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# Association of Cardiomyopathy With Adverse Cardiac Events in Pregnant Women at the Time of Delivery

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## ABSTRACT

**OBJECTIVES** The aim of this study was to determine the predictors of adverse events in pregnant women with cardiomyopathy (CDM) and CDM subtypes at the time of delivery.

**BACKGROUND** Investigation of patients' characteristics and outcomes in women with CDM at the time of delivery has been limited.

**METHODS** The Healthcare Cost and Utilization Project's National Inpatient Sample was screened for hospital admissions for delivery in pregnant women with CDM from 2006 to 2010. Clinical characteristics and maternal outcomes were identified in women with and without CDM and in CDM subtypes. The primary outcome of interest was major adverse clinical events (MACE), a composite of in-hospital death, acute myocardial infarction, heart failure, arrhythmia, cerebrovascular event, or embolic event.

**RESULTS** Our study population comprised 2,078 patients with CDM and 4,438,439 patients without CDM. Of those with CDM, 52 (2.5%) were hypertrophic, 1,039 (50.0%) were peripartum, and 987 (47.5%) were classified as other. Women with CDM were older, white, and insured by Medicaid. MACE rates were significantly higher in women with peripartum CDM (46%), compared with hypertrophic CDM (23%) and all others (39%) ($p < 0.001$). In multivariable analysis, the presence of peripartum cardiomyopathy (odds ratio [OR]: 2.2; 95% confidence interval [CI]: 1.1 to 4.6), valvular disease (OR: 2.11; 95% CI: 1.6 to 2.9), and eclampsia (OR: 5.0; 95% CI: 1.6 to 1.9) was independently associated with MACE.

**CONCLUSIONS** Presence of CDM is independently predictive of MACE during hospitalization for delivery. Patients with peripartum CDM had the highest likelihood of MACE compared with other CDM subtypes. (J Am Coll Cardiol HF 2015;3:257–66) © 2015 by the American College of Cardiology Foundation.

Cardiac complications have consistently been a leading cause of maternal death during pregnancy or delivery among developed nations (1-3). The progression of pregnancy is accompanied by hemodynamic demands on the maternal cardiovascular system and thus poses an increased risk for complications in women with limited cardiovascular reserve (4,5). A growing concern is the presence of pre-existing and new onset cardiomyopathy (CDM) during pregnancy that may result in clinical decompensation with overt heart failure, arrhythmias, and even maternal death, particularly at the time of delivery (6). Delivery of the fetus presents an additional hemodynamic insult for pregnant women with CDM and therefore a period of elevated risk. CDM in pregnancy, including peripartum CDM, has a low incidence, approximately 1 in 3,000 to 1 in 4,000 births (7,8). The incidence of other forms of CDM in pregnancy, including hypertrophic CDM and dilated CDM, is largely unknown, but these types

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**ABBREVIATIONS AND ACRONYMS**

**CDM** = cardiomyopathy

**HCUP** = Healthcare Cost and Utilization Project

**ICD-9** = International Classification of Diseases-9th Revision

**LOS** = length of stay

**MACE** = major adverse cardiac events

**NIS** = National Inpatient Sample

**THC** = total hospital charge

are considered uncommon, thus making epidemiological studies on women with CDM challenging. Investigation into the patients' characteristics and outcomes in CDM has been mainly limited to small cohorts of patients (9–12), with only 1 recent study using hospital records pooled from 6 states limited to women with peripartum CDM (13).

In this study, we sought to characterize the incidence of CDM in pregnant women in the United States and to determine the impact of CDM on maternal clinical outcomes and individual predictors of poor outcome at the time of delivery. In addition, we compared multiple types of CDM in terms of clinical characteristics and outcomes.

## METHODS

**DATA SOURCE.** We used data from the 2006 to 2010 National Inpatient Sample (NIS), collected by the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project (HCUP), which is the largest all-payer inpatient publicly available database in the United States (14). The NIS provides annual information on approximately 8 million inpatient stays from about 1,000 hospitals and estimates a 20% stratified sample from a sampling frame that comprises 90% of U.S. acute care hospital admissions. International Classification of Diseases-9$^{th}$ Revision (ICD-9) codes were used to ascertain hospitalizations for delivery, defined as any discharge record with a normal delivery or other indications for care in pregnancy, labor, and delivery-related diagnoses (ICD-9 codes 650 to 659 and V27.4 to V27.9) or delivery-related procedure (ICD-9 codes 72 to 75), as previously described (15). Our analysis was limited to delivery-associated hospitalizations to avoid including multiple hospitalizations for a given patient over the course of an individual pregnancy.

**STUDY POPULATION.** A total of 39,887,824 hospital discharges were reported to the NIS from 2006 to 2010 from 45 states (1,051 hospitals). We identified a cohort of 5,361,287 pregnant women admitted for delivery (vaginal or cesarean section) at U.S. hospitals. Patients with missing data on race (n = 918,585; 20.6%) and insurance status (n = 7,485; 0.2%) were excluded (n = 920,770; 20.8%), with a remaining study population of 4,440,521. The sample population was broadly separated into patients with CDM ("CDM") and those without CDM ("No CDM"), defined by the presence or absence of the following ICD-9 codes: 674.50 to 674.54; 425.1 to 425.18; 425.0; and 425.2 to 425.9. The CDM cohort was further divided as follows: peripartum CDM (ICD-9 codes 674.50 to 674.54); hypertrophic CDM (ICD-9 codes 425.1 to 425.18); and other CDM (ICD-9 codes 425.0 and 425.2 to 425.9), which includes disorders such as endomyocardial fibrosis, other primary CDM, alcoholic CDM, CDM in other diseases classified elsewhere, and secondary CDM unspecified. Patients diagnosed as having both hypertrophic CDM and peripartum CDM were classified into the hypertrophic CDM group (n = 13), and patients diagnosed as having both peripartum CDM and other CDM were classified into the peripartum CDM group (n = 204).

