A Case-Control Study of Peripartum Cardiomyopathy Using the Rochester Epidemiology Project

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Abstract

Background: The incidence of peripartum cardiomyopathy (PPCM) is known through referral center databases that may be affected by referral, misclassification, and other biases. We sought to determine the community-based incidence and natural history of PPCM using the Rochester Epidemiology Project.

Methods and Results: Incident cases of PPCM occurring between January 1, 1970, and December 31, 2014, were identified in Olmsted County, Minnesota. A total of 15 PPCM cases were confirmed yielding an incidence of 20.3 cases per 100,000 live births in Olmsted County, Minnesota. Clinical information, disease characteristics, and outcomes were extracted from medical records in a 27-county region of the Rochester Epidemiology Project including Olmsted County and matched in a 1:2 ratio with pregnant women without PPCM. A total of 48 women were identified with PPCM in the expanded 27-county region. There was 1 death and no transplants over a median of 7.3 years of follow-up. Six of the 23 women with subsequent pregnancies developed recurrent PPCM, all of whom recovered. Migraine and anxiety were identified as novel possible risk factors for PPCM.

Conclusions: The population-based incidence of PPCM was 20.3 cases per 100,000 live births in Olmsted County, Minnesota. Cardiovascular outcomes were generally excellent in this community cohort.

Keywords

Heart failure; incidence; migraine; pregnancy

Peripartum cardiomyopathy (PPCM) is defined as the development of cardiac failure in the last month of pregnancy or within 5 months of delivery in women with no history of heart disease and no other identifiable cause for cardiac failure. PPCM is characterized by left ventricular (LV) systolic dysfunction with an LV ejection fraction (LVEF) of 45% and confirmed by echocardiography,[1] as well as heart failure symptoms. Women with PPCM can experience complete recovery of heart function[2,3] with early diagnosis and treatment. Timely diagnosis is challenging because the symptoms of PPCM are similar to the physiological changes that occur during normal pregnancy and postpartum.[4,5]

The incidence estimates of PPCM vary widely between countries and within the United States from 25 cases per 100,000 live births in the United States[6] to 333 per 100,000 live births in Haiti.[7] Within the United States, rates vary from 25 cases per 100,000 live births in southern California to 185 per 100,000 live births in Georgia.[5,6,8–13] The first population-level estimate of PPCM incidence in the United States used the National Hospital Discharge Survey, relying on *International Classification of Diseases* (ICD) codes to confirm the diagnosis, and reported 31 cases per 100,000 live births.[13] A population-level study of PPCM with a complete medical record review for data abstraction has not been published previously. This study provides the first population-level epidemiologic study describing the incidence and outcomes of PPCM using a comprehensive medical record review through the Rochester Epidemiology Project (REP) using a case-control design to examine demographic and clinical characteristics, presentation, potential risk factors, and outcomes.

Methods

Participants

This project was approved by both the Mayo Clinic and Olmsted Medical Center Institutional Review Boards and conformed to the principles set forth in the Declaration of Helsinki 1975, as revised in 2013. All patients involved in the study provided written informed consent to allow the use of their medical records for research purposes as part of the REP. Patients who had not previously consented to participate in research through the REP were excluded from the study.

Source of Data

The REP has been used to conduct population-level epidemiologic research in Olmsted County, Minnesota, as described previously.[14] Briefly, the database links the medical record of most health care providers in the county, including Mayo Clinic and Olmsted Medical Center and their affiliated hospitals as well as a few private providers who provide 90%–96% of all health care to Olmsted County residents.[14–16] Data for this study was available

from 3 regions: Olmsted County (1 county), a 7-country region that included Olmsted County and 6 other surrounding counties, and a 27-county region that incorporated the 7 counties as well as other counties in southern Minnesota and western Wisconsin.[17] Olmsted County has a coverage rate of 99.9% from January 1, 1970, through December 31, 2014, and the 7-county region has a 93.8% coverage rate from January 1, 1976, through December 31, 2014. Starting January 1, 2010, the REP was expanded to include a total of 27 counties.[14–17] The 27-county region uses the same data linkage system as the REP and has an overall coverage rate of 60.9% from January 1, 2010, to December 13, 2014.[14–17] The lower coverage rate is due predominantly to not all heath care facilities within the region collaborating in the REP.[17] The REP has electronic indexes that include demographic information, diagnostic and procedure codes, health services use data, outpatient drug prescriptions, laboratory test results, imaging and procedure reports, and information about smoking, height, weight, and body mass index.[14–17] The demographic, racial, ethnic, and socioeconomic makeup of the 27 county region REP has been shown to be representative of the Minnesota/Wisconsin area and to a large segment of the US population.[17]

Study Population

Data were collected for all Olmsted County, Minnesota residents diagnosed with PPCM from January 1, 1970, through December 31, 2014. PPCM cases from the 1-county region were broadly identified from a list of 866 women 15–55 years of age living in Olmsted County, Minnesota, from 1970 to 2014 with a PPCM diagnosis code (ICD-9 674.5X, Hospital International Classification of Disease Adaptation [HICDA] 4251610, 4251310, BRK 0234 × 1) or a heart failure code (ICD-9 428.X, HIC 4270110, 4279133, BRK 23452); codes that were used for these disease classifications during this time period. The older HICDA code was used to identify PPCM cases during the years before the use of ICD-9 diagnosis codes. From the original 866 patients identified with possible PPCM, 15 cases were confirmed as PPCM. Population-level data were only available for Olmsted County, so the incidence of PPCM was based on Olmsted County data.

