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Peripartum cardiomyopathy with co-incident preeclampsia: A cohort study of clinical risk factors and outcomes among commercially insured women

Isabelle Malhamé[a,c], Natalie Dayan[a,b], Cristiano S Moura[b], Michelle Samuel[b,c], Evelyne Vinet[a,b,c], Louise Pilote[a,b,c,*]

[a] Department of Medicine, McGill University Health Centre, Montreal, Quebec, Canada
[b] Research Institute, McGill University Health Centre, Montreal, Quebec, Canada
[c] Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

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ABSTRACT

Background: Peripartum cardiomyopathy (PPCM) and preeclampsia are strongly associated, yet a description of risk factors for PPCM among women with preeclampsia is currently lacking. Additionally, the effect of preeclampsia on PPCM-related outcomes is not well known.
Methods: We constructed a cohort of delivery admissions from 2011 to 2014 using a large US administrative database (*Marketscan*). We assessed risk factors for the development of PPCM among women with preeclampsia. We compared the risks of major adverse cardiovascular events (MACE) at 6 months between PPCM with co-incident preeclampsia (pePPCM) and PPCM without preeclampsia (npePPCM).
Results: We included 1,024,035 pregnancies, of which 64,503 (6.3%) had preeclampsia. A total of 874 had PPCM (283 with preeclampsia and 591 without preeclampsia). Among women with preeclampsia, clinical risk factors for PPCM consisted in chronic kidney disease (OR 3.18, 95% CI [1.51, 6.69]), multiple pregnancy (OR 2.11, 95% CI [1.49, 2.98]), chronic hypertension (OR 1.88, 95% CI [1.43, 2.47]), advanced maternal age (OR 1.82, 95% CI [1.42, 2.33]), and type 2 diabetes (OR 1.58, 95% CI [1.00, 2.48]). Women with pePPCM had a higher risk of MACE than women with npePPCM (adjusted RR 1.29, 95% CI [1.06, 1.57]) due to increased rates of clinical heart failure and pulmonary embolism in the pePPCM group. Mortality did not differ between groups.
Conclusion: Preeclamptic women with risk factors for PPCM and women with pePPCM at increased risk of MACE should be followed closely. Further studies are required to determine whether preeclampsia affects the long-term prognosis of women with PPCM.

1. Introduction

Peripartum cardiomyopathy (PPCM) is defined by new-onset heart failure with reduced left ventricular ejection fraction (LVEF) during the peripartum period, in the absence of other identifiable cause [1]. This cardiomyopathy affecting 1/1000 to 1/4000 pregnancies in the United States (US) is associated with either death, need for transplantation, need for a left ventricular assist device, and persistently decreased ejection fraction in up to 13% of affected women [2,3].

Preeclampsia is a strong risk factor for PPCM since women with preeclampsia have a 10–20 times increased risk of PPCM when compared to non-hypertensive controls [4]. While an anti-angiogenic state might provide a theoretical basis to link the two conditions, not all women with preeclampsia go on to develop superimposed PPCM [5,6]. Identifying women with preeclampsia who are at highest risk of PPCM may lead to targeted quality improvement care interventions in order to facilitate early detection of this cardiomyopathy and decrease the burden of adverse outcomes related to late presentation [3]. However, risk factors for PPCM among women with preeclampsia are not well known.

Since less than 20% of women with PPCM have co-incident pre-eclampsia, knowledge of the effect of preeclampsia on PPCM-related

Abbreviations: ACE, Angiotensin converting enzyme; CI, Confidence interval; ICD-9, International Statistical Classification of Diseases and Related Health Problems, Ninth Revision; LVEF, Left ventricular ejection fraction; MACE, Major adverse cardiovascular events; npePPCM, Peripartum cardiomyopathy without preeclampsia; pePPCM, Peripartum cardiomyopathy with preeclampsia; PPCM, Peripartum cardiomyopathy; OR, Odds ratio; RR, Risk ratio

* Corresponding author at: McGill University Health Center and McGill University, Centre for Outcomes Research and Evaluation, 5252 De Maisonneuve Blvd, Office 2B.39, Montréal, QC H4A 3S5, Canada.
E-mail address: louise.pilote@mcgill.ca (L. Pilote).

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outcomes could help clinicians anticipate complications and counsel patients more accurately [7]. Well-described structural cardiac changes in preeclampsia, including left ventricular concentric remodeling and diastolic dysfunction, may affect the clinical course of women with PPCM [8–10]. While several small studies with discrepant results have addressed the impact of hypertensive disorders of pregnancy on outcomes of PPCM [3,11–16], only two with sample sizes of less than 40 patients focused on co-incident preeclampsia specifically [11,12].

