 controls at 6 months postpartum (supplementary Figure S2).

Outcomes

Patients with notching of the uterine arteries were classified retrospectively as having uncomplicated or complicated outcome (see supplementary Figure S1). The gestation was followed until term by an investigator who was blinded to the results of maternal echocardiography, and pregnancy was classified as complicated when one or more of the following adverse maternal, fetal and neonatal outcomes occurred: severe gestational hypertension (SBP > 160 mmHg and/or DBP > 110 mmHg)[33] with preterm delivery < 34 weeks; pre-eclampsia (proteinuria > 300 mg/24 h associated with gestational hypertension)[34]; placental abruption; other maternal complications (thrombocytopenia, elevated liver enzymes, HELLP syndrome, coagulation abnormalities); FGR; admission to neonatal intensive care unit due to fetal distress; perinatal death.

Postpartum follow-up

All patients underwent a clinical and an echocardiographic examination 6 months after delivery, performed by two operators (G.P.N. and H.V.) who were blinded to the outcome of pregnancy, in order to assess maternal SVR and LV functional and morphologic parameters.

Statistical analysis

Values are expressed as mean ± SD. Comparisons among groups were performed using one-way ANOVA with Student-Newman Keuls correction for multiple comparisons, whereas the intragroup comparison between pregnancy and postpartum data was performed using ANOVA for repeated measurements. The Mann–Whitney *U*-test was used for non-normally distributed data.

Since previous reports have shown LV relative wall thickness (RWT, ratio between diastolic wall thickness and LV diameter) and SVR to be independent predictors of complications in pregnancy[14,15], we tested the predictive power of FS%, mFS% and SCmFS% along with RWT and SVR. DBP and mean BP (MBP) were included in the univariate and stepwise logistic regression analysis, as increased BP is known to increase the risk of adverse outcome as well as to impair cardiac function. Receiver–operating characteristics (ROC) curves were constructed to find the cut-off value for the prediction of subsequent pregnancy complications for the following parameters at 24 weeks' gestation: SVR, FS%, mFS%, SCmFS%, SBP and MBP. The parameters were dichotomized according to the cut-off value found on ROC curve analysis, and univariate and multivariate stepwise regression logistic analysis was performed to identify independent predictors of complications.

Inter- and intraobserver variability of the echocardiographic measurements are reported in supplementary Appendix S2.

RESULTS

The main features at enrolment of the 54 controls and the 118 patients with bilateral notching of the uterine arteries who comprised the study population, divided according to uncomplicated ($n = 74$) or complicated ($n = 44$) outcome, are reported in Table 1. Maternal age was not significantly different between the controls and the patients with notching (32 ± 5 vs 33 ± 5 years), but was slightly higher in those with complicated outcome. Gestational age at delivery and birth-weight percentile were lower in the complicated pregnancies compared with the uncomplicated ones and with controls. Forty-four of 118 (37.3%) patients developed maternal and/or fetal complications (supplementary Table S1).

Hemodynamic and left ventricular morphological parameters

Table 2 shows the main hemodynamic and LV morphological features in controls and patients with uncomplicated and complicated outcome at 24 weeks' gestation and 6 months postpartum. In the intergroup comparison at 24 weeks, patients with complicated outcome showed, among other differences, higher SVR and RWT and lower

Table 1 Main characteristics of pregnancies in 118 high-risk women with bilateral notching of the uterine arteries with uncomplicated or complicated outcome and in 54 controls with normal uterine artery Doppler and normal pregnancy

Characteristic	*Controls (n = 54)*	*Uncomplicated outcome (n = 74)*	*Complicated outcome (n = 44)*	P*
Maternal age (years)	32 ± 5	31 ± 5	34 ± 3	< 0.05
Maternal height (m)	1.64 ± 0.05	1.65 ± 0.07	1.63 ± 0.06	NS
Maternal prepregnancy BMI (kg/m^2)	23 ± 3	24 ± 2	24 ± 2	NS
GA at delivery (weeks)	39 ± 1	38 ± 1	33 ± 4	< 0.05
Birth-weight centile	43 ± 23	44 ± 21	18 ± 4	< 0.05

Data are given as mean ± SD. *Complicated outcome vs controls and vs uncomplicated outcome. BMI, body mass index; GA, gestational age; NS, not significant.

