Persistent Maternal Cardiac Dysfunction After Preeclampsia Identifies Patients at Risk for Recurrent Preeclampsia

Herbert Valensise, Damiano Lo Presti, Giulia Gagliardi, Grazia Maria Tiralongo, Ilaria Pisani, Gian Paolo Novelli, Barbara Vasapollo

See Editorial Commentary, pp 690–692

Abstract—The purpose of our study was to assess cardiac function in nonpregnant women with previous early preeclampsia before a second pregnancy to highlight the cardiovascular pattern, which may take a risk for recurrent preeclampsia. Seventy-five normotensive patients with previous preeclampsia and 147 controls with a previous uneventful pregnancy were enrolled in a case-control study and submitted to echocardiographic examination in the nonpregnant state 12 to 18 months after the first delivery. All patients included in the study had pregnancy within 24 months from the echocardiographic examination and were followed until term. Twenty-two (29%) of the 75 patients developed recurrent preeclampsia. In the nonpregnant state, patients with recurrent preeclampsia compared with controls and nonrecurrent preeclampsia had lower stroke volume (63±14 mL versus 73±12 mL and 70±11 mL, P<0.05), cardiac output (4.6±1.2 L versus 5.3±0.9 L and 5.2±1.0 L, P<0.05), higher E/E′ ratio (11.02±3.43 versus 7.34±2.11 versus 9.03±3.43, P<0.05), and higher total vascular resistance (1638±261 dyne·s−1·cm−5 versus 1341±270 dyne·s−1·cm−5 and 1383±261 dyne·s−1·cm−5, P<0.05). Left ventricular mass index was higher in both recurrent and nonrecurrent preeclampsia compared with controls (30.0±6.3 g/m².7 and 30.4±6.8 g/m².7 versus 24.8±5.0 g/m².7, P<0.05). Signs of diastolic dysfunction and different left ventricular characteristics are present in the nonpregnant state before a second pregnancy with recurrent preeclampsia. Previous preeclamptic patients with nonrecurrent preeclampsia show left ventricular structural and functional features intermediate with respect to controls and recurrent preeclampsia. (Hypertension. 2016;67:748-753. DOI: 10.1161/HYPERTENSIONAHA.115.06674.)

Key Words: echocardiography ■ diastolic dysfunction ■ hemodynamics ■ hypertension ■ left ventricular remodeling ■ preeclampsia ■ pregnancy

Maternal cardiovascular health represents the key point for developing an uneventful pregnancy, and its proper function is important for a normal evolution of pregnancy. Serious pregnancy-related hypertensive disorders such as preeclampsia might entail severe future effects on women’s health even after delivery and influence the long-term quality of life as well as the following pregnancy outcomes. A proper maternal cardiovascular adaptation to the pregnancy plays a key role for preventing gestational hypertensive complications, such as preeclampsia.1–5

Preeclampsia affects the 3% to 8% of pregnancies and represents a cause of increased maternal and perinatal morbidity and mortality.6,7 According to the different onset time, the origin and hemodynamics, preeclampsia is classified as early (placental mediated, linked to defective trophoblast invasion with high incidence of altered uterine artery Doppler, and lower body mass index [BMI]) and late (related to higher BMI and no alteration of uterine artery Doppler)8 recurring in 15% of the following pregnancies.8–11 Former preeclampsics have a 7x higher risk of disease recurrence compared with women who have had a normal pregnancy.12,13

Patients with a previous preeclampsia show maternal cardiac dysfunction, and they are more likely to develop systemic hypertension and to die at an early age from cardiovascular disease.14–17 In particular, postpartum follow-up of women with a previous preeclampsia showed persistence of altered cardiac geometry and left ventricular dysfunction.18,19

The latest studies in literature highlight the importance of assessing maternal cardiac function and structure evaluating hemodynamics in terms of total vascular resistance (TVR), left ventricular geometric pattern with regard to the presence of concentric geometry, and diastolic dysfunction.20–22 It is of primary importance to understand how to select and identify those women at increased risk for recurrent preeclampsia. In a recent study, Scholten et al23 concluded that the risk of recurrent preeclampsia and fetal growth restriction in a subsequent pregnancy is inversely and linearly related to pregnancy plasma volume, and this condition might predispose to abnormal hemodynamic adaptation to pregnancy. In previously early preeclamptic women, given the high incidence of postpartum asymptomatic left ventricular abnormalities, the high
prevalence of hypertension, and the increased cardiovascular risk profile, a new pregnancy might develop in an impaired hemodynamic environment, which may prepare the ground for subsequent complications.