**PATIENT CHARACTERISTICS AND OUTCOME MEASURES.** All patient and hospital characteristics were obtained from the NIS. Demographic and medical history data extracted included maternal age, race, insurance status, valvular disease, diabetes mellitus, and delivery at a teaching hospital. The primary outcome of interest was major adverse cardiac events (MACE), defined as a composite of the following: in-hospital death; acute myocardial infarction (ICD-9 codes 410 and 411); heart failure (ICD-9 code 428); arrhythmia (ICD-9 codes 426 and 427); cerebrovascular events (ICD-9 codes 431 and 433 to 436); pulmonary embolism (ICD-9 code 515.1); arterial embolism (ICD-9 code 444); atheroembolism (ICD-9 code 445); obstetric pulmonary embolism (ICD-9 code 673); and cardiac complications of anesthesia or other sedation in labor and delivery (ICD-9 code 668.1). Additional covariates examined included the following: transient hypertension of pregnancy (ICD-9 codes 642.30 to 642.34); mild pre-eclampsia (ICD-9 codes 642.40 to 642.44); severe pre-eclampsia (ICD-9 codes 642.50 to 642.54); eclampsia complicating pregnancy/childbirth (ICD-9 codes 642.60 to 642.64); multiple gestation (ICD-9 code 651); postpartum hemorrhage (ICD-9 code 666); and cesarean delivery (ICD-9 code 74). Valvular heart disease was studied: diseases of the mitral valve (ICD-9 codes 394.0 to 394.9 and 424.0); tricuspid valve (ICD-9 codes 397.0 and 746.89); and aortic valve (ICD-9 codes 395.0 to 395.9).

**STATISTICAL ANALYSIS.** Data were summarized by descriptive statistics. Chi-square test was used to compare categorical variables, whereas Student *t* test or 1-way analysis of variance was used to compare continuous variables. The 5-year CDM incidence rate per 100,000 deliveries was reported as follows: n, CDM cases / (n, total number of deliveries) × 100,000. Multivariable logistic regression was used to evaluate the association of CDM with MACE while controlling for demographic and medical history. A separate multivariable logistic regression was performed to examine the association of CDM subtype with MACE

in pregnant women with CDM. Predictor variables included the following: CDM (in all women only) or subtypes of CDM (in women with CDM only); age; race; insurance status; diabetes mellitus; valvular disease; transient hypertension; pre-eclampsia status; multiple gestation; postpartum hemorrhage; cesarean delivery; year of delivery; hospital region; and delivery at a teaching hospital. Variables with a p value <0.1 in univariate logistic analyses were selected for inclusion in the multivariable logistic regression model with their 2-way interaction terms of interest (any 2-way interaction term involving race for the all women studied and all possible 2-way interaction terms for the women with CDM only) to study each variable's association with MACE after controlling for the rest of the demographics and medical history. Odds ratio (OR) and 95% confidence interval (CI) were reported. Linear regression models were performed to evaluate the influence of CDM on increased length of stay (LOS) or total hospital charge (THC). LOS and THC were log-transformed to meet the normality assumption for linear regression models. Variables with a p value <0.1 in univariate analyses were selected for inclusion in the multiple linear regression model with their 2-way interaction terms of interest. Backward selection with a significant level of 0.05 was used in all model selection. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, North Carolina).

## RESULTS

**INCIDENCE OF CARDIOMYOPATHY.** Among the 4,440,517 patients who comprised the study population, 2,078 (0.05%) had CDM and 4,438,439 (99.95%) did not. The 5-year CDM incidence rate per 100,000 deliveries is 46.8 per 100,000; for hypertrophic CDM, it is 1.2 per 100,000; for peripartum CDM, it is 23.4 per 100,000; and for other CDM types, it is 22.2 per 100,000.

**PATIENT CHARACTERISTICS.** Clinical and demographic characteristics for the CDM and No CDM groups, as well as for the 3 CDM subgroups (hypertrophic CDM, n = 52; peripartum CDM, n = 1,039; and Other CDM, n = 987) are summarized in Table 1. In the Other CDM category, 92% (n = 909) of these patients were classified as having dilated CDM. Patients with CDM compared with patients without CDM were slightly older and more likely to be black, insured by Medicaid or Medicare, have diabetes and valvular disease, and undergo delivery at a teaching hospital (p < 0.001 for all). With respect to the CDM subgroups, the peripartum cohort was more likely to be insured by Medicaid, and the patients with hypertrophic CDM were more likely to be insured by private companies including HMOs and undergo delivery at a teaching hospital (p < 0.01 for all). The group of patients with hypertrophic CDM had fewer black patients than the peripartum CDM and other CDM cohorts, and patients with hypertrophic CDM were more likely to be hospitalized in the Northeast region compared with the other groups, which were more likely to be hospitalized in the South. Multiple gestation was also significantly more common in the CDM cohort. Black women have a higher rate of peripartum CDM and all other CDM types (0.0005 and 0.0005, respectively) compared with white women (0.0002 and 0.0002, respectively). Disease of the mitral valve was present in 10% of patients with CDM (n = 220), aortic valve disease was present in 3 patients, and tricuspid valve disease was found in 50 patients. Patients with CDM were also noted to have higher rates of transient hypertension, pre-eclampsia events, postpartum hemorrhage, and cesarean delivery (p < 0.001 for all). Among the CDM subtypes, the peripartum CDM cohort had the highest rates of hypertensive disorders and pre-eclampsia/eclampsia, postpartum hemorrhage, and cesarean delivery.