Table 2 Main hemodynamic and echocardiographic features at 24 weeks' gestation and 6 months postpartum in 118 high-risk women with bilateral notching of the uterine arteries and uncomplicated or complicated outcome and in 54 controls with normal uterine artery Doppler and normal development of pregnancy

Parameter	*Controls* (n = *54)*	P†	*Uncomplicated outcome* (n = *74)*	P‡	*Complicated outcome* (n = *44)*	P§
24 weeks' gestation						
Heart rate (bpm)	84 ± 11	NS	83 ± 12	< 0.01	75 ± 15	< 0.01
Systolic BP (mmHg)	115 ± 11	NS	116 ± 10	NS	116 ± 17	NS
Diastolic BP (mmHg)	61 ± 9	NS	62 ± 9	< 0.001	68 ± 11	< 0.001
MBP (mmHg)	79 ± 7	NS	80 ± 7	< 0.01	85 ± 10	< 0.01
LVDd (cm)	4.91 ± 0.35	NS	4.90 ± 0.37	< 0.001	4.57 ± 0.31	< 0.001
LVDs (cm)	2.78 ± 0.41	NS	2.76 ± 0.41	NS	2.85 ± 0.36	NS
IVSd (cm)	0.80 ± 0.11	NS	0.79 ± 0.11	< 0.001	0.91 ± 0.12	< 0.001
PWd (cm)	0.76 ± 0.12	NS	0.76 ± 0.12	< 0.001	0.87 ± 0.13	< 0.001
PWs (cm)	1.51 ± 0.15	NS	1.44 ± 0.12	< 0.001	1.58 ± 0.25	< 0.001
LVMi (g/m$^{2.7}$)	34 ± 8	NS	33 ± 8	< 0.05	37 ± 9	NS
RWT	0.32 ± 0.06	NS	0.32 ± 0.06	< 0.001	0.39 ± 0.05	< 0.001
EF (%) (biplane Simpson)	66 ± 8	NS	68 ± 9	< 0.05	62 ± 4	< 0.05
Stroke volume (mL)	83 ± 13	NS	82 ± 14	< 0.001	66 ± 11	< 0.001
Cardiac output (L/min)	6.86 ± 1.01	NS	6.81 ± 1.23	< 0.001	4.96 ± 1.49	< 0.001
SVR (dynes × s/cm^5)	945 ± 168	NS	964 ± 192	< 0.001	1463 ± 363	< 0.001
6 months postpartum						
Heart rate (bpm)	72 ± 8***	NS	73 ± 8***	NS	71 ± 11	NS
Systolic BP (mmHg)	120 ± 11*	NS	117 ± 12	NS	122 ± 10	NS
Diastolic BP (mmHg)	66 ± 11*	NS	64 ± 12	< 0.05	71 ± 13	< 0.05
MBP (mmHg)	84 ± 9**	NS	82 ± 10	< 0.01	88 ± 10	< 0.01
LVDd (cm)	4.56 ± 0.23***	NS	4.55 ± 0.23***	NS	4.59 ± 0.31	NS
LVDs (cm)	2.65 ± 0.21*	NS	2.62 ± 0.26*	NS	2.66 ± 0.28*	NS
IVSd (cm)	0.72 ± 0.10***	NS	0.73 ± 0.10***	< 0.01	0.78 ± 0.10***	< 0.01
PWd (cm)	0.67 ± 0.12***	NS	0.67 ± 0.12***	< 0.001	0.76 ± 0.11***	< 0.001
PWs (cm)	1.33 ± 0.08***	< 0.001	1.37 ± 0.10***	< 0.001	1.54 ± 0.15	< 0.001
LVMi (g/m$^{2.7}$)	26 ± 6***	NS	26 ± 6***	< 0.001	30 ± 7***	< 0.001
RWT	0.30 ± 0.05	NS	0.31 ± 0.05	< 0.05	0.34 ± 0.06***	< 0.05
EF (%) (biplane Simpson)	65 ± 8	NS	64 ± 8	NS	65 ± 7	NS
Stroke volume (mL)	71 ± 9***	NS	71 ± 8***	NS	71 ± 13*	NS
Cardiac output (L/min)	5.13 ± 0.77	NS	5.17 ± 0.75***	NS	5.07 ± 1.32	NS
SVR (dynes × s/cm^5)	1334 ± 242***	NS	1297 ± 261***	< 0.05	1449 ± 299	< 0.05

