RISK FACTORS AND OUTCOMES OF PERIPARTUM CARDIOMYOPATHY WITH CO-INCIDENT PREECLAMPSIA AMONG COMMERCIALLY INSURED WOMEN IN THE UNITED STATES

Isabelle Malhamé

Department of Epidemiology, Biostatistics and Occupational Health
McGill University, Montreal

April 2019

ABSTRACT

Peripartum cardiomyopathy (PPCM) is a specific type of cardiomyopathy defined by new-onset heart failure with reduced systolic function during the peripartum period. Preeclampsia, a multisystem disorder affecting pregnant and postpartum women, is strongly associated with PPCM. Since PPCM and preeclampsia are frequently co-incident, and are both independently associated with adverse maternal outcomes, this work sought to further elucidate clinical risk factors and outcomes of their combined occurrence.

A cohort was constructed with delivery admissions from 2011 to 2014 using a large US administrative database (*Marketscan*). All pregnancies complicated by preeclampsia were identified, and clinical risk factors for the development of PPCM were assessed. The risks of Major Adverse Cardiovascular Events (MACE) at 6 months were compared between PPCM with co-incident preeclampsia (pePPCM) and PPCM and no preeclampsia (npePPCM).

In total, 1,024,035 pregnancies were included, of which 64,503 (6.3%) were complicated by preeclampsia. There were 283 women with pePPCM and 591 women with npePPCM. Among women with preeclampsia, risk factors for PPCM were chronic kidney disease, multiple pregnancy, chronic hypertension, advanced maternal age, and type 2 diabetes. Women with pePPCM were more likely to experience MACE than women with npePPCM (adjusted RR 1.29, 95% CI [1.06, 1.57]), which was explained by higher rates of acute heart failure, pulmonary edema, and pulmonary embolism in this patient group. There was no difference in mortality between groups.

Close follow-up of preeclamptic women with risk factors for PPCM should be considered. Preeclampsia conferred a greater risk of MACE at 6 months among women with PPCM. Further studies are required to determine whether preeclampsia affects the risk of PPCM recurrence in subsequent pregnancy.

ABRÉGÉ

La cardiomyopathie peripartum (PPCM) se définit par une insuffisance cardiaque avec fonction systolique réduite survenant *de novo* durant la période peripartum. La prééclampsie, une maladie multisystémique caractérisée par une hypertension artérielle ainsi qu'une atteinte d'organes cibles chez la femme enceinte et postpartum, est fortement associée à la PPCM. Puisque PPCM et prééclampsie sont deux conditions souvent coïncidentes, et toutes deux indépendamment associées à des issues maternelles défavorables, cette étude tenta d'élucider les facteurs de risques et les issues cliniques associés à leur incidence combinée.

Une cohorte fut construite avec l'ensemble des hospitalisations pour accouchement de 2011 à 2014 à l'aide d'une banque de données administrative Américaine (*Marketscan*). Toutes les grossesses atteintes par la prééclampsie furent identifiées, et les facteurs de risque associés au développement de la PPCM furent examinés. Le risque d'évènements cardiovasculaires majeurs fut comparé entre les femmes avec PPCM et prééclampsie (pePPCM) et celles avec PPCM sans prééclampsie (npePPCM).

Un total de 1,024,035 grossesse furent inclues, dont 64,503 (6.3%) furent compliquées par la prééclampsie. Il y eut 282 femmes avec pePPCM et 591 femmes avec npePPCM. Parmi les femmes atteintes de prééclampsie, les facteurs de risques pour la PPCM identifiés furent la maladie rénale chronique, la grossesse multiple, l'hypertension chronique, l`âge maternel avancé, et le diabète de type 2. Par ailleurs, les femmes avec pePPCM étaient à risque plus élevé de développer un évènement cardiovasculaire majeur (RR ajusté 1.29, 95% CI [1.06, 1.57]), ce qui put être expliqué par une plus grande

incidence d'insuffisance cardiaque aigüe, d'œdème pulmonaire, et d'embolie pulmonaires dans ce groupe de patientes. Il n'y eut pas de différence dans la mortalité entre les deux groupes.

Un suivi rapproché des femmes prééclamptiques avec facteurs de risqué pour la PPCM devrait être considéré. Parmi les femmes atteintes de PPCM, la prééclampsie conférait un risque accru d'évènements cardiovasculaires majeurs à 6 mois d'observation. Des études additionnelles sont requises afin de déterminer si la prééclampsie affecte le risque de récurrence de la PPCM dans les grossesses subséquentes.

PREFACE & CONTRIBUTION OF AUTHORS

This thesis is a manuscript-based thesis containing a single manuscript titled "Peripartum cardiomyopathy with co-incident preeclampsia: a cohort study of clinical risk factors and outcomes among commercially insured women". Chapter 1 defines peripartum cardiomyopathy (PPCM) and describes its pathophysiology, epidemiology, and risk factors. Chapter 1 also provides background information on preeclampsia and what is currently known about its co-incidence with PPCM. Chapter 2 explains the purpose and the relevance of the present study, exposes the main study questions, and presents a breakdown of the research methodology. Chapter 3 is the preface to the manuscript and chapter 4 is the manuscript of our study. Results of our sensitivity analysis are presented in Chapter 5. Chapter 6, the discussion and conclusion of the thesis, summarizes our main findings, addresses limitations of the thesis, and provides future research avenues.

I am the first author of the manuscript presented in this thesis document. I developed the study protocol, conducted the data analysis, interpreted the data, and prepared both the manuscript and the thesis document. All coauthors contributed to developing the study protocol, interpreting the data, and reviewing the study manuscript. Additionally, Natalie Dayan, my first co-supervisor, provided her content expertise and provided critical revisions to the thesis document. Evelyne Vinet, my second co-supervisor, contributed to developing the cohort used for this thesis work and reviewed the thesis document. Cristiano Soares de Moura prepared the datasets used in this thesis work and revised all statistical programming. Louise Pilote, my primary thesis supervisor, oversaw all aspects of this thesis.

ACKNOWLEDGEMENT

"Rien ne sert de courir; il faut partir à point"
Jean de La Fontaine, Le lièvre et la tortue (Permier Vers)

The end of this academic chapter marks an important transition in my personal and professional journey. This Master's opened the door to a world of possibilities and allowed me to develop instrumental tools to further support my dream of becoming an independent clinician investigator devoted to better understanding medical disorders during pregnancy.

This would not have been possible without the experienced guidance and unconditional support of my thesis supervisor and mentor Dr. Louise Pilote, who has not only patiently initiated me to epidemiology, but also shown me that research never ceases to be the source of novelty and excitement. I am profoundly grateful to my co-supervisor Dr. Natalie Dayan, who provided with her generous and kind mentorship as well as her unique perspective and caring attention to the details that make up the big picture throughout this project. I thank Dr. Evelyne Vinet for sharing her love of pregnancy-related research, Ms. Michelle Samuel for her practical insights, Ms. Jasmine Poole for her help in defying space and time, and Dr. Cristiano Soares de Moura, for steering this project forward with his unwavering calm and resourcefulness.

I am grateful to my teachers Ken, Nika, Sri, Erica, Ray, and Ghada who nurtured my passion for Obstetric Medicine research and supported the writing of this thesis during my Fellowship. I also want to thank Drs. Vicky Tagalakis, Thomas Maniatis, Patrick Willemot, Suzanne Morin, Michelle Elizov, and Alan Barkun, for believing in my academic endeavors.

Finalement, à mes chéris. Adrien, mon roc, merci d'avoir été là à mes côtés, me transmettant ton amour, ta force, ton courage, et ton soutien sans faille. Ariane et Mathilde, mes tendres amies, merci de m'avoir protégée et encouragée à chaque étape de ce long parcours. Pete, mon grand petit frère, merci de m'avoir offert tes sages conseils au quotidien. Maman et Papa, merci d'être mon inspiration, vous qui m'avez appris qu'avec une tête remplie d'idées, un cœur plein d'espoir, ainsi qu'une démarche honnête et sincère, on pouvait arriver à tout, dans la vie comme dans la recherche.

TABLE OF CONTENTS

INTRODUCTION

According to the Center for Disease Control's Mortality Surveillance System, cardiomyopathy from all causes combined accounts for 10.3% of maternal mortality cases in the United States (US) (1). Peripartum cardiomyopathy (PPCM) is a specific type of cardiomyopathy defined by new-onset systolic dysfunction with decreased left ventricular ejection fraction (LVEF) often below 45%, during the peripartum period, with no other identifiable cause of heart failure (2, 3). Peripartum cardiomyopathy has been associated with death, need for transplantation, need for a left ventricular assist device, and persistently decreased ejection fraction in up to 13% of affected women (4). Preeclampsia, a multisystem disorder affecting pregnant and postpartum women, is diagnosed in close to 22% of women with PPCM, which is four times the worldwide incidence (5). Along with other hypertensive disorders of pregnancy, preeclampsia is responsible for 6.8% of pregnancy-related deaths in the US (1).

Since PPCM and preeclampsia are frequently co-incident, and are both independently associated with adverse maternal outcomes, this work sought to further elucidate clinical risk factors and outcomes of their combined occurrence.

CHAPTER 1 – BACKGROUND

1.1 Defining peripartum cardiomyopathy: a brief historical perspective

According to the American Heart Association, cardiomyopathies are defined as "a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure–related disability" (6). Heart failure occurring in the peripartum period has long been recognized as a pregnancy complication, and descriptions of this phenomenon date back to the 19th century (1). New-onset cardiomyopathy as a cause of peripartum heart failure was first reported in 1937 by Gouley *et al* in a case-series of 7 patients (7). Through the years, this distinct and autonomous clinical entity was given a multitude of names such as "toxic postpartal heart disease", "postpartum heart disease", "postpartum myocardosis", "Meadows syndrome", and "postpartum myocarditis", before being called "peripartum cardiomyopathy (PPCM)" (8, 9).

In 1971, Demakis *et al* published a case-series of 27 patients and defined the following diagnostic criteria for PPCM: "(1) Development of heart failure in the last month of pregnancy or with the first 5 months postpartum, (2) Absence of a determinable etiology for the cardiac failure, (3) Absence of demonstrable heart disease prior to the last month of pregnancy" (8, 10). It is only later in the year 2000 that the National Heart, Lung, and Blood Institute and Office of Rare Diseases from the National Institutes of Health (NIH) reassembled experts in the fields of cardiovascular medicine, obstetrics, immunology, and

pathology, and resulted in a first set of official diagnostic criteria for PPCM (9, 10). These diagnostic criteria were the following: "Development of cardiac failure in the last month of pregnancy or within the 5 months of delivery; Absence of identifiable cause for the cardiac failure; Absence of recognizable heart disease prior to the last month of pregnancy; Left ventricular systolic dysfunction demonstrated by classic echocardiographic criteria such as depressed shortening fraction or ejection fraction" (2). The peripartum diagnostic interval established with those criteria (i.e. one month prior to delivery and 5 months postpartum) was initially put in place to ensure that women with PPCM were not merely women with preexisting cardiomyopathy aggravated by pregnancy but rather women with a truly new-onset of idiopathic cardiomyopathy during the peripartum period (2). Moreover, PPCM was deemed to be a diagnosis of exclusion occurring "only in those patients with no prior history of recognizable heart disease" and in the absence of an alternative explanation for the depressed ejection fraction seen in women with PPCM (2).

Both the American Heart Association and the European Society of Cardiology subsequently adopted this definition of PPCM, recognizing this disease as a distinct type of cardiomyopathy, attributable to pregnancy exclusively, and occurring within the peripartum period (6, 11). In 2010, however, the Heart Failure Association of the European Society of Cardiology Working Group on PPCM issued a position statement with a few modifications to the previous NIH definition (3). This statement deemed the peripartum timeline of one month prior to delivery and 5 months postpartum to be too arbitrary, potentially leading to under-diagnosis of the condition (3). Institution of strict echocardiographic criteria was also proscribed for similar reasons (3). As a result, this working group issued the following contemporary and updated definition of PPCM: "Peripartum cardiomyopathy is an idiopathic

cardiomyopathy presenting with heart failure secondary to left ventricular systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. It is a diagnosis of exclusion. The left ventricle may not be dilated but the ejection fraction is nearly always reduced below 45%" (3).

1.2 Peripartum cardiomyopathy: pathophysiology, epidemiology, and risk factors

Although the underlying pathophysiology for PPCM remains poorly understood, several mechanisms have been considered to contribute its development. These include autoimmune processes, myocarditis, maladaptive response to hemodynamic stress of pregnancy, stress activated cytokines, viral infections, and prolonged tocolysis (3). More recently, the "vascular/hormonal hypothesis" has become the predominant explanatory model, whereby a vascular and/or hormonal insult combined with host susceptibility is at the origin of the disease (12). Two main vasculotoxic hormonal environments have been highlighted (13). Firstly, Hilfiker-Kleiner *et al* identified that a 16-kDa fragment released towards the end of pregnancy via secretion of prolactin, had a central role in endothelial and cardiomyocyte damage, particularly in murine models with a genetic predisposition (13-15). Secondly, Patten *et al* discovered that, in animal models, mice lacking peroxisome proliferator-activated receptor-gamma co-activator- 1 alpha (PGC-1a), a powerful cardiac regulator of angiogenic imbalance, that were exposed to elevated circulating levels of sFlt-1 developed profound PPCM (14). This angiogenic imbalance was, later on, confirmed in a large cohort of women with PPCM, who also had higher sFlt-1 levels than controls (15). Therefore, a "two-hit" process, in which host susceptibility worsened by an anti-angiogenic

state caused by either a prolactin fragment or uteroplacental insufficiency may lead to the development of PPCM (16). Recently, the genetic sequencing of 172 women with PPCM for 43 genes associated with dilated cardiomyopathy highlighted a common genetic pathway between the two diseases (13-15). The great majority (65%) of genetic variants occurred in the gene encoding for *Titin*, one of three proteins constituting cardiac sarcomeres (17). As *Titin* mutations were found in 15% of tested women, this genetic predisposition may be a partial explanation as to why some women develop PPCM while others do not (17).

