Peripartum cardiomyopathy and hypertensive disorders of pregnancy and cardiovascular events among 1.6 million California pregnancies

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Abstract

Background—Cardiovascular complications during and soon after pregnancy present an opportunity to assess risk for subsequent cardiovascular disease. We sought to determine whether peripartum cardiomyopathy and hypertensive disorder of pregnancy subtypes predict future myocardial infarction, heart failure, or stroke independent of one another and independent of other risks like gestational diabetes, preterm birth, and intrauterine growth restriction.

Methods and Results—The California Healthcare Cost and Utilization Project database was used to identify all hospitalized pregnancies from 2005-2009, with follow-up through 2011, for a retrospective cohort study. Pregnancies, exposures, covariates and outcomes were defined by ICD-9 codes. Among 1.6 million pregnancies (mean age 28y; median follow-up time to event 2.7y), 558 cases of peripartum cardiomyopathy, 123,603 cases of hypertensive disorders of pregnancy, 107,636 cases of gestational diabetes, 116,768 preterm births, and 23,504 cases of intrauterine growth restriction were observed. Using multivariable Cox proportional hazards models, peripartum cardiomyopathy was independently associated with a 13.0-fold increase in myocardial infarction [95%CI, 4.1-40.9], a 39.2-fold increase in heart failure [95%CI, 30.0-51.9], and a 7.7-fold increase in stroke [95%CI, 2.4-24.0]. Hypertensive disorders of pregnancy were associated with a 1.4 [95%CI, 1.0-2.0] to 7.6 [95%CI, 5.4-10.7] fold higher risk of myocardial infarction, heart failure, and stroke. Gestational diabetes, preterm birth, and intrauterine growth restriction had more modest associations with CVD.

Conclusions—These findings support close monitoring of women with cardiovascular pregnancy complications for prevention of early subsequent cardiovascular events and further study of mechanisms underlying their development.

Key Words: peripartum cardiomyopathy, hypertensive disorders of pregnancy, cardiovascular disease, women

Introduction

Cardiovascular disease (CVD) is a significant and often underappreciated cause of morbidity and mortality in women(1). Pregnancy can often "unmask" CVD in women(2,3). In the estimated 85 percent of women who experience a pregnancy during their lifetime, cardiovascular complications during pregnancy and childbirth therefore present an opportunity to assess risk for later CVD(4). Indeed, leveraging early phenotypes to identify those at risk for CVD as soon as possible is an aspirational goal for both precision medicine(5,6) and for primary CVD disease prevention(7,8).

Peripartum cardiomyopathy (PPCM) and hypertensive disorders of pregnancy (HDP) are two major cardiovascular complications of pregnancy and have been reported to share a common underlying pathophysiology in animal studies(9-11). PPCM is characterized by the sudden onset of maternal heart failure presenting either in the last month of pregnancy or in the first five months postpartum. Hypertension in pregnancy is defined as a blood pressure equal to or greater than 140/90 mmHg; gestational onset is defined at or after 20 weeks' gestation (**Online Table 2**).

We hypothesized that specific subtypes of PPCM and HDP may carry different CVD risks(12),(13). Recent data from a Danish nationwide register–based cohort demonstrated that specific subtypes of HDP (i.e. severe preeclampsia, moderate preeclampsia and gestational hypertension) conferred differing risks of incident cardiomyopathy(14). Still, prior studies have not fully elucidated the independent risks of PPCM and HDP subtypes on specific CVD outcomes [i.e. myocardial infarction (MI), heart failure (HF), and stroke]. The availability of a large cohort of women directly representative of the general population of California in the California Healthcare Cost and Utilization Project (HCUP) allowed us to determine the risks of PPCM and HDP subtypes along a spectrum of chronicity and severity for subsequent MI, HF,

and stroke, while independently adjusting for other demographic and pregnancy-related factors that are known to be associated with later maternal CVD [i.e. gestational diabetes mellitus (GDM), preterm delivery and intrauterine growth restriction (IUGR)](15-17).

Methods

Study Sample

We used the California Healthcare Cost and Utilization Project (HCUP) database (https://www.hcup-us.ahrq.gov/), which provides state-specific data for all inpatient, emergency, and ambulatory visits. HCUP contains information collected as part of medical billing, including patient demographics, International Classification of Diseases, Ninth Revision (ICD-9) diagnoses, expected payer, dates of admission and discharge, and follow-up. We identified the first delivery from all patients ages 18 and older in HCUP from 2005-2009 by ICD-9 code (n=1,686,601). During the 2005-2009 study period, after excluding those with a non-California residence (n=2,734), missing information on age (n=2,742) or race/ethnicity (n=11,434), data were available in California HCUP for 1,669,691 pregnancies. Among those 1,669,691 remaining pregnancies we excluded those with pre-existing MI, HF, stroke, and congenital(18) or valvular heart disease using ICD-9 codes (n=7,646), leaving 1,662,045 eligible pregnancies for this study. Congenital heart disease diagnoses were classified according to methods previously described.(18) The number of pregnancies in our study cohort represents 7.8% of all pregnancies in the United States within the same time period(19). Analyses were performed in accordance with the HCUP Data Use Agreement. To preserve patient anonymity, any groups in which there were fewer than 10 patients are listed in Tables as <10.

Exposures

After pregnancies were identified, we defined instances of PPCM, HDP subtypes, GDM, preterm birth, and IUGR by ICD-9 code (**Online Table 1**). We considered both principal and secondary diagnoses to identify these pregnancy exposures.

We further divided PPCM into diagnoses made pre-partum (PPCM diagnoses already present at delivery) and those made post-partum (PPCM diagnosis appearing within 5 months post-delivery). We defined HDP as one of the following: chronic HTN, gestational HTN, preeclampsia, chronic HTN with gestational HTN, chronic HTN with preeclampsia and no HTN or PPCM (referent) (**Online Table 2**).