Data given as mean ± SD. *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ for intragroup comparison (24 weeks vs 6 months postpartum). †Controls vs uncomplicated outcome. ‡Uncomplicated outcome vs complicated outcome. §Controls vs complicated outcome. BP, blood pressure; EF%, ejection fraction of the left ventricle, percentage of reduction of the left ventricular volume from diastole to systole; IVSd, interventricular septal thickness in diastole from M-mode tracing; LVDd, left ventricular end-diastolic diameter from M-mode tracing; LVDs, left ventricular end-systolic diameter from M-mode tracing; LVMi, left ventricular mass index; MBP, mean blood pressure; PWd, left ventricular posterior wall thickness in diastole from M-mode tracing; PWs, left ventricular posterior wall thickness in systole from M-mode tracing; RWT, relative wall thickness of the left ventricle, ratio between the diastolic wall thickness and the left ventricular diameter; SVR, systemic vascular resistance, index of left ventricular afterload.

CO, SV and HR compared to patients with uncomplicated outcome and to controls. The intergroup comparison 6 months postpartum showed, among other differences, that LVMi, DBP and MBP were higher in the complicated compared to the uncomplicated outcome group and the controls; SVR was slightly higher.

The intragroup comparison in the controls and in the uncomplicated outcome group found, among other differences, lower SVR and higher CO, SV, LVMi and HR at 24 weeks compared with 6 months postpartum. In the complicated outcome group, LVMi was greater and SV lower at 24 weeks' gestation compared with 6 months postpartum.

Parameters of left ventricular systolic performance

The parameters of LV systolic performance are shown in Table 3. The intergroup comparison at 24 weeks showed that the patients with complicated outcome had lower FS%, mFS% and SCmFS% compared to the patients with uncomplicated outcome and to controls. In particular, at 24 weeks' gestation mean SCmFS% was 22.5% lower in those with complicated outcome compared to controls and 30% lower compared to patients with uncomplicated outcome. The patients with uncomplicated outcome had significantly higher SCmFS% (+7.5%) compared to controls. At 6 months postpartum the patients with complicated outcome had lower cESS and SCmFS% compared to patients with uncomplicated outcome and to controls.

The intragroup comparison showed that controls had a lower cESS at 24 weeks' gestation compared with postpartum, whereas FS%, mFS% and SCmFS% were unchanged. Patients with uncomplicated outcome had a higher SCmFS% at 24 weeks' gestation compared with 6 months postpartum (+7.5%). Patients with complicated

Table 3 Main left ventricular chamber function and midwall mechanics at 24 weeks' gestation and 6 months postpartum in 118 high-risk women with bilateral notching of the uterine arteries and uncomplicated or complicated outcome and in 54 controls with normal uterine artery Doppler and normal development of pregnancy

Parameter	*Controls* (n = 54)	P†	*Uncomplicated outcome* (n = 74)	P‡	*Complicated outcome* (n = 44)	P§
24 weeks' gestation						
FS%	43.6 ± 6.1	NS	43.8 ± 6.1	< 0.001	37.6 ± 6.4	< 0.001
mFS%	24.6 ± 4.8	NS	25.9 ± 4.8	< 0.001	18.8 ± 5.0	< 0.001
cESS (dynes/m^2)	98 ± 22	NS	102 ± 22	NS	102 ± 28	NS
Expected mFS%	24.6 ± 2.3	NS	24.1 ± 2.3	NS	24.3 ± 3.1	NS
SCmFS%	100.4 ± 18.5	< 0.001	107.9 ± 18.4	< 0.001	77.9 ± 20.7	< 0.001
6 months postpartum						
FS%	41.8 ± 4.7	NS	42.4 ± 6.0	NS	42.2 ± 4.8***	NS
mFS%	23.4 ± 4.4	NS	23.9 ± 5.7**	NS	21.6 ± 4.6**	NS
cESS (dynes/m^2)	108 ± 16**	NS	104 ± 17	< 0.01	96 ± 15	< 0.01
Expected mFS%	23.4 ± 1.7**	NS	23.8 ± 1.8	< 0.01	24.7 ± 1.7	< 0.01
SCmFS%	100.0 ± 17.7	NS	100.4 ± 21.6**	< 0.05	87.8 ± 19.1*	< 0.05