In the US, the incidence of PPCM is estimated at 1 in 1000 to 1 in 4000 pregnancies (18). In Canada, a population study based in Alberta measured an incidence of 1 in 2400 deliveries (19). Its incidence is disproportionately high in certain regions of the world, such as in Haiti, where it has been measured at 1 in 300 deliveries (20). Identified risk factors for PPCM include advanced maternal age, high parity, primiparity, multiple pregnancy, hypertension, anemia, substance abuse, asthma, autoimmune diseases, diabetes, prolonged tocolysis, obesity, and lower socio-economic status, as well as African heritage (18, 21, 22).

1.3 Preeclampsia: definition, pathophysiology, epidemiology, and risk factors

Preeclampsia is a complex and polymorphous systemic disease affecting pregnant and postpartum women worldwide. In North America, the diagnosis is made on the basis of a combination of both persistent hypertension (defined as values above 140/90 mmHg) and either significant proteinuria (defined as the equivalent of 0.3 g/24h on a 24h urine collection or a urinary protein/creatinine ratio), or any new onset neurologic manifestations, pulmonary edema, renal insufficiency, liver enzyme abnormalities, and thrombocytopenia, or other

adverse condition or severe complication (23, 24). The presence of fetal manifestations of placental insufficiency such as placental abruption, stillbirth, intra-uterine growth restriction (IUGR), and uteroplacental insufficiency also constitute severe manifestations of this disease (24).

While an understanding of its pathophysiology remains incomplete, preeclampsia is thought to originate from utero-placental insufficiency, caused by a combination of maternal, placental, and fetal risk factors and leading to an angiogenic imbalance favouring high levels of "soluble Fms-like tyrosine kinase-1" (sFlt-1) (24, 25). It evolves along a continuum of severity, and its manifestations can involve the maternal neurologic, cardiovascular, renal, gastrointestinal, and haematological systems (24). Gestational hypertension (GH), unlike preeclampsia, is characterized by hypertension diagnosed after 20 weeks of gestation, but without end organ damage (23, 24). Together with preeclampsia and chronic hypertension, they constitute the broader diagnostic category of "hypertensive disorders of pregnancy" (HDP) (23, 24). Although they are often grouped together as the HDP, these are, in fact, three distinct disorders manifesting with elevated blood pressures.

The incidence rate of preeclampsia in Canada, stable since 2004, is estimated at 11.5 per 1000 deliveries in 2012 (24). In the United States (US), it affected 3.8% of deliveries in 2010, rising slightly from 3.4% in 1990 (26). Risk factors most associated with the development of preeclampsia include a prior history of preeclampsia, multifetal gestation, assisted reproduction, chronic hypertension, type 1 and type 2 diabetes, renal disease, and autoimmune disease (23, 24, 27).

1.4 Preeclampsia and its association with cardiac changes during pregnancy

A systematic review of 36 studies evaluated echocardiographic changes associated with HDP; it included 7,189 normal pregnancies, 745 women with GH, and 815 women with preeclampsia (28). In this study, women with preeclampsia had lower cardiac output, increased vascular resistance, lower stroke volume, and decreased diastolic function (28). While left ventricular mass was increased in hypertensive women in general, concentric remodelling was more common in women with preeclampsia (28). These findings emphasize that preeclampsia is a multi-systemic disease associated with cardiac remodelling, independently from the development of PPCM. Yet, preeclampsia has not been found to be associated with a clinically significant reduction in LVEF (28).

1.5 The association between preeclampsia and peripartum cardiomyopathy

Preeclampsia is strongly associated with PPCM. Indeed, in a meta-analysis aimed at determining the prevalence of preeclampsia among women with PPCM, preeclampsia was estimated to occur in nearly 22% of women with PPCM (5). Since preeclampsia and PPCM both can originate from an anti-angiogenic environment, as previously described, the vasculotoxic environment characterizing the end of pregnancy may be a process linking both diseases (15, 25). Moreover, genetic studies conducted among 181 patients with preeclampsia revealed that they were more likely to carry mutations associated with various types of cardiomyopathies, including PPCM (29). This may constitute an additional pathophysiologic mechanism linking both conditions. Reflecting this common

pathophysiology, PPCM and preeclampsia share several risk factors such as advanced maternal age, multiple pregnancy, obesity, and diabetes mellitus (30). Despite these common risk factors, however, only a small proportion of women with severe preeclampsia develop superimposed PPCM, and at least 50% of women with PPCM do not present with co-incident PPCM (18). To our knowledge, specific risk factors for the development of PPCM among women with preeclampsia have not been described.

1.6 Prior research on clinical outcomes between with peripartum cardiomyopathy with and without hypertensive disorders of pregnancy

Several studies have compared cardiovascular outcomes between women with PPCM with co-incident HDP and those with PPCM without co-incident HDP, and their results are summarized in Table T1 (4, 31-36). Of these, only two, with sample sizes <50 patients, focused on the effects of preeclampsia alone on PPCM-related outcomes (31, 32). These two studies are described below.

In a small Swedish case series of 24 women with PPCM, 14 (58%) had preeclampsia (31). All cases of pulmonary edema and 80% of intensive care unit admissions were among women with preeclampsia (31). In the long-term, however, women with preeclampsia were found to have higher LVEF at follow-up, with overall better recovery than women with PPCM but no preeclampsia (31). Important distinctions in patterns of cardiac dysfunction have been revealed in a study by Lindley *et al* among 39 women with PPCM (32). In this cohort, women with PPCM with preeclampsia (n=17) had increased relative ventricular wall thickness and higher mean estimated pulmonary artery pressure whereas women with PPCM without preeclampsia (n=22) had greater end diastolic diameter and eccentric remodeling

(32). When looking at a composite of death and heart failure hospitalizations, women with PPCM and co-incident preeclampsia had a worse event-free survival at one year (32). On follow-up of survivors who had available echocardiograms, 80% of the 10 women with PPCM and co-incident preeclampsia, compared to 25% of the 16 women with PPCM without preeclampsia, had recovered their LVEF (32). The authors, however, mention that this may have been affected by survival bias (32).

Three other studies have highlighted differences in clinical outcomes between women with PPCM with and without HDP (33-35). Ntusi *et al* conducted a cohort study among 83 women with PPCM referred to a cardiology clinic in South Africa (33). They further defined a group of women with either GH or preeclampsia (n=53), and a group of women with neither GH nor preeclampsia (n=30) (33). In total, 85% of women with PPCM with GH/preeclampsia presented antepartum compared to 100% of women with PPCM without GH/preeclampsia who presented postpartum (33). Women with PPCM and GH/preeclampsia had more pre-existing chronic hypertension whereas women with PPCM without GH/preeclampsia had more multiple pregnancies (33). Echocardiograms of women with PPCM and GH/preeclampsia more frequently demonstrated left ventricular hypertrophy (33). Women with PPCM without GH/preeclampsia, had lower LVEF at presentation, and developed more chronic heart failure on follow-up, with a higher burden of symptoms at their last recorded visit (33). There were no deaths in the group with PPCM and GH/preeclampsia of pregnancy, whereas 5 women died in the group of women witth PPCM without GH/preeclampsia (33). Women with GH/preeclampsia and clinical evidence of heart failure were not required to have an echocardiography reporting to enter the cohort (33). Women without hypertension, however, were required to have an LVEF below 45% (33). It

is thus possible that differences may have been due to initial selection bias. In their population-based study from Denmark, Ersboll *et al* identified 61 women with PPCM over 10 years (35). Women with PPCM but no HDP (n=28) suffered a higher rate of death, heart transplantations, mechanical circulatory support, and persistent heart failure at 10-14 months of follow-up, suggesting a relative protective effect of HDP among women with PPCM (35). In a German registry of 115 women with peripartum cardiomyopathy, Haghikia *et al* reported that "pregnancy-associated hypertensive disorders" were associated with clinical improvement upon follow-up (34).

Despite some investigators reporting distinctions in clinical outcomes between women with PPCM with and without HDP, others have found no specific differences between both groups (4, 36). Indeed, in their retrospective nationwide survey in Japan, Kamiya *et al* compared characteristics of women with PPCM with and without HDP (including GH, preeclampsia, and chronic hypertension) (36). A questionnaire was distributed to over 1000 medical organizations in Japan to locate women with PPCM who were diagnosed over two years. In total, 102 cases were included, 42 of which with co-incident HDP (36). Patients with and without HDP had similar cardiac dimension, systolic function and BNP at presentation, and a similar death rate. The only difference was a shorter hospital stay for PPCM affected women with HDP when compared to PPCM affected women without HDP (36). This study, however, may have been subjected to selection bias given that women with more severe disease may have been better recalled and located in both HDP and non-HDP groups, decreasing clinical differences between both groups. Finally, McNamara *et al* in their "Investigations of Pregnancy-Associated Cardiomyopathy" (IPAC), the largest prospective cohort of women with PPCM, which included 100 patients,

did not find any significant differences between among women with and without hypertension (4).

In summary, existing literature examining the impact of preeclampsia on PPCM presentation and outcomes has been limited by small sizes, from heterogeneous populations, and as such, the results are conflicting. Discrepancies between studies may be due to several factors including differences in case-finding strategies, differing definitions of HDP, variable outcome definitions, and different durations of follow-up. To date, neither large study nor meta-analysis has ever addressed whether preeclampsia or HDP has an effect on either short-term or long-term outcomes of women with PPCM. As expressed by Parikh *et al*, this may be due to the fact that "Combining data from PPCM studies is challenging, as the effect measures used are heterogeneous and often cannot be combined in a meta-analytic fashion in order to yield an informative statistic" (30).

CHAPTER 2 – METHODOLOGY

2.1 Rationale for the study

Despite a common pathophysiology between PPCM and preeclampsia, not all women with preeclampsia develop PPCM and a description of risk factors associated with PPCM within this subgroup is currently lacking. Identification of preeclampsia-specific risk factors for PPCM could provide clinicians with deeper insights about who may develop PPCM and thereby benefit from closer cardiac. This, in turn, could lead to early detection of PPCM and decreased adverse outcomes related to late presentation or diagnostic delay (4).

Whether or not preeclampsia has an impact on PPCM-related outcomes remains controversial. Indeed, several small studies have addressed the impact of various HDP subtypes on PPCM-related outcomes with discrepant results (4, 31-36). Thus, large epidemiologic studies are warranted to determine whether preeclampsia affects the clinical course of women with PPCM. Understanding the effect of preeclampsia on PPCM-related outcomes may help clinicians anticipate complications, manage adverse events, and counsel affected patients more accurately.

2.2 Objectives and Hypotheses

2.2.1 Objectives:

1. To identify risk factors for PPCM among women with preeclampsia.

2. To estimate the relative risk of major adverse cardiovascular events (MACE) among women with PPCM exposed to preeclampsia compared with women with PPCM unexposed to preeclampsia.

3. To compare the long-term use of heart failure medications between women with PPCM exposed to preeclampsia and women with PPCM unexposed to preeclampsia, as an indirect reflection of time to left ventricular ejection fraction recovery.

2.2.2 Hypotheses:

1. Among women with preeclampsia, several clinical risk factors will be strongly associated with PPCM.

2. Women with PPCM exposed to preeclampsia will sustain more MACE within 6 months of follow-up than will women with PPCM unexposed to preeclampsia.

3. Women with PPCM unexposed to preeclampsia will be prescribed evidence based left ventricular ejection fraction recovery than women with PPCM exposed to preeclampsia.

2.3 Data source: The MarketScan database

We used the *Commercial Plans and Encounters Database* of the *Truven Health MarketScan Research Databases* (2010 to 2014) (37, 38). This claims-based database contains integrated longitudinal data for individuals covered by employer-sponsored private health insurance from payers across the United States (US) (37, 38). Raw data obtained from payers is frequently reviewed for quality, standardized, and aggregated (37). A unique enrollee identifier links patient-level demographic and enrollment information to inpatient, outpatient, and emergency department medical claims, and outpatient pharmacy claims (38, 39). 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. This database has previously been used to assess population trends of preeclampsia and severe maternal morbidity in the US (40, 41). Although the extent of misclassification of variables within the obstetric population of the *Marketscan* database is not known, the positive predictive value of ICD-9 codes for maternal comorbidities in similar health administrative databases has been estimated above 97% (42).

2.4 Construction of the base study cohort

We constructed a fixed base study cohort among women aged 15 to 55 years with obstetric deliveries between April 1st, 2011 and June 30th, 2014 and with insurance coverage for at least 6 months prior to the estimated date of conception (Figure T1). To identify obstetric deliveries, we used a previously validated algorithm using ICD codes in administrative databases (43). To establish the approximate time of conception, we used a previously published algorithm

(44): we subtracted 35 weeks from the date of delivery if a code for preterm delivery was present, and 39 weeks from the date of delivery in the absence of code for preterm delivery. We excluded women with an abortive outcome. Because PPCM is a diagnosis of exclusion defined by new-onset cardiomyopathy with reduced ejection fraction in the peripartum period in the absence other known causes of heart failure (see Introduction and Chapter 1.1 of thesis), we excluded women at highest risk of having non-PPCM related heart failure from our main study cohort (Figure T1) (2, 3). We excluded women with pre-existing cardiac disease (including codes for "personal history of heart disease", arrhythmia, cardiomyopathy, chronic rheumatic heart disease, heart surgery, ischemic heart disease, diseases of the pulmonary circulation, other forms of heart failure, and congenital heart disease) and women with malignancy who may have developed treatment-induced cardiomyopathy (including diagnostic codes for "personal history of malignancy", malignancy, or cancer therapy) within 6 months prior to estimated conception (Figure T1). By doing so, we aimed to avoid misclassifying those women with peripartum heart failure due to pre-existing cardiac conditions into the PPCM sub-cohort, and to enhance the specificity of our PPCM coding algorithm. See supplementary appendix for details of all the diagnostic and procedure codes used to construct the study cohort.

2.5 Assessment of risk factors for peripartum cardiomyopathy among women with preeclampsia

We used codes for non-severe preeclampsia, severe preeclampsia (including HELLP), and eclampsia to identify preeclampsia episodes. Pregnancies complicated by preeclampsia between 20th week of gestation and delivery were included in the preeclampsia sub-cohort (Figure T1). After inclusion in the preeclampsia sub-cohort, women with a diagnostic code for

PPCM and a procedure code for echocardiography within the peripartum period (i.e. between the last month of gestation and the first 5 months postpartum) were considered to have superimposed PPCM, herein referred to as pePPCM (Figure T2).