Using a large cohort of commercially insured women in the US, we identified clinical risk factors for PPCM among women with preeclampsia. We also compared the incidence of major adverse cardiovascular events (MACE) between women with PPCM and co-incident preeclampsia (pePPCM) and those with PPCM and no preeclampsia (npePPCM). We hypothesized that women with pePPCM were at higher risk of MACE than women with npePPCM due to additional preeclampsia-induced cardiovascular changes.

2. Methods

2.1. Data source

We used the *Commercial Plans and Encounters Database* of the *Truven Health MarketScan Research Databases* (2010–2014) [17,18]. This claims-based database contains integrated longitudinal data for individuals covered by employer-sponsored private health insurance from payers across the US [17,18]. Briefly, a unique enrollee identifier links patient-level demographic and enrollment information to inpatient, outpatient, emergency department, and outpatient pharmacy claims [18,19]. Within the database, diagnoses and procedures are coded using the *International Statistical Classification of Diseases and Related Health Problems, Ninth Revision* (ICD-9) diagnostic and procedure codes, the *Current Procedural Terminology*, and the *Diagnosis Related Groups* codes, whereas drugs are coded with the *National Drug Code* system.

2.2. Study population

We constructed a pregnancy cohort among women aged 15–55 years with obstetric deliveries between April 1st, 2011 and June 30th, 2014 and insurance coverage for at least 6 months prior to the estimated date of conception. We identified deliveries using a previously validated algorithm for administrative databases [20], and established the approximate time of conception with a published strategy for estimation of beginning of pregnancy [21] (Table S1 of the Supplementary Appendix). Successive delivery episodes separated by at least 180 days were included. Abortive outcomes were excluded (Table S1 of the Supplementary Appendix for list of codes). Since the diagnosis of PPCM relies on the absence of other known causes of heart failure [1,22], we excluded women with pre-existing cardiac disease or women with prior malignancy who may have developed treatment-related cardiotoxicity (Table S2 of the Supplementary Appendix for list of codes).

To identify pregnancies complicated by preeclampsia, we used diagnostic codes for non-severe preeclampsia, severe preeclampsia, and eclampsia occurring between 20 weeks of gestation and delivery (Table S1 of the Supplementary Appendix for list of codes). Women with a diagnostic code for PPCM and a procedure code for cardiac echocardiography between the last month of gestation and the first 5 months postpartum were considered as having PPCM (Table S1 of the Supplementary Appendix for list of codes). We only considered the first episode of PPCM per woman. Women with PPCM and co-incident preeclampsia constituted the pePPCM group. Women with PPCM in the absence of preeclampsia or gestational hypertension constituted the npePPCM group.

2.3. Risk factors

We extracted information on the following clinical risk factors potentially associated with superimposed PPCM among women with preeclampsia [2,23]: advanced maternal age (≥35 years), multiple pregnancy, chronic hypertension, chronic kidney disease, gestational diabetes, type 1 and type 2 diabetes, obesity, anemia, systemic autoimmune rheumatic disease (including rheumatoid arthritis, systemic lupus erythematous, and other connective tissue diseases), hyperthyroidism, hypothyroidism, asthma, tobacco use, and substance use disorder (including alcohol and drug use disorders) (Table S3 of the Supplementary Appendix for list of codes). All potential risk factors were recorded at time of preeclampsia diagnosis, except for age recorded at time of delivery.

2.4. Outcomes

The primary outcome of MACE was a composite of cardiovascular indicators of severe maternal morbidity previously developed for the obstetric population [24], and procedures pertinent to PPCM-related outcomes [25]. Thus, the occurrence of at least one of the following events defined MACE [24,25]: acute heart failure (ICD-9 diagnostic codes for acute pulmonary heart disease, left-sided heart failure, acute systolic heart failure, acute diastolic heart failure, ventricular fibrillation/flutter, cardiac arrest, cardiopulmonary resuscitation, and cardiac massage), acute respiratory distress, pulmonary edema, conversion of cardiac rhythm, pulmonary embolism, puerperal cerebrovascular disorder, mechanical ventilation, heart transplantation, mechanical circulatory support, intra-cardiac device implantation, permanent pacemaker implantation, or all-cause mortality (Table S4 of the Supplementary Appendix for list of codes). Acute heart failure, pulmonary edema, and acute respiratory distress were considered to be mutually non-exclusive indicators of clinical heart failure. In order to maximize capturing events directly attributable to pePPCM and npePPCM while minimizing losses to follow-up, we measured our primary outcome within 6-months of PPCM diagnosis. Thus, each 'case' of PPCM was diagnosed prior to July 1st 2014, or 6 months before the end of the study period.

