Peripartum Cardiomyopathy

Population-Based Birth Prevalence and 7-Year Mortality

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OBJECTIVE: To estimate the birth prevalence and 7-year case-fatality rate of peripartum cardiomyopathy for a statewide population by applying the National Institutes of Health Workshop on Peripartum Cardiomyopathy definition, including echocardiographic criteria for left ventricular dysfunction.

METHODS: This was an epidemiologic study of residents of North Carolina experiencing an obstetric delivery or a pregnancy-related death before delivery in 2002 through 2003 including 235,599 live births. Potential cases were identified from International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM), pregnancy and cardiovascular codes followed by medical record review, and from the state pregnancy-related mortality file. Only women meeting the established definition including echocardiographic criteria for left ventricular dysfunction and women with diagnoses at autopsy were included. The state death file and the U.S. Social Security Death Index were searched for the years 2002 through 2010 for all cases.

RESULTS: A total of 740 potential cases from 70 hospitals were identified from discharge ICD-9-CM codes. The medical records for 698 (94.3%) were located and reviewed. Seventy-eight met inclusion criteria. An additional seven women had diagnoses only at autopsy. The birth prevalence was 1 case for every 2,772 live births or 3.61 cases per 10,000 live births (95% confidence interval 2.88-4.46). The 7-year case-fatality rate was 16.5% (95% confidence interval 10–25.9%). Black non-Hispanic women experienced an almost fourfold increased prevalence and fatality compared with white women. Women older than age 35 years had the highest prevalence.

CONCLUSIONS: The racial disparity in both birth prevalence and case-fatality is striking; one in six women died within 7 years.

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In the 19th century, Ritchie and Virchow[1,2] recognized an association between cardiac failure and late pregnancy that was subsequently first described as a specific syndrome in 1937 by Gouley.[3] In 1997, peripartum cardiomyopathy was defined by the National Institutes of Health (NIH) Workshop convened by the National Heart, Lung, and Blood Institute and the Office of Rare Diseases as the development of cardiac failure in the last month of pregnancy or within 5 months after delivery, the absence of an identifiable cause for the cardiac failure, the absence of recognizable heart disease before the last month of pregnancy, and left ventricular dysfunction demonstrated by echocardiographic criteria such as decreased shortening fraction or ejection fraction.[4,5] The etiology of peripartum cardiomyopathy continues to be investigated; recent research supports a role for excess antiangiogenic signal in the peripartum period.[6,7]

Although peripartum cardiomyopathy is relatively rare, the proportion of pregnancy-related deaths attributed to this disease is increasing.[8-10] Current estimates of the birth prevalence and case-fatality rate of peripartum cardiomyopathy are based on case

series from single institutions,[11–13] are based on retrospective cohort studies from prepaid insurance plans,[14,15] or rely solely on International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes without clinical verification of the diagnostic criteria.[16] In addition, the initial presentation of peripartum cardiomyopathy may be sudden death outside of a clinical setting with the diagnosis made only at autopsy; such cases will be identified only from linked birth and death files and autopsy review. Accurate population-based estimates of the birth prevalence, risk factors, and case-fatality rates for peripartum cardiomyopathy are necessary to understand the burden of disease of this condition, to establish a baseline to monitor trends, and to work to develop better prevention strategies. In this article, we use statewide population-based data and apply clinical and echocardiographic criteria as defined by the NIH Workshop on Peripartum Cardiomyopathy and Hibbard[4,17] to estimate the birth prevalence and case-fatality rate for peripartum cardiomyopathy in North Carolina.

MATERIALS AND METHODS

The population studied included residents of the state of North Carolina experiencing an obstetric delivery or a pregnancy-related death before delivery in the years 2002 and 2003 including a total of 235,599 live births. Potential cases of peripartum cardiomyopathy were identified from the state hospital discharge database ICD-9-CM codes followed by clinical review of the actual hospital medical records. We also examined the surveillance database of pregnancy-related deaths in North Carolina from 2002 through 2004 to determine whether there were women not identified from the hospital discharge database who died of peripartum cardiomyopathy after an obstetric delivery or while pregnant during the study period.