We extracted information on the following clinical risk factors potentially associated with superimposed PPCM among women with preeclampsia (Figure T2) (12, 18): advanced maternal age (≥ 35 years), multiple pregnancy, obesity, chronic hypertension, anemia, type 1 and type 2 diabetes mellitus, gestational diabetes mellitus, hypothyroidism, hyperthyroidism, chronic kidney disease, systemic autoimmune rheumatic diseases (including rheumatoid arthritis, systemic lupus erythematous, and other connective tissue diseases), asthma, tobacco use, and substance use disorder (including alcohol and drug use disorders). All potential risk factors were captured at time of preeclampsia diagnosis, except for maternal age which was recorded at time of delivery. See supplementary appendix for details of all the diagnostic codes used for assessment of risk factors. Unadjusted and adjusted multivariable logistic regression models were performed for each potential risk factor, with all other variables included as covariates. Crude and adjusted odds ratio (OR) and their 95% confidence interval (CI) were obtained for each potential risk factor. We used generalized estimating equations (GEE) with robust standard error to account for successive preeclampsia pregnancies occurring in the same woman (45, 46).

2.6 Comparison of major adverse cardiovascular events between women with peripartum cardiomyopathy exposed and unexposed to preeclampsia

Women with PPCM and co-incident preeclampsia constituted the pePPCM group (Figure T1). Women who developed PPCM but who did not have codes for preeclampsia constituted the npePPCM group (Figure T1). Additionally, it was not possible to ascertain that women with

gestational hypertension and pulmonary edema in the setting of PPCM did not in fact meet diagnostic criteria for preeclampsia (23, 24). Thus, women with npePPCM and uncomplicated gestational hypertension were excluded from the main PPCM sub-cohort in order to ensure that the unexposed group (i.e. women with npePPCM) did not comprise any misclassified exposed women (i.e. women with pePPCM). We only considered first episodes of PPCM after which women could no longer contribute any further pregnancies to the cohort. Women with pePPCM and those with npePPCM together constituted the PPCM sub-cohort (Figure T1).

We compared the combined incidence of major adverse cardiovascular events (MACE) and all-cause mortality between women with pePPCM and women with npePPCM (Figure T2). The MACE outcome was a composite of diagnoses of severe cardiovascular maternal morbidity developed for use in administrative databases (47), and cardiovascular procedures (48); these outcomes have been previously reported in women with heart disease in pregnancy (48, 49). MACE included indicators of acute heart failure (with 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), pulmonary edema, acute respiratory distress, conversion of cardiac rhythm, pulmonary embolism, puerperal cerebrovascular disorder, mechanical ventilation, heart transplantation, mechanical circulatory support, intra-cardiac device implantation, permanent pacemaker implantation, and in-hospital death. See supplementary appendix for detail of all diagnostic and procedure codes used for our composite outcome.

We required the primary outcome to occur within 6-months from time of diagnosis of PPCM (Figure T2). Indeed, a majority of women who have PPCM in the US have been estimated to recover their left ventricular function within 6-months (6, 50). We thus selected this

observation period to ensure that MACE events captured were directly attributable to PPCM, while also balancing against potential losses to follow-up with longer time periods. A diagnosis of PPCM also occurred within 6 months from the end of the study period (December 31st, 2014) to allow for a similar observation period for outcomes of all women included.

We used log-binomial regression models to estimate the association between preeclampsia and MACE among women with PPCM reported as risk ratios (RR) with 95% CI. Estimates were adjusted for age, multiple pregnancy, and medical comorbidities (including chronic hypertension, chronic kidney disease, obesity, and diabetes mellitus).

2.7 Comparison of long-term use of heart failure pharmacotherapy between women with peripartum cardiomyopathy exposed and unexposed to preeclampsia

As a proxy for persistent left ventricular dysfunction, we estimated in all PPCM women the total duration in days of prescribed pharmacotherapy with evidence-based heart failure medication (including beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor agonists, loop diuretics, and combination of hydralazine and nitroglycerine) (51). Duration of therapy between women with pePPCM and women with npePPCM was compared with non-parametric testing using a Kruskal-Wallis test, as treatment duration followed a skewed distribution.

2.8 Sensitivity analyses

First, women with uncomplicated gestational hypertension were included in the npePPCM group (Figure T1). As explained in greater detail above, we had excluded women with npePPCM and uncomplicated gestational hypertension from our main analysis to ensure that our

comparison group (i.e. npePPCM) did not comprise any misclassified women with preeclampsia. This sensitivity analysis sought to assess whether inclusion/exclusion of women with npePPCM and uncomplicated gestational hypertension from the main comparison group affected our results. We repeated similar regression models estimating crude and adjusted RR for combined MACE while adjusting for age, multiple pregnancy, and medical comorbidities (including chronic hypertension, chronic kidney disease, obesity, and diabetes mellitus).

Second, women with pre-existing cardiac disease and PPCM diagnosis were included in the main PPCM sub-cohort. As previously mentioned, in order to optimize the validity of the coding algorithm used to capture women who developed PPCM in our pregnancy cohort, we had excluded women at highest risk of having peripartum heart failure from other causes. In consequence, even if some women with pre-existing cardiac disease truly had developed superimposed PPCM, they were systematically excluded from our cohort. The aims of this sensitivity analysis were 1) to assess whether the inclusion/exclusion of women with pre-existing cardiac disease and PPCM diagnosis altered conclusions about the association between preeclampsia and MACE among women with PPCM and 2) after inclusion of women with pre-existing cardiac disease in the main PPCM sub-cohort, to address whether pre-existing cardiac disease may be an important driver of MACE among women with PPCM. Thus, we included women who had pre-existing cardiac disease with a diagnostic code for PPCM as well as a procedure code for echocardiography between the last month of gestation and the first 5 months postpartum in the PPCM sub-cohort. We further categorized these women according to whether they also had preeclampsia or uncomplicated gestational hypertension (Figure T1). The proportion of women with diagnostic codes for PPCM who had pre-existing cardiac disease was measured. Types and frequencies of the various included cardiac conditions were described. We

again constructed log-binomial regression models to estimate RRs and their 95% CI of MACE among women with pePPCM compared to women with npePPCM using this new classification, adjusting for pre-existing cardiac disease, age, multiple pregnancy, and medical comorbidities. We also compared the risk of MACE between PPCM women with and without pre-existing cardiac disease in a multivariable log binomial regression, with pre-existing disease as the independent variable. For this analysis, we adjusted for preeclampsia, age, multiple pregnancy, and medical comorbidities.

2.9 Directed acyclic graph depicting the association between preeclampsia and major adverse cardiovascular events among women with peripartum cardiomyopathy, and relationships with confounders and factors in the causal pathway

Directed acyclic graphs (DAG)s were used to depict causal relationships between variables included in our conceptual framework (52, 53). Figures 3a and 3b represent the DAGs of the cohort study addressing the association between our main exposure of interest (i.e. preeclampsia) and our primary outcome (i.e. MACE) among women with PPCM (Figures T3a and T3b) (52). These DAGs were initially constructed using the "R" package "DAGitty", and transcribed in Figures T3a and T3b (54). Variables confounded the association between the exposure and outcome when they were 1) associated with the exposure 2) associated with the outcome 3) not an "intermediate variable in the causal pathway between exposure and outcome" (52, 53). Confounded associations were considered to be mediated by biasing paths (55). Variables in the pathway of the association between the exposure and outcome were considered to be intermediates in the causal path (55). A sufficient adjustment set of covariates was obtained when no biasing paths remained after adjustment for a parsimonious set of variables (55).

We considered the following covariates to illustrate the association between preeclampsia and MACE: age, multiple pregnancy, chronic hypertension, chronic kidney disease, obesity, diabetes mellitus, preterm labor, preterm delivery, use of tocolytics, use of magnesium sulfate, and mode of delivery (Figure T3a). As demonstrated in Figure T3b, adjusting for age, multiple pregnancy, chronic hypertension, chronic kidney disease, obesity, and diabetes mellitus was sufficient in removing all biasing paths (Figure T3b). These covariates composed the sufficient adjustment set for our analysis. As such, further adjustment was found not to be required for preterm labor, preterm delivery, use of tocolytics, use of magnesium sulfate, and cesarean delivery. Additionally, preterm labor, preterm delivery, use of tocolytics, use of magnesium sulfate, and cesarean delivery, were found to be in the causal path of the association between preeclampsia and MACE (Figures T3a and T3b).

Figure T1. Flow chart of study participants

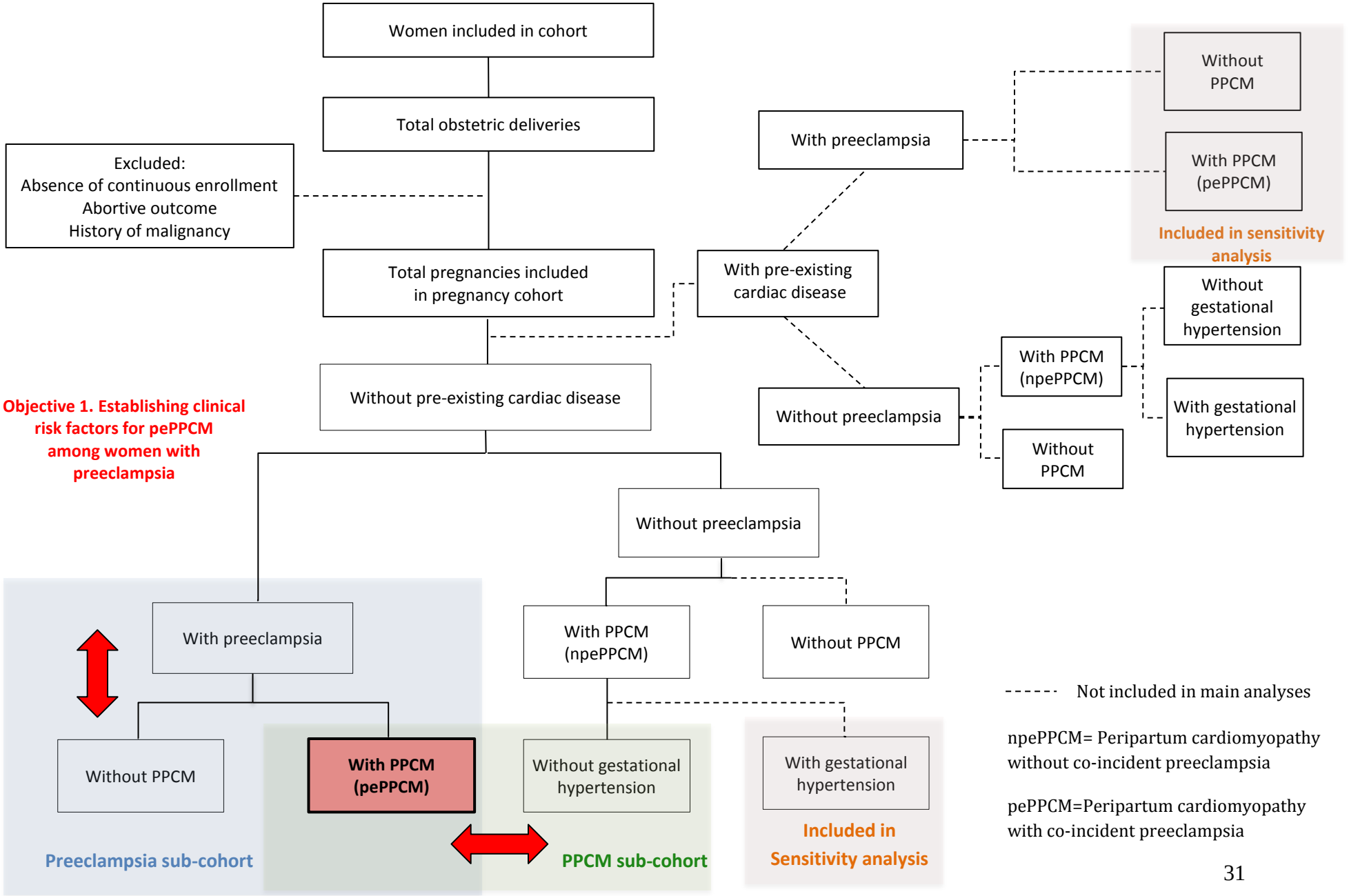
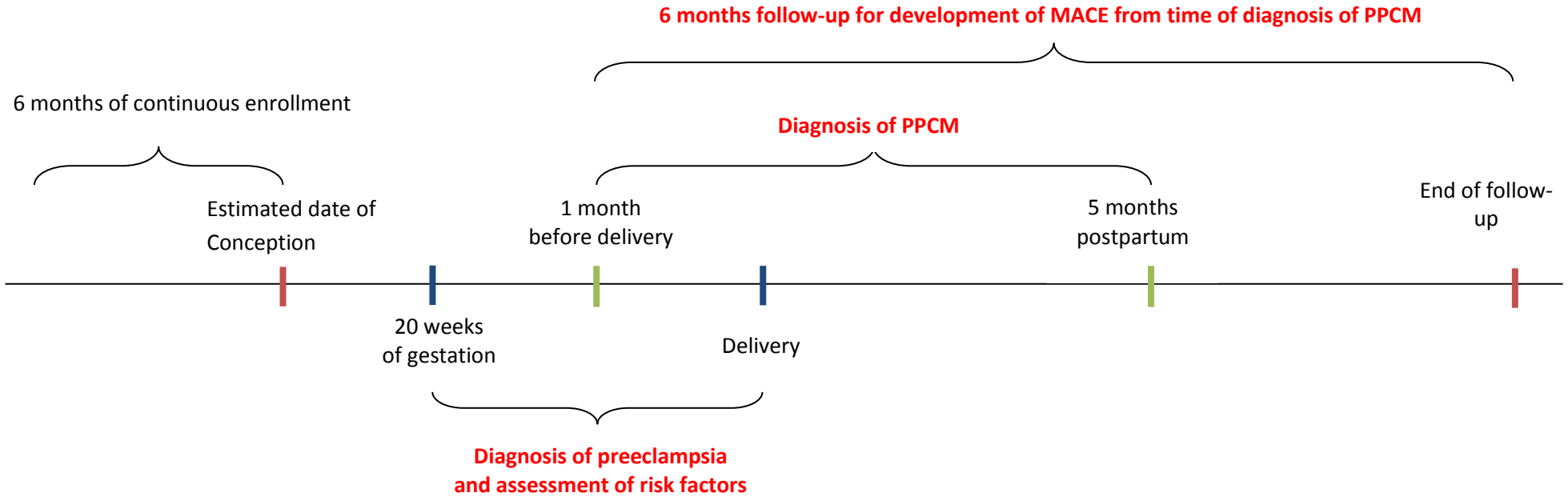