As a proxy for persistent left ventricular dysfunction, we estimated total duration of therapy with evidence-based heart failure medication initiated within 30 days of PPCM diagnosis (including beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor agonists, loop diuretics, and combination of hydralazine and nitroglycerine) (Table S5 of the Supplementary Appendix for list of medication) [26].

2.5. Statistical analysis

Descriptive statistics were presented as numbers and percentages, means with standard deviation (SD), or medians with interquartile range (IQR). Continuous variables were compared using *t*-test or Kruskal-Wallis test and categorical variables were compared using two-way Chi-square test or Fisher's exact tests, as appropriate. Cumulative incidence of PPCM was calculated as the total number of PPCM cases divided by the total number of deliveries during the study period. It was expressed in PPCM case/# of deliveries and # PPCM cases/1000 deliveries.

To assess clinical risk factors for PPCM among women with preeclampsia, we ran univariate and multivariable logistic regression models with all putative risk factor variables included as covariates. We used generalized estimated equations with robust standard error to estimate the odds ratio (OR) and their 95% confidence interval (CI) of having superimposed PPCM, while accounting for successive pregnancies with preeclampsia occurring in the same woman [27,28].

In order to estimate the risk of MACE at 6 months in women with pePPCM compared with women with npePPCM, we ran log-binomial regression models yielding risk ratios (RR)s and 95% CIs. We adjusted for maternal age, multiple pregnancy, and baseline medical co-morbidities (including chronic hypertension, chronic kidney disease, obesity, type 1, type 2, and gestational diabetes).

Duration of cardiac pharmacotherapy was compared between women with pePPCM and women with npePPCM using the Kruskal-Wallis test, since treatment durations followed a skewed distribution.

We conducted a sensitivity analysis in which women with npePPCM and uncomplicated gestational hypertension were included in the npePPCM group. We ran similar models as in the main outcome analysis and estimated RR for MACE with adjustment for the same covariates as outlined above. Since we wanted to maximize the probability that women included in the pePPCM group truly had preeclampsia, we did not include any women with gestational hypertension alone (i.e. with no codes for preeclampsia) in the pePPCM group.

We considered a two-sided p value ≤ 0.05 as statistically significant. Statistical analyses were performed using RStudio statistical package (version. 099.442 – 2009–2015).

2.6. Ethical considerations

Ethics approval for the current study was obtained from the Institutional Review Board of the Faculty of Medicine of McGill University in Montreal, Canada under the requirements of a data use agreement between the University of Alabama at Birmingham and McGill University.

3. Results

3.1. Study population

A total of 993,187 women contributed 1,024,035 pregnancies to the study cohort (Fig. 1). There were 874 cases of PPCM diagnosed during the study period. The cumulative incidence of PPCM in our total study cohort was ~ 1/1172 deliveries (i.e. 0.85/1000 deliveries). Among 64,503 pregnancies with preeclampsia, 283 had pePPCM (Fig. 1). Of the 959,532 pregnancies without preeclampsia, 591 had npePPCM (Fig. 1). Thus, the cumulative incidence of pePPCM among women with preeclampsia was 1/228 deliveries (i.e. 4.39/1000 deliveries with preeclampsia), whereas the cumulative incidence of npePPCM among women without preeclampsia was 1/1624 deliveries (i.e. 0.62/1000 deliveries without preeclampsia).

3.2. Baseline characteristics

Compared to women with preeclampsia alone, women with pre-eclampsia and PPCM were older and were more frequently delivered by cesarean section (Table 1). At time of preeclampsia diagnosis, more women with PPCM had multiple pregnancy and a secondary chronic health condition (including obesity, chronic hypertension, chronic kidney disease, as well as gestational and type 2 diabetes) than women with uncomplicated preeclampsia (Table 1). Baseline characteristics of patients with pePPCM and npePPCM at time of PPCM diagnosis are shown in detail on Table 2. On average, pePPCM was diagnosed earlier than npePPCM (Table 2).