Data given as mean ± SD. *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ for intragroup comparison (24 weeks vs 6 months postpartum). †Controls vs uncomplicated outcome. ‡Uncomplicated outcome vs complicated outcome. §Controls vs complicated outcome. cESS, circumferential end-systolic stress of left ventricle (LV) (index of LV afterload); FS%, fractional shortening of LV at endocardial level (index of LV chamber function); Expected mFS%, expected midwall fractional shortening from corresponding cESS; mFS%, midwall fractional shortening at midwall level (index of midwall mechanics of LV); SCmFS%, stress-corrected midwall fractional shortening (index of midwall mechanics adjusted for afterload of LV).

Table 4 Cut-off values identified by receiver–operating characteristics curves for prediction of subsequent pregnancy complications in 118 high-risk women with bilateral notching of the uterine arteries

Cut-off	*Sensitivity* (%)	*Specificity* (%)
Diastolic blood pressure > 60 mmHg	65.9	59.5
Mean blood pressure > 86.7 mmHg	45.5	89.2
Fractional shortening ≤ 40%	70.5	75.7
Midwall fractional shortening ≤ 22%	79.5	77.0
Stress-corrected midwall fractional shortening ≤ 95%	86.4	75.7
Relative wall thickness > 0.36	75.0	82.4
Systemic vascular resistance > 1349 dynes × s/cm^5	81.8	97.3

outcome had a lower FS%, mFS% and SCmFS% at 24 weeks' gestation vs 6 months postpartum.

Predictors of complications

The cut-off values identified by the ROC curves for the prediction of subsequent pregnancy complications are presented in Table 4, while Table 5 shows univariate and multivariate stepwise logistic regression analysis for the prediction of pregnancy complications for these cut-offs in the 118 patients with bilateral notching of the uterine arteries. SCmFS% appears to be an independent predictor of complications along with DBP, SVR and RWT.

Table 5 Univariate and multivariate stepwise binary logistic regression analysis for prediction of complications in 118 high-risk women with bilateral notching of the uterine arteries

Variable	*Odds ratio (95% CI)*
Univariate binary logistic regression analysis	
Diastolic blood pressure > 60 mmHg	0.6 (0.2–1.4)
Mean blood pressure > 86.7 mmHg	3.9 (1.7–9.1)*
Fractional shortening ≤ 40%	7.4 (3.2–17.4)*
Midwall fractional shortening ≤ 22%	13.0 (5.2–32.4)*
Stress-corrected midwall fractional shortening ≤ 95%	19.7 (7.2–54.2)*
Relative wall thickness > 0.36	14.1 (5.7–34.9)*
Systemic vascular resistance > 1349 dynes × s/cm^5	162.0 (32.7–802.7)*
Stepwise binary logistic regression analysis	
Diastolic blood pressure > 60 mmHg	8.1 (1.1–62.7)*
Stress-corrected midwall fractional shortening ≤ 95%	7.6 (1.3–44.5)*
Relative wall thickness > 0.36	24.9 (3.7–169.9)*
Systemic vascular resistance > 1349 dynes × s/cm^5	264.0 (22.0–3173.9)*

*$P < 0.05$.

DISCUSSION

This study suggests that, at 24 weeks' gestation, normotensive women have three different midwall mechanics patterns according to the subsequent development of pregnancy and uterine artery flow characteristics (see supplementary Figure S3):

1) myocardial function is impaired (SCmFS%, −22.5% vs controls) in patients with bilateral notching of the uterine arteries and a complicated outcome of pregnancy;
2) myocardial function is enhanced (SCmFS%, +7.5% vs controls) in patients with bilateral notching of the uterine arteries and an uncomplicated outcome of pregnancy;
3) myocardial function is unchanged compared with postpartum in women with a normal uterine artery Doppler flow pattern and normal pregnancy.