Figure T2. Timeline for preeclampsia diagnosis and assessment of risk factors, as well as peripartum cardiomyopathy diagnosis and assessment of major adverse cardiovascular events



MACE = Major Adverse Cardiovascular Event, PPCM = Peripartum cardiomyopathy (including women with peripartum cardiomyopathy with co-incident preeclampsia and women with peripartum cardiomyopathy without co-incident preeclampsia)

Figure T3a. Directed acyclic graph of the association between preeclampsia and major adverse cardiovascular events within the peripartum cardiomyopathy sub-cohort, prior to adjustment for confounders

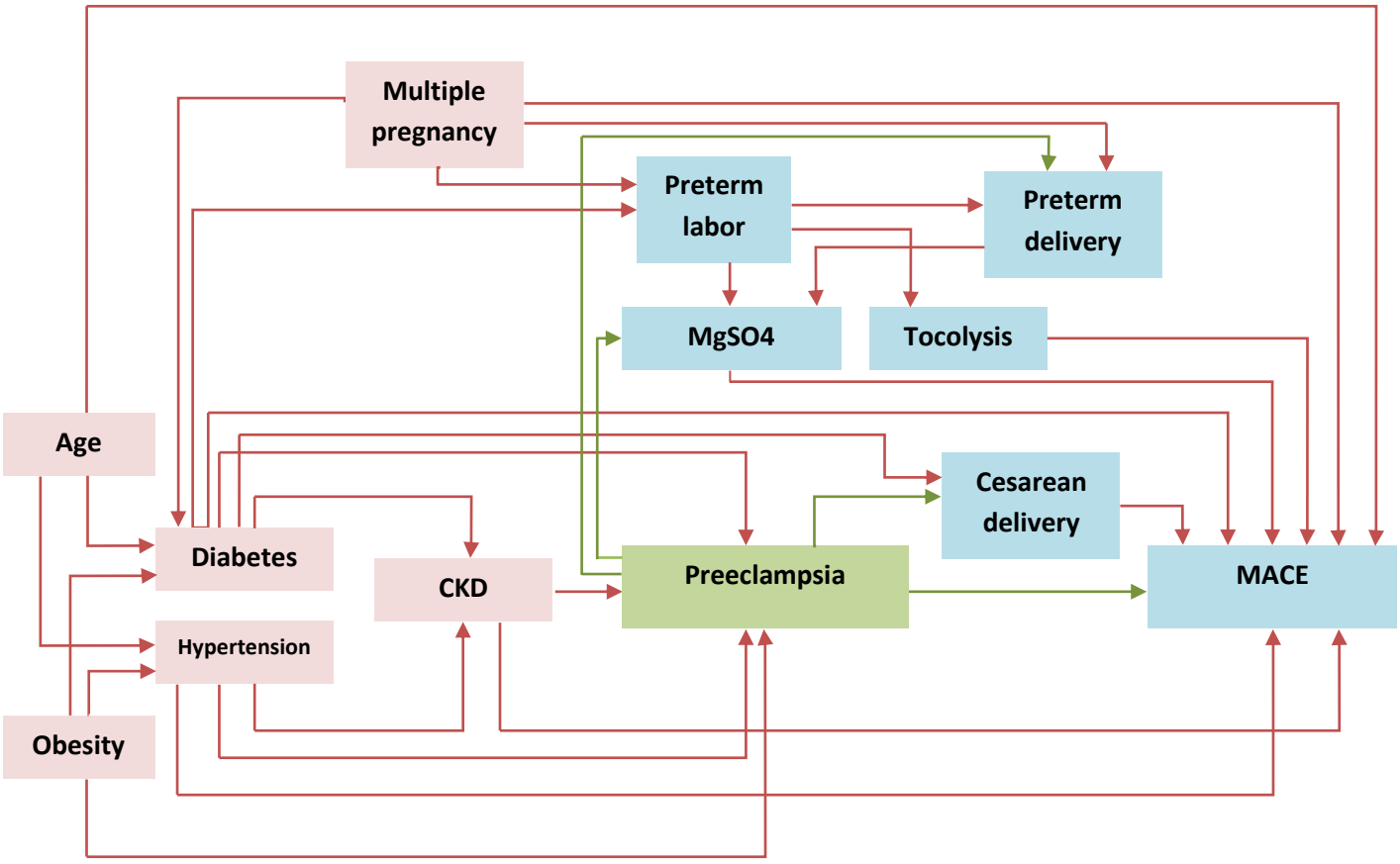
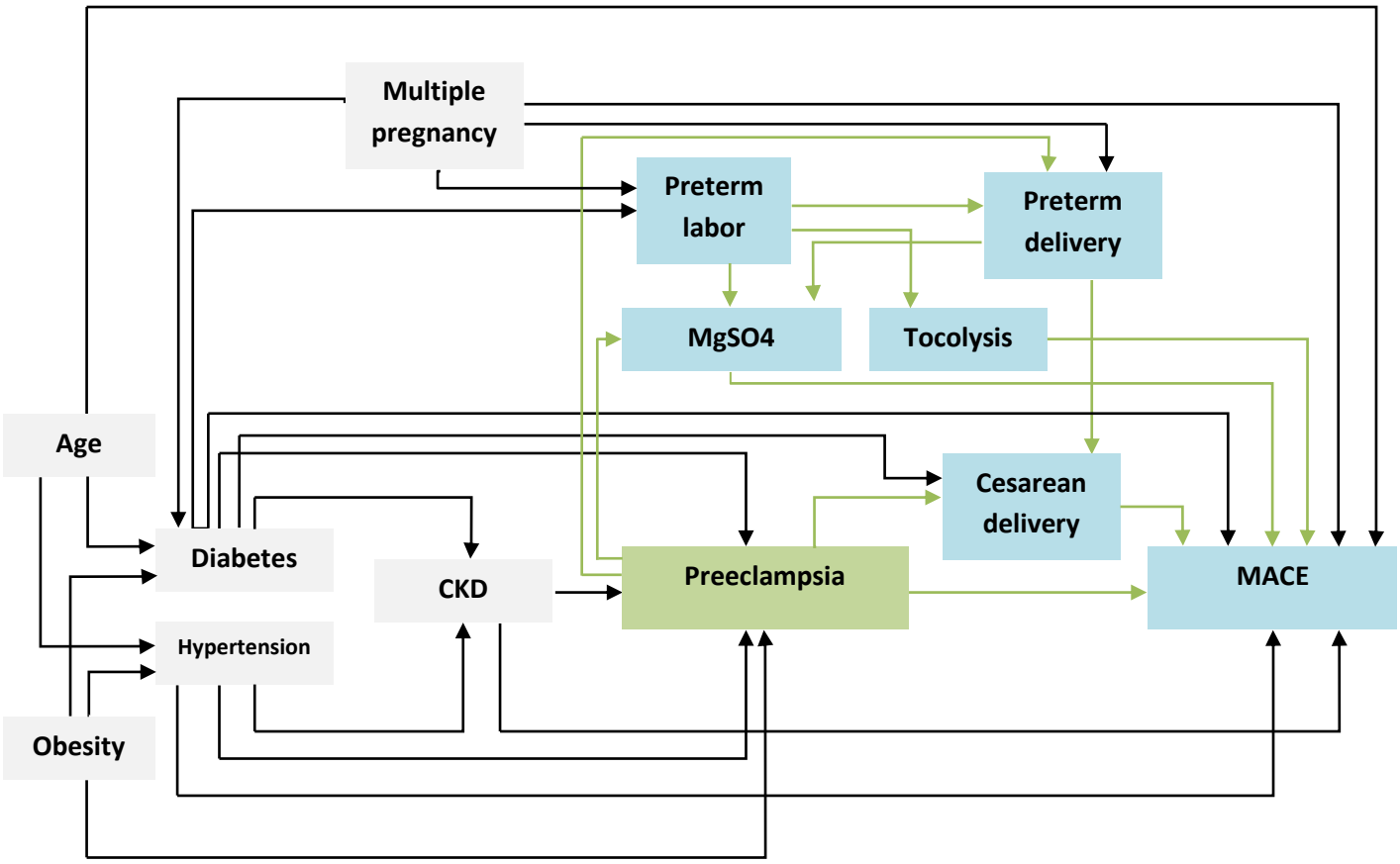
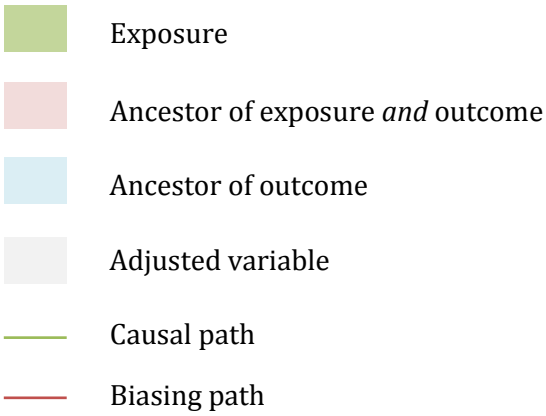


Figure T3b. Directed acyclic graph of the association between preeclampsia and major adverse cardiovascular events within the peripartum cardiomyopathy sub-cohort, after adjustment for confounders



Legend for Figures T3a and 3b:



CKD=Chronic kidney disease, MACE= Major adverse cardiovascular events

Table T1. Studies addressing outcomes of peripartum cardiomyopathy with and without hypertensive disorders

Authors	Country	Time period	Recruitment and data source	Total number included	Hypertensive disorder considered	N (%) with hypertensive disorder	Outcome observed
Ntusi *et al* (33)	South Africa	1996-2009	Consecutive referrals to a cardiology clinic	83	Gestational hypertension and preeclampsia	53 (63.9%)	Women without HD had lower LVEF at presentation (23.8% VS 49.9% p=0.001) and more chronic heart failure at last follow-up (28% VS 1.9% p<0.001). There were more deaths in the group without HD (5 deaths compared to none).
Kamiya *et al* (36)	Japan	2007-2008	Questionnaire survey sent to medical organizations in Japan	102	Chronic hypertension, gestational hypertension, and preeclampsia	42 (41.2%)	Women with HD had a shorter hospital stay (26.9 VS 40.9 days).
Ersboll *et al (35)*	Denmark	2005-2014	Danish national patient Register, Medical Birth Register, and Causes of Death Register	61	Chronic hypertension, gestational hypertension, and preeclampsia	33 (54.1%)	There was a higher rate of composite outcome of death, heart transplantations, mechanical circulatory support, and persistent heart failure at 10-14 months of follow-up among women without HD (32.1% VS 0%).
Barasa *et al (31)*	Sweden	NA	Identification by clinicians and identification by ICD coding in hospital's discharge database	24	Preeclampsia	14 (58.3%)	100% of cases with pulmonary edema and 80% of cases requiring intensive care unit admissions occurred in women with HD. Preeclampsia was associated with a higher LVEF at presentation and follow-up (p<0.001).
Haghikia *et al (34)*	Germany	2004-2012	Patient registry	115	Pregnancy-associated hypertensive disorders	50 (43.5%)	Having a HD was associated with clinical improvement on follow-up (49% of women with clinical improvement had HD VS 7% of women without clinical improvement who had HD).
McNamara *et al (4)*	United States	2009-2012	Prospective consecutive enrollment	100	Hypertension	45 (45.0%)	HD was not associated with a difference in prognosis.
Lindley *et al (32)*	United States	2004-2014	Retrospective chart review of electronic medical records	39	Preeclampsia/ Eclampsia/HELLP	15 (38.5%)	A composite of death and hospital readmission for heart failure was more frequent in women with HD on survival analysis (p=0.0466). There was improved LV recovery in women with HD (75.0% recovery with HD VS 30.8% without HD, p=0.047)

CHAPTER 3. PREFACE TO MANUSCRIPT

This manuscript explores associations between PPCM and preeclampsia. Using a retrospective cohort study design, our aims were to (1) identify clinical risk factors strongly associated with PPCM among women with preeclampsia, and (2) estimate the effect of preeclampsia on clinical outcomes within 6 months of PPCM diagnosis.

An abstract based on the results of the cohort study was presented as an oral presentation at the 5th International Congress on Cardiac Problems in Pregnancy in February 2018, in Bologna, Italy.

This manuscript has been submitted to *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health*.

CHAPTER 4. STUDY MANUSCRIPT

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

Authors :
Isabelle Malhamé MD[1,3]
Natalie Dayan MD MSc[1, 2]
Cristiano S Moura PhD[2]
Michelle Samuel MPH[2,3]
Evelyne Vinet MD PhD[1, 2, 3]
Louise Pilote MD MPH PhD[1, 2, 3]

Affiliations:
1. Department of Medicine, McGill University Health Centre, Montreal, Quebec, Canada
2. Research Institute, McGill University Health Centre, Montreal, Quebec, Canada
3. Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

Total word count (Abstract): 250

Total word count (Manuscript): 2,888

Subject term: Preeclampsia, Cardiomyopathy, Hypertension

Address of Correspondence:
Louise Pilote MD MPH PhD
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

Tel: 514-934-1934, x 44722 or 34667
Fax: 514-934-8293 or 514-843-1676

Email: louise.pilote@mcgill.ca

ABSTRACT

Background: Peripartum cardiomyopathy (PPCM) and preeclampsia are strongly associated, yet risk factors and outcomes following their combined occurrence are not well known.

Methods: A cohort was constructed with delivery admissions from 2011 to 2014 using a large US administrative database (*Marketscan*). All pregnancies complicated by preeclampsia were identified, and clinical risk factors for the development of PPCM were assessed. The risks of major adverse cardiovascular events (MACE) at 6 months were compared between PPCM with co-incident preeclampsia (pePPCM) and PPCM and no preeclampsia (npePPCM).