The procedures for identifying cases of peripartum cardiomyopathy during pregnancy or within 5 months of an obstetric delivery from the hospital discharge database are as follows. The North Carolina State Center for Health Statistics conducted an iterative match of the live birth files for the calendar years 2002 and 2003 against the statewide hospital discharge database of females aged between 10 and 50 years with any mentioned ICD-9-CM codes of 674.5, 674.8, 648.6, 425.4, or 428 and having hospital admission dates between January 1, 2002, and December 31, 2004. The data in the North Carolina Hospital Discharge database are retrieved claim forms used by facilities to bill payers. The database is maintained by the Cecil G. Sheps Center for Health Services Research under contract with the North Carolina Division of Health Service Regulation. More information about the database is available at http://www.shepscenter.unc.edu/research_programs/hosp_discharge/). Details of the iterative match are available on request. The ICD-9-CM codes correspond to the following diagnoses: 674.5, peripartum cardiomyopathy (this code was added to ICD-9-CM in 2003); 674.8, hepatorenal syndrome after delivery, postpartum cardiomyopathy, subinvolution of the uterus, uterine hypertrophy; 648.6, other cardiovascular disease in pregnancy; 425.4, primary cardiomyopathies; and 428, congestive heart failure. To refine the list of potential cases the following rules of exclusion were applied: 674.8 but no other codes for cardiac disease or pulmonary edema; 648.6 with codes for arrhythmia, rheumatic, or other valvular heart disease; 428 without 425.4; or 428 with any code for malignancy, toxic goiter, or major puerperal infection.

Permission was granted by the State Registrar for release of the resulting list of potential cases to the principal investigator. Institutional review board approval was obtained from the North Carolina State Center for Health Statistics, the Centers for Disease Control and Prevention, and the institutions with which the principal investigator was affiliated. Hospitals without an Institutional review board granted permission for record review under these institutional review board approvals. Institutional review board approval was obtained from all other participating hospitals. This project was considered a public health surveillance study by the North Carolina Division of Public Health; therefore, release of information without authorization from individuals, including Health Insurance Portability and Accountability Act authorization, was granted.

We worked with each hospital's medical records department to access records for review. Only those women meeting the diagnostic criteria as defined by the NIH Workshop and either echocardiographic criteria proposed by Hibbard in 1999 (ejection fraction less than 45% or fractional shortening less than 30%, or both, with or without end-diastolic dimension more than 2.7 cm/m^2 body surface area)[4,17] or, in the absence of recorded parameters, a description of moderately or severely reduced left ventricular systolic function and a dilated left ventricle were included as cases of peripartum cardiomyopathy. Women with hypertrophic cardiomyopathy or pulmonary edema with normal left ventricular function were excluded. Women with history of recent viral-like illness were also excluded. The charts of cases were abstracted for patient age, race, parity, medical history, complications of pregnancy, timing of onset relative to delivery, and results of echocardiograms and other

diagnostic studies. If a range was given for the ejection fraction, the midpoint of the range was used in the analysis. Prescribed therapies including medication, implantable defibrillator, and heart transplant were also abstracted.

In addition, the North Carolina enhanced pregnancy-related mortality database was searched for deaths attributable to peripartum cardiomyopathy occurring between January 1, 2002, and December 31, 2004, in women with an obstetric delivery or who were pregnant at time of death in the years 2002–2003. The details of the enhanced surveillance system for identifying pregnancy-related deaths in the state have been previously published.[9,18] Briefly, all death certificates with any mention of pregnancy, including reported underlying or contributing cause of death related to pregnancy, or with ICD 10th revision cause of death codes (O00–O99) were identified by computer search and were manually reviewed by a nosologist. In addition, all death records of females aged 10–50 years were computer-matched to live birth and fetal death files for the same and previous calendar years to identify deaths occurring during or within 1 year of a delivery. Finally, hospital discharge records were searched for women who die in hospital with a pregnancy-related discharge diagnosis to ascertain additional deaths not identified through vital records. Additional supporting clinical documentation was obtained when available, including medical records and autopsy reports. All autopsies performed through the State Medical Examiners' system were available from the Office of the Chief Medical Examiner. Each death was reviewed by a physician and classified as either pregnancy-related or not pregnancy-related, using definitions developed by the American College of Obstetricians and Gynecologists and Centers for Disease Control and Prevention Maternal Mortality Study Group.[19] For this study, peripartum cardiomyopathy cases from the enhanced maternal mortality surveillance file were included if there was an autopsy diagnosis of peripartum cardiomyopathy or dilated cardiomyopathy without other etiology occurring in late pregnancy or within 5 months of obstetric delivery.