Outcomes

Primary CVD outcomes were admissions for MI, HF, and stroke defined by ICD-9 codes (**Online Table 1**). MI subtypes were defined as MI with CAD (MICAD) and MI with non-obstructive coronary arteries (MINOCA). MINOCA includes MI from stress cardiomyopathy, hypercoagulable state, coronary artery dissection, coronary artery anomaly, and coronary vasospasm.(20) MINOCA was defined using its ICD-9 code as well as 1) having had a myocardial infarction using ICD-9 codes 410.00-410.92; 2) having had a cardiac catheterization or computed tomography coronary angiogram (inpatient or outpatient, defined by CPT code) within 7 days of index event; and 3) having had an ICD-9 code for a MINOCA subtype. ICD-9 codes used for MINOCA subtypes were 413.1 for coronary vasospasm; 414.12 for coronary artery dissection; 429.83 for Takotsubo/stress cardiomyopathy; 289.81 for hypercoagulable state; and 746.85 for coronary anomaly.

Stroke was further subdivided into ischemic, embolic, and hemorrhagic etiologies. Among our study cohort, systolic vs diastolic HF, and left vs right HF were not well specified and thus we were unable to distinguish among these HF subtypes. ICD-9 codes defining the outcomes are found in **Online Table 1**.

Covariates

We adjusted for covariates known to be associated with PPCM, hypertension, CVD, and peripartum morbidity and mortality(21) which could potentially confound the associations we were interested in studying. Covariates included age, race, insurance status, median household income, chronic kidney disease, pre-existing diabetes, obesity, drug abuse, smoking, multiple gestations, as well as each of the exposures. Patients with preexisting (prior to pregnancy) HTN were considered to have baseline chronic hypertension and were included within the HDP variable; therefore, we did not include HTN as a covariate.

Statistical Analyses

Primary analyses. We considered our baseline period in which initial delivery occurred from 2005-2009. Follow-up began 6 months after delivery in order to avoid double-counting an exposure and outcome, and it lasted until the end of 2011. Descriptive statistics were performed including n's, means and percentages with standard deviations and interquartile ranges as appropriate among all participants and within PPCM and HDP subtypes. We tested the assumption of proportionality of hazards for PPCM and HDP subtypes and MI, HF, and stroke. We found that one of the five HDP subtypes, *de novo* preeclampsia, violated the assumption ($p=0.02$). Therefore, in the case of *de novo* preeclampsia, our hazard ratio estimates represent an average across the length of study follow-up. We employed multivariable Cox proportional hazards models to determine the association between PPCM and HDP and subsequent CVD, adjusting for the potential confounders listed in the covariates section above. We considered GDM, preterm delivery and IUGR as secondary exposures and considered these in multivariable models adjusting for PPCM and HDP.

Secondary analyses. It is known that certain pregnancy complications beget further comorbidities: for example, hypertensive disorders of pregnancy can be risk factors for PPCM(14). *Overlap.* We assessed pregnancy exposures for overlap. Similarly, we assessed for overlap among our CVD outcomes of interest. Finally, since specific subtypes of MI and stroke may be more common in younger individuals and among women, we analyzed outcomes by subtype. For example, we assessed how many of the MI's in our population were due to MICAD vs MINOCA, and how many of the incident strokes were from hemorrhagic versus ischemic versus embolic etiologies. As mentioned above, ICD-9 codes for HF subtypes were not specified in the study cohort. We also considered PPCM as intra- or postpartum in order to determine whether timing of PPCM affected CVD outcomes. *Stratification*. In addition to our original multivariable Cox proportional hazards model (see Primary analyses), we re-ran the model i) stratifying on quintiles of age rather than using age as a covariate and ii) stratifying by preterm birth and PPCM, preeclampsia and PPCM, and IUGR and PPCM.

All analyses were performed using SAS version 9.4X. A p-value of 0.05 or less was considered statistically significant. Certification to use de-identified HCUP data was obtained from the University of California, San Francisco Committee on Human Research. No informed consent was required.

Results

Characteristics of study population.

Of the 1,662,045 study participants who delivered from 2005-2009 in HCUP-CA, 579,656 (35%) were non-Hispanic white women, 105,489 (6%) were African-American, 648,602 (39%) were Hispanic, and 200,908 (12%) were Asian or Pacific Islanders. 20,765 (1.2%) of pregnancies were complicated by drug abuse, and 11,248 (0.7%) of pregnancies were complicated by active smoking. 330, 946 deliveries were second pregnancies within the study period. In terms of additional risk factors for cardiovascular complications, 23,108 (1.4%) of pregnant women had pre-existing hypertension, 16,806 (1.0%) had pre-existing diabetes, and 538 (0.3%) had chronic kidney disease. Notably, the prevalence of African Americans, chronic HTN, and obesity was higher in the PPCM group than in the general population. The prevalence of Asian and Pacific Islanders was higher in the GDM group. **Table 1** summarizes these and other characteristics of the study cohort.

Prevalence of pregnancy exposures in study population.

There were 558 cases of PPCM, 97 of which were diagnosed before delivery, and 461 of which were diagnosed postpartum. There were 49,114 cases of gestational HTN and 62,162 cases of preeclampsia; broken down by HDP subtypes of interest, there were 12,458 cases of isolated chronic HTN, 43,073 cases of *de novo* gestational HTN, 56,419 cases of *de novo* preeclampsia, 4,907 pregnancies with both chronic HTN and superimposed gestational HTN, and 5,743 pregnancies with chronic HTN and superimposed preeclampsia (**Table 2**). There were 107,636 cases of GDM, 23,504 cases of IUGR, and 116,768 cases of preterm birth. Median follow-up time to event was 2.68 years, ranging from 1 day to 6.84 years, resulting in 0.99, 1.23, and 1.02

cases of MI, HF, and stroke, respectively, per 1000 person-years. **Online Table 3** demonstrates the overlap and correlations among pregnancy exposure categories. Preterm birth and preeclampsia were the most highly correlated (Kendall-Tau correlation coefficient 0.146) whereas IUGR and peripartum cardiomyopathy had the lowest correlation (Kendall-Tau correlation coefficient 0.0017) among pregnancy exposures studied.

Multivariable models demonstrated associations between exposures and future cardiovascular risk.