Results: 1,024,035 pregnancies were included, of which 64,503 (6.3%) were complicated by preeclampsia. There were 283 women with pePPCM and 591 women with npePPCM. Among women with preeclampsia, risk factors for PPCM were 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 were more likely to experience MACE than women with npePPCM (adjusted RR 1.29, 95% CI [1.06, 1.57]), which was explained by higher rates of clinical heart failure and pulmonary embolism in this patient group. There was no difference in mortality between groups.

Conclusion: Close follow-up of preeclamptic women with risk factors for PPCM should be considered. Preeclampsia conferred a greater risk of MACE at 6 months among women with PPCM. Further studies are required to determine whether preeclampsia affects the long-term prognosis of women with PPCM.

KEYWORDS

Cardiomyopathy, heart failure, preeclampsia

ABREVIATIONS

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

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) has been 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, a leading cause of maternal morbidity and mortality, is diagnosed in ~ 20% of women with PPCM, which is four times the worldwide incidence (4, 5).

While an anti-angiogenic state might provide a theoretical basis to link the two conditions, not all women with preeclampsia develop superimposed PPCM (6, 7). Assessment of risk factors for PPCM among this high-risk population could identify those who may benefit from closer surveillance for the development of cardiovascular complications. This, in turn, could lead to early detection of PPCM and decreased adverse outcomes related to late presentation or diagnostic delay (3). Moreover, well-described structural cardiac changes in preeclampsia, including left ventricular concentric remodeling and diastolic dysfunction, may further affect the clinical course of women with PPCM (8-10). A better understanding of the effect of preeclampsia on PPCM-related outcomes could help clinicians anticipate complications and counsel patients more accurately. While several small studies with discrepant results have addressed the impact of various 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 assessed 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.

METHODS

Data source

We used the *Commercial Plans and Encounters Database* of the *Truven Health MarketScan Research Databases* (2010 to 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, and emergency department medical claims, 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.

Study population

We constructed a pregnancy cohort among women aged 15 to 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.

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.

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).

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 cases/1000 deliveries and/or PPCM case/# of 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 estimating 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 comorbidities (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.

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).

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.

RESULTS

Study population

A total of 993,187 women contributed 1,024,035 pregnancies to the study cohort (Figure 1). There were 874 cases of PPCM diagnosed during the study period. The cumulative incidence of PPCM in our total study cohort was ~ 1/1,172 deliveries (i.e. 0.85/1,000 deliveries). Among 64,503 pregnancies with preeclampsia, 283 had pePPCM (Figure 1). Of the 959,532 pregnancies without preeclampsia, 591 had npePPCM (Figure 1). Thus, the cumulative incidence of pePPCM among women with preeclampsia was 1/228 deliveries (i.e. 4.39/1,000 deliveries with preeclampsia), whereas the cumulative incidence of npePPCM among women without preeclampsia was 1/1,624 deliveries (i.e. 0.62/1,000 deliveries without preeclampsia).

Baseline characteristics

Compared to women with preeclampsia alone, women with preeclampsia 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).

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]) (Figure 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 (Figure 2). Results of the univariate regressions are shown on Table S6 of the supplementary appendix.

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 (Figure 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 (Figure 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]).

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 (6, 7, 30-32). Further research is needed to determine whether adequate blood

pressure and glycemic control might mitigate the risk of developing PPCM among women with chronic hypertension and type 2 diabetes.

Cardiovascular disease, including cardiomyopathy are among leading causes of pregnancy-related deaths in the US (4). Prompt identification and early management of women at highest risk of cardiovascular disease might help to reduce this maternal mortality risk. Close follow-up of preeclamptic women with risk factors for PPCM should be considered and clinicians should maintain a low threshold for performing echocardiography in the appropriate clinical context within this high-risk 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 (33). 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 postpartum period (34, 35).

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 at a single center 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.

The lack of difference in duration of pharmacotherapy for heart failure between women with pePPCM and those with npePPCM, possibly reflects no differences in persistent left ventricular dysfunction in both groups. Differences in long-term prognosis, however, could not be firmly excluded due to lack of indications for medication initiation and discontinuation in our database. 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. As a result, findings may not be generalizable to state-insured pregnant women. Moreover, our data source did not have information about prior history of preeclampsia, parity, duration of symptoms, echocardiographic measurements, natriuretic peptide values, and out-of-hospital death. Lack of ethnicity data was also a limitation given its known influence on PPCM-related outcomes (3, 36). Despite our use of stringent criteria, the extent of misclassification of the diagnosis and procedure codes that we used remains to be determined. 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 long-term prognosis of women with PPCM and preeclampsia remains to be further described. 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.

FUNDING

No funding was received for this work. 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.

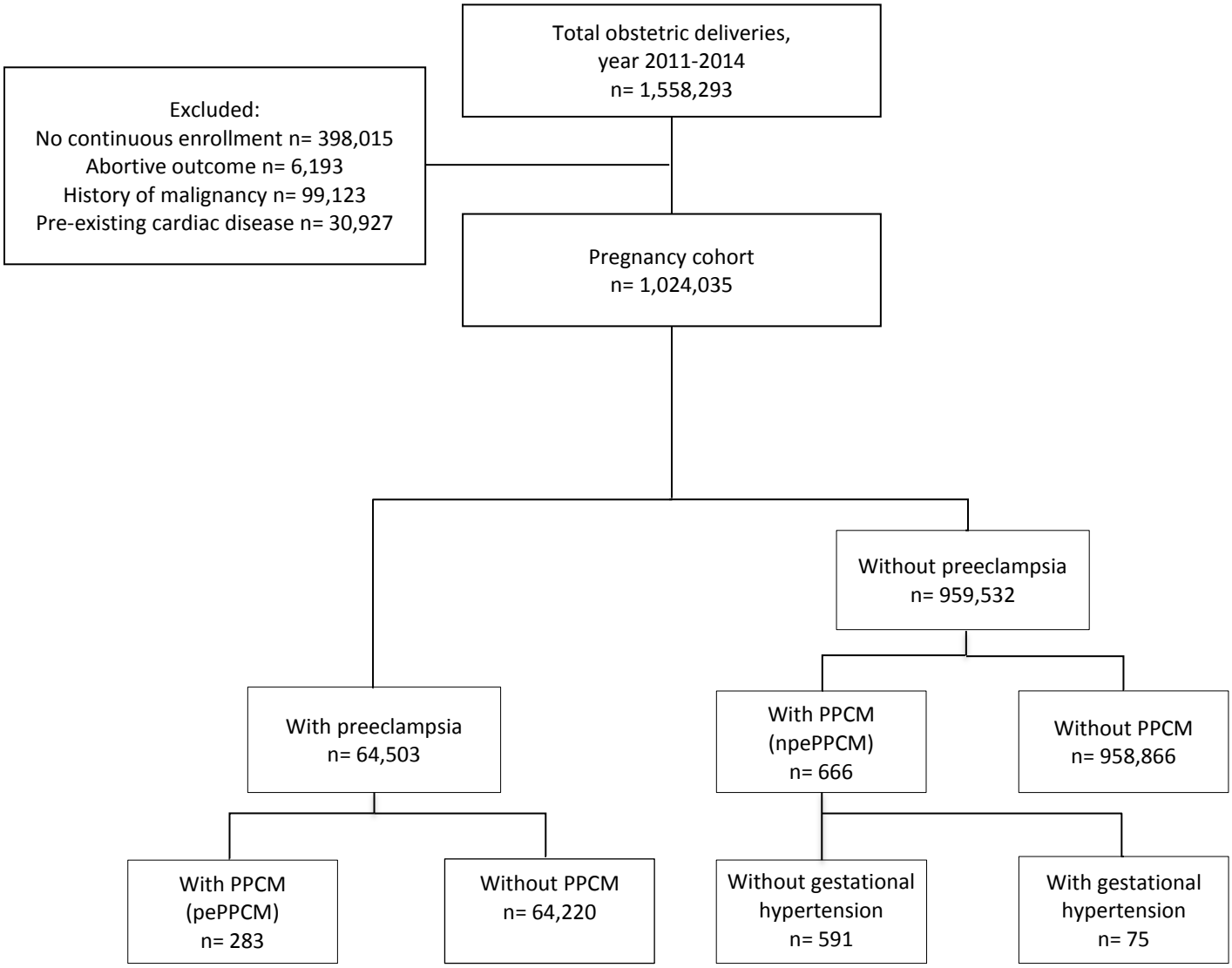
References

1. Sliwa K, Hilfiker-Kleiner D, Petrie MC, Mebazaa A, Pieske B, Buchmann E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. European journal of heart failure. 2010;12(8):767-78.
2. Arany Z, Elkayam U. Peripartum Cardiomyopathy. Circulation. 2016;133(14):1397-409.
3. McNamara DM, Elkayam U, Alharethi R, Damp J, Hsich E, Ewald G, et al. Clinical Outcomes for Peripartum Cardiomyopathy in North America: Results of the IPAC Study (Investigations of Pregnancy-Associated Cardiomyopathy). Journal of the American College of Cardiology. 2015;66(8):905-14.
4. Pregnancy Mortality Surveillance System [cited 2018 October 19th]. Available from: https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pmss.html.
5. Bello N, Rendon IS, Arany Z. The relationship between pre-eclampsia and peripartum cardiomyopathy: a systematic review and meta-analysis. Journal of the American College of Cardiology. 2013;62(18):1715-23.
6. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. The New England journal of medicine. 2004;350(7):672-83.
7. Damp J, Givertz MM, Semigran M, Alharethi R, Ewald G, Felker GM, et al. Relaxin-2 and Soluble Flt1 Levels in Peripartum Cardiomyopathy: Results of the Multicenter IPAC Study. JACC Heart failure. 2016;4(5):380-8.
8. Vaught AJ, Kovell LC, Szymanski LM, Mayer SA, Seifert SM, Vaidya D, et al. Acute Cardiac Effects of Severe Pre-Eclampsia. Journal of the American College of Cardiology. 2018;72(1):1-11.
9. Castleman JS, Ganapathy R, Taki F, Lip GY, Steeds RP, Kotecha D. Echocardiographic Structure and Function in Hypertensive Disorders of Pregnancy: A Systematic Review. Circulation Cardiovascular imaging. 2016;9(9).
10. Dennis AT. Transthoracic echocardiography in women with preeclampsia. Current opinion in anaesthesiology. 2015;28(3):254-60.
11. Barasa A, Goloskokova V, Ladfors L, Patel H, Schaufelberger M. Symptomatic recovery and pharmacological management in a clinical cohort with peripartum cardiomyopathy. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2017:1-8.
12. Lindley KJ, Conner SN, Cahill AG, Novak E, Mann DL. Impact of Preeclampsia on Clinical and Functional Outcomes in Women With Peripartum Cardiomyopathy. Circulation Heart failure. 2017;10(6).
13. Ntusi NB, Badri M, Gumedze F, Sliwa K, Mayosi BM. Pregnancy-Associated Heart Failure: A Comparison of Clinical Presentation and Outcome between Hypertensive Heart Failure of Pregnancy and Idiopathic Peripartum Cardiomyopathy. PLoS One. 2015;10(8):e0133466.

14. Haghikia A, Podewski E, Libhaber E, Labidi S, Fischer D, Roentgen P, et al. Phenotyping and outcome on contemporary management in a German cohort of patients with peripartum cardiomyopathy. Basic Res Cardiol. 2013;108(4):366.
15. Ersboll AS, Johansen M, Damm P, Rasmussen S, Vejlstrup NG, Gustafsson F. Peripartum cardiomyopathy in Denmark: a retrospective, population-based study of incidence, management and outcome. European journal of heart failure. 2017.
16. Kamiya CA, Kitakaze M, Ishibashi-Ueda H, Nakatani S, Murohara T, Tomoike H, et al. Different characteristics of peripartum cardiomyopathy between patients complicated with and without hypertensive disorders. -Results from the Japanese Nationwide survey of peripartum cardiomyopathy. Circulation journal : official journal of the Japanese Circulation Society. 2011;75(8):1975-81.
17. Truven Health MarketScan® Research Databases. [cited 2017 December 26th]. Available from: https://marketscan.truvenhealth.com/marketscanuniversity/userguide/2015 MarketScanCCAE-MDCRUserGuide.pdf.
18. Leigh G. Hansen SC. Health Research Data for the Real World: the Marketscan Research Databases 2011 [cited 2017 December 26th]. Available from: https://marketscan.truvenhealth.com/marketscanuniversity/userguide/2015 MarketScanCCAE-MDCRUserGuide.pdf.
19. Machado MAA, de Moura CS, Wang Y, Danieli C, Abrahamowicz M, Bernatsky S, et al. Comparative effectiveness of antihypertensive drugs in nondiabetic patients with hypertension: A population-based study. Journal of clinical hypertension (Greenwich, Conn). 2017;19(10):999-1009.
20. Kuklina EV, Whiteman MK, Hillis SD, Jamieson DJ, Meikle SF, Posner SF, et al. An enhanced method for identifying obstetric deliveries: implications for estimating maternal morbidity. Maternal and child health journal. 2008;12(4):469-77.
21. Margulis AV, Setoguchi S, Mittleman MA, Glynn RJ, Dormuth CR, Hernandez-Diaz S. Algorithms to estimate the beginning of pregnancy in administrative databases. Pharmacoepidemiology and drug safety. 2013;22(1):16-24.
22. Pearson GD, Veille JC, Rahimtoola S, Hsia J, Oakley CM, Hosenpud JD, et al. Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. Jama. 2000;283(9):1183-8.
23. Abboud J, Murad Y, Chen-Scarabelli C, Saravolatz L, Scarabelli TM. Peripartum cardiomyopathy: a comprehensive review. Int J Cardiol. 2007;118(3):295-303.
24. Sigakis MJ, Leffert LR, Mirzakhani H, Sharawi N, Rajala B, Callaghan WM, et al. The Validity of Discharge Billing Codes Reflecting Severe Maternal Morbidity. Anesthesia and analgesia. 2016;123(3):731-8.
25. Kolte D, Khera S, Aronow WS, Palaniswamy C, Mujib M, Ahn C, et al. Temporal trends in incidence and outcomes of peripartum cardiomyopathy in the United States: a nationwide population-based study. J Am Heart Assoc. 2014;3(3):e001056.
26. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomstrom-Lundqvist C, Cifkova R, De Bonis M, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. European heart journal. 2018;39(34):3165-241.