To ascertain deaths associated with peripartum cardiomyopathy beyond the period of 1 year after delivery, we conducted a computer search of the North Carolina death files through calendar year 2010 for classified cases based on the clinical review process described. We also searched the U.S. Social Security Death Index database for all cases to ascertain any additional deaths that were not identified in the North Carolina mortality files, such as those that may have occurred out of state.

Race and ethnicity were obtained from the medical record or from the informant's response on the decedent's death certificate. The birth prevalence of peripartum cardiomyopathy and the 7-year cumulative case-fatality rates with 95% confidence intervals were calculated using the exact binomial limits for the total population and by age, race, and ethnicity.[20]

RESULTS

From the hospital discharge database linked to the birth files, a total of 3,827 potential cases for the 2-year period were identified; after refinement of ICD-9-CM codes and deletion of duplicate cases (more than one admission for the same patient), 740 potential cases of peripartum cardiomyopathy remained (Fig. 1). These cases involved 70 different nonmilitary hospitals within the state, all of which agreed to allow access to the medical records. Forty-two records (5.7%) among 20 hospitals could not be located and the remaining 698 (94.3%) were reviewed and abstracted. Seventy-eight (11.2%) met the NIH Workshop criteria for peripartum cardiomyopathy, including echocardiographic evidence of left ventricular systolic dysfunction. An additional seven cases were identified from the pregnancy-related mortality files. A total of 85 cases of peripartum cardiomyopathy thus were identified in North Carolina for the 2-year period.

Autopsies and investigative reports by the medical examiner were obtained for all seven women identified from the pregnancy-related mortality files. All died postpartum, and none had peripartum cardiomyopathy diagnosed before autopsy. Only one died after admission to a hospital; peripartum cardiomyopathy was not suspected at the time of death and therefore was not coded on the hospital discharge record. The other six did not have a hospital admission; two died at home, three died in an emergency department, and one was dead on arrival at the hospital. Thus, hospital records from approximately the time of death were available for review for one of these seven women. Six had an autopsy diagnosis of peripartum cardiomyopathy. The seventh had an autopsy diagnosis of dilated cardiomyopathy with no history of heart disease and without evidence of inflammation or other etiology.

From January 1, 2002, through December 31, 2003, there were 235,599 live births within the state and 85 cases of peripartum cardiomyopathy, giving a birth prevalence of peripartum cardiomyopathy for this population of 1 case for every 2,772 live births or 3.61 cases per 10,000 live births (95% confidence interval 2.88-4.46). The distribution of cases and birth prevalence by race, ethnicity, and age are shown in