To increase the sample size of the study, data were also collected from January 1, 1976, through December 31, 2014, by individual record review for the 7-county and the 27-county regions. Because heart failure diagnosis codes had not yielded any additional cases of PPCM in the survey of 866 records in Olmsted County, only diagnosis codes for PPCM (ICD-9 674.5X) or cardiomyopathy (HICDA 4250310) were used for the expanded regions. From the 7-county region, we identified an additional 242 women with PPCM diagnoses, and a further 69 patients from the 27-county region with PPCM diagnoses. From these potential cases, medical record review confirmed 33 additional cases of PPCM, which combined with the 15 cases from Olmsted County, provided a total of 48 cases for the study (Fig. 1).

In total, 1177 potential cases of PPCM were individually screened from all 3 regions using a case definition for PPCM based on the criteria proposed by the National Heart, Lung and Blood Institute and the Office of Rare Diseases of the National Institutes of Health Workshop on Peripartum Cardiomyopathy[1] that included (1) the development of cardiac failure in the last month of pregnancy or within 5 months of delivery, (2) an absence of an identifiable cause for the cardiac failure, (3) an absence of recognizable heart disease before

the last month of pregnancy, and (4) a LV systolic dysfunction demonstrated by classical echocardiographic criteria with an EF of 45% (Fig. 1).

Control patients were selected from a pool of 52,682 women 15–55 years of age who lived and gave birth within the 27-county region of the REP from January 1, 1970, through December 31, 2014. Controls were matched on a 2:1 basis by age, race, and number of babies born during the index pregnancy (index pregnancy refers to the pregnancy related to initial PPCM diagnosis for cases and the matched pregnancy in each control).

Data Collection

Data regarding demographics, medical history, index pregnancy, and outcomes for the 48 confirmed PPCM cases and the 96 selected controls were abstracted from electronic and paper medical records available through the REP and entered into a Research Electronic Data Capture (REDCap) database.[18]

Statistical Analysis

The incidence was calculated for all Olmsted County female residents who were 15–55 years of age and considered to be at risk for PPCM. Annual birth rates for Olmsted County residents were obtained from the Minnesota Health Statistics Annual Summary Reports.[19,20] To compare cases and controls, the Student's t test or Wilcoxen–Mann–Whitney test were used to assess differences for continuous variables with normal or skewed distribution, respectively. The Fisher exact test or the χ^2 test were used to evaluate categorical variables. A P value of <.05 was considered statistically significant. Categorical data are presented as frequency (n) and percent (%) and numeric data as mean ± standard deviation for normally distributed data and median (interquartile range) for non-normally distributed data, unless otherwise specified. Missing data were excluded from the analyses. Column total percentages are based on excluding missing data. Data were analyzed using Stata/IC 15.[21]

Results

Fifteen women in the single county area of Olmsted County, Minnesota, who met the definition for a diagnosis of PPCM were identified. Based on vital statistics data from the Minnesota Department of Health,[19,20] the incidence of PPCM from 1970 through 2014 in Olmsted County, Minnesota, was determined to be 20.3 cases per 100,000 live births.

An additional 33 women who lived in the larger 27 county REP area and met the criteria for a diagnosis of PPCM were identified that, when added to the 15 cases from Olmsted County, provided the 48 overall number of cases for the case control study (Fig. 1).'Ninety-six women were identified as controls with a 2:1 matching based on age, race, and number of infants born during the index pregnancy. Demographics of cases and controls are listed in Table 1. The mean age of the cohort was 28 years (range 15–44 years) (Table 1). The cohort was 79.2% White, 18.7% Black (a mix of African American [6.2%] and African immigrants [12.5%]) and 1 woman (2.1%) who identified as both Native American and Hispanic. Women in the PPCM cohort had a higher median body mass index than women in the control cohort (25.2 kg/m^2 vs 23.6 kg/m^2, P = .01), were more likely to be overweight or obese (66.7% vs 41.7%, P = .005), and were more likely to have government-sponsored

health insurance (ie, Medicaid), whereas women in the control cohort were more likely to have private health insurance (53.3% vs 25.6%, *P* = .001) (Table 1). There were no statistically significant differences in marital status, education level, smoking status, and history of alcohol consumption or drug use between the 2 groups. The median length of follow-up was shorter for cases compared to controls (7.2 years vs 12.8 years, *P* < .001) (Table 1).

Comorbidities for the 2 groups are compared in Table 2. Women in the PPCM cohort were more likely to have a history of hypertension (8.3% vs 2.1%, *P* = .01), anxiety (25.0% vs 10.4%, *P* = .03) and migraine (43.8% vs 15.6%, *P* < .001) compared with controls (Table 2). There were no differences observed in hyperlipidemia, heart disease, cancer, depression, asthma, allergies, infections, diabetes, or chemical exposure between the 2 groups (Table 2). Among the women for whom these data were available, women diagnosed with PPCM were more likely to have a history of hypertensive disorders of pregnancy (HDP), predominantly gestational hypertension and preeclampsia (40.0% vs 4.2%, *P* = .02), and a higher likelihood of gestational diabetes (4.8% vs 3.1%, *P* = .04) in previous pregnancies (Table 3).