Patients with a complicated outcome of pregnancy still had depressed myocardial function 6 months postpartum (SCmFS% −12.2% vs controls and −12.6% vs patients with uncomplicated outcome).

A limitation of our study is related to the incomplete echocardiographic assessment, lacking investigation of LV diastolic chamber and longitudinal systolic function.

Hemodynamic and left ventricular morphological parameters

This study confirms previous observations[15] showing that, at 24 weeks' gestation, normotensive women who develop complications later in pregnancy have a more concentric shape of the LV (higher LVMi and RWT) and a substantially different hemodynamic pattern (higher SVR and lower CO, SV and HR) compared to normotensive women with an uncomplicated outcome. These hemodynamic and LV morphological characteristics of women who developed complications are also consistent with a volume underload, described previously in gestational hypertensive women who develop complications[14,25]. This volume underload might explain why patients with a complicated outcome show smaller LV dimensions and lower SV compared with women with a normal evolution of pregnancy.

Interestingly, in women with subsequent complications, the differences in the hemodynamics (higher SVR, DBP and MBP) and the LV geometry (higher LVMi and RWT) persist 6 months postpartum vs controls and women with an uncomplicated outcome.

LV systolic performance

The novel findings of this study are related to midwall mechanics. The patients with complicated outcome had depressed myocardial performance both prior to the development of complications (lower FS%, mFS% and SCmFS%) and postpartum (lower cESS and SCmFS%) compared to patients with uncomplicated outcome and to controls. At 24 weeks' gestation, the midwall mechanics (SCmFS%) were lower in patients with complicated outcome, by about 23% compared to controls and about 30% compared to patients with uncomplicated outcome. The impairment of midwall mechanics might be explained in part by the relationships existing between hemodynamic parameters and midwall mechanics. Previous reports have shown that the more hypertrophied is the ventricle, the more depressed is the myocardial function[29,35,36], whereas a reduction of SVR enhances midwall mechanics[37]. Since the group of patients with subsequent complications showed a hypertrophied ventricle and high SVR (which remained unchanged postpartum), the overall effect will have been determined by the increased LV mass not being balanced by a reduction of SVR, resulting in a reduction of midwall mechanics during pregnancy. These findings also suggest that LV remodelling, as indicated by the increased RWT, during complicated pregnancy is not sufficient to maintain normal LV mechanics.

In controls (absence of bilateral notching of the uterine arteries) at 24 weeks' gestation, the equilibrium reached by the reduction of SVR and the increment of LVMi maintained midwall mechanics so that they were unchanged postpartum.

In contrast, in patients with bilateral notching of the uterine arteries and uncomplicated pregnancy, myocardial function was surprisingly enhanced (increased SCmFS%) during pregnancy, both compared with controls and relative to postpartum findings. This is interesting and difficult to explain. In these patients, myocardial mass, LV wall thickness and peripheral resistance did not differ from those of controls, while SCmFS% was higher than that of controls by about 7%. We hypothesize that in these patients with impaired placentation (indicated by the notching of the uterine artery waveform), the enhancement of myocardial function might be crucial to maintain normal hemodynamic parameters (SVR) and, therefore, to an uncomplicated outcome of pregnancy.

Predictors of complications

Previous reports[14,15,25] have highlighted the importance of hemodynamic and morphological aspects of the maternal heart in predicting complications. Our study shows that, along with SVR and RWT, impaired midwall mechanics (SCmFS% $\leq$ 95%) also have a role to play in the prediction of complications. The development of complications is therefore caused by a global impairment of the maternal cardiovascular system, involving LV morphological, mechanical and hemodynamic aspects.

In the patients with complicated outcome, by 6 months postpartum the chamber function (FS%) had returned to normal levels and midwall mechanics (mFS% and SCmFS%) had increased (probably due to the reduction of RWT and LVMi), but remained lower compared to women with an uncomplicated outcome of pregnancy and to controls. This behavior of midwall mechanics is probably linked to the higher LV mass and wall thickness still present at 6 months postpartum compared to controls and to the uncomplicated outcome group. This difference between LV chamber function and midwall mechanics highlights a persisting subclinical impairment of systolic function after pregnancy. The question that arises is whether the impairment of midwall mechanics after a complicated pregnancy is pregestational or a memory of the cardiovascular maladaptation during the pregnancy. Although we cannot answer this question, requiring pregestational studies and long-term follow-up, we might consider, as elements for future discussion and research, that: a) pregnancy is a stress test for the cardiovascular system; and b) patients with hypertensive complications during pregnancy might show persisting differences in cardiac function many years after recovery from pre-eclampsia[38] and are at increased risk for future cardiovascular events[39,40]. It is possible that pregnancy reveals a pregestational predisposition to cardiovascular disease.

