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Left ventricular function many years after recovery from pre-eclampsia

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Objective Epidemiological observations have shown that women with pre-eclampsia are at increased risk for subsequent development of cardiovascular disease. We evaluated maternal haemodynamics in asymptomatic women many years after pre-eclampsia and HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome.

Design Case–control study.

Setting University-based department of obstetrics.

Population Forty-eight women, 13–18 years after the affected pregnancy: 17 women with a history of HELLP syndrome, 14 women with a history of pre-eclampsia and 17 women following normal pregnancy (control group).

Methods Echocardiographic examination was performed in all groups, recording the isovolumetric contraction time and isovolumetric relaxation time (ICT + IVRT), ejection time (ET), myocardial performance index (MPI), transmitral early to atrial filling velocity ratio (MV-E/MV-A), stroke volume (SV) and cardiac output (CO).

Main outcome measures Cardiac function.

Results Women with previous HELLP syndrome showed a significantly increased MPI (0.34 versus 0.26; $P = 0.008$) and ICT + IVRT (442.16 versus 415.03; $P = 0.01$); MV-E/A, SV, ET and CO were not significantly different. Women with a history of pre-eclampsia showed a significantly increased MPI (0.36 versus 0.26; $P = 0.006$) and decreased ET (317.3 versus 328.93; $P = 0.04$); ICT + IVRT, MV-E/A, SV and CO were not significantly different.

Conclusion This study confirms epidemiological observations that women with pre-eclampsia are at increased risk for subsequent development of cardiovascular disease. Many years after HELLP syndrome or pre-eclampsia, asymptomatic women have an increased risk for impaired cardiac function as shown by an increased MPI.

Keywords Cardiac function, maternal haemodynamics, pre-eclampsia.

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Introduction

Epidemiological studies[1–4] covering approximately 800 000 pregnancies have shown an increased risk for cardiovascular death or cardiovascular disease later in life in women with previous pre-eclampsia. These studies were retrospective, investigating death certificates, autopsy reports and hospital records. None of the studies investigated women prior to the manifestation of cardiovascular defects.

The myocardial performance index (MPI, also known as the Tei index) is used to evaluate systolic and diastolic left ventricular function. It is calculated by dividing the sum of the isovolumetric contraction time and isovolumetric relaxation time (ICT + IVRT) by the ejection time (ET). Because of the potent systolic parameters that contribute to MPI, such as ICT and ET, the index detects reliably alterations in left ventricular systolic function.[5–7] Thus, the index maintains a strong inverse relation with ejection fraction:[6] the higher the value of the index, the lower the ejection fraction. In addition, IVRT renders the index sensitive to the identification of impaired relaxation, and appears to be superior to conventional diastolic parameters in the detection of impaired relaxation, whereby the index is the higher for longer IVRT.[5,6] Several studies have demonstrated the value of MPI in a variety of heart diseases, including myocardial infarction, cardiac amyloidosis and heart failure.

In addition, MPI is a valuable tool in predicting cardiovascular mortality in subjects free of coronary heart disease.[8–13] MPI was established by Tei *et al.*[14] This index became a well-known parameter for the assessment of global cardiac function derived from simple time analysis.[8–13] Arnlöv *et al.*[13] showed MPI to be independent of other measurements of cardiac function and of traditional cardiovascular risk factors (hypertension, hyperlipidaemia, diabetes, left ventricular hypertrophy and smoking status) in elderly men free of coronary heart disease. MPI can easily be obtained noninvasively, and has shown good reproducibility, sensitively expressing systolic and diastolic left ventricular function.[14–16]

Numerous studies have reported the haemodynamics in women with established pre-eclampsia, mainly focusing on cardiac output (CO) measurements.[17–19] Moreover, it is now evident that the evaluation of maternal haemodynamics, especially CO measurements in early pregnancy, may be useful in predicting gestational hypertension.[20–22]

Vázquez-Blanco *et al.*[23] showed an increased MPI in pregnant women with established pregnancy-induced hypertension, 2–4 days after delivery. Twenty-eight pregnant women with pregnancy-induced hypertension showed an increased MPI when compared with healthy pregnant women. No follow-up was performed. Recently, Prefumo *et al.*[24] evaluated preliminary data on 15 women, 3 years after a pregnancy complicated by pre-eclampsia. They observed indices of decreased diastolic maternal cardiac function measured with tissue Doppler imaging, such as the Peak velocities early diastole to late diastole (Em/Am) ratio and early mitral inflow velocity to peak mitral annulus velocity (E/Em) ratio, and an increased carotid intima media thickness. We tested the hypothesis that asymptomatic women have impaired cardiovascular function, as shown by an elevated MPI, many years after a pregnancy complicated by HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome or pre-eclampsia.