Index pregnancy characteristics are listed in Table 4. Women in the PPCM cohort were more likely to have been diagnosed with HDP (56.3% vs 12.5%, *P* < .001) and more likely to have been placed on bed rest (28.2% vs 12.6%, *P* = .03) during their index pregnancy compared with women in the control group. The index pregnancies of women diagnosed with PPCM were less likely to have been planned pregnancies than those of controls (32.4% vs 54.4%, *P* = .03). Women in the PPCM cohort were also significantly more likely to have had an emergency cesarean section than women in the control cohort (43.8% vs 14.6%, *P* < .001). Women in the PPCM cohort were more likely to have had a cardiac indication for cesarean section than women in the control cohort (55.1% vs 7.1%, *P* = .01) (Table 4). Infants born to women in the PPCM cohort had a lower median gestational age (37 weeks vs 39 weeks, *P* = .004), were significantly more likely to be born prematurely (< 37 weeks gestation) (43.8% vs 22.9%, *P* = .003), had a significantly lower median birth weight (2445 g vs 3190 g, *P* = .01) and were more likely to be born at a low birth weight (<2500g) (45.8% vs 24.8%, *P* = .01). Women in the PPCM cohort seemed to be less likely to breastfeed, but this difference did not reach statistical significance (59.9% vs 75.8%, *P* = .06.) However, the rates of breastfeeding in the PPCM cohort decreased significantly after diagnosis (59.9% vs 24.3%, *P* = .009) (Table 4).

Table 5 presents characteristics, including physical examination at diagnosis, echocardiography findings, and treatments and outcomes for the 48 cases in our cohort. Eleven of the women (22.9%) were diagnosed with PPCM during pregnancy and the other 37 (77.1%) were diagnosed postpartum, with the median time of diagnosis being 4 days postpartum (Table 5). The majority of cases (41/48, 85.4%) presented with elevated blood pressure[22] and/or heart failure symptoms (44/48, 91.7%) with 1 patient missing information on symptoms at diagnosis. Indications for cardiac screening in the 3 cases without heart failure symptoms included arrhythmias and a new heart murmur. The median LVEF at diagnosis was 34% (range 12%–45%) and the median LV end diastolic diameter was 5.7 cm (range 4.0–7.4 cm). Forty-seven of the women (97.9%) were treated with medications, the most common being angiotensin-converting enzyme inhibitors (87.5%, *n* = 42), diuretics

(87.5%, $n = 42$), and beta-blockers (79.2%, $n = 38$) (Table 5). One patient had an intra-aortic balloon pump placed and subsequently died (Table 5, Fig. 1). This death was the only one in the cohort. No pacemakers or internal cardiac defibrillators were implanted and no patients underwent LV assist device implantation or transplantation during a median follow up time of 7.3 years (range 0.3–27.8 years) (Table 5, Fig. 1).

Supplementary Fig. 1 shows the trends in LVEF of the confirmed cases over the first 5 years of the study. Forty-three of the women (89.6%) diagnosed with PPCM recovered cardiac function (LVEF 50% per follow-up echocardiography) (Table 5, Fig. 1). The timing of the recovery ranged from 3 days to just >12 years, with the median time to recovery approximately 4.5 months (Table 5). Two women had residual cardiac dysfunction and no follow-up echocardiograms were recorded for 2 additional women in the PPCM cohort, so recovery status could not be determined (Fig. 1).

Among the control cohort of 96 women, 56 (62.6%) had a total of 105 subsequent pregnancies, resulting in 82 (78.1%) live births, 18 (17.1%) spontaneous abortions, and 5 (4.8%) terminations. Twenty-three of the 48 women (56.1%) diagnosed with PPCM had a total of 37 subsequent pregnancies resulting in 25 (67.6%) live births, 5 (13.5%) spontaneous abortions, and 7 (18.9%) terminations (Table 6). Pregnancy termination was significantly higher in cases compared with controls ($P = .01$) (Table 6). Among the women diagnosed with PPCM, 10 (30.3%) of the subsequent pregnancies were planned, 23 (65.2%) were unplanned, with information unavailable regarding planning for 6 pregnancies (Table 6). Twenty-two of the women (95.7%) recovered cardiac function (LVEF of 50% per follow-up echocardiography) before subsequent pregnancy. One woman had no follow-up echocardiograms after index pregnancy diagnosis, so recovery status at subsequent pregnancy was unknown (Fig. 1). Fifteen women (65.2%) were on cardiac medication during their subsequent pregnancies (Table 6). The relapse rate in the PPCM cohort was 12.5% ($n = 6$), but all 6 cases recovered normal LV function after their relapse (Table 6 and Fig. 1). Similar rates of women in each cohort underwent sterilization procedures after index delivery (33.3% vs 34.4%, $P = .90$).

Discussion

The estimate of the incidence of PPCM in Olmstead County, Minnesota from 1970 through 2014 was 20.3 cases per 100,000 live births, which is lower than previous estimates of 25 to 185 per 100,000 live births.[5–7,9,13,23] Fifteen cases were found in Olmsted County and an additional 33 cases for a total of 48 cases in the larger 27 county region. However, owing to the lower percentage coverage rate (61%) for the REP in the 27 county region, PPCM incidence for the larger region could not be calculated. From an initial 1177 patients identified using diagnosis codes for heart failure, cardiomyopathy and PPCM, only 48 (55%) of the 88 women with a diagnosis code for PPCM met the diagnostic criteria for PPCM after record review by a physician experienced with PPCM (Fig. 1).[1] The most common reasons for exclusion included a LVEF of >45% and a diagnosis of other types of cardiomyopathy (Fig. 1). Our study may reflect a more accurate population-level incidence than previously published studies, because all cases in this study were confirmed using medical record data, whereas previously published studies[5–7,9,13,23] relied on diagnosis codes and may have

overestimated the disease incidence by including women who had the diagnosis code for PPCM in their medical record but did not meet the diagnostic criteria for PPCM.