The purpose of our study was to assess cardiac function in normotensive women who have experienced a previous early pre-eclampsia before a second pregnancy to highlight the cardiovascular pattern, which may take a risk for recurrent preeclampsia.

Methods

Patient Selection
In a 5-year period (2009–2014), a group of 98 normotensive patients with a history of previous early pre-eclampsia in the first pregnancy were referred to the outpatient clinic of Tor Vergata University within 12 to 18 months after the first pregnancy for the cardiological evaluation as a routine follow-up, and they were submitted to clinical evaluation and maternal echocardiography. In their first pregnancy, 2 of the 98 early preeclamptic patients developed HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome and 1 had an intrapartum fetal death. Patients delivered in the first pregnancy at a mean gestational age of 33±2 weeks of gestation, with a mean neonatal weight centile of 17±10. Exclusion criteria were (1) echocardiography not performed 12 to 18 months after previous delivery, (2) no pregnancy within 24 months from echocardiography, (3) tobacco use, (4) maternal heart disease, (5) pre-existing maternal chronic medical problems, and (6) persistence of elevated blood systolic and diastolic blood pressure values (SBP and DBP, respectively; SBP>140 and DBP>90 mm Hg) before the next pregnancy.

Patients were then followed from the beginning of the new pregnancy until term to verify the fetomaternal outcomes. Patients underwent 24 weeks echocardiographic evaluation in the absence of any sign of preeclampsia to verify the cardiovascular adaptation to the second pregnancy.

The criteria of the International Society for the Study of Hypertension in Pregnancy were used to define preeclampsia. Preeclampsia was diagnosed if a previously normotensive woman had 2 consecutive (4 hours apart) DBP measurements of >90 mm Hg after the 20th week of gestation and proteinuria >300 mg in a 24-hour urine specimen.

Control Group
In the same period for each previously preeclamptic patients, 2 controls matched for age and BMI were included as controls in the study for a total of 208. These patients, whose first normotensive uneventful pregnancy was followed by the outpatient clinic of Tor Vergata, had to meet the following criteria: (1) they had to be submitted to maternal echocardiography 12 to 18 months after the first pregnancy; (2) they had to become pregnant within 36 months from the first pregnancy; and (3) they had to have a second uneventful normotensive pregnancy.

Also these women underwent echocardiographic evaluation at 24 weeks of gestation in their second pregnancy.

Echocardiographic Evaluation
The M-mode, 2-dimensional (2D), and Doppler echocardiographic investigation, evaluating TVR, systolic, diastolic, and morphological parameters of the left ventricle, was performed in the nonpregnant state in between the 2 pregnancies, at least 12 months after the first complicated pregnancy and before the second pregnancy.

The M-mode, 2D, and Doppler echocardiographic evaluations were performed with the patient in lateral position in harmonic imaging with an Aloka A 7 or Philips ie33 Ultrasound machine. Left ventricular end-diastolic and end-systolic diameters and interventricular septum and posterior wall diastolic thicknesses were detected as previously described according to the recommendation of the American Society of Echocardiography. Left ventricular mass in grams was calculated by the Devereux formula.
miscarriage, 2 had chromosomal abnormalities, 3 developed gestational hypertension, 8 were lost during the follow-up of the second pregnancy, totalling to 61 patients excluded from the study. The remaining 147 controls did not have complications by definition during pregnancy.

Table 1 reports baseline features of studied patients, the weeks, and the birth weight centile at delivery. No differences were found in age and BMI. Patients with a recurrent preeclampsia had lower birth weight centile and an earlier week at delivery.

Table 2 shows the main hemodynamic features of the study group at the visit after 12 to 18 months from the previous pregnancy. SBP and heart rate did not differ in the 3 groups. Patients with recurrent preeclampsia showed higher DBP, and higher TVR compared with controls and patients with nonrecurrent preeclampsia. LVMi was higher in both recurrent and nonrecurrent early-onset preeclampsia. Relative wall thickness was higher in recurrent, intermediate in nonrecurrent preeclampsia, and lower in controls.