**CLINICAL EVENTS AND OUTCOMES.** Adverse events at delivery for the CDM and No CDM patient groups and for the 3 CDM subgroups are listed in Table 2. Compared with patients with no CDM, patients with CDM had a significantly higher rate of MACE (42.1% vs. 0.4%), which was mainly related to higher rates of heart failure (33% vs. 0.02%). Other complications more commonly observed in the CDM cohort were as follows: cardiac arrhythmias (5.7% vs. 0.4%); maternal mortality (0.05% vs. 0%); cerebrovascular events (0.1% vs. 0.008%); and acute myocardial infarction (1.25% vs. 0.002%).

Among CDM subtypes, patients with peripartum CDM experienced the highest rates of MACE (46%), compared with patients with hypertrophic CDM (23%) or other CDM (38.9%). Heart failure was the most common cause of adverse events. The peripartum CDM subgroup experienced the highest rates of heart failure (36.5%), compared with patients with hypertrophic CDM (11.5%) or other CDM (30.4%). In-hospital mortality rates for patients with CDM in all 3 categories were low (<1%) and not significantly different from each other (p = 0.5).

**Predictors of MACE in all women.** After multivariable analysis, independent predictors of MACE in all women at the time of delivery included the presence of the following: CDM (OR: 90.25; 95% CI: 80.61 to 101.05); valvular disease (OR: 10.31; 95% CI: 9.50 to 11.16); multiple gestation (OR: 1.49; 95% CI: 1.36 to

**TABLE 1 Characteristics of Women With and Without CDM at Delivery and by CDM Subtype**

| | CDM (n = 2,078) | No CDM (n = 4,438,439) | p Value | Hypertrophic CDM (n = 52) | Peripartum CDM (n = 1,039) | Other CDM* (n = 987) | p Value |
|---|---|---|---|---|---|---|---|
| Age (yrs) | 29.7 ± 6.6 | 27.5 ± 6.2 | <0.001 | 28.4 ± 5.2 | 29.1 ± 6.9 | 30.3 ± 6.2 | <0.001 |
| Race | | | <0.001 | | | | 0.009 |
| White | 770 (47.86%) | 1,804,375 (51.18%) | | 32 (69.57%) | 388 (47.26%) | 350 (47.17%) | |
| Black | 497 (30.89%) | 487,729 (13.84%) | | 6 (13.04%) | 248 (30.21%) | 243 (32.75%) | |
| Hispanic | 215 (13.36%) | 857,133 (24.31%) | | 4 (8.7%) | 129 (15.71%) | 82 (11.05%) | |
| Asian | 49 (3.05%) | 174,824 (4.96%) | | 1 (2.17%) | 23 (2.8%) | 25 (3.37%) | |
| Other race | 78 (4.85%) | 201,262 (5.71%) | | 3 (6.52%) | 33 (4.02%) | 42 (5.66%) | |
| Insurance | | | <0.001 | | | | <0.001 |
| Private including HMO | 834 (40.19%) | 2,206,374 (49.8%) | | 29 (55.77%) | 395 (38.13%) | 410 (41.54%) | |
| Medicare | 90 (4.34%) | 28,606 (0.7%) | | 0 (0%) | 27 (2.61%) | 63 (6.38%) | |
| Medicaid | 1,009 (48.63%) | 1,902,309 (42.9%) | | 21 (40.38%) | 540 (52.12%) | 448 (45.39%) | |
| Other insurance | 142 (6.84%) | 293,672 (6.6%) | | 2 (3.85%) | 74 (7.14%) | 66 (6.69%) | |
| Valvular disease | 278 (13.38%) | 20,509 (0.46%) | <0.001 | 10 (19.23%) | 141 (13.6%) | 127 (12.9%) | 0.408 |
| Diabetes mellitus | 109 (5.25%) | 40,453 (0.91%) | <0.001 | 0 (0.0%) | 48 (4.6%) | 61 (6.2%) | 0.066 |
| Multiple gestation | 107 (5.15%) | 82,731 (1.86%) | <0.001 | 2 (3.8%) | 73 (7.0%) | 32 (3.2%) | <0.001 |
| Teaching hospital | 1,373 (66.98%) | 2,091,820 (47.5%) | <0.001 | 39 (75.0%) | 659 (63.4%) | 675 (68.4%) | 0.0064 |
| U.S. hospital region | | | <0.001 | | | | <0.001 |
| Northeast | 324 (15.59%) | 685,204 (15.44%) | | 17 (32.7%) | 170 (16.4%) | 137 (12.9%) | |
| Midwest | 481 (23.15%) | 935,474 (21.08%) | | 14 (27.0%) | 202 (19.4%) | 265 (26.8%) | |
| South | 923 (44.42%) | 1,699,122 (38.28%) | | 10 (19.2%) | 503 (48.4%) | 410 (41.5%) | |
| West | 350 (16.84%) | 1,118,639 (25.2%) | | 11 (21.2%) | 164 (15.8%) | 175 (17.7%) | |
| Transient hypertension | 111 (5.34%) | 139,398 (3.1%) | <0.001 | 2 (3.9%) | 76 (7.3%) | 33 (3.3%) | <0.001 |
| Pre-eclampsia status | | | <0.001 | | | | <0.001 |
| Mild pre-eclampsia | 143 (7.5%) | 100,251 (2.3%) | | 1 (1.9%) | 101 (9.7%) | 41 (4.2%) | |
| Severe pre-eclampsia | 215 (10.35%) | 54,898 (1.2%) | | 0 (0.0%) | 157 (15.1%) | 58 (5.9%) | |
| Eclampsia | 23 (1.1%) | 3,358 (0.1%) | | 0 (0.0%) | 22 (2.1%) | 1 (0.1%) | |
| Pre-eclampsia/eclampsia with pre-existing HTN | 157 (7.6%) | 21,453 (0.5%) | | 0 (0.0%) | 81 (7.8%) | 76 (7.7%) | |
| Postpartum hemorrhage | 126 (6.06%) | 118,439 (2.7%) | <0.001 | 0 (0.0%) | 86 (8.3%) | 40 (4.05%) | <0.001 |
| Cesarean delivery | 1,144 (55.05%) | 1,398,686 (31.51%) | <0.001 | 25 (48.1%) | 641 (61.7%) | 478 (48.4%) | <0.001 |