The mean age at PPCM diagnosis in this study was 28 years (Table 1), with 62.5% of cases occurring in women 30 years in contrast with previous studies that found an association between PPCM diagnosis and advanced maternal age.[6,8,9,13] Previous studies reported that Black women have the highest rates of PPCM, followed by non-Hispanic White women, with Hispanics and Asians having the lowest rates.[5,6,9,13,23–25] Based on US Census data, the population within the study area was 90.2 97.4% non-Hispanic White and 1.3 3.7% Black during the study period, whereas cases in this cohort were 79.2% non-Hispanic White and 18.8% Black, supporting previous reports that PPCM cases seem to occur at a higher rate among Black women compared with non-Hispanic White women.[15]

Previous reports have also suggested an increased risk of PPCM with multiparty[5,8–12,25] and multifetal gestation.[26] In the current study, we did not observe an association between multiparity and PPCM diagnosis, as 28 of the 48 women (58.3%) with PPCM were nulliparous (Table 3). Similar to previous studies, however, multifetal gestation during the index pregnancy (17.0%, $n = 8$ in cases) occurred at a higher rate in women diagnosed with PPCM compared with the national rates for multifetal gestation that ranged from 2.1% to 3.5% during the time period of this study.[27]

HDP have been associated with an increased risk of PPCM.[26,28,29] Twenty-seven of the cases (56.3%) in this study were diagnosed with HDP during their index pregnancy, a rate significantly higher than controls (12/96, 12.5%, P .001) (Table 4). Preeclampsia was the most common HDP diagnosis among cases, occurring in 18 of the 48 women (37.5%) (data not shown), which is more than nine times the 4% preeclampsia rate among women in the United States.[30] This finding aligns with previous studies that have reported that preeclampsia is one of the strongest risk factors for PPCM.[26,31]

This study identified prior diagnoses of anxiety or migraine as novel possible risk factors for PPCM (Table 2). Anxiety may increase the risk of cardiovascular disease by increasing inflammation and inducing endothelial dysfunction, 2 factors that are postulated to play a role in the pathogenesis of PPCM.[32] Migraine may also be a risk factor for developing PPCM, although with a small sample size of incident cases, this may also simply reflect migraine as a common disease state in women. It is important to note, however, that migraine is a known risk factor for cardiovascular and cerebrovascular disease, potentially increasing risk through pathways including HDP.[33–35] Migraine, preeclampsia, and PPCM have all been associated with vascular dysfunction owing to hormone imbalances and angiogenic factors including vascular endothelial growth factor, soluble fms-like tyrosine kinase-1, estrogen, relaxin-2, prolactin, and placental growth factor.[33,36–41] Further investigation, including determining whether or not migraine subtype (with or without aura, for example) is more predictive of PPCM and whether increased frequency of migraine during pregnancy or only postpartum heightens risk of PPCM, is warranted.

Similar to previous studies,[5,8,42,43] the findings from this study suggest that infants born to mothers with PPCM have an increased risk for adverse birth outcomes, including

prematurity and low birthweight (<2500 g) compared with those born to mothers in the control cohort (Table 4). These adverse outcomes are important to note, because premature birth and low birth weight are both associated with increased infant mortality and a variety of developmental and medical issues for the child.[44]

Another important finding in this study is that the rate of breastfeeding in women with PPCM decreased significantly after diagnosis (Table 4). Women discontinued breastfeeding for a variety of reasons, including their perceived compromised physical or mental health, not having ready access to their infants while hospitalized, a lack of awareness by treating physicians about the safety of cardiac medications during lactation, and/or a concern that breastfeeding may be detrimental to the mother's recovery based on the proposed mechanistic link between PPCM and the nursing hormone prolactin.[37,45] The World Health Organization recommends exclusive breastfeeding for 6 months and continued breastfeeding for 1–2 years[46] because the lack of breastfeeding is associated with an increased risk of diabetes, ovarian and breast cancers, and postpartum depression in women and higher rates of mortality, infections, eczema, asthma, childhood obesity, diabetes, leukemia, and lower intelligence in children.[47,48] Mothers with PPCM and their physicians would likely benefit from increased education and awareness regarding which cardiac medications are safe to use during lactation and that breastfeeding seems to have no detrimental effect on outcomes among women with PPCM according to several published reports.[49–51] Further investigation into the short- and long-term outcomes of infants born to mothers diagnosed with PPCM is necessary so that appropriate counseling and care can be provided to mothers and infants.

Nearly 90% of the women with PPCM in this study recovered normal LV function with a median recovery time of 4.5 months (Table 5). It should be noted that approximately one-half of the women who had not recovered by year one did not have follow-up echocardiograms until 1–12 years after diagnosis, at which time they had recovered. Owing to the retrospective nature of the study, the precise timing of recovery was difficult to establish. However, our data suggest that cardiac function can continue to improve for many years after PPCM diagnosis. Guideline-directed recommendations for follow-up assessment of women diagnosed with PPCM would likely enhance our understanding regarding degree and timing of LV recovery in patients.

