Impact of Preeclampsia on Clinical and Functional Outcomes in Women With Peripartum Cardiomyopathy

Kathryn J. Lindley, MD; Shayna N. Conner, MD, MSCI; Alison G. Cahill, MD, MSCI; Eric Novak, MS; Douglas L. Mann, MD

**Background**—Preeclampsia is a risk factor for the development of peripartum cardiomyopathy (PPCM), but it is unknown whether preeclampsia impacts clinical or left ventricular (LV) functional outcomes. This study sought to assess clinical and functional outcomes in women with PPCM complicated by preeclampsia.

**Methods and Results**—This retrospective cohort study included women diagnosed with PPCM delivering at Barnes-Jewish Hospital between 2004 to 2014. The primary outcome was one-year event-free survival rate for the combined end point of death and hospital readmission. The secondary outcome was recovery of LV ejection fraction. Seventeen of 39 women (44%) with PPCM had preeclampsia. The groups had similar mean LV ejection fraction at diagnosis (29.6 with versus 27.3 without preeclampsia; *P* = 0.5). Women with preeclampsia had smaller mean LV end-diastolic diameters (5.2 versus 6.0 cm; *P* = 0.001), greater relative wall thickness (0.41 versus 0.35 mm Hg; *P* = 0.009), and lower incidence of eccentric remodeling (12% versus 48%; *P* = 0.03). Clinical follow-up was available for 32 women; 5 died of cardiovascular complications within 1 year of diagnosis (4/15 with versus 1/17 without preeclampsia; *P* = 0.16). In time to event analysis, patients with preeclampsia had worse event-free survival during 1-year follow-up ( *P* = 0.047). Echocardiographic follow-up was available in 10 survivors with and 16 without preeclampsia. LV ejection fraction recovered in 80% of survivors with versus 25% without preeclampsia ( *P* = 0.014).

**Conclusions**—PPCM with concomitant preeclampsia is associated with increased morbidity and mortality and different patterns of LV remodeling and recovery of LV function when compared with patients with PPCM that is not complicated by preeclampsia. (Circ Heart Fail. 2017;10:e003797. DOI: 10.1161/CIRCHEARTFAILURE.116.003797.)

**Key Words:** cardiomyopathy ■ left ventricle ■ preeclampsia ■ pregnancy ■ pregnancy and postpartum

Peripartum cardiomyopathy (PPCM) is a distinct type of heart failure that occurs within the last month of pregnancy or within 5 months after delivery. It is defined as left ventricular ejection fraction (LVEF) ≤45%; left ventricular (LV) cavity dilation occurring during the peripartum period in the absence of preexisting heart disease or other identifiable causes of heart failure. As many as 72% of women may have recovery of their LVEF; 20% of cases are left ventricular dysfunction and given that there is a strong epidemiological link between preeclampsia and PPCM, it has been suggested that preeclampsia and PPCM share a common pathophysiological mechanism(s) that leads to the clinical manifestation of heart failure. However, the prior clinical and epidemiological studies that have associated preeclampsia with the development of PPCM have never separately compared and contrasted the longitudinal clinical and functional outcomes of PPCM associated with preeclampsia and PPCM that is not associated with preeclampsia. Accordingly, the objective of this study was to compare clinical and functional outcomes of PPCM patients with preeclampsia to those who did not have preeclampsia. To our surprise, we found the clinical and functional outcomes of PPCM with concomitant preeclampsia are distinctly different from those observed with PPCM that is not complicated by preeclampsia.
Methods
This is a retrospective cohort study performed at Barnes-Jewish Hospital between 2004 and 2014. Patients with PPCM were identified via detailed chart review of the electronic medical record. Patients were included in the analysis if they delivered at Barnes-Jewish Hospital and were diagnosed with PPCM between 1 month prior to delivery and 5 months postpartum. Inclusion criteria included initial LVEF ≤45% without any other identifiable causes of heart failure. Patients were excluded if their initial echocardiogram was performed elsewhere or was otherwise unavailable for review. Echocardiograms were interpreted by a cardiologist board-certified in echocardiography. The reader was blinded to preeclampsia diagnosis. Preeclampsia was diagnosed according to American College of Obstetricians and Gynecologists criteria (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on 2 occasions at least 4 hours apart after 20 weeks gestation and proteinuria ≥300 mg/24-hour urine collection or protein/creatinine ratio ≥0.3 or dipstick reading of 1+). Patients with preeclampsia without severe features, with severe features, with hemolysis elevated liver enzymes low platelet syndrome, and with eclampsia were all included as having preeclampsia for the purposes of our study.