Values are mean ± SD or n (%). *In the "other CDM" category, 92% (n = 909) of these patients were classified as having dilated cardiomyopathy.
CDM = cardiomyopathy; HMO = health maintenance organization; HTN = hypertension.

1.63); postpartum hemorrhage (OR: 2.23; 95% CI: 2.07 to 2.40); and hypertension and eclampsia statuses (Table 3). Race was a significant predictor of MACE, with the highest risk among blacks compared with whites.

**Predictors of MACE in women with cardiomyopathy and peripartum cardiomyopathy.** Table 4 demonstrates the adjusted OR of experiencing MACE in women with CDM at delivery. Among women with CDM, the presence of peripartum CDM (OR: 2.22; 95% CI: 1.07 to 4.55) was independently predictive of MACE. Several effects are notable among the risk factors for developing MACE in women with CDM. Overall, the presence of eclampsia was the strongest factor for increasing the odds of MACE in patients with CDM (OR: 5.03; 95% CI: 1.60 to 15.79). Other predictors included the following: valvular disease (OR: 2.11; 95% CI: 1.56 to 2.90); postpartum hemorrhage (OR: 1.57; 95% CI: 1.01 to 2.40); cesarean delivery (OR: 1.52; 95% CI: 1.22 to 1.89); CDM type (p = 0.036); and 2-way interaction terms age and insurance (p = 0.045) and race and teaching hospital (p = 0.030). After removal of patients who received a double diagnosis of CDM, 1,861 patients with CDM were analyzed. Peripartum CDM and other types of CDM remained independently predictive of MACE (OR: 7.2; 95% CI: 2.2 to 24.3 and OR: 5.9; 95% CI: 1.8 to 19.9, respectively) after controlling for other covariates. Factors such as valvular heart disease, eclampsia, postpartum hemorrhage, cesarean delivery, and black race remained significantly associated with MACE (p < 0.05). Disease of the mitral valve (n = 220; OR: 2.24; 95% CI: 1.6 to 3.2) and tricuspid valve (n = 50; OR: 2.71; 95% CI: 1.39 to 5.27) were significant predictors of MACE in women with CDM in the multivariable model.

In the 1,039 patients with peripartum CDM, 478 (46.1%) experienced MACE (Table 2). Independent predictors of MACE in this cohort included the presence of the following: valvular heart disease