In our study, 5 of 43 woman (11.6%) with PPCM who recovered LV function suffered a decline in cardiac function, between 6 months to 9.3 years after recovery, unrelated to a subsequent pregnancy (data not shown). One woman suffered cardiac toxicity from medications taken for an unrelated condition and recovered. A second woman recovered by one year and then had 2 occasions with deterioration in cardiac function despite remaining on cardiac medications throughout that time period with her most recent echocardiogram demonstrating a LVEF of 50%. Three women had discontinued all cardiac medications after recovery but then suffered declines in cardiac function at 3.5, 6.0, and 9.3 years after recovery. All 3 women recovered cardiac function after cardiac medications were restarted. Most medical experts agree that guideline-directed medical therapy for heart failure should be continued indefinitely in women with PPCM who have persistent cardiac dysfunction. However, there is no clear consensus on how to treat women with PPCM with recovered LV function.[2,52] Data regarding the long-term risk of cardiac deterioration

if medications are stopped is conflicting.[53,54] Two recent studies suggest that women with LV recovery may still have LV diastolic dysfunction, decreased exercise capacity, ongoing angiogenic imbalance, and residual myocardial injury.[55,56] Noting that 5 women in our PPCM cohort experienced decline in LV function after recovery unrelated to subsequent pregnancy highlights the difficulty in determining the duration of medical treatment after recovery and the importance of long-term regular cardiac follow-up for women diagnosed with PPCM, including those with recovered cardiac function.

Many women with PPCM desire to have additional pregnancies after diagnosis. Decisions regarding subsequent pregnancy are challenging, because all women with PPCM are at risk for a decrease in LV function and possibly even death. Experts agree that women with persistent significant cardiac dysfunction are at greatest risk for cardiac complications during subsequent pregnancy and should be counseled against future pregnancy, while women with recovered cardiac function may consider subsequent pregnancy.[2,57,58] There are no proven risk factors for relapse during subsequent pregnancy among women with recovered LVEF, so careful monitoring during and after pregnancy is indicated. Although the sample size is small, our study results support the consensus that women diagnosed with PPCM with recovered cardiac function can have successful subsequent pregnancies (Table 6). Of note, 4 of the women in our study who relapsed during subsequent pregnancy were on cardiac medications at the time of relapse, highlighting that heart failure therapy does not guarantee freedom from relapse (Table 6). In addition, the large number of unplanned subsequent pregnancies and the higher rate of terminations in women diagnosed with PPCM indicate that contraceptive counseling on an ongoing basis, not simply shortly after PPCM diagnosis, is critical.

There are several limitations to this study. The small sample size prevented any subgroup analysis. The lack of racial/ethnic diversity in the REP compared with other regions of the United States may limit the generalizability of the study. Owing to the retrospective nature of the study, data are restricted to what is available in medical records and therefore the timing of subsequent echocardiograms varied between patients, adding uncertainty to calculations such as length of time to recovery. In addition, some cases of PPCM may have been missed because the REP does not have complete coverage of medical records for all 27 counties. This factor prevented an incidence calculation for the entire study area. A major strength of our study, however, is the use of data from the REP, a well-established, high-quality, federally funded resource for epidemiologic research. In addition, the use of complete medical record review to confirm the diagnosis leading to a well-defined cohort of PPCM cases from a specific geographical area with long-term follow-up is particularly noteworthy. These strengths, as well as the almost complete capture rate of medical records for all residents of Olmsted County, Minnesota, made it possible to calculate a precise incidence estimate for that area.[14–16] These strengths, along with the verification of diagnosis by medical record review, minimized referral bias and misclassification, which are common in coding-based studies. This study was also strengthened by the range of data collected and analyzed, as well as the abundance of data in areas addressing knowledge gaps related to PPCM including long-term outcomes of mothers, infant outcomes, and outcomes of subsequent pregnancies.

Conclusions

The population-based incidence of PPCM was 20.3 cases per 100,000 live births in Olmsted County, Minnesota. Among the well-characterized cohort of women with PPCM in this study, a history of anxiety and a history of migraine emerged as novel risk factors. The majority of women recovered LV function days to years after diagnosis. A minority of women with recovered LV function experienced subsequent LVEF decline months to years after recovery. Infants of mothers with PPCM had an increased risk of prematurity and low birth weight. Finally, women with recovered LVEF before subsequent pregnancy experienced no long term decline in LVEF after pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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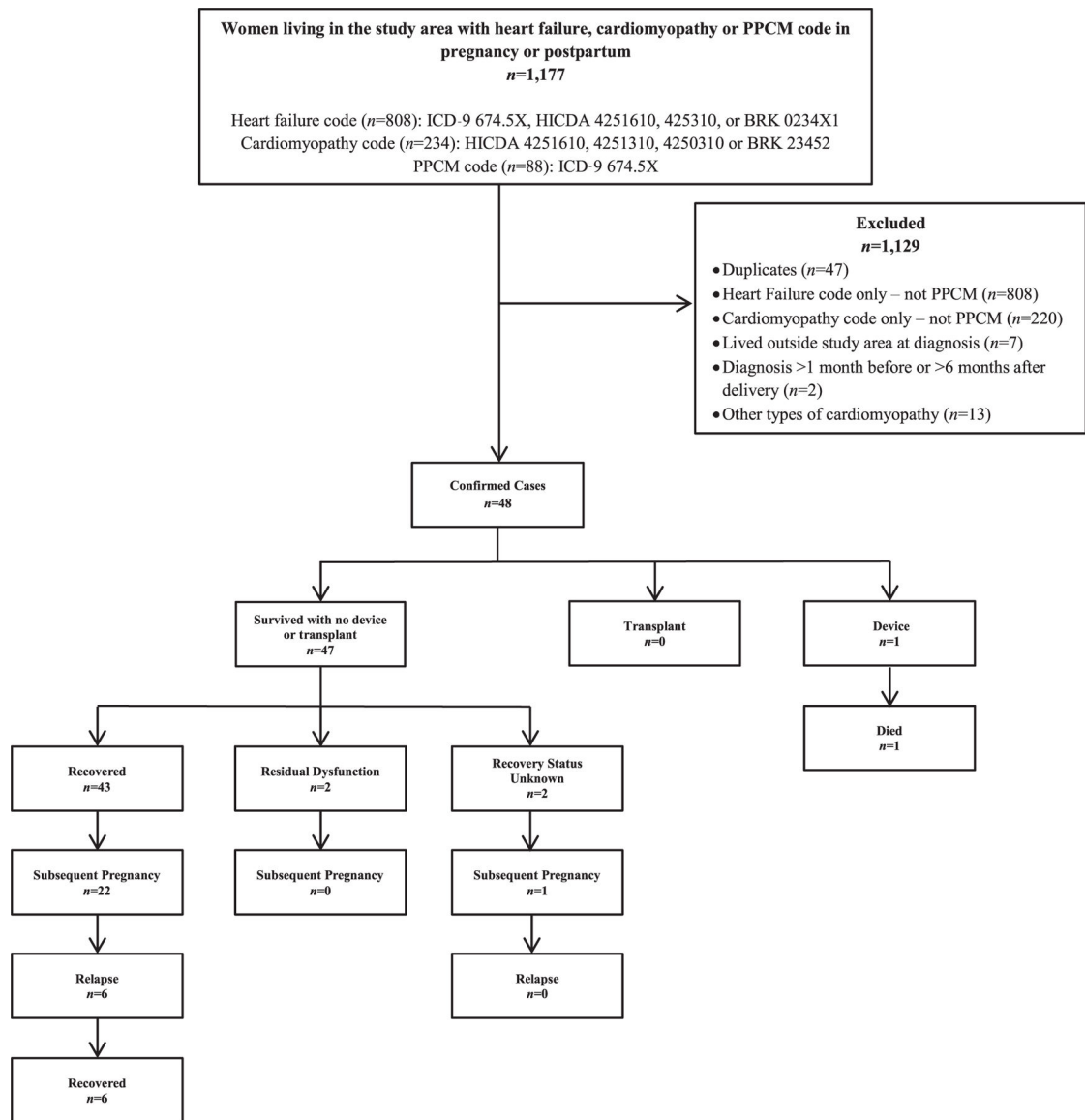
Fig. 1.