Among all women hospitalized during pregnancy from 2005-2009, there were 558 subsequent MIs, 3284 subsequent cases of HF, and 973 subsequent strokes. **Table 2** shows stroke, MI, and HF event numbers by pregnancy exposure category. Of the 330,946 pregnancies (of the total ~1.6 million pregnancies) which were second pregnancies within the study period, 24 had MI (24 of 558), 133 had HF (133 of 3284), and 37 had stroke (37 of 973). Using multivariable Cox proportional hazards models adjusting for all exposures and covariates, we found that PPCM was independently associated with a 13.0-fold increased risk of MI (95% CI 4.1-40.9), a 39.2-fold increased risk of HF (95% CI 30.0 – 51.9), and a 7.7-fold increased risk of stroke (95% CI 2.4-24.0; **Figure 1; Table 2).** The hazard ratios were similar for PPCM diagnosed at or before delivery when compared to PPCM diagnosed in the first five months postpartum **(Figure 1)**.

We investigated cardiovascular risks according to hypertensive disorder of pregnancy subtypes of differing chronicity and severity. We examined five subtypes: chronic hypertension alone, *de novo* gestational hypertension, *de novo* preeclampsia, chronic hypertension with superimposed gestational hypertension, and chronic hypertension with superimposed

preeclampsia **(Online Table 2)**. These subtypes carried a 2.3-6.3-fold increased risk for MI, a 2.5-5.4-fold increased risk for HF, and a 1.4-7.6-fold increased risk for stroke **(Figure 2; Table 2).** Although there was some overlap in 95% confidence intervals, chronic HTN alone, and with superimposed preeclampsia, carried the highest risks of MI, HF and stroke compared with other HDP subtypes. Chronic HTN with superimposed gestational hypertension did not demonstrate a statistically significant increased risk for MI; the n in this group was less than 10.

All of our models included additionally included GDM, preterm birth, and IUGR. IUGR was related to risk of MI but not HF or stroke [HR for MI=1.6 (95% CI: 1.0-2.5)]. Preterm delivery was significantly associated with MI, stroke and HF (Figure 2; Table 2). GDM was associated with risks of stroke and HF but not with MI **(Figure 2; Table 2).** Overall, these three pregnancy exposures conferred comparatively lower risks for cardiovascular diseases as compared to PPCM and HDP.

Tests for residual confounding in the multivariable model show robust associations between exposures and outcomes.

Age is a well-known and strong predictor both for both cardiovascular complications of pregnancy and for our outcomes of interest; (21,22) and increased prevalence of exposures and outcomes by age was again demonstrated in our study (**Online Table 4**). We therefore sought to test for residual confounding by age in our multivariable model. We compared hazard ratios derived from our original model to those obtained using an alternate approach stratifying on quintiles of age rather than using age as a covariate (thereby avoiding the assumptions of the proportional hazards model). We found that this alternate approach did not change hazard ratio point estimates or 95% confidence intervals by more than a point (data not shown).

We also ran additional models stratifying by preterm birth and PPCM, preeclampsia and PPCM, and IUGR and PPCM, and did not find substantial differences in hazard ratio point estimates or 95% confidence intervals (data not shown).

Secondary analyses.

With respect to exposures, excepting the HDP subtypes of gestational HTN & chronic HTN and preeclampsia & chronic HTN, where clinical overlap was present by design (10.3% and 9.24% overlap, respectively), there was notable overlap between PPCM and preeclampsia (26.1%), preeclampsia and preterm birth (26.0%) between chronic HTN and preterm birth (18.8%). Overlap among all other categories ranged from 1.49% to 10.6% (**Online Table 3**).

With respect to outcomes, PPCM is known to be a risk factor for HF but has not previously been described as a risk factor for MI or stroke (**Figure 1, Table 2**). To determine whether there was overlap in MI, HF, and stroke outcome diagnoses in patients with PPCM that might explain our observations, we queried ICD-9 diagnoses for each individual patient in the PPCM exposure group. Most categories of overlap had fewer than 10 patients; for example, fewer than 10 out of 58 patients with PPCM (6.9%) had overlapping outcome diagnoses (for HF/stroke and HF/MI). No single PPCM exposure had all three outcome diagnoses. Among patients with hypertensive disorder of pregnancy subtypes, GDM, preterm birth, and IUGR exposures, the percentage of patients with more than one outcome diagnosis ranged from 5.74% to 11.37%. Therefore, the majority of observed outcomes were separate cardiovascular events.

We then asked whether heart failure could be a mediator of MI and stroke among patients with PPCM and overlapping outcome diagnoses. We re-fitted our MI and stroke models with heart failure as a time-dependent covariate. With heart failure as a mediator, the risk of PPCM

for MI decreased from 13.0 (95% CI 4.1-40.9) to 4.6 (95% CI 1.4-14.8) and the risk of PPCM for stroke decreased from 7.6 (95% CI) to not significant (2.7 95% CI 0.8–8.5). Therefore, although there were novel significant associations between PPCM and MI and PPCM and stroke, heart failure mediated much of those associations.

Finally, we analyzed outcomes by MI and stroke subtypes (**Table 3**). Based on ICD-9 coding, we found that the predominant type of MI experienced within the follow-up period was MICAD, and the most common type of stroke was ischemic stroke.

Discussion

Summary of Findings.

In this retrospective cohort study of over 1.6 million deliveries representing nearly every completed pregnancy in California over a 5-year period, we report the following: i) PPCM is associated with risks for MI and stroke in addition to (and partly mediated by) HF; ii) HDP subtypes were associated with risks for MI, stroke, and HF; iii) subtypes of HDP representing a longer duration of hypertension and a higher severity (i.e. chronic HTN and chronic HTN with superimposed preeclampsia) had the greatest magnitudes of risks for MI, stroke and HF; iv) GDM, preterm birth, and IUGR were independently associated with risks for future CVD when accounting for PPCM and HDP; and v) PPCM and HDP were independently associated with CVD when accounting for these other CVD-related pregnancy complications. Stratification by age and by selected exposures did not significantly change observed hazard ratios, suggesting these findings are robust to potential residual confounding.