**TABLE 2 Outcomes of Women With or Without Cardiomyopathy at Delivery and by Cardiomyopathy Subtype**

| Outcome | CDM (n = 2,078) | No CDM (n = 4,438,439) | p Value | Hypertrophic CDM (n = 52) | Peripartum CDM (n = 1,039) | Other CDM (n = 987) | p Value |
|---|---|---|---|---|---|---|---|
| Major adverse cardiac events* | 874 (42.1%) | 16,344 (0.4%) | <0.001 | 12 (23.1%) | 478 (46.0%) | 384 (38.9%) | <0.001 |
| Mortality (maternal) | 17 (0.82%) | 291 (0.01%) | <0.001 | 0 (0%) | 7 (0.67%) | 10 (1.01%) | 0.4967 |
| Heart failure | 686 (33.01%) | 1,002 (0.02%) | <0.001 | 6 (11.54%) | 379 (36.48%) | 301 (30.5%) | <0.001 |
| Cardiac arrhythmias | 248 (11.93%) | 13,788 (0.31%) | <0.001 | 7 (13.46%) | 131 (12.61%) | 110 (11.14%) | 0.5593 |
| Cerebrovascular events | 3 (0.14%) | 396 (0.01%) | <0.001 | 0 (0%) | 3 (0.29%) | 0 (0%) | 0.3043 |
| Pulmonary embolism | 0 (0%) | 0 (0%) | NA | 0 (0%) | 0 (0%) | 0 (0%) | NA |
| Arterial embolism | 2 (0.1%) | 38 (0%) | <0.001 | 0 (0%) | 2 (0.19%) | 0 (0%) | 0.5315 |
| Atheroembolism | 0 (0%) | 1 (0%) | 1 | 0 (0%) | 0 (0%) | 0 (0%) | NA |
| Obstetric pulmonary embolism | 28 (1.35%) | 1,150 (0.03%) | <0.001 | 0 (0%) | 23 (2.21%) | 5 (0.51%) | 0.0067 |
| Cardiac complications of anesthesia or other sedation in labor and delivery | 0 (0%) | 0 (0%) | NA | 0 (0%) | 0 (0%) | 0 (0%) | NA |
| Acute myocardial infarction | 26 (1.25%) | 115 (0.002%) | <0.001 | 0 (0%) | 15 (1.44%) | 11 (1.11%) | 0.5303 |

Values are n (%). *Composite of the following: maternal death, heart failure, arrhythmia, cerebrovascular events, pulmonary embolism, arterial embolism, atheroembolism, obstetric pulmonary embolism, cardiac complications of anesthesia or other sedation in labor and delivery, and acute myocardial infarction. Some individuals experienced more than 1 type of major adverse cardiac event (MACE) subset; however, these events are counted only once in the composite MACE: this accounts for a composite MACE value lower than the sum of all subsets. Note: p values for multinomial variables and binary variables were calculated on the basis of chi-square test and Fisher exact test, respectively.

CDM = cardiomyopathy; NA = not applicable.

(OR: 2.16; 95% CI 1.49 to 3.14) (Table 5); severe pre-eclampsia (OR: 1.54; 95% CI: 1.08 to 2.21); multiple gestation (OR: 0.59; 95% CI: 0.36 to 0.98); and cesarean delivery (OR: 1.36; 95% CI: 1.04 to 1.78). Delivery at a teaching hospital was associated with a reduction in MACE in this cohort.

**LENGTH OF STAY AND TOTAL HOSPITAL COSTS.** Figure 1 delineates the mean LOS and THC for the CDM and No CDM cohorts. The CDM cohort had a more than 2-fold increased mean LOS and an approximately 4-fold increased THC. The average cost per day as a function of THC/LOS for the CDM cohort was $6,394.29 compared with $4,543.59 for the No CDM group (data not shown). Race, valvular disease, transient hypertension, pre-eclampsia status, postpartum hemorrhage, and cesarean delivery were significantly associated with a larger THCs (data not shown).

In multivariable analysis, race, valvular heart disease, delivery at a teaching hospital, pre-eclampsia status, multiple gestations, postpartum hemorrhage, and cesarean delivery were significantly associated with longer LOS (all $p < 0.05$). Coefficient estimates of the multiple linear regression models for LOS and THC in patients with CDM are noted in the Online Appendix (Online Tables 1 and 2, respectively). Patients with valvular disease had significantly longer LOS than those without valvular disease after adjusting for all other factors.

## DISCUSSION

With a national all-payer database of contemporary hospital inpatient stays in the United States, this is the first study of its kind (to our knowledge) to investigate the outcomes of CDM and subgroups of CDM in a large cohort of pregnant women at the time of delivery. Because of its large sample size, the NIS is useful for the study of unusual conditions such as

**TABLE 3 Multivariable Analysis: Individual Predictors of MACE in All Women at Delivery**

| Factor* | OR (95% CI) |
|---|---|
| Cardiomyopathy | 90.25 (80.61–101.05) |
| Valvular disease | 10.31 (9.50–11.16) |
| Multiple gestation | 1.49 (1.36–1.63) |
| Postpartum hemorrhage | 2.23 (2.08–2.40) |
| Transient hypertension | 1.31 (1.20–1.42) |
| Pre-eclampsia status | |
| Eclampsia vs. normal | 9.14 (7.50–11.13) |
| Severe pre-eclampsia vs. normal | 2.59 (2.38–2.82) |
| Mild pre-eclampsia vs. normal | 1.53 (1.40–1.68) |
| Pre-eclampsia or eclampsia with pre-existing HTN vs. normal | 2.88 (2.56–3.25) |
| Diabetes mellitus | 1.60 (1.42–1.80) |
| Teaching hospital | 1.32 (1.28–1.38) |
| Age | 1.10 (1.08–1.11) |
| Cesarean delivery | 1.74 (1.68–1.81) |
| Race | |
| Asian vs. white | 0.72 (0.66–0.78) |
| Black vs. white | 1.16 (1.1–1.22) |
| Hispanic vs. white | 0.69 (0.66–0.73) |
| Other vs. white | 0.80 (0.74–0.87) |

*Each factor is based on the final optimal multivariable logistic regression model in which all factors had a p value <0.1 in the univariate model were taken into account. Factors such as age, race, insurance, diabetes mellitus, valvular disease, teaching hospital, transient hypertension, pre-eclampsia status, multiple gestation, postpartum hemorrhage, cesarean delivery, year, and CDM were significantly associated with MACE after adjusting for these factors (all p values < 0.0001).