Follow-up echocardiographic analysis was performed for all women with an echo performed between 6 and 24 months after diagnosis. If women had an echo between 1 and 6 months after diagnosis that documented recovery of LV function, they were also included in the analysis. The primary outcome variable was 1-year event-free survival rate for the combined endpoint of death and hospital readmission. The secondary outcome was recovery of LV function, which was defined as LVEF ≥50% with an absolute improvement of ≥10%.2,19,20 This study was approved by the institutional review board, the Washington University Human Research Protection Office (institutional review board No 201107046). Informed consent was waived per institutional review board approval.

Statistical Analysis
All data are presented as mean±SD. The composite outcome of interest was death/readmission within 1 year. Event counts were compared using Fisher exact test. Student’s 2-sample t test for independent groups was used for analysis of continuous variables. Kaplan–Meier curves were created by preeclampsia status and compared using the log-rank test. Start time was date of diagnosis, and patients were followed until first readmission or death or were censored at last available follow-up or at 1 year. Analysis was conducted in SAS 9.4 (SAS Institute Inc, Cary, NC) and SPSS 23.0 (IBM Corp, Armonk, NY). Dr Lindley had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

Results

Patient Demographics
Fifty-seven women were identified with a diagnosis of PPCM, of whom 39 had an initial echo available for review and were included in the study (Figure 1). Table 1 shows the baseline demographics for the patients in this study. Seventeen women (44%) with PPCM had concomitant preeclampsia (2 mild preeclampsia, 14 severe preeclampsia, and 1 hemolysis elevated liver enzymes low platelet syndrome). As shown, the cohort was predominantly Black. There was no significant difference between groups with respect to underlying chronic hypertension or diabetes mellitus. The patients with concomitant preeclampsia delivered at an earlier gestational age. Systolic and diastolic blood pressures were both significantly higher in the patients with preeclampsia (P<0.001 and 0.004, respectively). As shown in Table 1, there were no significant differences in medical therapy after diagnosis, with the majority of both groups receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, and furosemide.

LV Structure and Function at Baseline
Table 2 shows the 2-dimensional echocardiographic variables at the time of entry in the study. Measurements of LV function, including LVEF, LV mean global longitudinal strain, and LV outflow tract velocity integral were all depressed at baseline, but were not significantly different between the 2 groups. Importantly, women with preeclampsia had significantly smaller LV end-diastolic diameter (5.2±0.51 versus 6.0±0.70 cm; P=0.001) and increased LV relative wall thickness (0.41±0.09 versus 0.35±0.06; P=0.009) when compared with patients without preeclampsia. Patients with preeclampsia were less likely to have an eccentric remodeling phenotype than patients without preeclampsia (12% versus 48%; P=0.03). Both groups of patients had increased estimated LV filling pressures (P=0.06), and patients with preeclampsia had significantly higher mean estimated pulmonary artery pressures (P=0.04).

Effect of Preeclampsia on Clinical and Functional Outcomes
We were able to obtain vital status on 32 of 39 women in this study, including 15 women with preeclampsia and 17 women without preeclampsia. Five women died of cardiovascular complications within 1 year of diagnosis, of whom 4 had preeclampsia and 1 did not have preeclampsia (P=0.16). Figure 2 shows the 1-year event-free survival for the combined end point of death or hospital readmission in women with and without preeclampsia and includes patients immediately lost to follow-up (n=7; 2 preeclampsia and 5 no preeclampsia) among those at risk. As shown, there was a significantly lower (P=0.047) event-free survival in the patients with preeclampsia than in patients without preeclampsia during 1-year follow-up.