We found that the above cardiovascular pregnancy complications were associated with substantial risks for MI, HF, and stroke even within the first six years post-delivery. In contrast to long-held belief that heart disease largely affects women who are long past their child-bearing years, we demonstrate that the presence of cardiovascular complications of pregnancy can identify a sub-population of younger women who are at high risk for premature cardiovascular disease. Our findings are relevant given the recent call to attention and study concerning the growing epidemic of MI in younger women by scientific experts(7) and support initiatives designed to follow younger at-risk women more closely for CVD prevention(22).

PPCM is hypothesized to have several different causes, including genetic mutations, fetal autoimmunity, vascular dysfunction, in addition to HDP itself(23-25). Furthermore, PPCM

presenting during pregnancy may represent a different clinical entity as compared to PPCM presenting postpartum(12) and may have different underlying genetic underpinnings(13). Despite this, our findings did not suggest that intrapartum and postpartum PPCM as coded in HCUP conferred differing risks for CVD. Despite overlapping pathophysiology between PPCM and HDP(26), PPCM has a relatively greater magnitude of risk for incident CVD than any of the HDP subtypes studied.

Given that preterm birth, IUGR, and GDM have demonstrated associations with CVD(27-29) and are commonly seen with HDP and PPCM, we studied these as secondary exposures and did find that each was significantly associated with one or more subtypes of CVD, confirming findings from prior investigations. HDP is a common reason for medically indicated preterm delivery. Several lines of evidence suggest that a common pathology in many cases of preterm birth and IUGR, as well as subtypes of HDP and PPCM and HDP, is vascular dysfunction of varying chronicity and severity.(30-34) GDM is a risk factor for future diabetes and its attendant microvascular and macrovascular effects(35) which may explain the associations seen between GDM and stroke, as well as HF.

Strengths and Limitations.

As a statewide record, California HCUP provided generalizable data from a large and ethnically diverse population and has been used to uncover several insights into cardiovascular disease(18,36,37). Age, race, and ethnicity in the study cohort were similar to those of national CDC birth records for the same time period(19). HCUP captures over 95 percent of California's population, which comprises over 38 million people. Large datasets like HCUP can facilitate defining phenotypes at greater resolution, such as the pregnancy complication subtypes analyzed

in this paper and in other work from our group(18). In addition to several exposures, we were also able to adjust for several potential confounders, which clarified the effects of each exposure on future cardiovascular risk. Increasing phenotypic resolution at scale can help uncover new associations and inspire new hypotheses on the mechanisms of disease. Here we demonstrate for the first time that PPCM, a relatively rare event, carried risks not only for future HF but also for MI and stroke as well, and that these associations, while mediated in part by HF, are not simply explained by overlap of outcome diagnoses.

In terms of magnitude, PPCM conferred the highest magnitude of hazard ratios for future CVD, followed by chronic HTN with superimposed preeclampsia, and then chronic HTN alone. Whereas PPCM and HDP have been demonstrated to exist on a common pathophysiologic spectrum(11,26), we demonstrate that their respective association with later cardiovascular disease differ in magnitude of risk. Further basic and translational studies are needed to determine the specific pathophysiologic mechanisms that connect PPCM and HDP with later CVD.

Relatively short follow-up time (maximum of 6.84 years) likely resulted in an underestimation of risk along the lifetimes of the individuals studied. Also, with small numbers in some groups after adjustment for several covariates, 95% confidence intervals for several exposure subtypes were wide. Given the significant associations found despite these caveats, the hazard ratios measured in this study may in fact be underestimates of true cardiovascular risk following a pregnancy complicated by PPCM and/or HDP.

Despite using a large dataset like HCUP, our analysis of exposure and outcome subtypes were potentially limited due to misclassification bias and to a lack availability of certain diagnostic codes. We attempted to assess the extent of misclassification bias in our study. HCUP

data is anonymized, precluding the ability to perform manual chart review of the ICD-9 coding used to define exposures, covariates, and outcomes. We found that prevalence of preterm birth was similar to national estimates; prevalence of PPCM, and GDM were similar to previous reports in smaller California cohorts in which diagnoses were confirmed by manual chart review(19,21). Literature review of ICD-9 coding for preeclampsia, gestational HTN, and hypertensive disorders of pregnancy shows low sensitivity and high specificity(38) while ICD-9 coding for outcomes like MI, HF, and stroke shows high sensitivity and specificity(39-41). If these trends are also true within HCUP, it would suggest that the hazard ratios reported in this study are likely accurate, but could be underestimates of true risk. Despite these shortcomings, our analysis shows several robust signals indicating increased CVD risk among exposures of interest.

Finally, the lack of certain diagnostic codes limited our ability to perform detailed analysis of outcome subtypes (e.g., HF subtypes) or distinguish between HF class. When defining MI and stroke by outcome subtype, there were not enough numbers to perform statistical analysis; the national HCUP database may provide adequate numbers for such an analysis.

In this study, we demonstrated that PPCM is associated with near-term HF, MI and stroke in women in California, independent of HDP, GDM, preterm delivery and IUGR. Among HDP subtypes, chronicity and severity of HTN increased risk of subsequent HF, MI and stroke. While these results are independent of age, the increased prevalence of exposures and outcomes with age in the face of national birth patterns with women giving birth at older ages mean that we can expect even more PPCM, HDP, and CVD in pregnant women. The importance of pregnancy as a cardiovascular ‘stress test’ will, therefore, only further expand in the future.

Conclusions

Our findings support close monitoring of women with cardiovascular pregnancy complications for prevention of subsequent, near-term CVD events and begs further study of potential mechanisms underlying the development of these early CVD events.

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Disclosures:

The authors have no disclosures.

References

1. Mosca L, Hammond G, Mochari-Greenberger H et al. Fifteen-year trends in awareness of heart disease in women: results of a 2012 American Heart Association national survey. Circulation 2013;127:1254-63, e1-29.

2. Khan NA, Daskalopoulou SS, Karp I et al. Sex differences in prodromal symptoms in acute coronary syndrome in patients aged 55 years or younger. Heart 2016.

3. Hemal K, Pagidipati NJ, Coles A et al. Sex Differences in Demographics, Risk Factors, Presentation, and Noninvasive Testing in Stable Outpatients With Suspected Coronary Artery Disease: Insights From the PROMISE Trial. JACC Cardiovasc Imaging 2016;9:337-46.