Patient cohort with outcomes. From an initial cohort of 1177 women, 48 cases of peripartum cardiomyopathy (PPCM) were confirmed. 47 out of 48 women survived. One woman received an intra-aortic balloon pump and subsequently died. There were no transplants in this cohort. 43 women recovered cardiac function (left ventricular ejection fraction of   50% on echocardiogram), 2 had residual left ventricular dysfunction, and 2 had no follow-up echocardiograms so the recovery status could not be determined, but both were functionally recovered. At least 22 of the recovered women had subsequent pregnancies, as well as 1 woman whose recovery status was unknown. One woman with unknown recovery status (functionally recovered) had 1 subsequent pregnancy and did not relapse symptomatically, but no echocardiogram was conducted. Six of the recovered cases relapsed (12.5% rate of relapse) with at least 1 pregnancy, but all 6 subsequently recovered after relapse.

Table 1.

Maternal Demographic Characteristics of Cases and Controls[*]

Patient Characteristics	Case (*n* = 48)	Control (*n* = 96)	P Value
Age (y)	28 ± 7.0	28 ± 7.0	—
Prepregnancy BMI (kg/m^2)	25.2 (20.5–36.6)	23.6 (21.6–28.0)	.01
BMI category			.005
<25.0	16 (33.3)	56 (58.3)	
25.0	32 (66.7)	40 (41.7)	
Race/ethnicity			—
White	38 (79.2)	76 (79.2)	
American Indian	1 (2.1)	2 (2.1)	
Black	9 (18.7)	18 (18.7)	
African American	3 (6.2)	7 (6.2)	
African Immigrant	6 (12.5)	11 (12.5)	
Hispanic	1 (2.1)	2 (2.1)	
Marital status			.07
Single	13 (27.1)	26 (27.1)	
Married	24 (50.0)	61 (63.5)	
Domestic partner	11 (22.9)	9 (6.4)	
Education			.84
<High school	6 (13.3)	13 (13.7)	
High school or GED	12 (26.7)	19 (20.0)	
Some college or associate degree	15 (33.3)	36 (37.9)	
College degree	12 (26.7)	27 (28.4)	
Health insurance			.001
Private	21 (46.7)	70 (74.4)	
Medical assistance/Medicaid	24 (53.3)	24 (25.6)	
Smoking			.16
At diagnosis	15 (31.2)	16 (18.0)	
Before pregnancy	8 (16.7)	23 (25.8)	
Never	25 (52.1)	50 (56.2)	
Alcohol use			.44
At diagnosis	3 (6.5)	1 (1.6)	
Before pregnancy	24 (52.2)	37 (57.8)	
Never	19 (41.3)	26 (40.6)	
Drug use			.82
Current	3 (6.2)	3 (3.8)	
Past	7 (14.6)	11 (14.1)	
Never	38 (79.2)	64 (82.1)	
Length of follow-up[†] (y)	7.2 (4.1–12.6)	12.8 (8.2–18.8)	<.001

Data are number (%), mean ± standard deviation, or median (interquartile range) unless otherwise specified.

*
Percentages are based on column totals excluding unknown data.

†
Follow-up was defined as years of medical records available for review after the index pregnancy delivery.

Abbreviations: BMI, body mass index; GED, general educational development or general education diploma.

Table 2.