Methods

This is a case–control study covering 17 women with HELLP syndrome, 14 women with pre-eclampsia and 17 women with uncomplicated pregnancies, all of whom received prenatal care at Innsbruck Medical University Hospital, Innsbruck, Austria between 1991 and 1996. During this period, a total of 13 094 women gave birth at our hospital, namely 12 473 women with uncomplicated pregnancies, 547 women with pre-eclampsia and 74 women with HELLP syndrome. A power calculation, based on a pilot study (unpubl. obs., Strobl I, Schweigmann U, Windbichler G, Scheier M), showed a mean MPI of 0.26 in the pre-eclamptic group and 0.19 in the control group (with a common standard deviation of 0.06). Therefore, we estimated a sample size of $n = 13$ per group to show a statistically significant difference at a two-sided α level of 0.05 between groups with 80% power using Student's t test. For this reason, we aimed to have 20 participants allocated to echocardiographic measurements in each group, who were 'randomly' selected from each category described above. The randomisation was performed as follows. All women who gave birth in our hospital during the period 1991–1996 were categorised into one of three groups, namely normal pregnancy, pre-eclamptic pregnancy or HELLP syndrome. The statistician randomly selected 32 women in the normal group, 34 women in the pre-eclamptic group and 32 women in the HELLP group. (The statistician did this by scrolling through the lists, whilst a person, who could not see the computer screen, told him to stop after an arbitrary time interval. The third patient thereafter in the list was selected and the process was repeated until all women had been selected.) The correct assignment to the different groups (normal, pre-eclampsia, HELLP) was checked and women were invited to the study in the sequence of selection of the cases by the statistician. If the woman declined to participate in the study, or we were unable to contact a woman, the next person was contacted. The groups were matched for body mass index (BMI) and blood pressure. We were able to examine 17, 14 and 17 women in the normal group, pre-eclamptic group and HELLP group, respectively (Figure 1). For different reasons, the following women were excluded from the study: chronic hypertension ($n = 7$), BMI > 30 kg/m^2 ($n = 4$; high BMI is correlated with an increased MPI), coronary heart disease ($n = 1$), serious depression ($n = 1$), breast cancer ($n = 2$), aortic stenosis ($n = 1$), tetraplegia ($n = 1$) and pacemaker ($n = 1$). One woman had died of a heart attack, 16 women were not traceable and 11 women declined participation. Four women did not attend the clinic after allocation.

ICT + IVRT, ET, transmitral early to atrial filling velocity ratio (MV-E/MV-A) and the atrioventricular velocity time integral (AV-VTI) were measured prospectively in all groups, and the stroke volume (SV), CO and MPI were calculated. HELLP syndrome was defined as the presence of all of the following criteria: haemolysis (characteristic peripheral blood smear and serum lactate dehydrogenase > 600 U/l or serum total bilirubin ≥ 1.2 mg/dl), elevated liver enzymes (serum aspartate aminotransferase ≥ 70 U/l) and low platelet count (<100 000 cells/μl). Pre-eclampsia was defined as blood pressure ≥ 140/90 mmHg after 20 weeks of pregnancy, as measured on more than two occasions at least 6 hours apart, and significant proteinuria (≥300 mg/24 hours or urine dipstick of ≥1+ on two occasions at least 6 hours apart).[25,26]

Echocardiographic examination was performed according to the guidelines of the American Society of Echocardio-