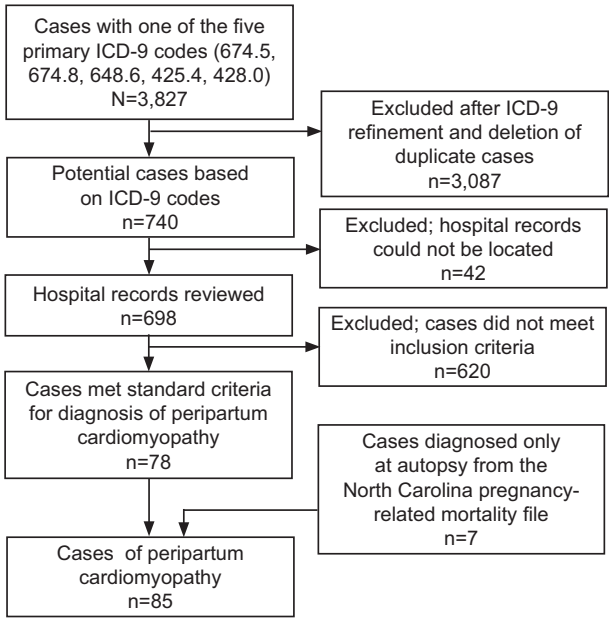

Fig. 1. Identification of cases of peripartum cardiomyopathy from the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes followed by chart review, and the enhanced North Carolina pregnancy-related mortality files, 2002–2003.

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Table 1. Black non-Hispanic women experienced birth prevalence almost four-times that of white non-Hispanic women. There tended to be an increasing prevalence with increasing age, with women older than 35 years having the highest birth prevalence. The median time from delivery to onset of symptoms or sudden death could be accurately determined for 81 of the 83 women with occurrence postpartum and was 2 weeks (range <1 week–5 months). Two women had diagnoses late in pregnancy.

Over the course of the subsequent 7 years after delivery, 14 of the 85 women died of peripartum cardiomyopathy or its direct complications, 7 identified from the hospital discharge database (included 2 deaths from heart transplant rejection) and 7 identified from the enhanced maternal mortality file, for a case-fatality rate of 16.5% (95% confidence interval 10–25.9%). Case-fatality rates varied by race, ethnicity, and age (Table 1). The case-fatality rate among black non-Hispanic women was almost four-times that of white non-Hispanic women, 24% compared with 6.1%. The median time from delivery to death for the 14 decedents was 4.1 months, with a range of 7 days to 6 years and 9 months. Ten (71.4%) of the deaths occurred within the first year after delivery, for a first-year case-fatality rate of 11.8%. Two of the remaining 75 women (2.7%) died between 3 and 5 years after delivery. Two of the remaining 73 (2.7%) died between 5 and 7 years after delivery. Seven, or 50%, of the deaths occurred among women who did not have diagnoses until autopsy.

Table 2 shows the number and percentage with specific medical complications of pregnancy for the 79 women with charts available for review (78 identified through the hospital discharge database plus one case diagnosed only after autopsy but with hospital admission) and also by survival status; 64.6% of the women had some type of hypertension (29.1% preeclampsia or eclampsia) and 8.9% were multifetal gestations. An ejection fraction at the time of diagnosis

Table 1. Distribution of Cases, Birth Prevalence, and Case-Fatality by Race, Ethnicity, and Age

Race and Ethnicity	Distribution of All Cases	Cases Per Live Birth	Prevalence, Cases Per 10,000 Live Births (95% CI)	No. of Deaths (Fatality Rate Per 100 Cases)
Total	85 (100)	1/2,772	3.61 (2.88–4.46)	14 (16.5)
Race and ethnicity				
White non-Hispanic	33 (38.9)	1/4,266	2.34 (1.61–3.29)	2 (6.1)
Black non-Hispanic	50 (58.9)	1/1,087	9.20 (6.83–12.12)	12 (24.0)
Hispanic	1 (1.1)	1/31,140	0.32 (0–1.79)*	0
Asian or Pacific Islander	1 (1.1)	1/5,954	1.68 (0.04–9.35)*	0
Age (y)				
Younger than 18	2 (2.3)	1/4,763	2.10 (0.25–7.58)*	0
18—24	23 (27.1)	1/3,563	2.81 (1.78–4.21)	4 (17.4)
25—29	16 (18.8)	1/3,904	2.56 (1.46–4.16)	4 (25.0)
30—34	17 (20.0)	1/3,188	3.14 (1.82–5.02)	1 (5.9)
35—39	23 (27.1)	1/997	10.03 (6.36–15.04)	4 (17.4)
Older than 39	4 (4.7)	1/1,134	8.82 (2.40–22.56)	1 (25.0)

CI, confidence interval. Data are n (%) unless otherwise specified.
* These estimates are unstable because of small numbers.

was available for six of the seven women who died and had diagnoses before death; the median was 0.18 (range 0.10-0.20). Among survivors the median ejection fraction at the time of diagnosis was 0.30 (range 0.08-0.50). The rates of prescribed therapies could be determined for 77 of the 78 women identified from the hospital discharge database; those are shown in Table 3.