4. Parikh NI, Jeppson RP, Berger JS et al. Reproductive Risk Factors and Coronary Heart Disease in the Women's Health Initiative Observational Study. Circulation 2016;133:2149-58.

5. Robinson PN. Deep phenotyping for precision medicine. Hum Mutat 2012;33:777-80.

6. Delude CM. Deep phenotyping: The details of disease. Nature 2015;527:S14-5.

7. Nabel EG. Heart Disease Prevention in Young Women: Sounding an Alarm. Circulation 2015;132:989-91.

8. Goff DC, Jr., Lloyd-Jones DM, Bennett G et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:S49-73.

9. Aoyama K, Suzuki Y, Sato T et al. Cardiac failure caused by severe pre-eclampsia with placental abruption, and its treatment with anti-hypertensive drugs. J Obstet Gynaecol Res 2003;29:339-42.

10. Mann DL, Zipes DP, Libby P, Bonow RO, Braunwald E. Braunwald's heart disease : a textbook of cardiovascular medicine. Tenth edition. ed. Philadelphia, PA: Elsevier/Saunders, 2015.

11. Patten IS, Rana S, Shahul S et al. Cardiac angiogenic imbalance leads to peripartum cardiomyopathy. Nature 2012;485:333-8.

12. Krishnamoorthy P, Garg J, Palaniswamy C et al. Epidemiology and outcomes of peripartum cardiomyopathy in the United States: findings from the Nationwide Inpatient Sample. J Cardiovasc Med (Hagerstown) 2016;17:756-61.

13. Ware JS, Seidman JG, Arany Z. Shared Genetic Predisposition in Peripartum and Dilated Cardiomyopathies. N Engl J Med 2016;374:2601-2.

14. Behrens I, Basit S, Lykke JA et al. Association Between Hypertensive Disorders of Pregnancy and Later Risk of Cardiomyopathy. JAMA : the journal of the American Medical Association 2016;315:1026-33.

15. Savitz DA, Danilack VA, Elston B, Lipkind HS. Pregnancy-induced hypertension and diabetes and the risk of cardiovascular disease, stroke, and diabetes hospitalization in the year following delivery. Am J Epidemiol 2014;180:41-4.

16. Wenger NK. Recognizing pregnancy-associated cardiovascular risk factors. The American journal of cardiology 2014;113:406-9.

17. Manten GT, Sikkema MJ, Voorbij HA, Visser GH, Bruinse HW, Franx A. Risk factors for cardiovascular disease in women with a history of pregnancy complicated by preeclampsia or intrauterine growth restriction. Hypertens Pregnancy 2007;26:39-50.

18. Hayward RM, Foster E, Tseng ZH. Maternal and Fetal Outcomes of Admission for Delivery in Women With Congenital Heart Disease. JAMA cardiology 2017;2:664-671.

19. Martin JA, Hamilton BE, Ventura SJ, Osterman MJ, Wilson EC, Mathews TJ. Births: final data for 2010. Natl Vital Stat Rep 2012;61:1-72.

20. Pasupathy S, Tavella R, Beltrame JF. Myocardial Infarction With Nonobstructive Coronary Arteries (MINOCA): The Past, Present, and Future Management. Circulation 2017;135:1490-1493.

21. Gunderson EP, Croen LA, Chiang V, Yoshida CK, Walton D, Go AS. Epidemiology of peripartum cardiomyopathy: incidence, predictors, and outcomes. Obstetrics and gynecology 2011;118:583-91.

22. Cusimano MC, Pudwell J, Roddy M, Cho CK, Smith GN. The maternal health clinic: an initiative for cardiovascular risk identification in women with pregnancy-related complications. Am J Obstet Gynecol 2014;210:438 e1-9.

23. Fett JD. Peripartum cardiomyopathy: A puzzle closer to solution. World J Cardiol 2014;6:87-99.

24. 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:e0133466.

25. Ware JS, Li J, Mazaika E et al. Shared Genetic Predisposition in Peripartum and Dilated Cardiomyopathies. N Engl J Med 2016;374:233-41.

26. 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;62:1715-23.

27. Tanz LJ, Stuart JJ, Williams PL et al. Preterm Delivery and Maternal Cardiovascular Disease in Young and Middle-Aged Adult Women. Circulation 2017;135:578-589.

28. Srinivas SK, Edlow AG, Neff PM, Sammel MD, Andrela CM, Elovitz MA. Rethinking IUGR in preeclampsia: dependent or independent of maternal hypertension? J Perinatol 2009;29:680-4.

29. Cirillo PM, Cohn BA. Pregnancy complications and cardiovascular disease death: 50-year follow-up of the Child Health and Development Studies pregnancy cohort. Circulation 2015;132:1234-42.

30. Tomimatsu T, Mimura K, Endo M, Kumasawa K, Kimura T. Pathophysiology of preeclampsia: an angiogenic imbalance and long-lasting systemic vascular dysfunction. Hypertens Res 2017;40:305-310.

31. Grand'Maison S, Pilote L, Okano M, Landry T, Dayan N. Markers of Vascular Dysfunction After Hypertensive Disorders of Pregnancy: A Systematic Review and Meta-Analysis. Hypertension 2016;68:1447-1458.

32. Di Martino D, Zullino S, Casati D et al. C1. Maternal hemodynamic profile in hypertensive disorders of pregnancy (HDP) and intrauterine growth restriction. J Matern Fetal Neonatal Med 2016;29:11.

33. Boeldt DS, Bird IM. Vascular adaptation in pregnancy and endothelial dysfunction in preeclampsia. J Endocrinol 2017;232:R27-R44.

34. Banerjee M, Cruickshank JK. Pregnancy as the prodrome to vascular dysfunction and cardiovascular risk. Nat Clin Pract Cardiovasc Med 2006;3:596-603.

35. Gunderson EP, Chiang V, Pletcher MJ et al. History of Gestational Diabetes Mellitus and Future Risk of Atherosclerosis in Mid-life: The Coronary Artery Risk Development in Young Adults Study. Journal of the American Heart Association 2014;3:e000490.

36. Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. JAMA : the journal of the American Medical Association 2011;306:2248-54.

37. Dewland TA, Olgin JE, Vittinghoff E, Marcus GM. Incident atrial fibrillation among Asians, Hispanics, blacks, and whites. Circulation 2013;128:2470-7.

38. Klemmensen AK, Olsen SF, Osterdal ML, Tabor A. Validity of preeclampsia-related diagnoses recorded in a national hospital registry and in a postpartum interview of the women. Am J Epidemiol 2007;166:117-24.

39. McCormick N, Bhole V, Lacaille D, Avina-Zubieta JA. Validity of Diagnostic Codes for Acute Stroke in Administrative Databases: A Systematic Review. PLoS One 2015;10:e0135834.

40. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of heart failure diagnoses in administrative databases: a systematic review and meta-analysis. PLoS One 2014;9:e104519.

41. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of myocardial infarction diagnoses in administrative databases: a systematic review. PLoS One 2014;9:e92286.

Figure Legends

Figure 1. Adjusted associations between peripartum cardiomyopathy and myocardial infarction, heart failure, and stroke. Hazard ratios for all PPCM (black diamond), as well as PPCM diagnosed prior to delivery (open square) and postpartum (black triangle). Covariates included age, race, insurance status, median household income, chronic kidney disease, pre-existing diabetes, obesity, drug abuse, smoking, multiple gestations, as well as for each of the exposures (PPCM, HDP subtypes, GDM, IUGR, and preterm birth).

Figure 2. Adjusted associations between hypertensive disorder of pregnancy subtypes and myocardial infarction, heart failure, and stroke. Hazard ratios for HDP subtypes, GDM, IUGR and preterm birth and MI, HF, and stroke. Covariates included age, race, insurance status, median household income, chronic kidney disease, pre-existing diabetes, obesity, drug abuse, smoking, multiple gestations, as well as for each of the exposures (PPCM, HDP subtypes, GDM, IUGR, and preterm birth).

Tables

Table 1. Patient characteristics. Baseline characteristics for patients included in the analysis; those with preexisting MI, heart failure, stroke, and congenital or valvular heart disease were excluded.

	PPCM	Gestational HTN	Preeclampsia	GDM	Uncomplicated Pregnancies†
N	558	47,980	62,162	107,636	1,455,554
Mean Age (SD)	31 (7)	28 (7)	28 (7)	32 (6)	28 (6)
Race/Ethnicity					
non-Hispanic white	174 (31%)	18801 (39%)	19994 (32%)	28153 (26%)	515843 (35%)
Black	116 (21%)	4427 (9%)	5693 (9%)	4774 (4%)	91344 (6%)
Hispanic	133 (24%)	17198 (36%)	26458 (43%)	44794 (42%)	565042 (39%)
Asian/Pacific Islander	82 (15%)	4236 (9%)	5572 (9%)	21705 (20%)	171072 (12%)
Other	47 (8%)	2658 (6%)	3610 (6%)	6553 (6%)	77394 (5%)
Native American	<10 (<2%)*	660 (1%)	835 (1%)	1657 (2%)	34859 (2%)
Income					
First quartile	155 (28%)	13088 (27%)	18729 (30%)	26292 (24%)	389006 (27%)
Second quartile	145 (26%)	12637 (26%)	16252 (26%)	27992 (26%)	378219 (26%)
Third quartile	132 (24%)	11509 (24%)	14619 (24%)	26721 (25%)	350629 (24%)
Fourth quartile	126 (23%)	10746 (22%)	12562 (20%)	26631 (25%)	337700 (23%)
Insurance Status					
Medicare	<10 (<2%)*	166 (0.35%)	317 (1%)	441 (0.4%)	4380 (0.3%)

Medicaid	222 (40%)	17903 (37%)	24814 (40%)	33902 (32%)	536653 (37%)
Private insurance	311 (56%)	28530 (59%)	35165 (57%)	71157 (66%)	869142 (60%)
Self-pay	11 (2%)	588 (1%)	874 (1%)	824 (0.8%)	20183 (1%)
Other	<10 (<2%)*	793 (2%)	992 (2%)	1312 (1%)	25196 (2%)
Hospitalization					
Mean Cost (SD)	$36,979 ($49,863)	$17316 ($15642)	$30194 ($29414)	$21068 ($22192)	$16458 ($13948)
Days to re-hospitalization	74 (204)	679 (381)	642 (399)	676 (378)	665 (386)
Comorbidities					
Drug Abuse	21 (4%)	792 (2%)	1244 (2%)	691 (0.6%)	18145 (1%)
Diabetes	22 (4%)	1146 (2%)	2554 (4%)	656 (0.6%)	12570 (0.8%)
Chronic HTN	50 (9%)	4907 (10%)	5743 (9%)	4261 (4%)	10016(0.7%)
Obesity	71 (13%)	3842 (8%)	5215 (8%)	7858 (7%)	32986 (2%)
Chronic Kidney Disease	<10 (<2%)*	30 (0.07%)	236 (0.4%)	50 (0.05%)	246 (0.02%)
Cesarean Section	87 (16%)	4794 (10%)	6323 (10%)	20619 (19%)	182361 (13%)
Multiple births	<10 (<2%)*	44 (0.1%)	237 (0.4%)	164 (0.15%)	644 (0.04%)
Smoking (active)	12 (2%)	374 (0.8%)	537 (0.9%)	605 (0.6%)	9807 (0.7%)
Still Birth	<10 (<2%)*	286 (0.6%)	621 (1%)	485 (0.5%)	8661 (0.6%)
Preterm birth	100 (18%)	4565 (10%)	16167 (26%)	10654 (10%)	87895 (6%)
Intrauterine growth restriction	14 (3%)	1267 (3%)	3217 (5%)	1609 (1%)	17779 (1%)
Family history of CVD	<10 (<2%)*	94 (0.2%)	303 (0.5%)	346 (0.3%)	2578 (0.2%)
Baseline DM	15 (3%)	881 (2%)	2009 (3%)	1979 (2%)	10081 (0.7%)

* In accordance with HCUP policies, categories in which there were fewer than 10 patients are represented simply as <10.