Table 3 shows diastolic function parameters. Diastolic function was different in the controls compared with both recurrent and nonrecurrent early-onset preeclampsia. In particular, E/E′ was higher in the recurrent early-onset patient, intermediate in nonrecurrent early-onset patients, and lower in controls.

Table 4 shows the hemodynamic and left ventricular morphological features of patients and controls at 24 weeks of gestation during the second pregnancy. A low CO with high TVR characterized recurrent preeclamptic patients when compared with nonrecurrent preeclampsia and controls. Moreover, recurrent preeclampsia showed an increased LVMi and relative wall thickness showing a tendency to a concentric geometry of the left ventricle.

Discussion

This study shows how cardiovascular abnormalities detected through echocardiography in a nonpregnant woman with a history of early preeclampsia might identify the risk for recurrent preeclampsia in a subsequent pregnancy. Doubtless, cardiac function integrity and the adaptive mechanisms during pregnancy play a key role for the proper evolution and outcome of gestation. An impaired hemodynamic adaptation in a previous pregnancy and the subsequent complications, such as preeclampsia, might imply an increased risk profile for the woman and for the fetus during a second pregnancy.

Altered cardiovascular adaptation was noted in patients going through several disorders of pregnancy, such as fetal growth restriction and preeclampsia. This condition is often related to an altered process of trophoblast invasion of the spiral arteries with a subsequent abnormal placentation. For a long time, the detection of abnormal uterine artery Doppler waveform (elevated resistance index and notching) during the second trimester of pregnancy was considered as a good tool for the screening of high-risk pregnancies, although it shows a low positive predictive value.32–35

Previous reports highlighted how TVR and CO can improve the uteroplacental screening test.20 In our previous studies, cardiac functional and structural alterations were present in normotensive pregnant women before the early-onset preeclampsia, and in gestational hypertension before the appearance of subsequent complications. In this study, we focused on nonpregnant previously early preeclamptic women before a second pregnancy to assess the hemodynamic state and cardiac function possibly involved in a subsequent unfavorable outcome in terms of recurrence of preeclampsia.

There is growing evidence of an asymptomatic left ventricular systolic and diastolic dysfunction, left ventricular hypertrophy, and prehypertension state 1-year postpartum in patients with previous early preeclampsia.38 and 40% of patients with persistent cardiac alterations develop essential hypertension within 2 years after early preeclampsia. Estensen et al7 demonstrated a higher resistance throughout the arterial system persisting over time in women with a previous preeclampsia. Our study is consistent with these data, confirming the high cardiovascular risk profile of previously preeclampsia patients 12 to 18 months postpartum. In particular, we found that patients with recurrent preeclampsia in the nonpregnant state show signs of diastolic and systolic dysfunction, and high TVR. These cardiovascular features might represent the prepregnancy predisposition involved in the genesis of recurrent preeclampsia.

**Table 1. Baseline Characteristics of the Study Groups**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>147 Controls</th>
<th>53 Nonrecurrent PE</th>
<th>22 Recurrent PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>34±4</td>
<td>34±4</td>
<td>35±4</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.63±0.05</td>
<td>1.64±0.05</td>
<td>1.63±0.07</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23±3</td>
<td>23±3</td>
<td>24±5</td>
</tr>
<tr>
<td>Birth weight centile</td>
<td>47±22</td>
<td>39±22*</td>
<td>18±9*†</td>
</tr>
<tr>
<td>Weeks at delivery</td>
<td>39±1 wk</td>
<td>38±1 wk</td>
<td>33±4 wk*†</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; and PE, preeclampsia.

*P<0.05 vs controls.
†P<0.05 vs nonrecurrent PE.

