Peripartum Cardiomyopathy

National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) Workshop Recommendations and Review

Objective Peripartum cardiomyopathy (PPCM) is a rare life-threatening cardiomyopathy of unknown cause that occurs in the peripartum period in previously healthy women. In April 1997, the National Heart, Lung, and Blood Institute (NHLBI) and the Office of Rare Diseases of the National Institutes of Health (NIH) convened a Workshop on Peripartum Cardiomyopathy to foster a systematic review of information and to develop recommendations for research and education.

Participants Fourteen workshop participants were selected by NHLBI staff and represented cardiovascular medicine, obstetrics, immunology, and pathology. A representative subgroup of 8 participants and NHLBI staff formed the writing group for this article and updated the literature on which the conclusions were based. The workshop was an open meeting, consistent with NIH policy.

Evidence Data presented at the workshop were augmented by a MEDLINE search for English-language articles published from 1966 to July 1999, using the terms peripartum cardiomyopathy, cardiomyopathy, and pregnancy. Articles on the epidemiology, pathogenesis, pathophysiology, diagnosis, treatment, and prognosis of PPCM were included.

Recommendation Process After discussion of data presented, workshop participants agreed on a standardized definition of PPCM, a general clinical approach, and the need for a registry to provide an infrastructure for future research.

Conclusions Peripartum cardiomyopathy is a rare lethal disease about which little is known. Diagnosis is confined to a narrow period and requires echocardiographic evidence of left ventricular systolic dysfunction. Symptomatic patients should receive standard therapy for heart failure, managed by a multidisciplinary team. If subsequent pregnancies occur, they should be managed in collaboration with a high-risk perinatal center. Systematic data collection is required to answer important questions about incidence, treatment, and prognosis.

Author Affiliations: Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md (Dr Pearson); Department of Obstetrics and Gynecology, Bowman Gray School of Medicine, Winston-Salem, NC (Dr Veille); Division of Cardiology, University of Southern California, Los Angeles (Dr Rahimtoola); Division of Cardiology, George Washington University School of Medicine and Health Sciences, Washington, DC (Dr Hsia); Emeritus Professor of Cardiology, Imperial College Medical School, London, England (Dr Oakley); Division of Cardiovascular Medicine, Medical College of Wisconsin, Milwaukee (Dr Hosenpud); Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, Ga (Dr Ansari); and Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, Md (Dr Baughman).

Corresponding Author and Reprints: Gail D. Pearson, MD, ScD, National Heart, Lung, and Blood Institute, Room 9146, MSC 7940, Bethesda, MD 20892-7940 (e-mail: pearson@nhlbi.nih.gov).

Clinical Cardiology Section Editors: Bruce Brundage, MD, University of California, Los Angeles, School of Medicine; Margaret A. Winker, MD, Deputy Editor, JAMA. This article is one of a series sponsored by the American Heart Association.
stetrics, immunology, and pathology met to discuss the available information and make recommendations (a list of participants appears at the end of this article). The objectives for the Workshop on PPCM, modeled on a previous NHLBI Workshop on Idiopathic Dilated Cardiomyopathy, were to (1) summarize existing information on PPCM, specifically its definition, epidemiology, cause, clinical characteristics, treatment, and prognosis; (2) review diagnostic criteria and discuss means of differentiating early symptoms of heart failure from normal physiological changes associated with pregnancy, such as tachypnea and fatigue during the third trimester of pregnancy; (3) develop recommendations for future research on PPCM; and (4) discuss educational measures to increase awareness of PPCM and thus facilitate prompt diagnosis. A representative subgroup of 8 participants and NHLBI staff formed the writing group for this article and updated the literature on which the conclusions concerning cause, includes the majority of articles identified through these processes covering epidemiology, pathogenesis, pathophysiology, diagnosis, treatment, and prognosis of PPCM.

**PPCM: LITERATURE REVIEW**

Data presented at the workshop were augmented with a MEDLINE literature search (English language) for the years 1966 to July 1999 that included the terms *peripartum cardiomyopathy*, *cardiomyopathy*, and *pregnancy*. The literature search was updated following the workshop to provide the most timely references. The bibliographies of articles identified in this fashion were searched for additional references, and the search was further supplemented with articles recommended by workshop participants. This review, which workshop participants felt to be important because of the reported rarity of the condition, the consensus that the condition may be more prevalent than reported, and because of new data concerning cause, includes the majority of articles identified through these processes covering epidemiology, pathogenesis, pathophysiology, diagnosis, treatment, and prognosis of PPCM.