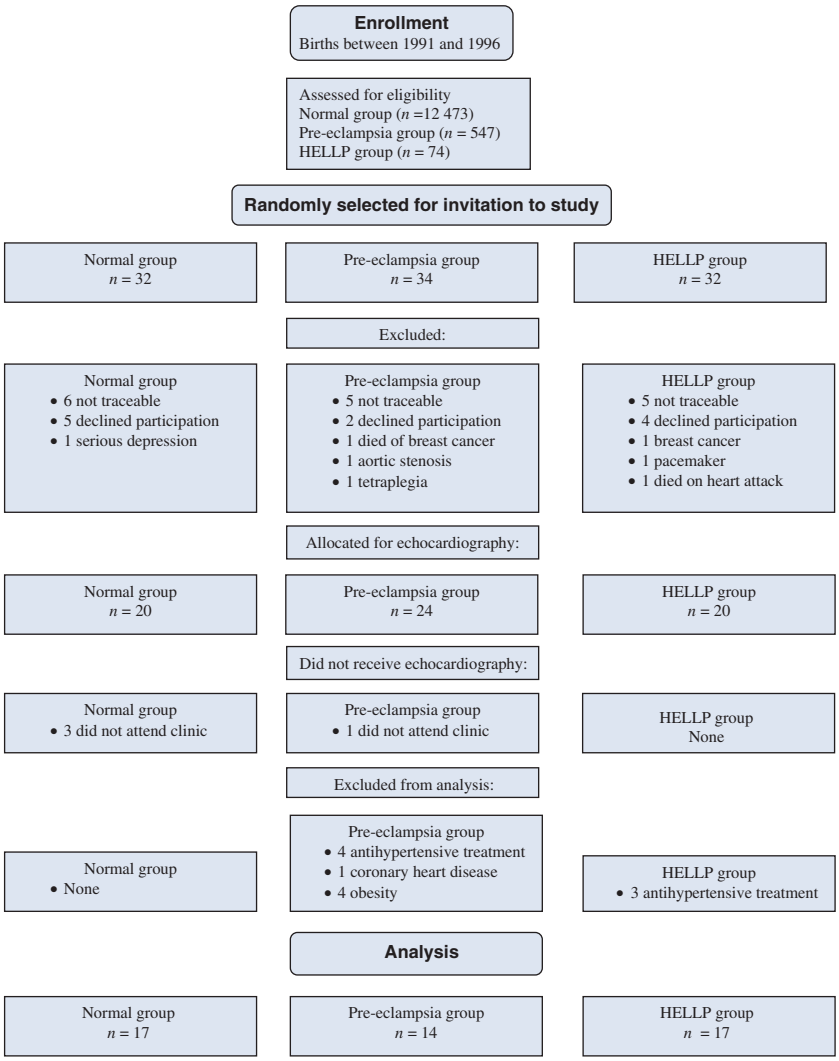

Figure 1. Flow diagram of patients.

graphy[27] using Aloka SSD 3500 ultrasound equipment (Aloka Corporation, Tokyo, Japan) with a phased-array transducer Aloka UST-5299 (2.1–3.8 MHz changeable).

Maternal CO was assessed with the women in the left lateral decubitus position with her left arm behind her head. The transducer was placed on the chest wall at the site corresponding to the cardiac apex and tilted to show the five-chamber view of the heart. Pulsed-wave Doppler was used. The sample volume was placed at the tips of the mitral leaflets during diastole and, subsequently, in the left ventricular outflow tract just below the aortic valve. Three measurements were made in each woman and the average was recorded. Time intervals were measured from mitral and aortic flow velocity profiles. Interval A from cessation to the onset of mitral flow is equal to the sum of ICT, ET and IVRT. Interval B (ET) was measured as the duration of ventricular ejection flow. Thus, the sum ICT + IVRT was obtained by subtracting interval B from interval A. Doppler-derived MPIs combining systolic and diastolic function were calculated as (A − B)/B. As these time intervals are a function of the heart rate, we adjusted them according to the formula of Bazett.[28] The transmitral flow velocity was recorded from the apical transducer position with the sample volume situated between the mitral leaflet tips. The peak velocities from the early (MV-E) and late (MV-A) transmitral flow velocities were recorded, and the ratio of E to A (E:A ratio) was calculated.

The left ventricular outflow tract diameter was measured 1 cm proximal to the aortic valve, and its cross-sectional area was calculated. SV was computed as the product of the cross-sectional area of the aorta and the VTI, and CO was calculated as the product of SV and heart rate. All measurements were taken by one operator (I.S.), who was blind to the woman's previous history.

Twenty-three consecutive women were examined by the same operator (I.S.) in order to calculate the intra-observer repeatability for the MPI measurement. The investigator took two sets, each of three measurements of the MPI, in every woman, and was blind to the results of the measurements on the screen. From each set of three measurements, the mean was used to calculate the intra-observer repeatability according to the method of Bland and Altman.[29]

An automated and calibrated device (3BTO-A2; Microlife, Taipei, Taiwan) was used to measure blood pressure. The measurements were taken with the woman in a sitting position with the cuff on the upper arm at the level of the heart. A small (length < 22 cm), normal (length, 22–32 cm) or large (length, 33–42 cm) adult cuff was used, depending on the mid-arm circumference. After 5 minutes of rest, the blood pressure was measured in both arms simultaneously. A series of recordings was made at 1-minute intervals until variations between consecutive readings were within 10 mmHg in systolic and 6 mmHg in diastolic blood pressure in both arms.[30] Systolic and diastolic blood pressure measurements from the arm with the highest mean arterial pressure were chosen for analysis.