**Table 2. Hemodynamic Features 12 to 18 Months After Pregnancy and Before a Second Pregnancy**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>147 Controls</th>
<th>53 Nonrecurrent PE</th>
<th>22 Recurrent PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>120±10</td>
<td>123±10</td>
<td>122±11</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>68±10</td>
<td>69±13</td>
<td>77±11*†</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>73±8</td>
<td>74±9</td>
<td>76±15</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>73±11</td>
<td>70±11</td>
<td>63±14*†</td>
</tr>
<tr>
<td>Cardiac output, L</td>
<td>5.3±0.9</td>
<td>5.2±1.0</td>
<td>4.6±1.2*†</td>
</tr>
<tr>
<td>TVR, dyne·s⁻¹·cm⁻³</td>
<td>1341±270</td>
<td>1383±261</td>
<td>1638±261*†</td>
</tr>
<tr>
<td>LVd, cm</td>
<td>4.62±0.25</td>
<td>4.68±0.26</td>
<td>4.52±0.26†</td>
</tr>
<tr>
<td>LVds, cm</td>
<td>2.75±0.32</td>
<td>2.83±0.40</td>
<td>2.82±0.39</td>
</tr>
<tr>
<td>LVMi, g/m²</td>
<td>24.8±5.0</td>
<td>30.4±6.8*</td>
<td>30.0±6.3*</td>
</tr>
<tr>
<td>RWT</td>
<td>0.28±0.04</td>
<td>0.33±0.04*</td>
<td>0.35±0.04*</td>
</tr>
</tbody>
</table>

DBP indicates diastolic blood pressure; LVd, left ventricular diameter in diastole; LVds, LVd in systole; LVMi, left ventricular mass index; PE, preeclampsia; RWT, relative wall thickness; SBP, systolic blood pressure; and TVR, total vascular resistance.

*P<0.05 vs controls.
†P<0.05 vs nonrecurrent PE.
The role of echocardiography at 24 weeks of gestation was confirmed in this study and may help identifying normotensive asymptomatic patients weeks before the onset of complications, through the evaluation of TVR, CO, and the geometry of the left ventricle (Table 4). The main characteristics of patients with recurrent preeclampsia were the low CO, and the altered cardiac structure with a hypertrophied ventricle at 24 weeks of gestation. High TVR and low CO might be considered signs of an underfilled cardiovascular system with a pressure overload, although blood pressure is within the normal range. The underfilled cardiovascular system together with the signs of cardiovascular systolic and diastolic dysfunction, dating before pregnancy, might cooperate to the development of recurrent preeclampsia. In previous studies, TVR was found to be the best independent predictor for the identification of subsequent development of complications in pregnancy and the best value for a negative outcome is 1400 dyne·s⁻¹·cm⁻⁵ with a positive predictive value of 77%. 20 Cardiac structural alterations were also independent predictors. In this study, left ventricular morphological and functional parameters in recurrent preeclampsia were found to be different at 24 weeks of gestation with more concentric geometry and hypertrophied ventricle, as well as a lower SV and CO, and a higher TVR. These data, though, suggest also that cardiac dysfunction and cardiovascular maladaptation precedes the appearance of a recurrent preeclampsia months before the second pregnancy.

Schooten et al 23 have shown that recurrent preeclampsia is characterized by an underfilled cardiovascular system in the nonpregnant status. The questioning is if this underfilling state is also associated to cardiac structural and functional alterations. Our report shows that in recurrent preeclampsia, 12 to 18 months after the first preeclampsia pregnancy and months before a second pregnancy, TVR, left ventricular mass, and left ventricular systolic and diastolic function are altered. We observed a significantly lower SV, CO, and elevated TVR values in recurrent preeclampsia women compared with both controls and nonrecurrent preeclampsia women. The other important finding relates to left ventricular features with a significantly higher mass in both groups of patients with a previous preeclampsia and higher diastolic dimensions in patients with recurrent preeclampsia. We also found a progressive impairment of diastolic function in previous preeclampsia patients with the worst condition in recurrent preeclampsia compared with patients with nonrecurrent preeclampsia (E/E' progressively higher).

Our data are somehow different from those reported by Ghossein-Doh et al 38 in recurrent preeclampsia because they observed lower left ventricular mass in patients with recurrent preeclampsia compared with nonrecurrent preeclampsia. These discrepancies might be explained by differences in the selected population. In our study, age was higher, BMI was lower, and chronic hypertension was excluded. Ghossein-Doh et al 38 included chronic hypertensive patients. In these patients, the pharmacological treatment might have affected the results of left ventricular mass and function, as well as the pathogenesis of the recurrent preeclampsia; when excluding these chronic hypertensive patients the numbers become too small to have comparable data with our series. The interesting similarities with Ghossein-Doh et al 38 are the lower SV in our patients with recurrent preeclampsia, denoting that there might be a low plasma volume before pregnancy. The overall result is that patients developing preeclampsia have TVR, and left ventricular mass higher than controls, and parameters of diastolic and systolic function different from both controls and nonrecurrent preeclampsia. Moreover, patients with nonrecurrent preeclampsia show different left ventricular mass and diastolic function parameters compared with controls.