CI = confidence interval; HTN = hypertension; MACE = major adverse cardiac events; OR = odds ratio.

**TABLE 4 Multivariable Analysis of MACE in Women With CDM**

| Factor* | OR (95% CI) |
|---|---|
| CDM type (ref. hypertrophic) | |
| Peripartum CDM | 2.22 (1.07–4.55) |
| Other CDM | 1.85 (0.88–3.85) |
| Cesarean delivery | 1.52 (1.22–1.89) |
| Postpartum hemorrhage | 1.57 (1.01–2.45) |
| Pre-eclampsia status (ref. normal) | |
| Eclampsia | 5.03 (1.60–15.79) |
| Severe pre-eclampsia | 1.84 (1.31–2.58) |
| Mild pre-eclampsia | 1.19 (0.78–1.81) |
| Pre-eclampsia or eclampsia with pre-existing HTN | 1.62 (1.09–2.40) |
| Valvular disease | 2.11 (1.56–2.90) |
| Mitral valve disease | 2.24 (1.60–3.12) |
| Tricuspid valve disease | 2.71 (1.39–5.27) |
| Age (units = 5 years) | |
| Medicaid | 1.15 (1.02–1.29) |
| Medicare | 2.09 (1.19–3.66) |
| Other insurance | 0.88 (0.63–1.22) |
| Private including HMO | 1.04 (0.91–1.19) |
| Teaching hospital (ref. yes vs. no with specified race) | |
| White | 0.95 (0.69–1.29) |
| Black | 0.60 (0.39–0.94) |
| Hispanic | 0.43 (0.23–0.79) |
| Asian | 0.95 (0.27–3.34) |
| Other race | 2.63 (0.82–8.41) |
| Race (ref. white at non-teaching hospital) | |
| Black | 1.61 (1.02–2.56) |
| Hispanic | 2.30 (1.31–4.04) |
| Asian | 0.59 (0.22–1.58) |
| Other race | 0.42 (0.15–1.20) |
| Race (ref. white at teaching hospital) | |
| Black | 1.03 (0.77–1.39) |
| Hispanic | 1.04 (0.69–1.56) |
| Asian | 0.59 (0.25–1.38) |
| Other race | 1.16 (0.65–2.08) |
| Insurance (ref. private including HMO at age 29.65 years) | |
| Medicare | 0.95 (0.51–1.77) |
| Medicaid | 1.35 (1.06–1.72) |
| Other insurance | 1.39 (0.89–2.16) |

*Factors (e.g., hospital region) are delineated by specific effects (e.g., Midwest, South, and West) as listed in the table, or otherwise, if not listed, the effect on the factor is yes vs. no. The multivariable logistic regression model for patients with CDM was performed in which all factors had a p value <0.1 in univariate models and their 2-way interaction terms were taken into account.

CDM = cardiomyopathy; HMO = health maintenance organization; MACE = major adverse cardiac events; other abbreviations as in Table 3.

CDM in a young cohort, to evaluate outcomes at the time of delivery. It has been previously used to investigate trends in hospitalization of pregnancy and heart disease, as well as trends in admission for heart failure or in myocardial infarction (16–20). In our study, MACE occurred in more than 40% of the CDM cohort at the time of delivery compared with the less than 1% in the No CDM cohort. Adverse events in the CDM cohort were mainly driven by heart failure. MACE was also noted to be prevalent in all 3 CDM subgroups, with the highest overall incidence in the peripartum CDM subgroup. This cohort of patients with peripartum CDM is the largest cohort of patients reported to date. The presence of CDM is associated with a more than 90-fold increase in the odds of developing MACE in all women who undergo delivery. Black women experienced the overall highest odds of MACE compared with other races. Significant predictors of MACE in the CDM cohort were CDM subgroup, race, valvular disease, pre-eclampsia/eclampsia status, cesarean delivery, and postpartum hemorrhage. Peripartum CDM is a significant predictor of MACE. Patients with CDM had more than double the LOS and nearly quadruple the THCs compared with patients without CDM.

A number of earlier studies identified risk factors for adverse maternal outcomes during pregnancy in women with heart disease (1,5,7,9,10,21–25). A left ventricular ejection fraction of <40% has been shown to predict adverse events in pregnancy (5). Grewal et al. (9) demonstrated that in women with known dilated CDM, 39% of pregnant women developed cardiac events. Similarly, the European Registry on Pregnancy and Heart disease (ROPAC) demonstrated the worst outcomes in women with a diagnosis of CDM, with 2.4% mortality, 24% heart failure, 11% ventricular arrhythmias, 3.4% hypertension, and 58% cesarean delivery (1). We demonstrated a low mortality in the CDM cohort, likely a reflection of heightened awareness of cardiac disease in pregnancy, as well as early diagnosis and coordinated management among obstetric, cardiology, and anesthesia teams at the time of delivery. Overwhelmingly, the most common adverse outcome was heart failure, regardless of subtype of CDM, with more than one-third of the patients with peripartum CDM experiencing this outcome. Notably, heart failure was present in patients without CDM (**Table 1**), presumably related to other cardiac conditions that are associated with heart failure in pregnancy (valvular disease, pulmonary hypertension, congenital heart disease). Recently, the ROPAC registry demonstrated that in a diverse group of patients, including those with congenital heart disease, CDM, and valvular heart disease, the most common adverse outcome was heart failure and was associated with higher adverse maternal and fetal outcome (26).