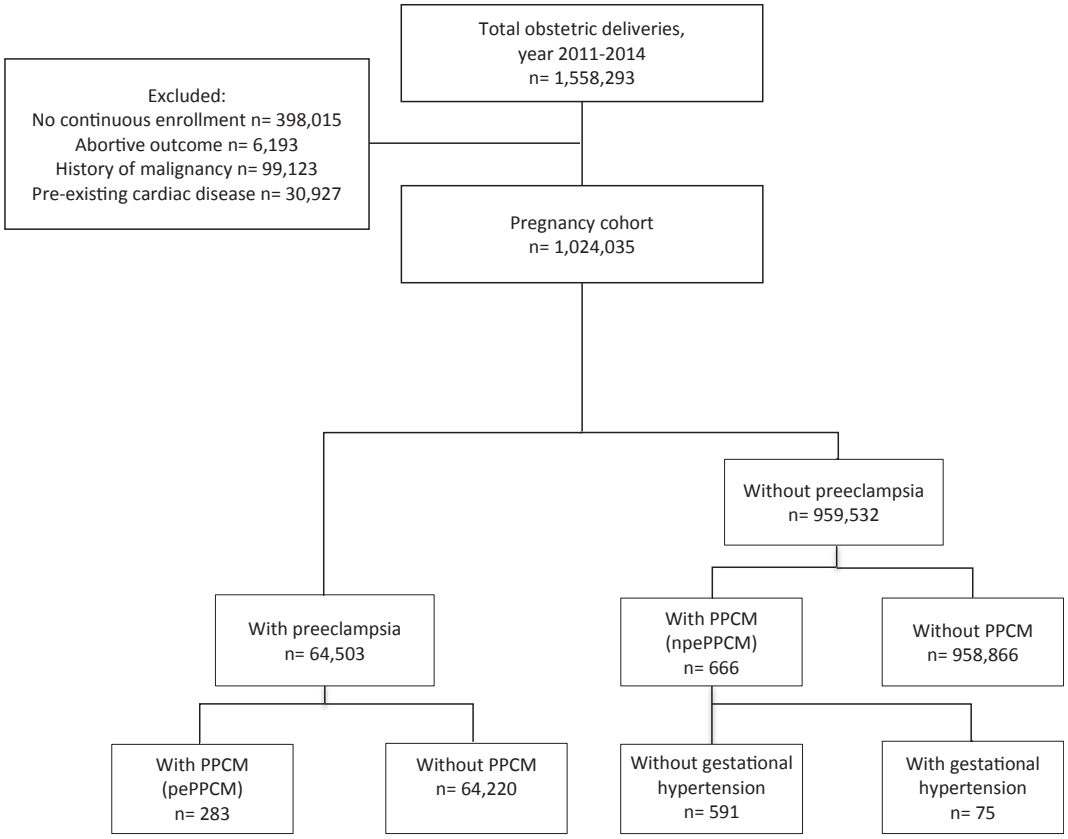

Fig. 1. Flowchart of study participants. Selection of participants from cohort entry to diagnosis of preeclampsia, and peripartum cardiomyopathy. npePPCM = Peripartum cardiomyopathy without preeclampsia, pePPCM = Peripartum cardiomyopathy with preeclampsia, PPCM = Peripartum cardiomyopathy.

Table 1
Descriptive characteristics of women with preeclampsia and superimposed PPCM compared to women with preeclampsia alone*.

	Preeclampsia with PPCM n = 283	Preeclampsia without PPCM n = 64,220	*P* value
Mean age in years (SD)	31.8 (6.8)	30.2 (5.8)	< 0.01
Advanced maternal age (≥35 years)	109 (38.5%)	14,797 (23.0%)	< 0.01
Urban geographic location	238 (87.5%)	53,527 (85.5%)	0.36
Preterm delivery	70 (24.7%)	13,027 (20.3%)	0.06
Cesarean section delivery	189 (66.8%)	34,119 (53.1%)	< 0.01
Multiple pregnancy	39 (13.8%)	4,491 (7.0%)	< 0.01
Chronic hypertension	89 (31.4%)	10,865 (16.9%)	< 0.01
Chronic kidney disease	7 (2.5%)	328 (0.5%)	< 0.01
Gestational diabetes	79 (27.9%)	13,417 (20.9%)	< 0.01
Type 1 diabetes	8 (2.8%)	1,128 (1.8%)	0.17
Type 2 diabetes	30 (10.6%)	3,296 (5.1%)	< 0.01
Obesity	64 (22.6%)	10,629 (16.6%)	< 0.01
Anemia	26 (9.2%)	4,359 (6.8%)	0.11
SARD	4 (1.4%)	568 (0.9%)	0.32
Hyperthyroidism	5 (1.8%)	726 (1.1%)	0.26
Hypothyroidism	21 (7.4%)	5,168 (8.0%)	0.70
Asthma	23 (8.1%)	4,124 (6.4%)	0.23
Tobacco use	8 (2.8%)	1,143 (1.8%)	0.18
Substance use disorder	5 (1.8%)	475 (0.7%)	0.06

pePPCM = Peripartum cardiomyopathy with preeclampsia, SARD = Systemic autoimmune rheumatic disease (Includes juvenile and rheumatoid arthritis, systemic lupus erythematous, and other connective tissue diseases), SD = Standard deviation.