DISCUSSION

We estimated the birth prevalence of peripartum cardiomyopathy in a geographically defined population (North Carolina) for 2002–2003 to be 3.61 cases per 10,000 live births (1 in 2,772 live births). The prevalence varied by race, ethnicity, and age. Fourteen of the 85 identified case group individuals (16.5%) died of peripartum cardiomyopathy or its direct complications within 7 years.

Our estimate of the birth prevalence is similar to those of other recent studies from the United States, which range from 1 in 2,066 to 1 in 4,025 live births.[14–16] In addition, studies of prevalence, including ours, have reported wide variation by race and ethnicity. Differences in population demographics are likely one reason for variation in reported prevalence from different geographic locations. To screen for potential cases for chart review, both California studies used ICD-9-CM codes for heart disease, heart failure, and nonpregnancy-related cardiomyopathy; they did not use code 674.8, which is complications in the puerperium, including peripartum cardiomyopathy. To identify cases for review, we used both generic codes for heart failure and cardiomyopathy as well as pregnancy-specific codes for cardiovascular disease, 674.8, and the code specific for peripartum cardiomyopathy, 674.5, which was only added to the ICD-9-CM in 2003. The study from the National Hospital Discharge Survey found a prevalence of 1 in 3,189 live births for the period 1990–2002 but a prevalence of 1 in 2,229 live births for the period 2000–2002.[16] This study completely relied on combinations of ICD-9-CM codes for inclusion criteria, because the investigators could not verify the criteria used for making the diagnosis. Neither of the California cohorts or the National Hospital Discharge Survey included any cases identified only by autopsy. In our study, cases ascertained by autopsy accounted for 8.2% of cases.

Our estimated case-fatality rate of 16.5% from peripartum cardiomyopathy or associated complications is much higher than those in other recent reports from populations within the United States of 0–9%.[14–16,21–23] There are several potential explanations. The addition of cases identified by autopsy from the pregnancy-related mortality files increased our estimate from 9% to 16.5%. Also, we followed-up case group individuals to 7 years and found two deaths that occurred more than 5 years after delivery. In addition, women in our population may have had more severe disease because we used strict criteria for inclusion. Supporting this, the mean ejection fraction was 0.28 compared with 0.32 among the Southern California case group individuals; also, 6.5% of our case group individuals were considered candidates for heart transplant. A total of 88.3% of women recognized as having peripartum cardiomyopathy in this

Table 2. Rates of Pregnancy-Related Complications and Mean Ejection Fraction at Time of Diagnosis

Pregnancy-Related Complications	All (N=79)*	Survivors (n=71)	Decedents (n=8)†
Chronic hypertension	10 (12.7)	9 (12.7)	1 (12.5)
Gestational hypertension	18 (22.8)	15 (21.1)	3 (37.5)
Preeclampsia	11 (13.9)	9 (12.7)	2 (25.0)
HELLP syndrome	1 (1.3)	1 (1.4)	0
Eclampsia	1 (1.3)	1 (1.4)	0
Preeclampsia superimposed on chronic hypertension	10 (12.7)	8 (11.3)	2 (25.0)
Gestational diabetes	7 (8.9)	7 (9.9)	0
Pregestational diabetes	5 (6.3)	5 (7.0)	0
Multifetal gestation	7 (8.9)	5 (7.0)	2 (25.0)
Ejection fraction at time of diagnosis	0.28 (0.08-0.50)‡	0.30 (0.08-0.50)§	0.18 (0.10-0.20)‖

HELLP, hemolysis, elevated liver enzymes, low platelets. Data are n (%) or median (range).