Statistical analysis

Continuous data, normally distributed, are presented as the mean with standard deviation (SD); for skewed data, medians and ranges are shown. A normal distribution of the data was assessed using the Kolmogorov–Smirnoff test. For skewed data, logarithmic transformation was applied. Differences between study groups were assessed using the independent samples t test for continuous variables, and chi-squared and Fisher's exact tests for categorical variables, as appropriate. Two-sided $P < 0.05$ was deemed to be statistically significant. All analyses were conducted with SPSS 15.0 statistical software (SPSS Inc., Chicago, IL, USA).

Results

No statistically significant differences in relevant clinical data were seen between case and control groups during the study (Table 1). Details of the pregnancies are shown in Table 2.

Intra-observer repeatability for MPI according to Bland and Altmann[29] showed the mean at −0.014 and 95% of all measurements within −0.074 and +0.045.

MPI was increased significantly in the HELLP group when compared with the control group (0.34 ± 0.08 versus 0.26 ± 0.08; $P = 0.008$) (Figure 2). The HELLP group showed a significant increase in the sum of ICT and IVRT (442.16 ± 34.64 versus 415.03 ± 29.36; $P = 0.019$) when compared with the control group. MV-E, MV-A, MV-E/MV-A, AV-VTI, SV, ET and CO were not significantly different (Table 3). In the HELLP group, 29% of the women showed an MPI above the 95th centile, according to the reference values established in the control group.

No statistically significant correlation was found between MPI and serum lactate dehydrogenase (624 ± 365 U/l, $r = -0.167$, $P = 0.52$) and serum glutamate oxaloacetate transaminase (106.2 ± 70.6 U/l, $r = 0.24$, $P = 0.34$) at the time of the index pregnancy for the HELLP group. An inverse correlation was found between MPI and the serum bilirubin concentration (1.5 ± 0.6 mg/dl, $r = -0.52$, $P = 0.03$) and between MPI and the platelet count (65 529 ± 22 660 cells/μl, $r = 0.50$, $P = 0.04$).

Women with a history of pre-eclampsia showed a significantly increased MPI (0.36 ± 0.11 versus 0.26 ± 0.08;

Table 1. Baseline characteristics of case and control groups at the time of the study

	HELLP group	Pre-eclampsia group	Control group
Subjects (n)	17	14	17
Age (years), mean ± SD	43.2 ± 4.1	43.6 ± 2.9	43.9 ± 3.8
Previous pregnancies, median (range)	1.0 (1–3)	2.0 (1–3)	2.0 (1–5)
Caucasian (%)	100	100	100
Smokers (%)	17	14	17
Alcohol daily (%)	0	0	0
Drug use (%)	0	0	0
Mean arterial pressure (mmHg), mean ± sd	92.4 ± 6.6	93.6 ± 7.1	94.8 ± 4.3
Years after the index pregnancy, mean ± SD	14.35 ± 1.3	15.78 ± 2.2	14.94 ± 1.6
Current body mass index (kg/m^2), mean ± sd	23.3 ± 2.1	24.9 ± 2.7	24.1 ± 3.06
Sport (%) (>2.5 hours/week)	29	28	23

HELLP group, women with previous pregnancies affected by HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome; Pre-eclampsia group, women with previous pregnancies affected by pre-eclampsia; Control group, women with previous uncomplicated pregnancies.
No statistically significant differences between case and control groups.

Table 2. Baseline characteristics of case and control groups at the time of the pregnancy

	HELLP group	Pre-eclampsia group	Control group
Subjects (*n*)	17	14	17
Woman's age at pregnancy (years), mean ± SD (*P* value)	29.1 ± 4.3 (0.9)	27.9 ± 3.0 (0.3)	29.3 ± 4.3
Gestational age at delivery (weeks), mean ± SD (*P* value)	32.1 ± 8.7 (0.002)	38.5 ± 3.1 (0.29)	39.4 ± 1.9
Birth weight (g), mean ± SD (*P* value)	1970 ± 837 (0.00)	3083 ± 873 (0.43)	3301 ± 663
Maximum mean arterial pressure during hospitalisation (mmHg), mean ± SD (*P* value)	134.2 ± 16.5 (0.00)	130.3 ± 17.3 (0.00)	90.5 ± 8.1
Proteinuria during hospitalisation (mg/dl), mean ± SD (*P* value)	275 ± 288.8 (0.00)	190.7 ± 163.1 (0.00)	8.2 ± 13.2

HELLP group, women with previous pregnancies affected by HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome; Pre-eclampsia group, women with previous pregnancies affected by pre-eclampsia; Control group, women with previous uncomplicated pregnancies.
P value between HELLP group and control group, and between pre-eclampsia group and control group.