* All covariates were measured between 6 months prior to conception and time of preeclampsia diagnosis (except age, preterm delivery and cesarean section delivery measured at time of delivery).

Table 2
Descriptive characteristics of women with peripartum cardiomyopathy with coincident preeclampsia compared to women with peripartum cardiomyopathy without preeclampsia*.

	pePPCM n = 286	npePPCM n = 591	*P* value
Mean age in years (SD)	31.8 (6.8)	32.0 (5.7)	0.57
Advanced maternal age (≥35 years)	109 (38.5%)	211 (35.7%)	0.42
Median days from delivery (IQR)	6 (20.5)	8 (36.5)	0.01
Urban geographic location	2388 (87.5%)	497 (86.1%)	0.59
Preterm delivery	70 (24.7%)	71 (12.0%)	< 0.01
Cesarean section delivery	189 (66.8%)	339 (57.4%)	< 0.01
Multiple pregnancy	39 (13.8%)	42 (7.1%)	< 0.01
Chronic hypertension	154 (54.4%)	128 (21.7%)	< 0.01
Chronic kidney disease	8 (2.8%)	6 (1.0%)	0.08
Gestational diabetes	84 (29.7%)	108 (18.3%)	< 0.01
Type 1 diabetes	9 (3.2%)	7 (1.2%)	0.06
Type 2 diabetes	35 (12.4%)	30 (5.1%)	< 0.01
Obesity	75 (26.5%)	89 (15.1%)	< 0.01
Anemia	37 (13.1%)	85 (14.4%)	0.60
SARD	4 (1.4%)	8 (1.4%)	0.94
Hyperthyroidism	5 (1.8%)	7 (1.2%)	0.49
Hypothyroidism	47 (8.0%)	25 (8.8%)	0.66
Asthma	29 (10.2%)	46 (7.8%)	0.22
Tobacco use	8 (2.8%)	21 (3.6%)	0.58
Substance use disorder	5 (1.8%)	3 (0.5%)	0.12

pePPCM = Peripartum cardiomyopathy with preeclampsia, SARD = Systemic autoimmune rheumatic disease (Includes juvenile and rheumatoid arthritis, systemic lupus erythematous, and other connective tissue diseases), SD = Standard deviation.

* All covariates were measured between 6 months prior to conception and time of peripartum cardiomyopathy diagnosis (except age, preterm delivery and cesarean section delivery measured at time of delivery).

3.3. Clinical risk factors for PPCM among women with preeclampsia

The strongest clinical risk factors for PPCM among women with preeclampsia were chronic kidney disease (OR 3.18, 95% CI [1.51, 6.69), multiple pregnancy (OR 2.11, 95% CI 1.49, 2.98]), and chronic hypertension (OR 1.88, 95% CI [1.43, 2.47]) (Fig. 2). Advanced maternal age (OR 1.82, 95% CI [1.42, 2.33]) and type 2 diabetes (OR 1.58, 95% CI [1.00, 2.48]) were also independently associated with superimposed PPCM (Fig. 2). Results of the univariate regressions are shown on Table S6 of the supplementary appendix.

3.4. Clinical outcomes of women with pePPCM compared to women with npePPCM

Overall, the primary outcome occurred in 301 (34.4%) women: 121 (42.8%) with pePPCM and 180 (30.5%) with npePPCM ($p < 0.01$). Women with pePPCM were 1.29 times more likely to experience MACE than were women with npePPCM when adjusting for age, multiple pregnancy, and medical comorbidity (crude RR 1.40, 95% CI [1.16, 1.67], adjusted RR 1.29, 95% CI [1.06, 1.57]). Specifically, more women with pePPCM experienced clinical heart failure (41.7% versus 28.1%, $p < 0.01$) and pulmonary embolism (4.6% versus 2.2% $p = 0.05$) than women with npePPCM (Fig. 3). No heart transplantations were observed during the 6-months timeline for observation of outcomes. Although the proportion of women with puerperal cerebrovascular disorders, need for mechanical circulation, and/or permanent pacemaker insertion was higher in the npePPCM group than in the pePPCM group, differences between groups were not statistically significant (Fig. 3). Moreover, there was no significant difference in all-cause mortality between groups.

We did not detect a difference in median duration of pharmacotherapy for heart failure between the pePPCM and the npePPCM groups (Table 3).