### Definition

Peripartum cardiomyopathy is defined on the basis of 4 criteria, adapted from work by Demakis et al and summarized in Table 1. The importance of adhering to the interval from 1 month before delivery to 5 months postpartum was emphasized to exclude preexisting causes of cardiomyopathy that may be exacerbated by pregnancy rather than arising as a result of pregnancy. For example, heart failure occurring earlier in pregnancy may be caused by previously unsuspected dilated cardiomyopathy unmasked by the hemodynamic or hormonal stress of pregnancy. Peripartum cardiomyopathy is defined as occurring only in those patients with no prior history of recognizable heart disease and can be diagnosed only in the absence of another explanation for the cardiomyopathy.

### Incidence and Risk Factors

The incidence of PPCM is not known because population-based estimates are not available, and the diagnosis of this rare disease is not always straightforward. Incidence rates reported in individual studies are based on the experience at a particular institution and may reflect referral bias as well as individual practice patterns. Although the reported incidence rates range from 1 per 14 858 to 1 per 15 000, the currently accepted estimate of incidence is approximately 1 per 3000 to 1 per 4000 live births, which would translate to between 1000 and 1300 women affected each year in the United States. Risk factors for PPCM classically identified in the literature include multiparity, advanced maternal age, multifetal pregnancy, preeclampsia and gestational hypertension, and African American race. It is unclear whether race represents an independent risk factor or whether it is the interaction of race with hypertension that increases the risk of PPCM. Until risk factors can be delineated confidently, it is difficult to develop recommendations for screening high-risk populations.

### Etiology

Workshop participants concurred that PPCM is a distinct entity, rather than a clinically silent underlying cardiomyopathy unmasked by the hemodynamic stresses of pregnancy, because the reported incidence is higher than the incidence of idiopathic cardiomyopathy, and because the high frequency of myocarditis would not be expected in a population presenting with decompensation of preexisting heart disease due to hemodynamic stress. However, reliable data comparing the incidence of cardiomyopathy in pregnant women compared with age-matched nonpregnant women are not available. A number of possible causes have been proposed for PPCM, including myocarditis, abnormal immune response to pregnancy, maladaptive response to the hemodynamic stresses of pregnancy, stress-activated cytokines, and prolonged tocolysis. In addition, there have been a few reports of familial PPCM, raising the possibility that some cases of PPCM are actually familial dilated cardiomyopathy unmasked by pregnancy. The key hypotheses are presented below.

### Myocarditis

There is more evidence for myocarditis as a cause of PPCM than for other purported etiologies. Melvin and colleagues first reported myocarditis by endomyocardial biopsy in 3 consecutive patients with PPCM. The incidence of myocarditis in subsequent authors’ series has varied. The variability is likely due to the inclusion of patients outside the accepted time frame of PPCM, the inherent difficulties in establishing the diagnosis of myocarditis by endomyo-

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**Table 1. Definition of Peripartum Cardiomyopathy**

<table>
<thead>
<tr>
<th>Classic</th>
<th>Development of cardiac failure in the last month of pregnancy or within 3 months of delivery</th>
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<td></td>
<td>Absence of an identifiable cause for the cardiac failure</td>
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<tr>
<td></td>
<td>Absence of recognizable heart disease prior to the last month of pregnancy</td>
</tr>
<tr>
<td>Additional</td>
<td>Left ventricular systolic dysfunction demonstrated by classic echocardiographic criteria, such as depressed shortening fraction or ejection fraction</td>
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cardiac biopsy, the variability in the inclusion of patients with borderline myocarditis with those with histologic myocarditis as defined by the Dallas histologic criteria, the potential geographic variability of patient populations affected, and the variable interval between presentation and the performance of the endomyocardial biopsy. The highest incidence of myocarditis in PPCM (76%) was performed by Midei and colleagues. This group performed endomyocardial biopsies on patients with symptoms of congestive heart failure at the time of presentation and included patients with histologic borderline myocarditis as well as those with active myocarditis.

The absent or muted immune response during pregnancy may allow for unchecked viral replication and thus a greater likelihood of myocarditis in the setting of a viral infection. Studies in pregnant mice demonstrate enhanced susceptibility to cardiac viral cardiomyopathies due to coxsackieviruses and echoviruses. In the near future, electron micrography combined with molecular biological techniques should permit not only identification of viral particles in myocardium, but also the putative viruses implicated. The presumption is that if viral genetic products are evident, the postviral immune response of the patient may have been inappropriately directed against otherwise cryptic cardiac tissue proteins, leading to ventricular dysfunction.