Conclusion

The importance of studying LV midwall mechanics resides in their ability to identify patients with subclinical impaired cardiac function. In fact, LV diastolic abnormalities are predicted by LV midwall dysfunction but not by LV systolic chamber function[41,42]. This study highlights the role of midwall mechanics during pregnancy.

In particular, we found that at 24 weeks' gestation, midwall mechanics are impaired in normotensive patients who develop pregnancy complications, in the presence of normal BP values and prior to the development of complications. This impairment persists at 6 months postpartum. The implications of the persisting alteration of midwall mechanics after pregnancy might change the preventive approach to cardiovascular events later in these women's lives.

REFERENCES

1. Harrington K, Cooper D, Lees C, Hecher K, Campbell S. Doppler ultrasound of the uterine arteries: the importance of bilateral notching in the prediction of pre-eclampsia, placental abruption or delivery of a small-for-gestational-age baby. *Ultrasound Obstet Gynecol* 1996; **7**: 182–188.
2. North RA, Ferrier C, Long D, Townend K, Kincaid-Smith P. Uterine artery Doppler flow velocity waveforms in the second trimester for the prediction of preeclampsia and fetal growth retardation. *Obstet Gynecol* 1994; **83**: 378–386.
3. Todros T, Ferrazzi E, Arduini D, Bastonero S, Bezzeccheri V, Biolcati M, Bonazzi B, Gabrielli S, Pilu GL, Rizzo G, Valensie H. Performance of Doppler ultrasonography as a screening test in low risk pregnancies: results of a multicentric study. *J Ultrasound Med* 1995; **14**: 343–348.
4. Zimmermann P, Eirio V, Kujansuu E, Ranta T. Doppler assessment of the uterine and uteroplacental circulation in the second trimester in pregnancies at high risk for preeclampsia and/or intrauterine growth retardation: comparison between different Doppler parameters. *Ultrasound Obstet Gynecol* 1997; **9**: 330–338.
5. Valensise H, Bezzeccheri V, Rizzo G, Tranquilli AL, Garzetti GG, Romanini C. Doppler velocimetry of the uterine artery as a screening test for gestational hypertension. *Ultrasound Obstet Gynecol* 1993; **3**: 18–22.
6. Kurdi W, Campbell S, Aquilina J, England P, Harrington K. The role of color Doppler imaging of the uterine arteries at 20 weeks' gestation in stratifying antenatal care. *Ultrasound Obstet Gynecol* 1998; **12**: 339–345.
7. Albaiges G, Missfelder-Lobos H, Lees C, Parra M, Nicolaides KH. One-stage screening for pregnancy complications by color Doppler assessment of the uterine arteries at 23 weeks' gestation. *Obstet Gynecol* 2000; **96**: 559–564.
8. Papageorghiou AT, Yu CKH, Bindra R, Pandis G, Nicolaides KH. Multicenter screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. *Ultrasound Obstet Gynecol* 2001; **18**: 441–449.
9. Becker R, Vonk R, Vollert W, Entezami M. Doppler sonography of uterine arteries at 20–23 weeks: risk assessment of adverse pregnancy outcome by quantification of impedance and notch. *J Perinat Med* 2002; **30**: 388–394.
10. Harrington K, Fayyad A, Thakur V, Aquilina J. The value of uterine artery Doppler in the prediction of uteroplacental complications in multiparous women. *Ultrasound Obstet Gynecol* 2004; **23**: 50–55.