Our results were unchanged when women with uncomplicated gestational hypertension (n = 75) were included in the npePPCM group (crude RR 1.39, 95% CI [1.16, 1.65]; adjusted RR 1.27, 95% CI [1.05, 1.53]).

4. Discussion

In this large study of insured pregnant women in the US, we found that chronic kidney disease, multiple pregnancy, chronic hypertension, advanced maternal age, and type 2 diabetes were independently associated with superimposed PPCM among women diagnosed with preeclampsia. Women with pePPCM experienced a higher risk of MACE within the first 6 months following diagnosis than did women with npePPCM. This was mostly driven by indicators of clinical heart failure and pulmonary embolism within the pePPCM group as compared to the npePPCM group. There was no difference in duration of pharmacotherapy for heart failure between both groups.

Chronic kidney disease, multiple pregnancy, chronic hypertension, advanced maternal age, and type 2 diabetes are well-known risk factors for hypertensive disorders of pregnancy [29]. Our findings suggest that their role in the development of PPCM is not solely mediated by the presence of preeclampsia. Whether these associated risk factors worsen the anti-angiogenic milieu linking both PPCM and preeclampsia or whether they confer greater vulnerability to cardiotoxicity in the setting of preeclampsia remains to be determined [5,6,30–32]. Further research is needed to assess whether adequate blood pressure and glycemic control might mitigate the risk of developing PPCM among women with chronic hypertension and type 2 diabetes.

Cardiovascular diseases, including cardiomyopathy, are among leading causes of pregnancy-related deaths in the US [33]. Prompt identification and early management of women at highest risk of cardiovascular morbiditiy might help to reduce maternal mortality. Close follow-up of preeclamptic women with risk factors for PPCM should be

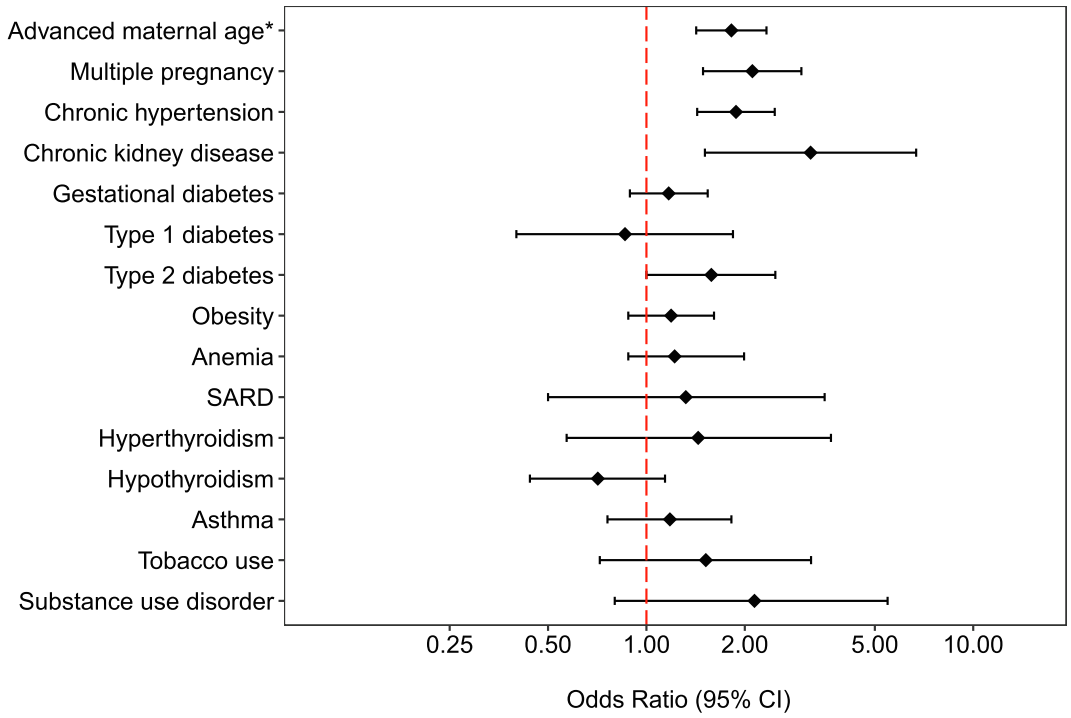

Fig. 2. Forest plot of the association between potential risk factors and peripartum cardiomyopathy among women with preeclampsia. Chronic kidney disease, multiple pregnancy, chronic hypertension, advanced maternal age, and type 2 diabetes were independent risk factors for the development of PPCM among women with preeclampsia. * Age above 35 years. CI = Confidence interval, SARD = Systemic autoimmune rheumatic diseases (Includes juvenile and rheumatoid arthritis, systemic lupus erythematous, and other connective tissue diseases).