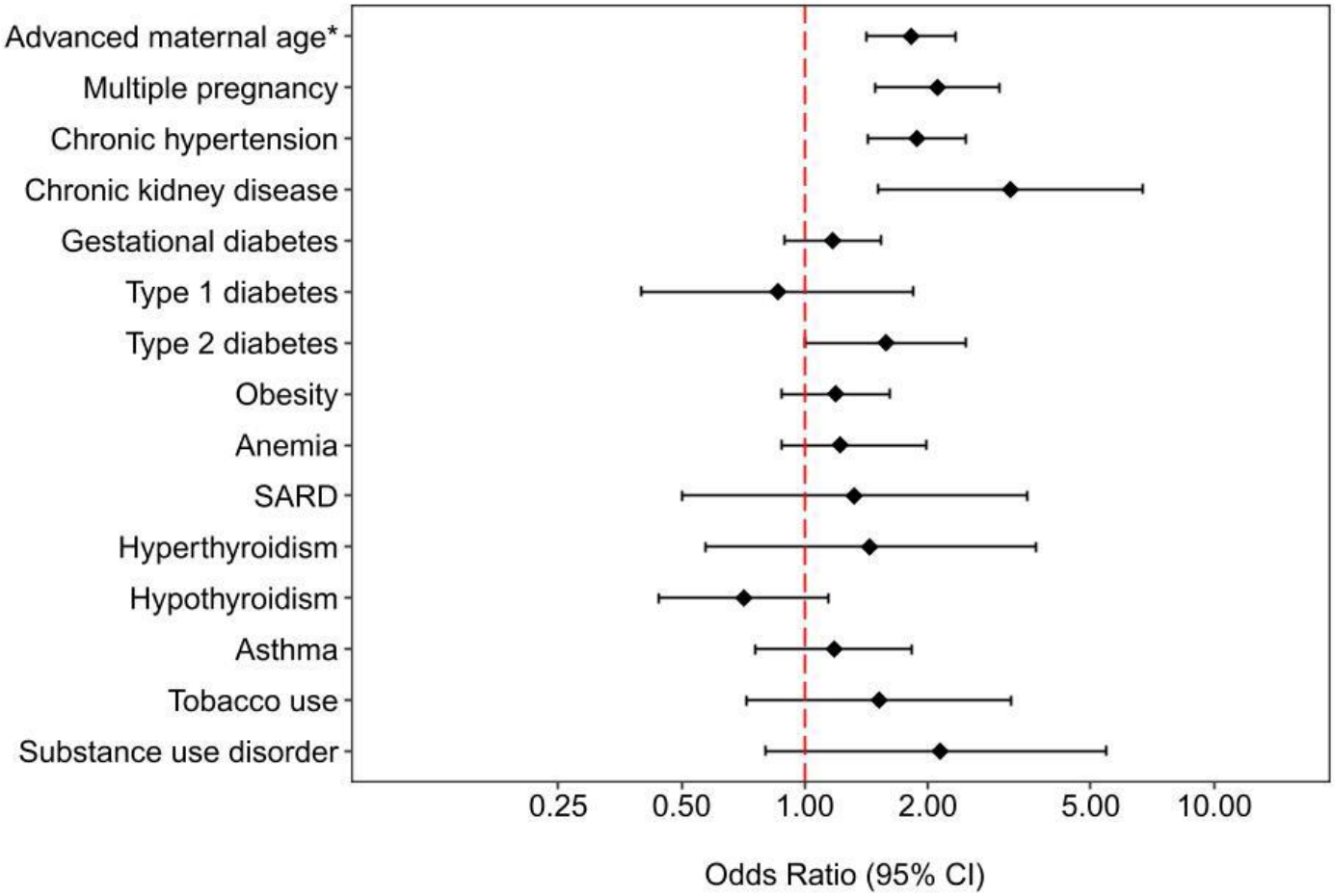
27. Auger N, Luo ZC, Nuyt AM, Kaufman JS, Naimi AI, Platt RW, et al. Secular Trends in Preeclampsia Incidence and Outcomes in a Large Canada Database: A Longitudinal Study Over 24 Years. The Canadian journal of cardiology. 2016;32(8):987.e15-23.
28. Louis GB, Dukic V, Heagerty PJ, Louis TA, Lynch CD, Ryan LM, et al. Analysis of repeated pregnancy outcomes. Statistical methods in medical research. 2006;15(2):103-26.
29. Hypertension in pregnancy / developed by the Task Force on Hypertension in Pregnancy.: American College of Obstetricians and Gynecologists. ; 2013 [cited 2017 December 11th]. Available from: https://www.acog.org/~/media/Task Force and Work Group Reports/public/HypertensioninPregnancy.pdf.
30. Patten IS, Rana S, Shahul S, Rowe GC, Jang C, Liu L, et al. Cardiac angiogenic imbalance leads to peripartum cardiomyopathy. Nature. 2012;485(7398):333-8.
31. Goland S, Weinstein JM, Zalik A, Kuperstein R, Zilberman L, Shimoni S, et al. Angiogenic Imbalance and Residual Myocardial Injury in Recovered Peripartum Cardiomyopathy Patients. Circulation Heart failure. 2016;9(11).
32. Bello NA, Arany Z. Molecular mechanisms of peripartum cardiomyopathy: A vascular/hormonal hypothesis. Trends in cardiovascular medicine. 2015;25(6):499-504.
33. Dennis AT, Solnordal CB. Acute pulmonary oedema in pregnant women. Anaesthesia. 2012;67(6):646-59.
34. Chan WS, Rey E, Kent NE, Chan WS, Kent NE, Rey E, et al. Venous thromboembolism and antithrombotic therapy in pregnancy. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC. 2014;36(6):527-53.
35. Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium 2015 [cited 2018 December 10th]. Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf.
36. Irizarry OC, Levine LD, Lewey J, Boyer T, Riis V, Elovitz MA, et al. Comparison of Clinical Characteristics and Outcomes of Peripartum Cardiomyopathy Between African American and Non-African American Women. JAMA cardiology. 2017;2(11):1256-60.

Figure 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

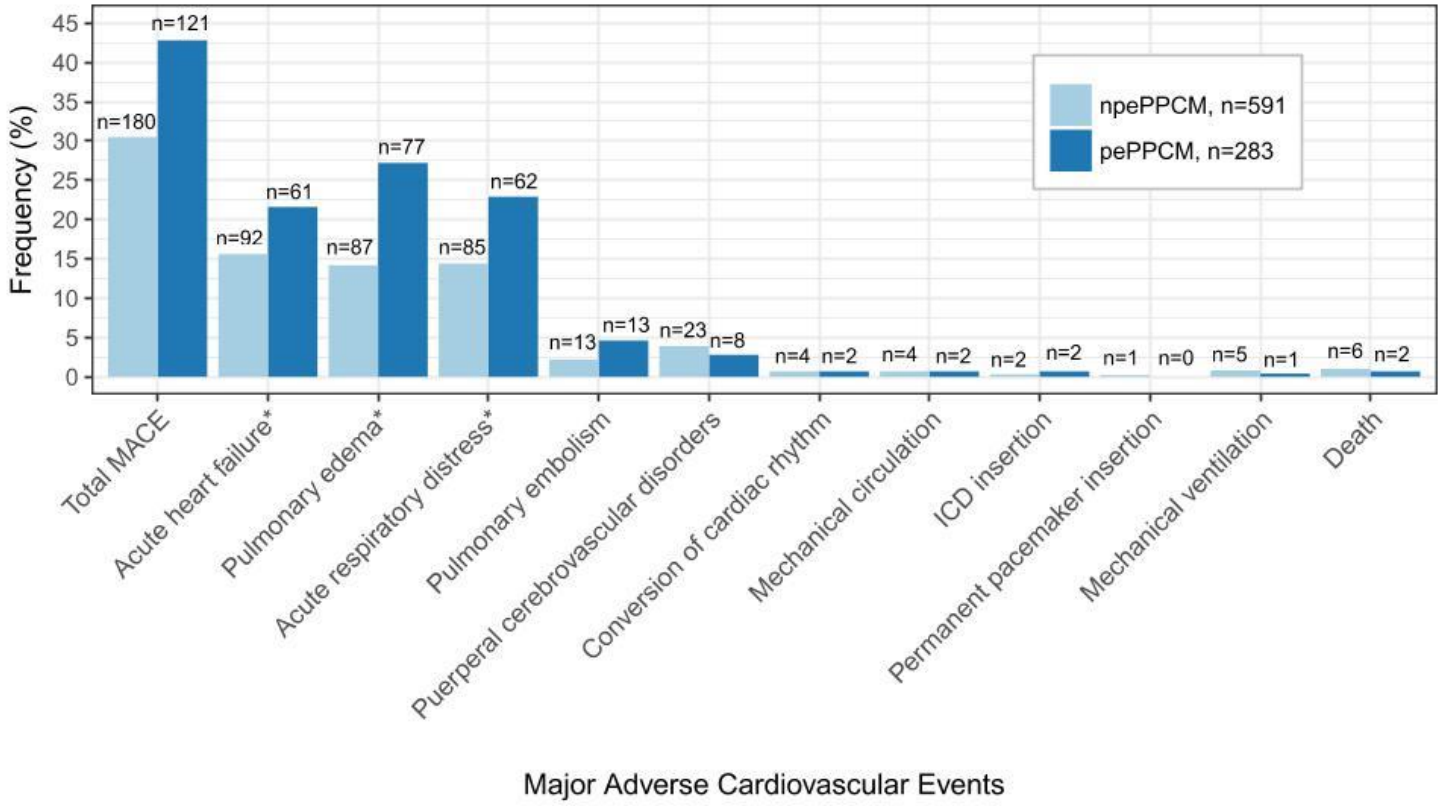
Figure 2. Forest plot of the association between potential risk factors and peripartum cardiomyopathy among women with preeclampsia- Chronic kidney disease, multiple pregnancy, chronic hypertension, advanced maternal age, and type 2 diabetes were independent risk factors for the development of PPCM among 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)

Figure 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

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

*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).

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

Table 2. Descriptive characteristics of women with peripartum cardiomyopathy with co-incident preeclampsia compared to women with peripartum cardiomyopathy without preeclampsia*

	pePPCM n = 283	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

* 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).

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

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

SUPPLEMENTARY APPENDIX

Table S1. Algorithm for Identification of deliveries*

Variable	ICD-9 diagnosis	CPT	ICD-9 procedure	DRG code
Identification of Delivery	V27, 650, 669.5x, 669.7x	59400, 59409, 59410, 59610, 59612, 59614, 59510, 59514, 59515, 59618, 59620, 59622	72.0, 72.1, 72.21, 72.29, 7231, 72.39, 72.4, 72.6, 72.51, 72.52, 72.53, 72.54, 71, 72.29, 72.8, 72.9, 73.22, 73.59, 73.6, 74.0, 74.1, 74.2, 74.4, 74.99, 74.0, 74.1, 74.2, 74.4, 74.99	370, 372, 373, 374, 375, 765, 766
Exclusion of abortive outcome	63x	59820, 59821, 59850-59852, 59840, 59841, 59822, 59850-59852, 59855-59857	69.01, 69.51, 74.91, 75.0, 74.3, 74.91	777, 779, 770

*Based on an algorithm described by *Kuklina et Al.* (1)

Table S2. Exclusion of women with a history of cardiac conditions and malignancy at baseline

Variable	ICD-9 diagnosis	CPT	ICD-9 procedure	DRG code
Cardiomyopathy	425.x, 425.1x			
Chronic rheumatic heart disease	393, 394.0-2, 394.9, 395.0-2, 395.9, 396.0-3, 396.8-9, 397.0-1, 397.9, 398.x			
Non rheumatic valvular heart disease	424.x			
Heart surgery		3310-33999, 34001-37799,	35, 36, 37, 38, 39	215-274
Personal history of heart disease	V15.1			
Ischemic heart disease	410.x, 411.x, 412.x, 413.x, 414.x			
Diseases of pulmonary circulation	416.x, 417.x			
Other forms of heart failure	402.x, 404.x, 420.x, 421.x, 422.0, 423.x, 428.x, 429.x, 426.x, 427.x			
Congenital heart disease	745.x, 746.x, 747.0-747.4x			
Personal history of malignancy	V10			
Malignancy or chemotherapy or radiotherapy	140-209, 230-234, 235-239, V10.x, V15.3	77295-77373, 77385-77425, 77399, 77422-77423, 77427-77499, 77520-77525, 77600-77615, 77620, 77750-77799, 96401-96402, 96405-96411, 96413-96417, 96420-96425	92.x	

Table S3. Diagnosis and procedure codes for diagnosis of covariates

Variable	ICD-9 diagnosis	CPT	ICD-9 procedure
Peripartum Cardiomyopathy	674.5x		
Caesarean section delivery	669.7	59510, 59514, 59515, 59618, 59620, 59622	
Preterm labor	644.0, 644.1, 644.2		
Chronic hypertension	401.x, 405.x, 642.2, 642.0x, 642.1x		
Gestational hypertension	642.3x,		
Preeclampsia	642.4x, 642.7x, 642.5x, 642.6x		
Multiple gestation	651		
Tobacco smoking	305.1, 649.0		
Alcohol use disorder	303.0		
Drug use disorder	304.6x, 304.8x, 304.5x, 304.1x, 304.9x, 304.7x, 304.4x, 304.0x, 648.3		
Asthma	493.0x, 493.1x, 493.2x, 493.8x, 493.9x		
Vitamin b deficiency	266.0x, 266.1x, 266.2x, 266.9x		
Diabetes type 1	250.x1, 250.x3		
Diabetes type 2	250.x0, 250.x2		
Gestational diabetes	648.8x		
Anemia during pregnancy	648.2x		
Obesity	278.0x, 649.1		
Systemic rheumatic autoimmune diseases	710.0, 710.1-5, 710.8, 710.9, 714.0, 714.1, 714.2, 714.3		
Hyperthyroidism	242.0-4, 242.8, 242.9		
hypothyroidism	244.0-3, 244.8, 244.9		
Chronic kidney disease	585.1-6, 585.9, 403.x, 404.x		
HIV	042, V08		
Hypercoagulable state	289.81, 289.82		
Echocardiography procedure		93303, 93304, 93306, 93307, 93308, 93312-93314, 93315-93317, 93318, 93320-93321, 93325, 93350, 93350-93352, 93352, 93355	00.02, 88.72, 37.28