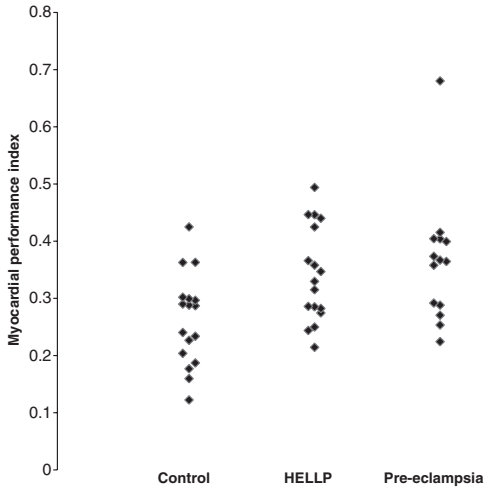

Figure 2. Myocardial performance index in women with previous uncomplicated pregnancies (control group) and in women with previous pregnancies affected by HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome or by pre-eclampsia.

Table 3. Echocardiographic measurements in women with previous pregnancies affected by HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome (HELLP group) and in women with previous uncomplicated pregnancies (control group)

	HELLP group	Control group	*P* value
MPI	0.34 ± 0.08	0.26 ± 0.08	0.008
ICT + IVRT	442.16 ± 34.64	415.03 ± 29.36	0.019
MV-E	79.13 ± 14.35	81.81 ± 18.19	0.637
MV-A	63.31 ± 16.22	59.78 ± 12.31	0.479
MV-E/MV-A	1.37 ± 0.36	1.38 ± 0.28	0.929
AV-VTI	22.43 ± 4.19	23.00 ± 3.65	0.675
SV	70.05 ± 12.25	72.76 ± 12.95	0.536
ET	329.65 ± 15.82	328.93 ± 15.65	0.894
CO	4.82 ± 0.98	4.90 ± 1.02	0.825

AV-VTI, atrioventricular velocity time integral; CO, cardiac output; ET, ejection time; ICT, isovolumetric contraction time; IVRT, isovolumetric relaxation time; MPI, myocardial performance index; MV-A, transmitral atrial filling velocity; MV-E, transmitral early filling velocity; MV-E/MV-A, transmitral early to atrial filling velocity ratio; SV, stroke volume.

$P = 0.006$) (Figure 2) and decreased ET (317.3 ± 15.05 versus 328.93 ± 15.65; $P = 0.045$). MV-A showed a slight trend towards higher values in the case group (67.20 ± 9.58 versus 59.78 ± 12.31; $P = 0.076$). ICT + IVRT, MV-E, MV-E/MV-A, AV-VTI, SV and CO were not significantly different (Table 4). In the pre-eclampsia group, 7% of the women showed an MPI above the 95th percentile, as defined by our reference values.

Discussion

Although it is known that women with current gestational hypertension have an elevated MPI,[23] to our knowledge, this is the first study to assess MPIs in asymptomatic women many years after a pregnancy affected by HELLP syndrome or pre-eclampsia. It has demonstrated that apparently healthy, asymptomatic women at a mean age of 43 years with a history of HELLP syndrome or pre-eclampsia have significantly elevated MPIs when compared with women of the same age following uncomplicated pregnancy.

The published reference ranges for MPI differ.[16,31–38] There is evidence that MPI increases slightly with increasing age.[37,38] However, clinically significant age- and gender-specific cut-off points are not well defined.[23] The 95th percentile of MPI in our control group was 0.42. Accordingly, five women (29%) in the HELLP group and one woman (7%) in the pre-eclampsia group showed an MPI above this cut-off point.