† Uncomplicated pregnancies in this context are defined as pregnancies uncomplicated by PPCM, gestational HTN, preeclampsia, or GDM.

SD = Standard Deviation; CVD = Cardiovascular Disease; PPCM = Peripartum Cardiomyopathy; HTN = Hypertension; DM = Diabetes Mellitus; GDM = Gestational DM; IUGR = Intrauterine Growth Restriction.

Table 2. Multivariable-adjusted associations between pregnancy complications and myocardial infarction, heart failure, and stroke.

All eligible pregnancies N = 1,662,045	Myocardial Infarction MV adjusted HR (95% CI) n = 558	Heart Failure MV adjusted HR (95% CI) n = 3,284	Stroke MV adjusted HR (95% CI) n = 973
PPCM n = 558 1.66 per 1000 person-years	13.0 (4.1-40.9) n = <10* N/A	39.2 (30.0 – 51.9) n = 56 2.19 per 1000 person-years	7.7 (2.4-24.0) n = <10* N/A
No PPCM (referent) n=1,661,487 0.58 per 1000 person-years	1.0 n=549 0.98 per 1000 person-years	1.0 n=3228 1.22 per 1000 person-years	1.0 n=964 1.01 per 1000 person-years
HP subtypes:			
Chronic HTN n = 12,458 0.54 per 1000 person-years	6.3 (4.6-8.7) n = 47 0.90 per 1000 person-years	3.9 (3.3-4.7) n = 152 1.12 per 1000 person-years	3.4 (2.4-4.8) n = 37 0.88 per 1000 person-years
De novo gestational HTN n = 43,073 5.98 per 1000 person-years	2.3 (1.6-3.4) n = 28 0.98 per 1000 person-years	2.5 (2.1-2.9) n = 188 1.39 per 1000 person-years	1.4 (1.0-2.0) n = 33 1.15 per 1000 person-years
De novo preeclampsia n = 56,419	2.5 (1.9-3.4) n = 49	3.0 (2.7-3.4) n = 355	2.3 (1.8-3.0) n = 79

0.59 per 1000 person-years	0.89 per 1000 person-years	1.69 per 1000 person-years	1.08 per 1000 person-years
Chronic HTN & Gestational HTN n = 4,907 0.54 per 1000 person-years	2.0 (0.8-4.8) n = <10* N/A	3.3 (2.5-4.5) n = 45 1.16 per 1000 person-years	3.0 (1.7-5.4) n = 12 1.67 per 1000 person-years
Chronic HTN & Preeclampsia n = 5,743 0.61 per person-years	5.0 (3.1-8.0) n = 22 1.01 per 1000 person-years	5.4 (4.5-6.6) n = 135 1.36 per 1000 person-years	7.6 (5.4-10.7) n = 43 1.03 per 1000 person-years
No HTN/preeclampsia/gestational htn (referent) n = 1,539,445 0.57 per 1000 person-years	1.0 n=407 1.00 per 1000 person-years	1.0 n = 2,409 1.17 per 1000 person-years	1.0 n = 769 1.01 per 1000 person-years
Gestational DM n = 107,636 0.59 per 1000 person-years	1.0 (0.8-1.4) n=57 0.88 per 1000 person-years	1.3 (1.1-1.4) n = 320 1.36 per 1000 person-years	1.42(1.2-1.8) n = 103 1.09 per 1000 person-years
No Gestational DM (referent) n=1,554,409 0.58 per 1000 person-years	1.0 n=501 1.00 per 1000 person-years	1.0 n=2964 1.22 per 1000 person-years	1.0 n=870 1.01 per 1000 person-years
IUGR n = 23,504 0.59 per 1000 person-years	1.6 (1.1-2.5) n = 23 1.11 per 1000 person-years	1.1 (0.9-1.4) n = 86 1.22 per 1000 person-years	1.5 (1.0-2.1) n =30 1.09 per 1000 person-years
No IUGR (referent) n=1,638,541	1.0 n=535	1.0 n=3198	1.0 n=943

0.58 per 1000 person-years	0.98 per 1000 person-years	1.23 per 1000 person-years	1.02 per 1000 person-years
Preterm birth n=116,768 0.58 per 1000 person-years	1.8 (1.4-2.3) n=105 1.05 per 1000 person-years	1.6 (1.4-1.7) n=532 1.25 per 1000 person-years	1.4 (1.1-1.6) n=134 1.05 per 1000 person-years
Preterm birth(referent) n=1,545,277 0.58 per 1000 person-years	1.0 n=453 0.97 per 1000 person-years	1.0 n=2752 1.23 per 1000 person-years	1.0 n=839 1.01 per 1000 person-years

* In accordance with HCUP policies, categories in which there were fewer than 10 patients are represented simply as <10.

MV = Multivariate; HR = Hazard Ratio; CI = Confidence Interval; HDP = Hypertensive Disorders of Pregnancy; PPCM = Peripartum Cardiomyopathy; HTN = Hypertension; DM = Diabetes Mellitus; IUGR = Intrauterine Growth Restriction.

Table 3. Number of patients in study cohort with CVD outcomes of interest by outcome subtype.