Table S4. Algorithm for Identification of Severe maternal morbidity (1, 2)

Variable	**ICD9-diagnosis**	**CPT**	**ICD9-procedure**
Acute heart failure	415, 427.21, 427.42, 427.5, 428.1, 428.21, 428.34, 428.31, 428.33, 428.41, 428.43, 997.1	92950	99.63 99.60
Conversion of heart rhythm		92960, 92961	99.6
Pulmonary edema	428.1, 514, 518.4		
Acute respiratory distress	518.0, 518.5, 518.81, 518.82, 518.84, 799.1		
Thromboembolism	415.1, 673.0, 673.1, 673.2, 673.3, 673.8		
Ventilation		94002, 94003	93.9, 96.03-96.05, 96.7
Shock	669.11, 785.5, 995.0, 995.4, 995.94, 998.0, 999.4		
Puerperal cerebrovascular disorders	325, 346.4, 348.1, 348.3, 348.5, 430-432, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436, 437, 674.0, 671.5, 997.02		
Heart transplant		33945	37.51, 33.6
Mechanical circulatory support		0051T , 0052T , 0053T , 33975 , 33976 , 33979, 33981, 33982, 33983	37.60, 37.61, 37.62, 37.65, 37.66, 37.68, 39.65
ICD implantation		33249 93641– 26/51	37.94, 37.95, 37.96, 37.97, 37.98, 00.51, 00.54
PPM implantation		33206 33207 33208	37.70-37.70, 37.80-37.89 00.50, 00.52, 00.53

Table S5. Identification of Medication

Loop Diuretics	Furosemide, bumetanide, tosemide, Ethacrynic acid
ACE inhibitors	Benazepril, Enalapril, lisinopril, perindopril, ramipril, captopril, fosinopril, moexipril, quinapril, trandolapril
ARB	Candesartan, irbesartan, olmesartan, valsartan, losartan, eprosartan, losartan, telmisartan, azilsartan medoxomil
Beta blockers	Atenolol, bisoprolol, esmolol, metoprolol, nebivolol, pindolol, sotalol, propranolol, timolol, betaxolol, carvedilol, nadolol, labetalol
Nitrates + hydralazine	Hydralazine+ Isosorbide dinitrate, isosorbide monitrate
Aldosterone antagonists	Epleronone, spironolactone

Table S6. Unadjusted odds ratio for the association between potential clinical risk factors and peripartum cardiomyopathy among women with preeclampsia

	Unajusted OR (95% CI)
Advanced maternal age (≥35 years)	2.09 (1.65, 2.66)
Multiple pregnancy	2.13 (1.51, 2.98)
Chronic hypertension	2.25 (1.75, 2.9)
Chronic kidney disease	4.94 (2.31, 10.55)
Gestational diabetes	1.47 (1.13, 1.9)
Type 1 diabetes	1.63 (0.8, 3.29)
Type 2 diabetes	2.19 (1.5, 3.21)
Obesity	1.47 (1.11, 1.95)
Anemia	1.39 (0.93, 2.08)
SARD	1.61 (0.6, 4.33)
Hyperthyroidism	1.57 (0.65, 3.82)
Hypothyroidism	0.92 (0.59, 1.43)
Asthma	1.29 (0.84, 1.98)
Tobacco smoking	1.61 (0.79, 3.25)
Substance use disorder	2.41 (0.99, 5.87)

CI = Confidence interval, OR = odds ratio, SARD = Systemic autoimmune rheumatic disease (includes juvenile and rheumatoid arthritis, systemic lupus erythematous, and other connective tissue diseases)

References

1. Sigakis MJ, Leffert LR, Mirzakhani H, Sharawi N, Rajala B, Callaghan WM, et al. The Validity of Discharge Billing Codes Reflecting Severe Maternal Morbidity. Anesthesia and analgesia. 2016;123(3):731-8.

2. Kolte D, Khera S, Aronow WS, Palaniswamy C, Mujib M, Ahn C, et al. Temporal trends in incidence and outcomes of peripartum cardiomyopathy in the United States: a nationwide population-based study. J Am Heart Assoc. 2014;3(3):e001056.

3. Ntusi NB, Badri M, Gumedze F, Sliwa K, Mayosi BM. Pregnancy-Associated Heart Failure: A Comparison of Clinical Presentation and Outcome between Hypertensive Heart Failure of Pregnancy and Idiopathic Peripartum Cardiomyopathy. PloS one. 2015;10(8):e0133466.

4. Kamiya CA, Kitakaze M, Ishibashi-Ueda H, Nakatani S, Murohara T, Tomoike H, et al. Different characteristics of peripartum cardiomyopathy between patients complicated with and without hypertensive disorders. -Results from the Japanese Nationwide survey of peripartum cardiomyopathy. Circulation journal : official journal of the Japanese Circulation Society. 2011;75(8):1975-81.

5. Ersboll AS, Johansen M, Damm P, Rasmussen S, Vejlstrup NG, Gustafsson F. Peripartum cardiomyopathy in Denmark: a retrospective, population-based study of incidence, management and outcome. European journal of heart failure. 2017.

6. Barasa A, Goloskokova V, Ladfors L, Patel H, Schaufelberger M. Symptomatic recovery and pharmacological management in a clinical cohort with peripartum cardiomyopathy. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2017:1-8.

7. Haghikia A, Podewski E, Libhaber E, Labidi S, Fischer D, Roentgen P, et al. Phenotyping and outcome on contemporary management in a German cohort of patients with peripartum cardiomyopathy. Basic Res Cardiol. 2013;108(4):366.

8. McNamara DM, Elkayam U, Alharethi R, Damp J, Hsich E, Ewald G, et al. Clinical Outcomes for Peripartum Cardiomyopathy in North America: Results of the IPAC Study (Investigations of Pregnancy-Associated Cardiomyopathy). Journal of the American College of Cardiology. 2015;66(8):905-14.

9. Lindley KJ, Conner SN, Cahill AG, Novak E, Mann DL. Impact of Preeclampsia on Clinical and Functional Outcomes in Women With Peripartum Cardiomyopathy. Circulation Heart failure. 2017;10(6).

CHAPTER 5. RESULTS OF SENSITIVITY ANALYSES

Of the 30,927 women with pre-existing cardiac disease in the cohort, 209 women also had a PPCM diagnosis. As such, women with pre-existing cardiac disease represented 19.3% of all women included in the PPCM sub-cohort (n=1,083). The exact pre-existing cardiac diagnoses in this patient group are shown on Table T2. Underlying cardiomyopathy (58.4%) and congestive heart failure (36.8%) were the two most common conditions.

Upon inclusion of women with pre-existing cardiac disease in the main PPCM sub-cohort, a total of 336 (31.0%) women experienced MACE: 133 (40.4%) with co-incident preeclampsia and 203 (26.9%) without preeclampsia ($p < 0.01$). The crude RR for the association between preeclampsia and MACE was 1.5 (95% CI [1.26, 1.79]). With adjustment, the RR for the association between preeclampsia and the primary outcome was 1.33 (95% CI [1.1, 1.61]), which was similar to results obtained in the main analysis. The primary outcome occurred in 34 (16.3%) women with pre-existing cardiac disease as compared to 302 (34.6%) women without pre-existing cardiac disease ($p < 0.01$). The crude RR for the association between pre-existing cardiac disease and the primary outcome was 0.47 (95% CI [0.33, 0.64]), and the adjusted RR was 0.5 (95% CI [0.35, 0.67]).

Women with pre-existing cardiac disease represented a minority of all women with a PPCM diagnosis. More than half the women with pre-existing cardiac disease and a PPCM diagnosis were found to have a cardiomyopathy prior to conception. As per international diagnostic criteria for PPCM, pre-existing cardiomyopathy precluded the diagnosis of PPCM from being established in these women (2, 3). Nevertheless, results from the main analysis were robust and preeclampsia was still independently associated with a ~30% increase in the risk of MACE. Conclusions regarding the association of preeclampsia and MACE among

women with PPCM were thus verified even with the addition of women with pre-existing cardiac disease to the main PPCM sub-cohort.

We found that women with pre-existing cardiac disease had a lower risk of MACE than women without pre-existing cardiac disease in the PPCM sub-cohort. This could have been due to several factors. Firstly, an important portion of women with pre-existing cardiac disease were likely misclassified as having PPCM when in fact they had peripartum heart failure secondary to their underlying diagnoses. Secondly, women with pre-existing cardiac disease who became pregnant could have represented a "healthier" subset of women with cardiac disease, and their clinical course could have been less severe than that of women with PPCM. Finally, women known to have pre-existing cardiac disease were perhaps followed more closely during pregnancy and postpartum leading to better outcomes than women with PPCM occurring de novo during the peripartum period.

Table T2. Distribution of cardiac diagnoses among women with pre-existing cardiac disease*

Cardiac conditions	n (%)
Congenital heart disease	15 (7.2)
Rheumatic heart disease	18 (8.6)
Valvular heart disease	71 (34)
Hypertensive heart disease	11 (5.3)
Cardiomyopathy	122 (58.4)
Pericardial disease	75 (35.9)
Congestive heart failure	77 (36.8)
Diseases of the pulmonary circulation	6 (2.9)
Cardiac surgery	12 (5.7)
Ischemic heart disease	22 (10.5)
Conduction disorders	74 (35.4)
Total	209 (100)

*Women may have had more than one pre-existing cardiac condition

CHAPTER 6. THESIS DISCUSSION

6.1 Thesis summary

This thesis sought to explore the interplay between two frequently co-incident and potentially highly morbid cardiovascular diseases affecting pregnant and postpartum women: PPCM, an idiopathic type of cardiomyopathy occurring de novo in the peripartum period, and preeclampsia, a hypertensive disorder of pregnancy.

Firstly, we assessed clinical risk factors for PPCM among women with preeclampsia. We constructed a pregnancy cohort with commercially insured women in the US and included all pregnancies complicated by preeclampsia in a separate sub-cohort. We identified risk factors for the development of PPCM within this patient group. Confirming thesis hypothesis #1, we found several independent risk factors for PPCM among women with preeclampsia. These included chronic kidney disease, multiple pregnancy, chronic hypertension, advanced maternal age, and type 2 diabetes. Thus, women with any of these risk factors may benefit from close clinical surveillance after their preeclampsia diagnosis, particularly in the first week after discharge from hospital admission for delivery when women tended to develop superimposed PPCM. To our knowledge, such risk factors among preeclamptic women have not been previously assessed. As such, our novel findings may help to improve early identification of women at highest risk for cardiac complications occurring de novo in the peripartum period.

Secondly, we sought to ascertain the effect of preeclampsia on clinical outcomes of PPCM in a large patient sample. We developed a sub-cohort of women with PPCM, and categorized them according to whether they were exposed (i.e. pePPCM) or unexposed (i.e. npePPCM) to preeclampsia. We compared the incidence of a composite

outcome of MACE within 6 months of PPCM diagnosis. As suggested in thesis hypothesis #2, preeclampsia conferred a greater risk of the primary outcome of MACE at 6 months among women in the PPCM sub-cohort. This association was robust to sensitivity analyses in which women with uncomplicated gestational hypertension and women with pre-existing cardiac disease were included into the main PPCM sub-cohort. A higher frequency of indicators of clinical heart failure and pulmonary embolism explained the observed increased risk of the primary outcome in the pePPCM group compared to the npePPCM group. In addition to reasons mentioned in the manuscript, preterm birth and delivery by cesarean section, both more frequent among women with pePPCM than women with npePPCM, may have been causal intermediates in the association between preeclampsia and MACE. Moreover, the administration of magnesium sulfate for seizure prophylaxis to women with preeclampsia may also have led to more heart failure events in this patient group (56). Our findings were aligned with results from the two prior small studies of <40 patients examining the effect of preeclampsia on PPCM-related outcomes (31, 32). Based on these results, clinicians caring for women with PPCM and co-incident preeclampsia should pay particular attention to afterload reduction strategies and early diuresis.

Thirdly, we compared duration of medical therapy for heart failure between women with pePPCM and those with npePPCM, as a proxy for persistent left ventricular dysfunction. Although we found trends for longer duration of therapy with loop diuretics in the pePPCM group, and trends for longer duration of therapy with nitroglycerine-hydralazine, beta-blockers, and angiotensin converting enzyme inhibitors in the npePPCM group, these differences were not statistically significant. Therefore, we had

insufficient evidence to reject the null hypothesis #3. Several other investigators, however, have described higher long-term PPCM recovery rates among hypertensive women when compared to non-hypertensive women (31-35).

6.2 Thesis limitations and potential sources of biases

In addition to those mentioned in the manuscript, this study had several potential limitations to its internal and external validity.

Internal validity

Selection bias is defined by a "systematic error in the recruitment or retention of study subjects" which may result in a distortion of the association between the exposure and outcome of interest (52). In our study, women from the preeclampsia sub-cohort and those from the PPCM sub-cohort were selected from the same underlying pregnancy cohort and inclusion/exclusion criteria were applied similarly among all groups. Thus, it is unlikely that selection bias occurred at time of cohort entry. Additionally, women had to have continuous enrollment from 6 months prior to conception until time of delivery. Loss to follow-up therefore could only occur in the postpartum period. Since both the postpartum observation period for PPCM and the observation period for primary outcome were short (i.e. 5 and 6 months, respectively), the risk of attrition was low.