Echocardiographic follow-up was available in a total of 26 of the 39 patients (67%), of whom 10 had preeclampsia and 16 did not have preeclampsia. As shown in Figure 3A and 3B, all but 1 patient with preeclampsia had some degree of improvement in LVEF. Overall, patients with preeclampsia had higher mean LVEF on follow-up echo (P=0.046). Patients with preeclampsia were also significantly more likely to meet criteria for recovery of LV function (defined as LVEF ≥50% with absolute increase of ≥10%) at follow-up (Figure 3C; P=0.014). Persistent diastolic dysfunction was common in both groups of patients (60% versus 81%; P=0.5; Table 3). There was no significant difference between the 2 groups in mean systolic or diastolic blood pressures or in being diagnosed with chronic hypertension at 1-year follow-up (P=0.8, 0.5, 0.7; Table 3).

Although our analysis included only outcomes to 1-year follow-up, it is important to note that there were 3 late heart failure deaths—in the group without preeclampsia at 64 months and the 2 preeclampsia patients who failed to recover their ejection fraction on follow-up (69 and 70 months). The patient without preeclampsia had partial recovery of her LVEF to 47%, but then was noncompliant with medical therapy and had subsequent decline in her LV function and ultimately
One patient with preeclampsia developed mixed functional/degenerative severe mitral regurgitation and died of postoperative complications after valve repair. The other patient with preeclampsia had partial recovery of LVEF and then marked decompensation after a subsequent pregnancy complicated by preeclampsia. She ultimately died of infectious complications of her LV assist device.

### Effect of Timing of Diagnosis on Clinical Outcomes

Five (23%) of the patients without preeclampsia and 4 (24%) of them with preeclampsia were diagnosed prior to delivery ($P=1.0$). Patients without preeclampsia were diagnosed a mean 40.7 (±43.7) days postpartum, compared with patients with preeclampsia who were diagnosed a mean 15.6 (±46.2) days postpartum, $P=0.09$. Of the 32 patients with 1-year clinical follow-up, none of the 7 patients who were diagnosed prior to delivery (3 with preeclampsia and 4 without preeclampsia) had recovery of LVEF, whereas 13 of 25 (52%) patients diagnosed postpartum had recovery of LVEF, $P=0.03$. Preeclampsia patients diagnosed postpartum were more likely to have recovery of LVEF than patients without preeclampsia diagnosed postpartum (75% versus 31%; $P=0.047$).

### Discussion

The results of this study show for the first time that the clinical and functional outcomes of patients with PPCM with concomitant preeclampsia are distinctly different from those observed with PPCM that is not complicated by preeclampsia. Two distinct lines of evidence support this statement. First, despite a similar degree of LV dysfunction at the time of initial diagnosis, PPCM diagnosed in the setting of preeclampsia was associated with significantly worse 1-year morbidity and mortality in this predominantly Black cohort (Figure 2). Importantly, the differences in clinical event rates between these 2 groups emerged as early as 4 to 5 months after the time of diagnosis. While the mortality rate in this study is relatively high, it has previously been identified that Black patients with PPCM have worse outcomes than patients of other races. The second major finding of this study is that the pattern of LV remodeling in PPCM with preeclampsia is distinctly different from the pattern of remodeling in PPCM that is not associated with preeclampsia. Patients with PPCM without preeclampsia underwent greater LV dilation and had a decrease in relative LV wall thickness consistent with the classic eccentric LV remodeling. In contrast, the decrease in LVEF in patients with PPCM with preeclampsia was not associated with LV dilation nor a decrease in relative wall thickness, which is more consistent with a concentric pattern of LV remodeling. Viewed together, the results of this study raise the intriguing question of whether the preeclampsia-induced LV dysfunction and PPCM represent 2 different disease processes that share a common clinical presentation, namely heart failure.