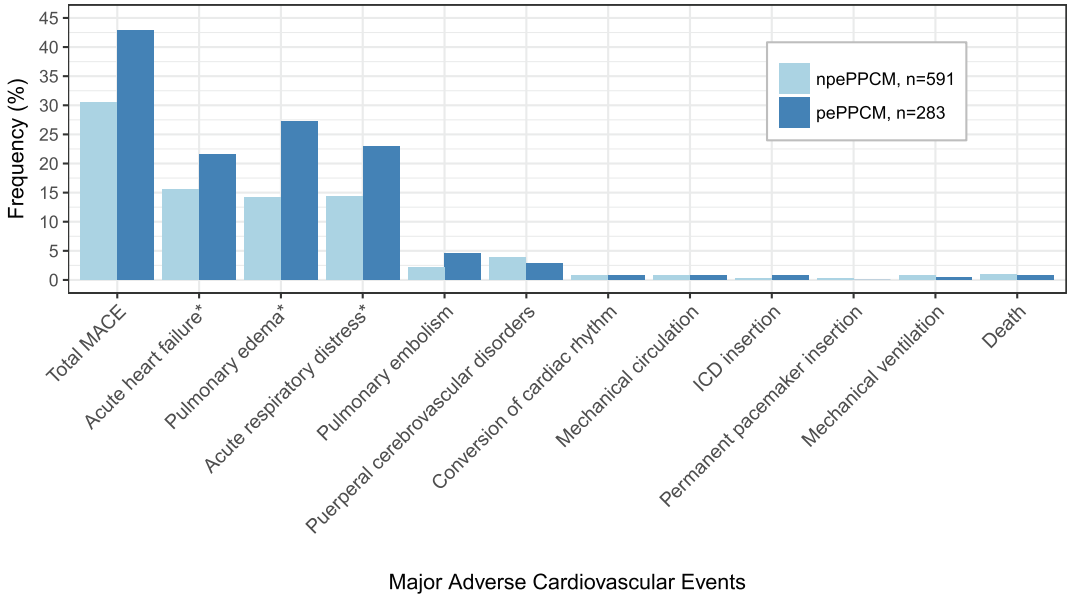

Fig. 3. Rates of major adverse cardiovascular events and all-cause mortality at 6 months among women with peripartum cardiomyopathy with and without co-incident preeclampsia. * Acute heart failure, pulmonary edema, and acute respiratory distress were mutually non-exclusive indicators of clinical heart failure. ICD = Implantable Cardioverter Defibrillator, npePPCM = Peripartum cardiomyopathy without preeclampsia, MACE = Major adverse cardiovascular events, pePPCM = Peripartum cardiomyopathy with preeclampsia.

considered and clinicians should maintain a low threshold for performing echocardiography in the appropriate clinical context within this patient group.

The reason why women with pePPCM experienced more cardiovascular morbidity than women with npePPCM is uncertain. The occurrence of pulmonary edema secondary to increased afterload, decreased oncotic pressure, and impaired diastolic function in ~3% of women with preeclampsia may partially explain our findings [34]. It is also possible that distinct remodeling patterns may account for differences in clinical outcomes. Indeed, upon echocardiographic assessment, women with PPCM and co-incident preeclampsia were found to have concentric remodeling as opposed to eccentric remodeling more frequently seen in women with PPCM without preeclampsia [12]. Additionally, the higher incidence of pulmonary embolism among women with pePPCM may reflect the fact that preeclampsia is a known risk factor for thromboembolic disease during pregnancy and the

Table 3
Duration of medical therapy for heart failure among women with peripartum cardiomyopathy with and without co-incident preeclampsia.

	Median duration in days (IQR)		*P* Value
	pePPCM	npePPCM	
	n = 83	n = 126	
Loop diuretics	63 (96.5)	30 (85.75)	0.16
	n = 6	n = 7	
Nitroglycerine-hydralazine	30 (17.25)	48 (160.5)	0.20
	n = 113	n = 156	
Beta-blockers	115 (165.00)	120 (205.75)	0.37
	n = 32	n = 38	
Mineralocorticoid receptor antagonists	137.5 (157.5)	89 (228.0)	0.53
	n = 98	n = 121	
Angiotensin converting enzyme inhibitors	85.5 (136.25)	97.0 (215.00)	0.22
	n = 7	n = 16	
Angiotensin receptor blockers	128 (184.5)	121 (139.5)	1

npePPCM = Peripartum cardiomyopathy without preeclampsia, pePPCM = Peripartum cardiomyopathy with preeclampsia, IQR = Interquartile range.

postpartum period [35,36].