Pregnancy is a stress model for the cardiovascular system, and the deleterious effect of the first pregnancy in some predisposed patients might persist. In these women, a new pregnancy might unmask the abnormal hemodynamic adaptation with left ventricular structural alterations leading to recurrent preeclampsia. In our series, recurrent and nonrecurrent patients had a similar clinical severity of the preeclamptic disease in the first pregnancy, suggesting that it is not the severity of the first episode of early preeclampsia to determine the response to the second pregnancy.
TVR links together peripheral (blood pressure) and central (CO) hemodynamic factors. Its increase is because of both a low CO and a high mean blood pressure, probably favored by a altered peripheral vascular reactivity. We think that the underfilling state present before and during pregnancy, described by Ghossein-Doh et al.,3,4 and confirmed by our data might play a key role for the abnormal response of the cardiovascular system, leading to a second complicated pregnancy. Interestingly, in the nonpregnant state nonrecurrent and recurrent preeclampsia patients have similar left ventricular mass, although they drastically differ for TVR, SV, and CO. All these parameters are consistent with the underfilling state and the pressure overload present in recurrent preeclampsia in the nonpregnant state, and persisting in the second pregnancy (Table 4). We think that the personal susceptibility in recurrent preeclampsia, probably determined by genetic factors, influences the further response to the second pregnancy, during which the pressure overload probably induces a significant increase in the LVMI and relative wall thickness to counterbalance the underfilling state. This particular left ventricular structural and functional pattern in the recurrent preeclampsia before (Tables 2 and 3) and during the second pregnancy (Table 4) highlights a possible ineffective attempt of the maternal cardiovascular system to overcome the hemodynamic maladaptation, leading to the complication.

Limitation of the Study

The choice of including the 4 patients with gestational hypertension and the patient with intrauterine growth restriction in the nonrecurrent preeclampsia group might be considered as an arbitrary choice because, as observed for the HYPITAT trial,39 induced labor in these patients might have reduced the chance to develop further complications, such as preeclampsia. Nevertheless, as there is no certainty that these patients would develop preeclampsia, we chose to include them in the nonrecurrent group to analyze the outcome recurrent preeclampsia without other complications that might affect the importance of the results.

Perspectives

This data confirm the strong relationship between the recurrence of preeclampsia and a possible pregestational asymptomatic predisposition characterized by a vascular maladaptation, and a cardiac systolic and diastolic dysfunction, as a ground on which a pregnancy could evolve. Therefore, the cardiovascular assessment after a severely complicated pregnancy might confer the proper level of risk to the future pregnancy and give important information to the obstetrician, who might be able to identify and manage these patients even before the beginning of pregnancy itself.

Disclosures

None.

References

Valensise et al.  

Cardiac Dysfunction in Recurrent Preeclampsia  

753


28. 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. doi: 10.1016/j.echo.2005.10.005.


### Novelty and Significance

**What Is New?**

- Patients with previous preeclampsia with persistent cardiac alterations 1 year after pregnancy are at risk for recurrent preeclampsia in the subsequent pregnancy.

**What Is Relevant?**

- There is a strong relationship between the recurrence of gestational hypertension disorders, such as a new preeclamptic pregnancy and the impaired but asymptomatic woman cardiovascular system dysfunction.

**Summary**

We studied 75 previously preeclamptic patients in the nonpregnant state before a second pregnancy. Patients developing recurrent preeclampsia in the second pregnancy more often presented with systolic and diastolic dysfunction, and hemodynamic features resembling an underfilling state of the cardiovascular system in the nonpregnant state.
Persistent Maternal Cardiac Dysfunction After Preeclampsia Identifies Patients at Risk for Recurrent Preeclampsia
Herbert Valensise, Damiano Lo Presti, Giulia Gagliardi, Grazia Maria Tiralongo, Ilaria Pisani, Gian Paolo Novelli and Barbara Vasapollo

_Hypertension_. 2016;67:748-753; originally published online February 22, 2016; doi: 10.1161/HYPERTENSIONAHA.115.06674

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/67/4/748

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Hypertension_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Hypertension_ is online at:
http://hyper.ahajournals.org//subscriptions/