### Preeclampsia and PPCM

Preeclampsia is a common hypertensive disorder of pregnancy that is associated with short-term and long-term postpartum morbidity and mortality secondary to cardiovascular dysfunction. Although LVEF is generally unchanged or minimally decreased in patients with preeclampsia, subtle echocardiographic changes in LV function have been observed repeatedly in preeclampsia. Indeed, previous studies have shown that women with preeclampsia have a greater degree of diastolic dysfunction and greater reductions in LV global strain when compared with age-matched pregnant women with preeclampsia, despite preservation of global LVEF. Moreover, preeclampsia-induced LV dysfunction persists for at least 1 to 2 years after delivery, even after normalization of blood pressure.

Epidemiological studies have shown that preeclampsia is present in ~20% of PPCM cases. Given that preeclampsia...
leads to LV dysfunction and given that there is a strong epidemiological link between preeclampsia and PPCM, it has been suggested that preeclampsia and PPCM share a common pathophysiological mechanism leading to cardiomyopathy. However, it is important to recognize that none of the prior clinical and epidemiological studies that conflated preeclampsia and PPCM examined longitudinal clinical and functional outcomes in patients with PPCM and preeclampsia. As noted earlier, the results of this study show that the clinical outcomes and patterns of LV remodeling are distinctly different in PPCM patients with preeclampsia versus patients with PPCM without preeclampsia. Moreover, the percentage of PPCM patients with recovery of LV function is ≈ 3-fold greater in patients with preeclampsia than in those without preeclampsia, which has also not been reported for PPCM. Viewed together, these results suggest that preeclampsia-induced LV dysfunction that meets the diagnostic criteria for PPCM may be a different pathophysiological disease process than PPCM that is not associated with preeclampsia. An alternative interpretation of our data is that PPCM with preeclampsia represents a more severe PPCM phenotype with worse outcome. However, it is difficult to reconcile this interpretation with the differing patterns of LV remodeling and the greater degrees of recovery of LV function in PPCM associated with preeclampsia.

There is one additional unique aspect of this study that warrants further discussion. As noted, our data suggest that women with PPCM with preeclampsia were more likely to recover LVEF to a normal range than women with PPCM without preeclampsia. While the reason(s) for this finding are not known, there are several potential explanations. First, this finding may be the result of survival bias because we only obtained 2-dimensional echoes on patients who were alive at the time of follow-up. It is likely that the PPCM patients with...
preeclampsia who died did not have recovery of LV function. A second explanation is that LV wall stress (i.e., relative wall thickness) was not increased in patients with PPCM with preeclampsia. Given that LVEF is load-sensitive, the increased LVEF in the patients with preeclampsia-induced LV dysfunction may have been because they were able to normalize their wall stress, whereas the PPCM patients with increased wall stress were not. A third explanation could be related to timing of disease onset. While patients with preeclampsia were as likely to be diagnosed prior to delivery as those without preeclampsia, there was a trend toward diagnosis at an earlier postpartum date for those who were diagnosed after delivery. The lack of recovery of LVEF in any patient diagnosed prior to delivery is consistent with prior studies, suggesting that earlier presentation may represent a more aggressive form of the disease.26 However, of patients diagnosed postpartum in our cohort, those with preeclampsia remained more likely to have LVEF recovery, despite the trend toward an earlier diagnosis date.