Information bias, defined as an "imperfect definitions of study variables or flawed data collection procedures", may have led to misclassification of study variables (52). Depending on whether misclassification was differential or non-differential, study results may have been affected (52). In order to minimize the risk of misclassification of women

with PPCM, we used a coding algorithm combining a diagnostic code for PPCM, a strict peripartum timeline, and the addition of a procedure code for echocardiography. Moreover, women at highest risk of misclassification – i.e. those with pre-existing cardiac disease and prior malignancy – were excluded from the main PPCM sub-cohort. To minimize information bias, risk factors were assessed from cohort entry until time of preeclampsia diagnosis for all women in the preeclampsia sub-cohort regardless of whether or not they developed PPCM. Although risk factors for PPCM could have been under-reported due to the nature of our administrative database relying on billing codes for medical conditions, the possibility of an observation bias whereby risk reporting was done more intensely in a specific subgroup was mitigated by the fact that all women were known to have preeclampsia. Moreover, exposure to preeclampsia was assessed using the same diagnostic coding algorithm for all women included in the PPCM sub-cohort, irrespective of whether or not they subsequently developed the MACE outcome. Thus, misclassification of exposure to preeclampsia was most likely non-differential, therefore biasing our estimate to the null value and underestimating the effect that we found.

Although we adjusted for all measurable confounders, unmeasured confounders may have been present. For instance, measurements of socio-economic status were not available in the database. However, given that our study was conducted among commercially ensured women mostly living in urban areas (as shown in Table 1 of the main manuscript), socio-economic disparities were likely to be minimal.

External validity

Our study had important external validity limitations. Indeed, our cohort was composed exclusively of commercially insured women in the US. A statistical brief with data from the Healthcare Cost and Utilization Project Nationwide Inpatient Sample on the source of payment for pregnancy and childbirth for the year 2011 reported that 3.6 million deliveries occurred among women with Medicaid or private insurance (57). While there were more deliveries among women with private insurance (1.9 million versus 1.6 million), ~ 46% of the total sample was composed of deliveries covered by Medicaid (57). Thus, it is important to note that our results may not have been applicable to a large proportion of deliveries in the US. However, this factor did not affect the internal validity of our results.

CONCLUSION

In summary, we identified several risk factors for PPCM among women with preeclampsia. Women with PPCM and co-incident preeclampsia had a higher risk of MACE at 6 months than women with PPCM without preeclampsia. Optimal follow-up frequency and modality for preeclamptic women with risk factors for PPCM requires further study. Whether or not obstetrical determinants such as use of magnesium sulfate, preterm delivery, and delivery method may further modify PPCM-related outcomes remains to be determined. Future research is also needed to assess whether the risk of PPCM recurrence with subsequent pregnancy differs between women with and without co-incident preeclampsia.

Bibliography

1. Pregnancy Mortality Surveillance System [cited 2018 October 19th]. Available from: https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pmss.html.
2. Pearson GD, Veille JC, Rahimtoola S, Hsia J, Oakley CM, Hosenpud JD, et al. Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. Jama. 2000;283(9):1183-8.
3. Sliwa K, Hilfiker-Kleiner D, Petrie MC, Mebazaa A, Pieske B, Buchmann E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. European journal of heart failure. 2010;12(8):767-78.
4. McNamara DM, Elkayam U, Alharethi R, Damp J, Hsich E, Ewald G, et al. Clinical Outcomes for Peripartum Cardiomyopathy in North America: Results of the IPAC Study (Investigations of Pregnancy-Associated Cardiomyopathy). Journal of the American College of Cardiology. 2015;66(8):905-14.
5. Bello N, Rendon IS, Arany Z. The relationship between pre-eclampsia and peripartum cardiomyopathy: a systematic review and meta-analysis. Journal of the American College of Cardiology. 2013;62(18):1715-23.
6. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation. 2006;113(14):1807-16.
7. Gouley BA MT, Bellet S. Idiopathic myocardial degeneration associated with pregnancy and especially the puerperium. American Journal of Medical Science. 1937;19:185-99.
8. Demakis JG, Rahimtoola SH. Peripartum cardiomyopathy. Circulation. 1971;44(5):964-8.
9. Veille JC. Peripartum cardiomyopathies: a review. American journal of obstetrics and gynecology. 1984;148(6):805-18.
10. Demakis JG, Rahimtoola SH, Sutton GC, Meadows WR, Szanto PB, Tobin JR, et al. Natural course of peripartum cardiomyopathy. Circulation. 1971;44(6):1053-61.
11. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. European heart journal. 2008;29(2):270-6.
12. Abboud J, Murad Y, Chen-Scarabelli C, Saravolatz L, Scarabelli TM. Peripartum cardiomyopathy: a comprehensive review. Int J Cardiol. 2007;118(3):295-303.
13. Bello NA, Arany Z. Molecular mechanisms of peripartum cardiomyopathy: A vascular/hormonal hypothesis. Trends in cardiovascular medicine. 2015;25(6):499-504.

14. Hilfiker-Kleiner D, Kaminski K, Podewski E, Bonda T, Schaefer A, Sliwa K, et al. A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. Cell. 2007;128(3):589-600.
15. Patten IS, Rana S, Shahul S, Rowe GC, Jang C, Liu L, et al. Cardiac angiogenic imbalance leads to peripartum cardiomyopathy. Nature. 2012;485(7398):333-8.
16. Damp J, Givertz MM, Semigran M, Alharethi R, Ewald G, Felker GM, et al. Relaxin-2 and Soluble Flt1 Levels in Peripartum Cardiomyopathy: Results of the Multicenter IPAC Study. JACC Heart failure. 2016;4(5):380-8.
17. Ware JS, Li J, Mazaika E, Yasso CM, DeSouza T, Cappola TP, et al. Shared Genetic Predisposition in Peripartum and Dilated Cardiomyopathies. The New England journal of medicine. 2016.
18. Arany Z, Elkayam U. Peripartum Cardiomyopathy. Circulation. 2016;133(14):1397-409.
19. Dhesi S, Savu A, Ezekowitz JA, Kaul P. Association Between Diabetes During Pregnancy and Peripartum Cardiomyopathy: A Population-Level Analysis of 309,825 Women. The Canadian journal of cardiology. 2017;33(7):911-7.
20. Fett JD, Christie LG, Carraway RD, Murphy JG. Five-year prospective study of the incidence and prognosis of peripartum cardiomyopathy at a single institution. Mayo Clin Proc. 2005;80(12):1602-6.
21. Kao DP, Hsich E, Lindenfeld J. Characteristics, adverse events, and racial differences among delivering mothers with peripartum cardiomyopathy. JACC Heart failure. 2013;1(5):409-16.
22. Gunderson EP, Croen LA, Chiang V, Yoshida CK, Walton D, Go AS. Epidemiology of peripartum cardiomyopathy: incidence, predictors, and outcomes. Obstetrics and gynecology. 2011;118(3):583-91.
23. Hypertension in pregnancy / developed by the Task Force on Hypertension in Pregnancy.: American College of Obstetricians and Gynecologists. ; 2013 [cited 2017 December 11th]. Available from: https://www.acog.org/~/media/Task Force and Work Group Reports/public/HypertensioninPregnancy.pdf.
24. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy hypertension. 2014;4(2):105-45.
25. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. The New England journal of medicine. 2004;350(7):672-83.
26. Maternal Hypertension in Canada [cited 2018 October 28th]. Available from: https://www.canada.ca/content/dam/canada/health-canada/migration/healthy-canadians/publications/healthy-living-vie-saine/maternal-hypertension-maternelle/alt/maternal-hypertension-maternelle-eng.pdf.
27. Henderson JT, Whitlock EP, O'Conner E, Senger CA, Thompson JH, Rowland MG. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. Low-Dose Aspirin for the Prevention of Morbidity and Mortality From Preeclampsia: A Systematic Evidence Review for the US Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014.
28. Castleman JS, Ganapathy R, Taki F, Lip GY, Steeds RP, Kotecha D. Echocardiographic Structure and Function in Hypertensive Disorders of Pregnancy: A Systematic Review. Circulation Cardiovascular imaging. 2016;9(9).

29. Gammill HS, Chettier R, Brewer A, Roberts JM, Shree R, Tsigas E, et al. Cardiomyopathy and Preeclampsia: Shared Genetics? Circulation. 2018.
30. Parikh P, Blauwet L. Peripartum Cardiomyopathy and Preeclampsia: Overlapping Diseases of Pregnancy. Current hypertension reports. 2018;20(8):69.
31. Barasa A, Goloskokova V, Ladfors L, Patel H, Schaufelberger M. Symptomatic recovery and pharmacological management in a clinical cohort with peripartum cardiomyopathy. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2017:1-8.
32. Lindley KJ, Conner SN, Cahill AG, Novak E, Mann DL. Impact of Preeclampsia on Clinical and Functional Outcomes in Women With Peripartum Cardiomyopathy. Circulation Heart failure. 2017;10(6).
33. Ntusi NB, Badri M, Gumedze F, Sliwa K, Mayosi BM. Pregnancy-Associated Heart Failure: A Comparison of Clinical Presentation and Outcome between Hypertensive Heart Failure of Pregnancy and Idiopathic Peripartum Cardiomyopathy. PloS one. 2015;10(8):e0133466.
34. Haghikia A, Podewski E, Libhaber E, Labidi S, Fischer D, Roentgen P, et al. Phenotyping and outcome on contemporary management in a German cohort of patients with peripartum cardiomyopathy. Basic Res Cardiol. 2013;108(4):366.
35. Ersboll AS, Johansen M, Damm P, Rasmussen S, Vejlstrup NG, Gustafsson F. Peripartum cardiomyopathy in Denmark: a retrospective, population-based study of incidence, management and outcome. European journal of heart failure. 2017.
36. Kamiya CA, Kitakaze M, Ishibashi-Ueda H, Nakatani S, Murohara T, Tomoike H, et al. Different characteristics of peripartum cardiomyopathy between patients complicated with and without hypertensive disorders. -Results from the Japanese Nationwide survey of peripartum cardiomyopathy. Circulation journal : official journal of the Japanese Circulation Society. 2011;75(8):1975-81.
37. Truven Health MarketScan® Research Databases. [cited 2017 December 26th]. Available from: https://marketscan.truvenhealth.com/marketscanuniversity/userguide/2015 MarketScanCCAE-MDCRUserGuide.pdf.
38. Leigh G. Hansen SC. Health Research Data for the Real World: the Marketscan Research Databases 2011 [cited 2017 December 26th]. Available from: https://marketscan.truvenhealth.com/marketscanuniversity/userguide/2015 MarketScanCCAE-MDCRUserGuide.pdf.
39. Machado MAA, de Moura CS, Wang Y, Danieli C, Abrahamowicz M, Bernatsky S, et al. Comparative effectiveness of antihypertensive drugs in nondiabetic patients with hypertension: A population-based study. Journal of clinical hypertension (Greenwich, Conn). 2017;19(10):999-1009.
40. Martin AS, Monsour M, Kawwass JF, Boulet SL, Kissin DM, Jamieson DJ. Risk of Preeclampsia in Pregnancies After Assisted Reproductive Technology and Ovarian Stimulation. Maternal and child health journal. 2016;20(10):2050-6.
41. Martin AS, Monsour M, Kissin DM, Jamieson DJ, Callaghan WM, Boulet SL. Trends in Severe Maternal Morbidity After Assisted Reproductive Technology in the United States, 2008-2012. Obstetrics and gynecology. 2016;127(1):59-66.
42. Lain SJ, Hadfield RM, Raynes-Greenow CH, Ford JB, Mealing NM, Algert CS, et al. Quality of data in perinatal population health databases: a systematic review. Medical care. 2012;50(4):e7-20.

43. Kuklina EV, Whiteman MK, Hillis SD, Jamieson DJ, Meikle SF, Posner SF, et al. An enhanced method for identifying obstetric deliveries: implications for estimating maternal morbidity. Maternal and child health journal. 2008;12(4):469-77.
44. Margulis AV, Setoguchi S, Mittleman MA, Glynn RJ, Dormuth CR, Hernandez-Diaz S. Algorithms to estimate the beginning of pregnancy in administrative databases. Pharmacoepidemiology and drug safety. 2013;22(1):16-24.
45. Auger N, Luo ZC, Nuyt AM, Kaufman JS, Naimi AI, Platt RW, et al. Secular Trends in Preeclampsia Incidence and Outcomes in a Large Canada Database: A Longitudinal Study Over 24 Years. The Canadian journal of cardiology. 2016;32(8):987.e15-23.
46. Louis GB, Dukic V, Heagerty PJ, Louis TA, Lynch CD, Ryan LM, et al. Analysis of repeated pregnancy outcomes. Statistical methods in medical research. 2006;15(2):103-26.
47. Sigakis MJ, Leffert LR, Mirzakhani H, Sharawi N, Rajala B, Callaghan WM, et al. The Validity of Discharge Billing Codes Reflecting Severe Maternal Morbidity. Anesthesia and analgesia. 2016;123(3):731-8.
48. Kolte D, Khera S, Aronow WS, Palaniswamy C, Mujib M, Ahn C, et al. Temporal trends in incidence and outcomes of peripartum cardiomyopathy in the United States: a nationwide population-based study. J Am Heart Assoc. 2014;3(3):e001056.
49. Silversides CK, Grewal J, Mason J, Sermer M, Kiess M, Rychel V, et al. Pregnancy Outcomes in Women With Heart Disease: The CARPREG II Study. Journal of the American College of Cardiology. 2018;71(21):2419-30.
50. Elkayam U. Clinical characteristics of peripartum cardiomyopathy in the United States: diagnosis, prognosis, and management. Journal of the American College of Cardiology. 2011;58(7):659-70.
51. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomstrom-Lundqvist C, Cifkova R, De Bonis M, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. European heart journal. 2018;39(34):3165-241.
52. Moyses Szklo FJN. Epidemiology, Beyond the Basics, Third Edition: Jones & Bartlett Publishers; 2014.
53. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC medical research methodology. 2008;8:70.
54. Textor J, van der Zander B, Gilthorpe MS, Liskiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. International journal of epidemiology. 2016;45(6):1887-94.
55. Textor J. DAGitty User Manual 2011 [cited 2019 January 1st]. Available from: http://www.dagitty.net/history/v1.0/manual.pdf.
56. Gandhi S, Sun D, Park AL, Hladunewich M, Silversides CK, Ray JG. The Pulmonary Edema Preeclampsia Evaluation (PEPE) Study. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC. 2014;36(12):1065-70.
57. Moore JE, Witt WP, Elixhauser A. Complicating Conditions Associated With Childbirth, by Delivery Method and Payer, 2011: Statistical Brief #173. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville (MD): Agency for Healthcare Research and Quality (US); 2006.