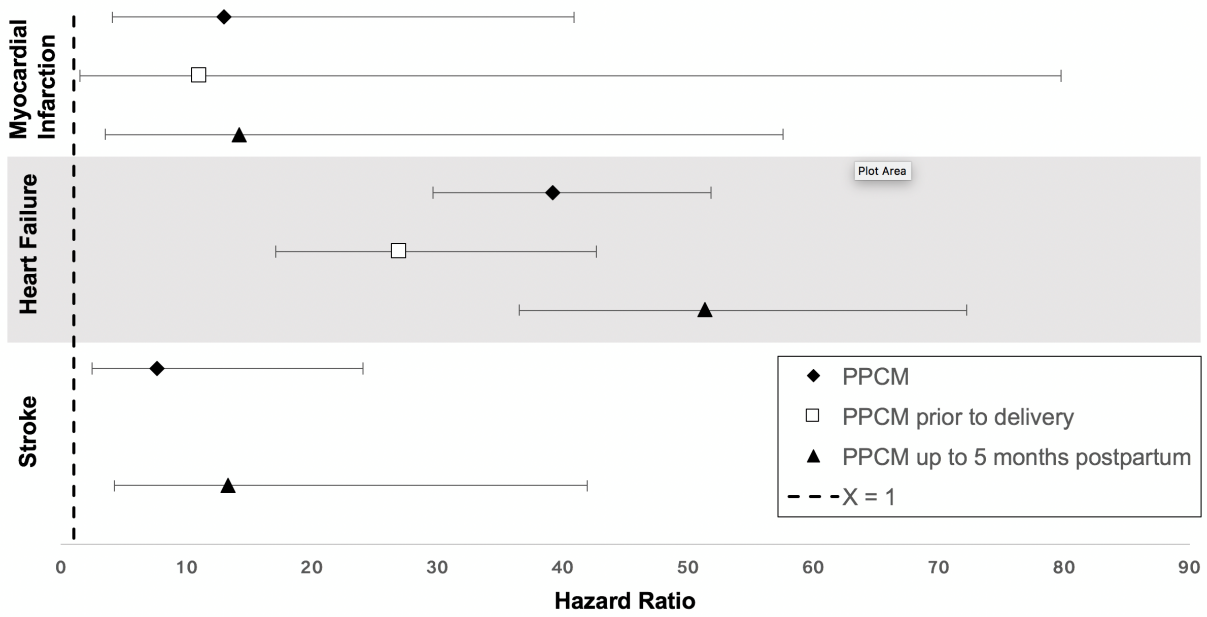
	MI		Stroke			Heart Failure
	MICAD	MINOCA	Embolic	Ischemic	Hemorrhagic	
PPCM (n=558)	<10*	<10*	<10*	<10*	0	56
Chronic HTN (n=12,458)	14	<10*	<10*	28	<10*	152
De Novo Gestational HTN (n=43,073)	<10*	<10*	<10*	22	<10*	188
De Novo Preeclampsia (n=56,419)	16	<10	<10	60	14	355
Chronic HTN & Gestational HTN (n=4,907)	<10*	0	<10*	<10*	<10*	45
Chronic HTN & Preeclampsia (n=5,743)	<10*	0	<10*	35	<10*	135
Gestational DM (n=107,636)	24	<10*	12	62	29	320
Preterm Birth (n=116,768)	42	15	13	96	25	532
IUGR (n=23,504)	<10*	<10*	<10*	17	<10*	86
Total	126	40	53	333	91	1251

* In accordance with HCUP policies, categories in which there were fewer than 10 patients are represented simply as <10.

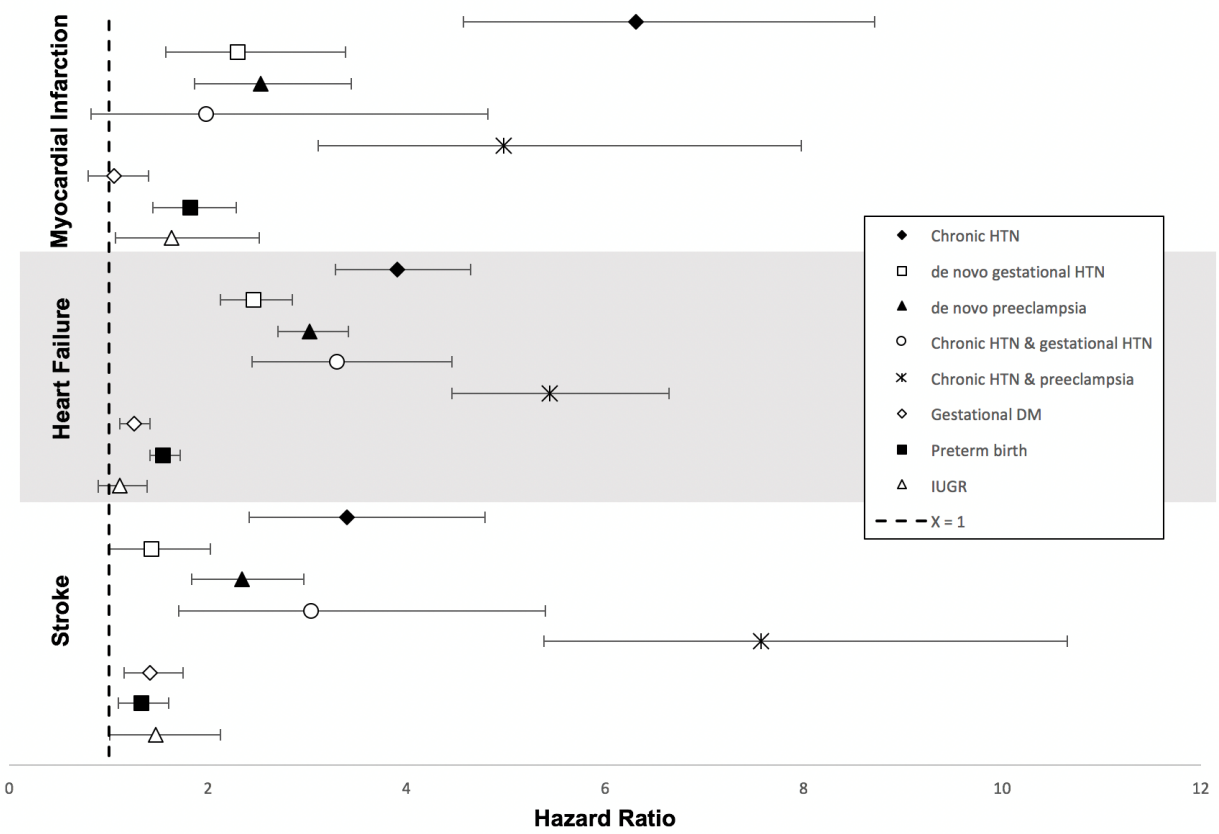
MI = Myocardial Infarction; MICAD = MI with obstructive coronary artery disease; MINOCA = MI without obstructive coronary artery disease; PPCM = Peripartum Cardiomyopathy; HTN = Hypertension; DM = Diabetes Mellitus; IUGR = Intrauterine Growth Restriction.

Figures

Figure 1.



37 **Figure 2.**



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