A final, albeit speculative, potential explanation for the differences in LV functional recovery is that the systemic angiogenic imbalance that occurs in PPCM is accentuated by preeclampsia.5 In humans, the placenta secretes VEGF inhibitors such as sFLT1.5 While sFLT1 levels are elevated above controls in women with PPCM, they are elevated to a much greater degree in patients with preeclampsia.5,27 sFLT1 levels decline rapidly after delivery.28 A recent analysis of the IPAC (Investigators of Pregnancy-Associated Cardiomyopathy) study identified that higher sFLT1 levels correlated with more severe symptoms and major adverse events in women with PPCM.28 Accordingly, higher levels of sFLT1 would be expected in the setting of preeclampsia and could account for the increased early mortality and heart failure hospitalizations in the preeclampsia group in our study, as well as the greater recovery of LV function after the rapid decline in sFLT1 levels after pregnancy. Thus, resolution of the antiangiogenic insult in preeclampsia-induced LV dysfunction may result in higher likelihood of recovering LV function than in patients with PPCM in the absence of preeclampsia. Additional studies will be necessary to address this interesting possibility.

Our study has several limitations. First, our findings are limited by the small sample size and the retrospective nature...
of the study design which was conducted in a single tertiary care center. As such, we did not have adequate power to detect moderate differences between groups. Further, we were not able to obtain vital status for all patients who comprised the initial patient cohort. Accordingly, these results of this study must be regarded as provisional until they can be confirmed by additional studies.

### Table 3. Clinical and Echocardiographic Follow-Up

<table>
<thead>
<tr>
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<th>No Preeclampsia</th>
<th>Preeclampsia</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-year clinical follow-up (n=32)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite death/ readmission at 1 y, n (%)</td>
<td>5 (29)</td>
<td>8 (53)</td>
<td>0.28</td>
</tr>
<tr>
<td>Death at 1 y, n (%)</td>
<td>1 (6)</td>
<td>4 (27)</td>
<td>0.16</td>
</tr>
<tr>
<td>Readmission at 1 y, n (%)</td>
<td>5 (29)</td>
<td>6 (40)</td>
<td>0.71</td>
</tr>
<tr>
<td>Chronic hypertension diagnosis, n (%)</td>
<td>5/16 (31)</td>
<td>2/10 (20)</td>
<td>0.7</td>
</tr>
<tr>
<td>Mean systolic blood pressure</td>
<td>123 (19.1)</td>
<td>126 (29.7)</td>
<td>0.8</td>
</tr>
<tr>
<td>Mean diastolic blood pressure</td>
<td>79 (13.9)</td>
<td>83 (20.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>Diagnosed prior to delivery (n=7)</td>
<td>4 (57)</td>
<td>3 (43)</td>
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<tr>
<td>LV recovery</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>Diagnosed postpartum (n=25)</td>
<td>13 (52)</td>
<td>12 (48)</td>
<td>1.0</td>
</tr>
<tr>
<td>LV recovery</td>
<td>4 (30.8)</td>
<td>9 (75.0)</td>
<td>0.047†</td>
</tr>
</tbody>
</table>

Survivors with echo follow-up (n=26)‡:

- LV recovery, n (%) (LVEF ≥50% with absolute increase ≥10%) | 4 (25) | 8 (80) | 0.014† |
- LV ejection fraction | 41.8 (12.9) | 51.7 (9.5) | 0.046† |
- % improvement from baseline LVEF | 16.8 (11.5) | 21.9 (11.1) | 0.27 |
- Average global strain | −16.3% (4.1) | −13.8% (4.6) | 0.4 |
- LV end-diastolic diameter, cm | 5.2 (0.63) | 5.1 (0.72) | 0.13 |
- LVOT VTI | 18.0 (4.6) | 19.3 (4.3) | 0.5 |
- Diastolic dysfunction, n (%) | 13 (81) | 6 (60) | 0.5 |
- Average E/e′ | 12.7 (7.4) | 10.47 (5.2) | 0.3 |
- E/A ratio | 1.3 (0.7) | 1.7 (0.8) | 0.1 |
- Estimated PASP, mmHg | 25.3 (5.8) | 32.4 (12.3) | 0.6 |
- LA volume index | 26.8 (9.8) | 29.7 (14.9) | 0.5 |
- Normal RV function, n (%) | 15 (94) | 8 (80) | 0.5 |

Values reported as mean (SD) except where indicated. E/A indicates ratio of mitral valve E wave inflow velocity to mitral valve A wave inflow velocity; E/e′, ratio of mitral valve E wave inflow velocity to e′ mitral annulus tissue doppler velocity; LA, left atrium; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; RV, right ventricle; and VT1, velocity time integral.