Counseling women with known CDM of any subtype of these risks before pregnancy or during pregnancy is of critical importance. Moreover, reduction in heart failure frequency and severity should be a

**TABLE 5 Multivariable Analysis of MACE in Women With Peripartum CDM**

| Factor* | OR (95% CI) | p Value |
|---|---|---|
| Valvular disease | 2.16 (1.49–3.14) | <0.001 |
| Teaching hospital | 0.76 (0.59–0.99) | 0.043 |
| Pre-eclampsia status (ref. normal) | | |
| Eclampsia | 2.02 (0.85–4.8) | 0.112 |
| Severe pre-eclampsia | 1.54 (1.08–2.21) | 0.018 |
| Mild pre-eclampsia | 1.26 (0.82–1.94) | 0.290 |
| Pre-eclampsia | 1.50 (0.94–2.42) | 0.090 |
| Multiple gestation | 0.59 (0.36–0.98) | 0.045 |
| Cesarean delivery | 1.36 (1.04–1.78) | 0.022 |

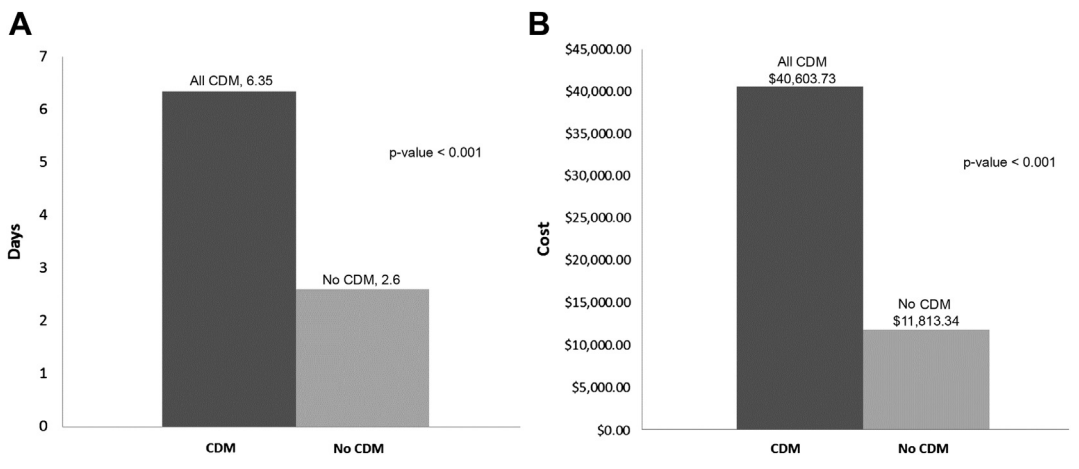
*Each factor is based on a multivariable logistic regression model in which all factors had a p value <0.1 in univariate models. Patients' characteristics such as having valvular disease, hospital type, having multiple gestation, and cesarean delivery were significantly associated with MACE after adjusting for these factors ($p < 0.0001$, $p = 0.0438$, $p = 0.0452$, and $p = 0.0228$, respectively).

MACE = major adverse cardiac events; other abbreviations as in Table 3.

goal, particularly at the time of delivery and in the days to weeks that follow. Although the observed in-hospital mortality appears to be low in this cohort, and in others (9,13), a finding that is reassuring, it is possible that in these high-risk women, maternal death could occur after hospitalization for delivery. The data represent an index hospitalization for delivery and do not allow us to follow patients over time or to document those women who may have died outside the hospital before or after delivery. Late effects of pregnancy on the diseased ventricle can occur months after the pregnancy is complete, with a decrement in ejection fraction as a relatively common finding in women with known dilated CDM (9). These late negative effects on left ventricular systolic function have a detrimental effect on long-term outcomes. They may be related to the discontinuation of optimal medical therapy for heart failure because of contraindications and/or a patient's preference during pregnancy or the early postpartum period. The long-term effects of pregnancy on women with CDM, particularly those with an abnormal ejection fraction, require further investigation.

We demonstrated an increased incidence of hypertensive-related and/or pre-eclampsia/eclampsia disorders in our CDM cohort, particularly in the group with peripartum CDM. In addition, eclampsia status was found to be a significant predictor of MACE in our CDM cohort, as well as in the peripartum CDM cohort. Earlier evidence has suggested that pre-eclampsia/eclampsia was more common in women with peripartum CDM (8,27,28), and it was a risk factor for the development of peripartum CDM (13). Pre-eclampsia/eclampsia may be a contributor to impairment in cardiac function. Consistent with this concept, several studies have shown that women with pre-eclampsia have evidence of diastolic dysfunction as well as impaired myocardial strain

**FIGURE 1 Length of Stay and Total Hospital Charges for Pregnant Women With CDM and Without CDM at Hospitalization for Delivery**




**(A)** Average length of stay for pregnant women at hospitalization for delivery in the United States from 2006 to 2010. The **black bar** represents the all forms of cardiomyopathy (CDM) cohort; the **gray bar** represents the patient cohort without cardiomyopathy. **(B)** Average total hospital charges for pregnant patients who underwent delivery in the United States from 2006 to 2010. The **black bar** represents the all forms of cardiomyopathy cohort; the **gray bar** represents the patient cohort without cardiomyopathy.

despite preservation of global systolic function (29,30). Gestational hypertension without pre-eclampsia does not cause similar cardiac dysfunction or clinical heart failure, a finding indicating that other factors or the acuity of a clinical syndrome are likely important. Most patients with pre-eclampsia do not develop clinical heart failure or peripartum CDM. A distinct but important clinical entity is pre-eclampsia-associated pulmonary edema, which occurs in the presence of high blood pressure and increased cardiac afterload. Unlike peripartum CDM, however, pre-eclampsia-associated pulmonary edema occurs in the presence of a normal ejection fraction. Misclassification of diagnoses is possible with this type of dataset, but it is unlikely because other investigators have also found a similar association (26,27).