Medical History of Cases and Controls

Comorbidity	Case ($n = 48$)	Control ($n = 96$)	P Value
Hypertension	4 (8.3)	2 (2.1)	.01
Hyperlipidemia	1 (2.1)	6 (6.3)	.43
All heart disease [*]	3 (6.3)	7 (7.3)	.99
Arrhythmia	3 (6.3)	3 (3.1)	.39
Other heart disease [†]	0 (0.0)	4 (4.2)	.55
Cancer [‡]	2 (4.2)	2 (2.1)	.60
Any mental health diagnosis	26 (54.2)	35 (36.5)	.04
Depression	22 (45.8)	31 (32.3)	.14
Anxiety	12 (25.0)	10 (10.4)	.03
Other mental health diagnosis	15 (31.3)	18 (18.8)	.10
Asthma	11 (22.9)	18 (18.8)	.66
Allergies	23 (47.9)	33 (34.4)	.15
Infections	28 (58.3)	55 (57.3)	.91
Diabetes	0 (0.0)	2 (2.1)	.55
Migraine	21 (43.8)	15 (15.6)	<.001
Autoimmune disease [§]	0 (0.0)	5 (5.2)	.17
Chemical exposure [¶]	6 (12.5)	4 (4.2)	.08

Data are number (%).

Percentages are based on column totals excluding unknown data.

[*] Three cases with arrhythmia.

[†] Three controls with mitral valve prolapse, and 1 control with patent foramen ovale.

[‡] Two cases had malignant melanoma, both treated only with excision. One control had thyroid cancer treated with excision and iodine ablation and one control had laryngeal squamous cell carcinoma treated with excision. No cases or controls were treated with chemotherapy or chest radiation.

[§] One control with ulcerative colitis, one control with Graves' disease and 3 controls with Hashimoto's thyroiditis.

[¶] Two cases with black mold exposure, 2 cases with pesticide exposure, 2 cases with occupational exposure.

Table 3.

Obstetric History of Cases and Controls Before the Index Pregnancy[*]

Obstetric history	Case (*n* = 48)	Control (*n* = 96)	*P* Value
Parity			
Median parity[†]	1 (0 – 2.5)	1 (0 – 2.5)	.34
Nulliparous	28 (58.3)	43 (44.8)	.16
Primipara or multipara	20 (41.7)	53 (55.2)	.16
Primipara or multipara women	*n* = 20	*n* = 53	
Multifetal gestations	0 (0.0)	0 (0.0)	—
Hypertensive disorders of pregnancy[‡]	8 (40.0)	4 (4.2)	.02
Gestational diabetes[§]	1 (4.8)	3 (3.1)	.04

Data are number (%) or median (interquartile range) unless otherwise specified.

Percentages are based on column totals excluding unknown data.

[*] The index pregnancy is the pregnancy associated with initial peripartum cardiomyopathy diagnosis for cases and the matched pregnancy for controls.

[†] Parity ranged from 0 to 6 for cases and 0 to 5 for controls.

[‡] Hypertensive disorders of pregnancy includes gestational hypertension, preeclampsia, eclampsia, preeclampsia superimposed on chronic hypertension, and unspecified types. Six missing.

[§] Five missing.

Table 4.

Index Pregnancy Characteristics of Cases and Controls[*]

Characteristics	Case (*n* = 48)	Control (*n* = 96)	*P* Value
Assisted reproduction	4 (8.3)	13 (13.5)	.42
Access to standard medical care during pregnancy	27 (75.0)	78 (82.1)	.36
Planned pregnancy	11 (32.4)	50 (54.4)	.03
Single parenting	10 (20.8)	21 (23.1)	.96
Hypertensive disorders of pregnancy	27 (56.3)	12 (12.5)	<.001
Gestational diabetes	2 (4.4)	9 (9.5)	.50
Antibiotic use during pregnancy	21 (70.0)	53 (56.4)	.19
Bed rest	11 (28.2)	12 (12.6)	.03
Tocolytic therapy	2 (4.3)	11 (11.6)	.22
Method of delivery			.001
Spontaneous vaginal	16 (33.3)	59 (61.5)	.001
Assisted vaginal	6 (12.5)	12 (12.5)	.99
Planned caesarean section	5 (10.4)	11 (11.5)	.85
Emergency caesarean section	21 (43.8)	14 (11.6)	<.001
Indication for caesarean section			
Cardiac	11 (55.4)	1 (7.1)	.01
Obstetric	10 (47.6)	13 (92.9)	
No. of neonates			
Single	40 (83.3)	80 (83.3)	—
Twins	7 (14.9)	14 (14.9)	
Triplets	1 (2.1)	2 (2.1)	
Neonate sex			0.68
Male	23 (41.8)	51 (45.1)	
Female	32 (58.2)	62 (54.9)	
Gestational age (wk)	37 (33–39)	39 (37–40)	.004
Premature (<37)	21 (43.8)	22 (22.9)	.003
Birthweight (g)	2445 (2012–3459)	3190 (2550–3562)	.01
Low birth weight (<2500)	22 (45.8)	28 (24.8)	.01
Breastfeeding			
Yes	22 (59.5)	69 (75.8)	.06
Breastfeeding in cases only			
After delivery	22 (59.5)	—	.009
Post diagnosis	9 (24.3)	—	

Data are number (%) or median (interquartile range) unless otherwise specified.

Percentages are based on column totals excluding unknown data.

[*] The index pregnancy is the pregnancy associated with initial peripartum cardiomyopathy diagnosis for cases and the matched pregnancy for controls.

Table 5.