*No preeclampsia, n=17; preeclampsia, n=15.
†Indicates statistically significant values.
‡No preeclampsia, n=16; preeclampsia, n=10.

### Conclusions

This study is the first to investigate the impact of preeclampsia on outcomes in women with PPCM. We observed that there was a high incidence of preeclampsia in this predominantly Black population of women diagnosed with PPCM. Despite comparable LVEF in the 2 groups, PPCM with preeclampsia is associated with excess early morbidity and mortality. Moreover, the patterns of LV remodeling and recovery of LV function were distinctly different in PPCM patients with preeclampsia than in PPCM patients without preeclampsia. Apart from the novelty of these findings, this study has several important clinical implications. First, while future pregnancies have been considered absolutely contraindicated only in women with PPCM with residual LV dysfunction, it is unknown if the risk of future pregnancy is equivalent for women with prior PPCM with versus without associated preeclampsia and whether residual diastolic dysfunction affects this risk. Our results suggest that despite complete normalization of LVEF in PPCM associated with preeclampsia, these patients remain at high risk of recurrent hospitalization or death. If our results are replicated in a larger patient cohort, they may lead to a rethinking of recommendations for future pregnancies in PPCM with PE. Second, although the incidence of recovery of LV ejection ≥50% was as high as 72% in the recent IPAC study, 45% of the patients in this study had hypertensive disorders of pregnancy. As noted earlier, the high incidence of recovery of LVEF in PPCM associated with PE is potentially misleading because the resolution of LVEF seems to be dissociated from increased cardiovascular events. Although the optimal duration of medical therapy for PPCM patients with recovered LVEF is unclear, a minimum of 1 year has been considered reasonable. If the results of our study are replicated in a larger patient cohort, they may also lead to changes in recommendations for the optimal duration of medical therapy in PPCM associated with preeclampsia. In summary, while the results of this study must be regarded as provisional because of the inherent limitations, this study serves the heuristic purpose of emphasizing the need to re-evaluate the complex relationship between PPCM and preeclampsia in an effort to better understand how these 2 disease processes are interrelated, as well as how they may be different.

### Disclosures

Dr Mann is funded by National Institutes of Health grant U10HL110309.

### References


**CLINICAL PERSPECTIVE**

Despite the co-occurrence of preeclampsia in ~20% of peripartum cardiomyopathy (PPCM) cases, there is surprisingly little known about how preeclampsia impacts outcomes in women with PPCM. Recent evidence suggests that PPCM may be a vascular disease and that PPCM and preeclampsia may share a common underlying vascular pathophysiological mechanism. Accordingly, we sought to determine whether these 2 disease processes are related or whether they are different diseases with a common phenotype (ie, heart failure). We observed that despite comparable decreases in left ventricular ejection fraction in the 2 groups, PPCM with preeclampsia is associated with excess early morbidity and mortality. Moreover, the patterns of left ventricular remodeling and recovery of left ventricular function were distinctly different in PPCM patients with preeclampsia. PPCM patients with preeclampsia had less eccentric remodeling and seem to be more likely to recover left ventricular ejection fraction at follow-up. Both groups had a high incidence of persistent diastolic dysfunction at follow-up. Given the relatively small sample size of this study, these results will need to be replicated in a larger patient cohort before counseling patients regarding prognosis and recommendations for future pregnancies in women with PPCM associated with preeclampsia. Nonetheless, our results emphasize the need to further evaluate the complex relationship between PPCM and preeclampsia.
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Circ Heart Fail. 2017;10:
doi: 10.1161/CIRCHEARTFAILURE.116.003797

Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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