Our findings are aligned with results of two prior smaller studies examining the effect of preeclampsia on PPCM-related clinical outcomes [11,12]. Among 24 women with PPCM conducted in Sweden 100% of women with pulmonary edema and 80% of women requiring admission to an intensive care unit had co-incident preeclampsia [11]. Additionally, in a cohort of 39 women in the US, women with PPCM and co-incident preeclampsia were more likely to experience adverse events when compared to women with PPCM without co-incident preeclampsia [12]. A reasonable clinical strategy for women with PPCM and co-incident preeclampsia would be to promote early and proactive afterload reduction and diuresis to avoid symptomatic heart failure. Whether the presence of preeclampsia may represent an indication for prophylactic anticoagulation among women with PPCM remains to be determined.

Although we did not find any difference in the duration of pharmacotherapy for heart failure between both groups, differences in long-term prognosis, could not be firmly excluded. Indeed, our database did not comprise any information on indications for medication initiation and discontinuation. While some investigators have described higher rates of long-term LVEF recovery among women PPCM and hypertensive disorders [11–15], others have found no differences in clinical outcomes between women with PPCM with and without hypertensive disorders [3,16]. Variation of results may be explained by differences in geographic settings and case-finding strategies, heterogeneous definitions of exposure to hypertensive disorders, varying primary outcomes, and different duration of follow-up. More studies are needed to determine whether PPCM with co-incident preeclampsia is associated with a better long-term prognosis than PPCM without preeclampsia in order to properly counsel women with PPCM.

This study was one of the largest cohorts of PPCM using comprehensive criteria for case definition, including a precise time window for the peripartum period, and a requirement for the use of diagnostic echocardiography. Additionally, the primary outcome was composed of indicators specifically developed for use in a pregnant and postpartum population [24]. Another strength of this study was the description of the incidence and risk factors for PPCM among women with preeclampsia. Although prior smaller and single-center studies have assessed outcome differences in women with PPCM with and without preeclampsia, our work addressed this clinical question on a much larger scale [11,12].

This study also had limitations. It was conducted retrospectively with an administrative database using private insurance claims only. Importantly, external validity was limited by the fact that our cohort was composed exclusively of commercially insured women in the US. In consequence, our results may not be applicable to other populations. Our data source did not have information about prior history of preeclampsia, parity, duration of symptoms, blood pressure values, echocardiographic measurements, natriuretic peptides, indications for medication initiation and discontinuation, and out-of-hospital death. Our study was also limited by the lack of ethnicity data given its known influence on PPCM-related outcomes [3,37]. In addition, we did not have information on neonatal outcomes; therefore the additional burden of pePPCM on neonatal health could not be assessed. Despite our use of stringent criteria, the diagnosis of PPCM was not confirmed by manual review of medical records. As a result, the extent of misclassification of the ICD code for PPCM remains to be determined. However, our database has previously been used to assess population trends of preeclampsia and severe maternal morbidity in the US [38,39], and the positive predictive value of ICD-9 codes for maternal morbidities in similar health administrative databases has been estimated above 80% [24,40]. Finally, MACE and all-cause mortality events occurring after 6 months were not recorded and conclusions about long-term prognosis could not be inferred.

We identified that chronic kidney disease, multiple pregnancy, chronic hypertension, advanced maternal age, and type 2 diabetes were independent clinical risk factors for PPCM among women with preeclampsia. Women with PPCM and co-incident preeclampsia had a greater risk of combined MACE at 6 months than women with PPCM without co-incident preeclampsia. More research is needed to explore optimal preventive and early detection strategies for PPCM in preeclamptic women. The prognosis of women PPCM and gestational hypertension alone as well as the long-term prognosis of women with PPCM and preeclampsia and PPCM require further study. Studies are warranted to determine whether preeclampsia affects the risk of PPCM recurrence with future pregnancy.

Authors contribution

IM, ND, CM, MS, EV, and LP designed the study. CM constructed the datasets. IM and CM had access to de-identified datasets and performed the statistical analyses. All authors contributed to result interpretation. IM drafted the manuscript. ND, CM, MS, EV, and LP critically revised the manuscript. All authors approved the final manuscript.

Conflict of interest

The authors report no conflict of interest.

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Dr. L Pilote holds a James McGill chair at McGill University; Drs. N Dayan and E Vinet hold a Fonds de Recherche du Quebec-Santé (FRQS) Career award.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.05.014.

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