Table 4. Echocardiographic measurements in women with previous pregnancies affected by pre-eclampsia and in women with previous uncomplicated pregnancies (control group)

	Pre-eclampsia group	Control group	*P* value
MPI	0.36 ± 0.11	0.26 ± 0.08	0.006
ICT + IVRT	432.15 ± 32.49	415.03 ± 29.36	0.134
MV-E	84.11 ± 14.32	81.81 ± 18.19	0.703
MV-A	67.20 ± 9.58	59.78 ± 12.31	0.076
MV-E/MV-A	1.28 ± 0.34	1.38 ± 0.28	0.365
AV-VTI	23.27 ± 3.95	23.00 ± 3.65	0.848
SV	70.35 ± 14.73	72.76 ± 12.95	0.632
ET	317.30 ± 15.05	328.93 ± 15.65	0.045
CO	5.39 ± 1.04	4.90 ± 1.02	0.216

AV-VTI, atrioventricular velocity time integral; CO, cardiac output; ET, ejection time; ICT, isovolumetric contraction time; IVRT, isovolumetric relaxation time; MPI, myocardial performance index; MV-A, transmitral atrial filling velocity; MV-E, transmitral early filling velocity; MV-E/MV-A, transmitral early to atrial filling velocity ratio; SV, stroke volume.

To date, the only study investigating MPI in women with pregnancy-induced hypertension was published by Vázquez-Blanco *et al.*[23] They found no significant differences in left ventricular diastolic dimension, left ventricular systolic dimension, shortening fraction, E velocity or E/A ratio between women with uncomplicated pregnancies and those with pregnancy-induced hypertension. The relative wall thickness and A velocity were increased significantly ($P = 0.03$ and $P = 0.04$, respectively) in women with pregnancy-induced hypertension when compared with normal healthy controls. Nevertheless, MPI distinguished even more clearly between healthy pregnant women and those with pregnancy-induced hypertension ($P < 0.01$). Therefore, we focused on MPI for our study. It is influenced by several conditions, such as hypertension and increased BMI.[39] We therefore matched our control and case groups for blood pressure and BMI, and excluded women on antihypertensive drugs or with diabetes. As pre-eclampsia is associated with increased BMI, hypertension and diabetes, one should be aware that, by matching for BMI and blood pressure, there will be a decrease in the difference in MPI between the case and control groups, emphasising the significance of the results.

Our study was not designed to compare between women with a history of HELLP syndrome and women who developed pre-eclampsia. However, we did not find any suggestion that impaired cardiac function differs between women who develop HELLP syndrome and women with prior pre-eclampsia. Furthermore, no correlation was found between MPI and serum lactate dehydrogenase or serum glutamate oxaloacetate transaminase concentration, and only a minor correlation was found between total bilirubin concentration and platelet count at the time of the index pregnancy.

One limitation of our study was the relatively small number of cases, which was mainly a result of the difficulty in recruiting women more than a decade after their disease had occurred. Moreover, this study did not examine long-term cardiovascular outcomes in women with and without increased MPIs, which would be necessary to test any prediction of an increase in cardiovascular disease in this high-risk population. However, women with a raised MPI are known to have a higher risk of myocardial infarction, cardiac death and heart failure,[32] adverse cardiac events during hospitalisation (cardiac death, cardiogenic shock, abdominal aneurysm, arrhythmias)[40,41] and adverse cardiac events in general.[42] In addition, an elevated index has been shown to have a prognostic value in patients with dilated cardiomyopathy, amyloidosis, coronary heart disease and symptomatic heart failure.[5,7,32–34,36] Further studies are needed to address this issue in relation to pregnancy sequelae.

Conclusion

Our study suggests that asymptomatic women have impaired cardiac function many years after a pregnancy complicated by pre-eclampsia or HELLP syndrome. There is evidence that this is a risk factor for cardiovascular disease. It is not known whether this elevated risk is a reflection of a common aetiology of these diseases, or whether cardiovascular disease in these women is caused by HELLP syndrome or pre-eclampsia. The association between increased MPI and a history of pre-eclamptic pregnancy raises the question of which comes first. This question should be addressed in further studies. Nevertheless, this study confirms epidemiological observations that women with pre-eclampsia are at increased risk for the subsequent development of cardiovascular disease. In addition, this study provides functional evidence that women with HELLP syndrome or pre-eclampsia have a cardiac disorder that is subclinical in nature.

Disclosure of interest

We declare no conflicts of interest.

Contribution to authorship

IS conceived and designed the research, acquired the echocardiographic measurements and drafted the manuscript. GW conceived and designed the research. AS performed statistical analysis. VWS and AR acquired the data of the affected pregnancies. US analysed and interpreted the data. MS made critical revisions of the manuscript for important intellectual content.

Details of ethics approval

This study was approved by the Ethics Committee of Innsbruck Medical University (date of approval, 23 January 2008; reference number, UN3024), and written informed consent was obtained from all women.

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