11. Ohkuki A, Minakami H, Sato I, Mori H, Nakano T, Tateno M. Predicting the risk of pre-eclampsia and a small-for-gestational-age infant by quantitative assessment of the diastolic notch in uterine artery flow velocity waveforms in unselected women. *Ultrasound Obstet Gynecol* 2000; **16**: 171–178.
12. Phupong V, Dejthevaporn T, Tanawattanacharoen S, Manotaya S, Tannirandorn Y, Charoenvidhya D. Predicting the risk of preeclampsia and small for gestational age infants by uterine artery Doppler in low-risk women. *Arch Gynecol Obstet* 2003; **268**: 158–161.
13. Valensise H, Novelli GP, Vasapollo B, Di Ruzza G, Romanini ME, Marchei M, Larciprete G, Manfellotto D, Romanini C, Galante A. Maternal diastolic dysfunction and LV geometry in gestational hypertension. *Hypertension* 2001; **37**: 1209–1215.
14. Novelli GP, Valensise H, Vasapollo B, Larciprete G, Altomare F, Di Pierro G, Casalino B, Galante A, Arduini D. LV concentric geometry as a risk factor in gestational hypertension. *Hypertension* 2003; **41**: 469–475.
15. Vasapollo B, Novelli GP, Valensise H. Total vascular resistance and LV morphology as screening tools for complications in pregnancy. *Hypertension* 2008; **51**: 1020–1026.
16. de Simone G, Devereux RB, Roman MJ, Ganau A, Saba PS, Alderman MH, Laragh JH. Assessment of LV function by the midwall fractional shortening/end systolic stress relation in human hypertension. *J Am Coll Cardiol* 1994; **23**: 1444–1451.
17. Palmon L, Reichek N, Yeon S, Clark N, Brownson D, Hoffman E, Axel L. Intramural myocardial shortening in hypertensive LV hypertrophy with normal pump function. *Circulation* 1994; **89**: 122–131.
18. Aurigemma GP, Gaasch WH, McLaughlin M, McGinn R, Sweeney A, Meyer TE. Reduced systolic pump performance and depressed myocardial contractile function in patients with normal ejection fraction and high relative wall thickness. *Am J Cardiol* 1995; **76**: 702–705.
19. Aurigemma GP, Silver KH, Priest MA, Gaasch WH. Geometric changes allow normal ejection fraction despite depressed myocardial shortening in hypertensive LV hypertrophy. *J Am Coll Cardiol* 1995; **26**: 195–202.
20. Sadler DB, Aurigemma GP, Williams DW, Reda DJ, Materson BJ, Gottdiener JS. Systolic function in hypertensive men with concentric remodelling. *Hypertension* 1997; **30**: 777–781.
21. Prefumo F, Muiesan ML, Perini R, Paini A, Bonzi B, Lojacono A, Agabiti-Rosei E, Frusca T. Maternal cardiovascular function in pregnancies complicated by intrauterine growth restriction. *Ultrasound Obstet Gynecol* 2008; **31**: 65–71.
22. Davey DA, MacGillivray I. The classification and definition of the hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 1988; **158**: 892–898.
23. Parazzini F, Cortinovis I, Bortolus R, Fedele L, Recarli A. Weight at birth by gestational age in Italy. *Hum Reprod* 1995; **10**: 1862–1863.
24. Vasapollo B, Valensise H, Novelli GP, Altomare F, Galante A, Arduini D. Maternal cardiac function as a key to differentiate small for gestational age from fetal growth restriction. *Ultrasound Obstet Gynecol* 2004; **24**: 23–29.
25. Valensise H, Vasapollo B, Novelli GP, Pasqualetti P, Galante A, Arduini D. Maternal total vascular resistance and concentric geometry: a key to identify uncomplicated gestational hypertension. *BJOG* 2006; **113**: 1044–1052.
26. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; **18**: 1440–1463.