Valvular heart disease was found to be a significant predictor of MACE in the CDM and peripartum CDM cohorts. Mitral and tricuspid valve disease were found to be significant predictors of MACE, likely related to functional mitral and/or tricuspid regurgitation secondary to mitral valve tethering resulting from an underlying cardiomyopathic process and possibly a marker of more severe left ventricular dysfunction. Aortic disease was not common or predictive. In the cohort reported by Grewal et al. (9), approximately 20% to 25% of patients with dilated CDM had significant mitral or tricuspid regurgitant lesions. Severe mitral regurgitation was a significant predictor of adverse cardiac events. Similarly, pregnancy increases the degree of regurgitant valve lesions (31), which can be associated with maternal adverse events (32).

There is increasing evidence for the relationship of race with pregnancy complications in women with peripartum CDM (13,33). Peripartum CDM has been traditionally characterized by prominent rates among black women (33,34), but it is recognized that this depends on the population studied and the incidence varies in women of different racial backgrounds (11,33,34). We noted in our analyses that white women overall represented the highest number of cases per CDM cohort. However, the white race also represented the largest overall sample size among the races in our study. When assessing for frequency of cases classified by race, we noted that black women had more than a 2-fold higher rate of peripartum CDM and all other CDM types (0.0005 and 0.0005, respectively) compared with white women (0.0002 and 0.0002, respectively). Elkayam et al. (12) similarly described this finding in their study, in which white women were the most represented race in their sample and therefore also had the highest weight on the peripartum CDM frequencies across races.

Cesarean delivery was most common in the CDM cohort overall, and most common in the peripartum CDM cohort, and it was a predictor of adverse events. This likely reflects the degree of clinical acuity and the severity of illness. However, an interaction related to anesthesia in the maternal outcomes cannot be excluded.

**STUDY LIMITATIONS.** The limitations are inherent to retrospective studies using administrative data, such as the NIS. The study likely reflects the incidence of symptomatic patients, rather the total number of patients with CDM and pregnancy. Notably, patients with American College of Cardiology/American Heart Association stage B heart failure could have been missed because of their asymptomatic status. Moreover, the OR for MACE for CDM may be overestimated by the presence of cardiac complications that led to the diagnosis of CDM. Unfortunately, there is no statistical model that can adjust for this.

Importantly, because of the characteristics of the HCUP NIS dataset, it is not possible to extract clinical characteristics, echocardiographic findings, and laboratory parameters vitally important to the analysis, as well as to confirm the diagnosis. Moreover, information regarding pre-existing conditions or pre-existing CDM, maternal comorbidities, left ventricular ejection fraction, or use of medical therapy was not available. In addition, neonatal outcomes were not available. The NIS does not longitudinally track patients over time after the hospitalization, nor is there a method to determine whether a pre-existing diagnosis of CDM was present before the hospitalization. Previously undiagnosed CDM versus known CDM and acute (i.e., peripartum) CDM versus chronic CDM are limitations of the current data. Patients with known CDM can be followed closely during their pregnancy and risk stratified, particularly at the time of delivery, and presumably some of their risk can be mitigated through this knowledge.

Hospital admissions for delivery in women with and without CDM were identified through ICD-9 codes and therefore were unable to be independently adjudicated. Errors in ICD-9 coding and documentation are possible, although the error rate has been found to be low in this database (16). ICD-9-Clinical Modification (ICD-9-CM) coding has demonstrated a high specificity and positive predictive value for related diseases such as heart failure and hypertensive disorders (18,35–37). Although diagnostic accuracy remains a concern, it is reassuring that our data are similar to others with regard to incidence, demographic data, and known risk factors.

## CONCLUSIONS

With a large all-payer population of U.S. pregnant women at delivery, we observed that MACE occurred in more than 40% of the CDM cohort at the time of delivery compared with the less than 1% in the No CDM cohort, with a strikingly low overall mortality rate in the CDM group. MACE in the CDM cohort was mainly driven by heart failure and, to a lesser extent, arrhythmias. MACE was also noted to be prevalent in all 3 CDM subgroups, with the highest overall incidence in the peripartum CDM subgroup. The presence of CDM significantly increased the odds of developing MACE. Significant predictors of MACE were CDM subtype, race, valvular disease, eclampsia status, cesarean delivery, and postpartum hemorrhage. Peripartum CDM was a significant predictor of MACE in the CDM group. Patients with CDM had more than double the LOS and nearly quadruple the THCs compared with patients without CDM.

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**KEY WORDS** cardiomyopathy, delivery, hypertrophic cardiomyopathy, maternal outcomes, peripartum cardiomyopathy, pregnancy

**APPENDIX** For supplemental tables, please see the online version of this article.