* Seventy-nine case group individuals had hospital records available: 78 identified from hospital discharge database and 1 case diagnosed at autopsy.

† Seven cases diagnosed before death and one death that occurred during hospital admission with records reviewed but diagnosed only at autopsy.

‡ Seventy-five of 78 records from the hospital discharge database included the ejection fraction at time of diagnosis; the other three records (two survivors and one decedent) described moderately or severely reduced left ventricular systolic function and a dilated left ventricle.

§ Sixty-nine of 71 survivors.

‖ Six of seven women who died and had diagnoses before death.

Table 3. Rates of Prescribed Therapies

Therapies (n=77)*	n (%)
Angiotensin-converting enzyme inhibitor	68 (88.3)
Beta-blocker	62 (80.16)
Anticoagulation with heparin or Coumadin	20 (26.0)
Implantable defibrillator	6 (7.8)
Placed on heart transplant list	5 (6.5)
Received a heart transplant	3 (3.9)

* Records of 77 of the 78 case group individuals identified from the hospital discharge database contained information regarding therapies.

North Carolina cohort were prescribed an angiotensin-converting enzyme inhibitor and 80.6% were prescribed a beta-blocker. These rates for the Southern California Kaiser series were 88% and 55%, respectively, suggesting that differences in medical management did not explain differences in mortality.

Preeclampsia and multifetal gestation are recognized risk factors for peripartum cardiomyopathy.[4] Of our 79 case group individuals with medical records available for review, 29.1% had preeclampsia, eclampsia, or preeclampsia superimposed on chronic hypertension, and 8.9% had multifetal pregnancies. Recent research has linked antiangiogenic soluble FMS-like tyrosine kinase-1 to peripartum cardiomyopathy in mice and humans. These investigators suggest that the antiangiogenic states of preeclampsia and multifetal gestation increase susceptibility to the high expression of soluble FMS-like tyrosine kinase-1 during late gestation.[6]

Our study has several strengths. This was a population-based study of a geographically well-defined, racially and ethnically diverse population. This should increase the generalizability of the findings and remove the selection bias inherent in studies that use enrollment in health insurance programs or other nonpopulation-based criteria to identify study participants. We used a broader range of ICD-9-CM codes to identify potential cases for chart review to improve our ascertainment of cases. We further refined our case selection process by reviewing medical records and included only those women who met the strict diagnostic criteria of the NIH Workshop, including echocardiographic diagnosis of left ventricular systolic dysfunction. Finally, we were also able to identify cases diagnosed only after autopsy, which had a major effect on both the estimated prevalence and case-fatality rates.

As with any study, ours has several weaknesses. First, it is a retrospective analysis. Although we used a wide range of ICD-9-CM codes, it is possible these codes did not capture all cases. We were unable to access 42 charts, which may have affected our prevalence estimate. Assuming the same proportion of cases among these 42 that we observed for the other 698, the revised estimated prevalence would be 1 case in 2,627 live births or 3.81 cases per 10,000 live births. There may have been a few women who died of peripartum cardiomyopathy without a diagnosis or autopsy, although in North Carolina this is unlikely, because all unexplained deaths are referred to the medical examiner's office. The case-fatality rate may be underestimated if deaths otherwise unknown to us were not included in the North Carolina death files or the U.S. Social Security Death Index.

Peripartum cardiomyopathy is recognized as a serious pregnancy-related morbidity and a significant cause of mortality. Taking into account differences in methods and population demographics of four recent studies of birth prevalence, including ours, we conclude that the birth prevalence of peripartum cardiomyopathy appears to be between 1 in 2,000 and 1 in 2,800 live births in the United States, but it varies by age, race, and ethnicity. One in six women with peripartum cardiomyopathy in this cohort died of the disease or its direct complications within 7 years. It is important for providers caring for pregnant or recently pregnant women to be aware of peripartum cardiomyopathy and to investigate symptoms of dyspnea and fatigue, which otherwise may be attributed to normal physiologic changes of pregnancy and the puerperium.

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