27. Devereux RB, Casale PN, Kligfield P, Eisenberg RR, Miller D, Campo E, Alonso DR. Performance of primary and derived M-mode echocardiographic measurements for detection of LV hypertrophy in necropsied subjects and in patients with systemic regurgitation and dilated cardiomyopathy. *Am J Cardiol* 1986; **57**: 1388–1393.
28. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, Alderman MH. LV mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. *J Am Coll Cardiol* 1992; **20**: 1251–1260.
29. Mayet J, Ariff B, Wasan B, Chapman N, Shahi M, Poulter NR, Sever PS, Foale RA, Thom SA. Improvement in midwall myocardial shortening with regression of LV hypertrophy. *Hypertension* 2000; **36**: 755–759.
30. de Simone G, Devereux RB, Roman MJ, Ganau A, Saba PS, Alderman MH, Laragh JH. Assessment of LV function by the midwall fractional shortening/end systolic stress relation in human hypertension. *J Am Coll Cardiol* 1994; **23**: 1444–1451.
31. de Simone G, Devereux RB, Daniels SR, Koren MJ, Meyer RA, Laragh JH. Effect of growth on variability of LV mass: assessment of allometric signals in adults and children and their capacity to predict cardiovascular risk. *J Am Coll Cardiol* 1995; **25**: 1056–1062.
32. de Simone G, Devereux RB, Koren MJ, Mensah GA, Casale PN, Laragh JH. Midwall LV mechanics. An independent predictor of cardiovascular risk in arterial hypertension. *Circulation* 1996; **93**: 259–265.
33. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. *Obstet Gynecol* 2003; **102**: 181–192.
34. ACOG Committee on Practice Bulletins – Obstetrics. Diagnosis and management of preeclampsia and eclampsia. *Obstet Gynecol* 2002; **99**: 159–167.
35. Wachtell K, Palmieri V, Olsen MH, Gerdts E, Papademetriou V, Nieminen MS, Smith G, Dahlöf B, Aurigemma GP, Devereux RB. Change in systolic LV performance after 3 years of antihypertensive treatment: the Losartan Intervention for Endpoint (LIFE) Study. *Circulation* 2002; **106**: 227–232.
36. Palmieri V, Russo C, Arezzi E, Pezzullo S, Sabatella M, Minichiello S, Celentano A. Relations of longitudinal LV systolic function to LV mass, load, and Doppler stroke volume. *Eur J Echocardiogr* 2006; **7**: 348–355.
37. Devereux RB, de Simone G, Pickering TG, Schwartz JE, Roman MJ. Relation of left ventricular midwall function to cardiovascular risk factors and arterial structure and function. *Hypertension* 1998; **31**: 929–936.
38. Strobl I, Windbichler G, Strasak A, Weiskopf-Schwendinger V, Schweigmann U, Ramoni A, Scheier M. Left ventricular function many years after recovery from pre-eclampsia. *BJOG* 2011; **118**: 76–83.
39. Valdés G, Quezada F, Marchant E, von Schultzendorff A, Morán S, Padilla O, Martínez A. Association of remote hypertension in pregnancy with coronary artery disease: a case-control study. *Hypertension* 2009; **53**: 733–738.
40. Lykke JA, Langhoff-Roos J, Lockwood CJ, Triche EW, Paidas MJ. Mortality of mothers from cardiovascular and non-cardiovascular causes following pregnancy complications in first delivery. *Paediatr Perinat Epidemiol* 2010; **24**: 323–330.
41. Schussheim AE, Diamond JA, Jhang JS, Phillips RA. Midwall fractional shortening is an independent predictor of left ventricular diastolic dysfunction in asymptomatic patients with systemic hypertension. *Am J Cardiol* 1998; **82**: 1056–1059.
42. Bella JN, Palmieri V, Liu JE, Kitzman DW, Oberman A, Hunt SC, Hopkins PN, Rao DC, Arnett DK, Devereux RB; Hypertension Genetic Epidemiology Network Study Group. Relationship between left ventricular diastolic relaxation and systolic function in hypertension: The Hypertension Genetic Epidemiology Network (HyperGEN) Study. *Hypertension* 2001; **38**: 424–428.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Flow chart summarizing enrolment of patients.

Figure S2 Distribution of midwall fractional shortening (mFS%) vs circumferential end-systolic stress (cESS) 6 months postpartum in the 54 controls and the corresponding equation for calculation of expected mFS.

Figure S3 Flow chart summarizing myocardial function in the study groups according to outcome of pregnancy.

Appendix S1 Detailed description of echocardiographic method.

Appendix S2 Inter- and intraobserver variability of the echocardiographic measurements.

Table S1 Main maternal and fetal/neonatal complications that subsequently developed in 118 patients with bilateral notching of the uterine arteries.