Disease Characteristics of Women Diagnosed With Peripartum Cardiomyopathy ($n = 48$)

Disease Characteristic	Value
Timing of diagnosis [*] (days)	4 (0–12)
During pregnancy	11
Postpartum	37
Clinical features	
Blood pressure	
Systolic (mm Hg)	140 (126 – 154)
Diastolic (mm Hg)	89 (79 – 104)
Elevated [†]	41 (85.4)
Heart rate (bpm)	103.5 (88 – 120)
Murmurs [‡]	14 (29)
Signs suggestive of left heart failure [§]	
Yes	36 (75.0)
Unknown	2 (4.2)
Signs suggestive of right heart failure [¶]	
Yes	33 (68.8)
Unknown	5 (10.4)
Echocardiograph parameters	
EF (%)	34 (24 – 40)
LVEDD (cm)	5.7 (5.1–6.0)
LVESD (cm)	4.5 (4.1–4.9)
Ventricular septal wall thickness (cm)	1.0 (0.9–1.1)
Posterior wall thickness (cm)	0.9 (0.9–1.1)
RV enlargement [‡]	9 (18.8)
RV hypokinesis [‖]	16 (33.3)
LA volume index (mL/m^2)	34 (27 – 38)
Valvular heart disease, [#,‖]	20 (41.7)
Pericardial effusion [‖]	20 (41.7)
Treatments	
Treatment with medication	47 (97.9)
ACE inhibitor	42 (87.5)
Angiotensin II receptor blocker	2 (4.2)
Beta blocker	38 (79.2)
Diuretic	42 (87.5)
Blood thinner	17 (35.4)
Bromocriptine	0 (0.0)
Vasodilator	10 (20.8)

Disease Characteristic	Value
Anti-arrhythmic	10 (20.8)
Calcium channel blocker	2 (4.2)
Nitroglycerin	3 (6.3)
Potassium	4 (8.3)
Magnesium sulfate	4 (8.3)
Mechanical circulatory support	0 (0.0)
Cardiac device implantation [**]	1 (2.1)
VAD	0 (0.0)
Outcomes	
Length of follow-up after diagnosis (y)	7.3 (4.1 – 12.2)
Transplant	0 (0.0)
Death	1 (2.1)
Left ventricular recovery [††,‡‡]	43 (89.6)
Persistent cardiac dysfunction [§§]	2 (4.2)

Data are number (%) or median (interquartile range) unless otherwise specified.

Percentages are based on column totals excluding unknown data.

[*] Diagnosis timing ranged from 2 days before delivery to 185 days (6 months) postpartum with 7 women diagnosed on the day of delivery.

[†] Elevated blood pressure as defined as a systolic blood pressure of 140 mm Hg and/or a diastolic blood pressure of 90 mm Hg as in the 2020 International Society of Hypertension Global Hypertension Practice Guidelines.[22]

[‡] Seven missing.

[§] Rales, wheezing, pulmonary edema.

[¶] Jugular venous distension, ascites, peripheral edema.

[‖] Eight missing.

[#] Designation of valvular heart disease was based on echocardiogram interpretations and included disease categorized as mild/moderate, moderate, moderate/severe, or severe. Valvular disease was found in just the mitral valve in 11 patients and in just the tricuspid valve in 6 patients. An additional 2 patients had disease in both the mitral and tricuspid valves and 1 patient had disease in the mitral, tricuspid, and pulmonary valve.

[**] Intra-aortic balloon pump.

[††] Left ventricular recovery defined as a left ventricular ejection fraction of 50% by echocardiogram.

[‡‡] Recovery time ranged from 3 days to just >12 years with a median of 4.5 months. Two patients had residual dysfunction, 1 died, and 2 had no follow-up echocardiogram, so the official recovery status is not known, but both were functionally recovered.

[§§] Persistent cardiac dysfunction defined as a left ventricular ejection fraction of 50%.

Abbreviations: ACE, angiotensin-converting enzyme; bpm, beats per minute; EF, ejection fraction; LA, left atrial; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; RV, right ventricle; VAD, ventricular assist device.

Table 6.

Obstetric and Cardiac Outcomes of Subsequent Pregnancies of Cases and Controls

Outcomes	Cases (*n* = 48)	Controls (*n* = 96)	P Value
No. of women with subsequent pregnancies [*]	23 (56.1)	56 (62.6)	.46
Subsequent pregnancies [†]	(*n* = 37)	(*n* = 105)	
Planned	10 (30.3)	[‡]	—
Unplanned	23 (69.7)	[‡]	—
Pregnancy outcome			
Delivered	25 (67.6)	82 (78.1)	.20
Spontaneous abortion	5 (13.5)	18 (17.1)	.80
Terminated	7 (18.9)	5 (4.8)	.01
Women on cardiac medication	15 (65.2)	[‡]	—
Beta blocker [§]	14	[‡]	—
Calcium channel blocker	1	[‡]	—
Digoxin	1	[‡]	—
Maternal outcome			
Relapse [¶]	6 (12.5)	[‡]	—
On cardiac medication at time of relapse	4 (66.7)	[‡]	—
Recovery after relapse [∥]	6 (100.0)	[‡]	—
Sterilization	16 (33.3)	33 (34.4)	.90

Data are number (%) unless otherwise specified.

Percentages are based on column totals excluding unknown data.

[*] For 7 cases and 7 controls subsequent pregnancy status is unknown.

[†] For 4, subsequent status, no data are available regarding planning of pregnancy.

[‡] Data either not applicable or not obtained.

[§] One woman was treated with both a beta blocker and a calcium channel blocker.

[¶] Relapse defined as decrease in the left ventricular ejection fraction to 45%.

[∥] LV recovery defined as a left ventricular ejection fraction of 50% by echocardiogram.