Abnormal Immune Response to Pregnancy. Several reports have documented the occurrence of chimerism of the hematopoietic lineage cells from the fetus to the mother during pregnancy. It is postulated that fetal cells may escape into the maternal circulation and remain there without being rejected, due to weak immunogenicity of the paternal haplotype of the chimeric cells, or to the naturally occurring immunosuppressive state of the mother, or both. If chimeric hematopoietic cells take up residence in cardiac tissue during the immunosuppressed pregnant state and, following postpartum recovery of immune competence, are recognized as nonself by the maternal immune system, a pathologic autoimmune response may be triggered. Prior exposure to paternal major histocompatibility complex antigens expressed by spermatozoa or previous immunization from prior pregnancies may play a role in inducing local tissue inflammatory response. Cytokines and similar signaling molecules are then released, leading to nonspecific bystander myocardotoxicity and myocarditis. The evidence (TABLE 2) that PPCM is associated with high titers of autoantibodies against select cardiac tissue proteins (eg, adenosine triphosphate translocator, branched chain a-keto acid dehydrogenase) supports abnormal immunologic activity as a possible cause of PPCM.

**Response to Hemodynamic Stresses of Pregnancy.** During pregnancy, blood volume (preload) and cardiac output increase and afterload decreases. An echocardiographic assessment of cardiac hemodynamics in normal pregnancies performed by Geva et al demonstrated a 10% increase in left ventricular end-diastolic volume, a 45% increase in cardiac output, and a 26% to 28% decrease in end-systolic wall stress, a sensitive measure of myocardial afterload. In addition, the left ventricle remodels in response to the hemodynamics of pregnancy, resulting in transient hypertrophy. The research by Geva et al and other studies have shown a reversible decrease in left ventricular systolic function in the second and third trimesters that persisted into the early postpartum period, but returned to baseline shortly thereafter. It is possible that PPCM may be due, in part, to an exaggeration of this decrease in systolic function, although there are no data in women supporting this hypothesis.

**Other Etiologic Factors.** Other causes for PPCM that merit further study have been suggested and include the following: (1) prolonged tocolysis; (2) stress-activated proinflammatory cytokines such as tumor necrosis factor alpha or interleukin 1 that have been implicated in the pathophysiology of idiopathic dilated cardiomyopathy, (3) abnormalities of relaxin, primarily an ovarian hormone produced during pregnancy, recently found in cardiac atria, shown to have positive inotropic and chronotropic properties and potentially involved in excessive relaxation of the cardiac skeleton; and (4) deficiency of selenium, which may make the heart more susceptible to injury from viral infection, hypertension, or hypocalcemia.

### Table 2. Serum Levels of Antibodies to Cardiac Muscle Proteins in Patients With Peripartum Cardiomyopathy (CM) and Idiopathic Dilated Cardiomyopathy*

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Antibody Titer Levels†</th>
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<tr>
<td></td>
<td>&lt;1:20</td>
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<tr>
<td><strong>ANT</strong></td>
<td></td>
</tr>
<tr>
<td>Idiopathic CM</td>
<td>16/56 (28)</td>
</tr>
<tr>
<td>Peripartum CM</td>
<td>1/10 (10)</td>
</tr>
<tr>
<td><strong>BCKD</strong></td>
<td></td>
</tr>
<tr>
<td>Idiopathic CM</td>
<td>30/56 (53)</td>
</tr>
<tr>
<td>Peripartum CM</td>
<td>0/10 (0)</td>
</tr>
<tr>
<td><strong>Myosin</strong></td>
<td></td>
</tr>
<tr>
<td>Idiopathic CM</td>
<td>18/56 (32)</td>
</tr>
<tr>
<td>Peripartum CM</td>
<td>1/10 (10)</td>
</tr>
</tbody>
</table>

†Reciprocal of the highest dilution of serum samples showing reactivity arbitrarily divided into those with low (<1:20), medium (1:20-1:160), and high (>1:160) titers. ANT indicates adenosine triphosphate translocator; BCKD, branched chain a-keto acid dehydrogenase. Data presented as No./Total (%) of patients in each group.
Peripartum Cardiomyopathy

Peripartum cardiomyopathy may, therefore, go unrecognized, leading to underestimation of incidence. Symptoms and signs that might raise the suspicion of heart failure include paroxysmal nocturnal dyspnea, chest pain, cough, neck vein distention, new murmurs consistent with atrioventricular valve regurgitation, and pulmonary crackles. There are no specific criteria for differentiating subtle symptoms of heart failure from normal late pregnancy, so it is important that a high index of suspicion be maintained to identify the rare case of PPCM.

The diagnosis of PPCM requires excluding other causes of cardiomyopathy and is confirmed by standard echocardiographic assessment of left ventricular systolic dysfunction, including depressed fractional shortening and ejection fraction. Strong consideration should be given to screening family members of PPCM patients because PPCM may be the forme fruste of a genetic predisposition to cardiomyopathy.

In the absence of systematic studies comparing therapeutic approaches in PPCM, standard heart failure therapy (diuretics, vasodilators, and digoxin) as needed should be initiated. Careful attention must be paid to fetal safety and to excretion of drug or drug metabolites during breastfeeding after delivery. Collaboration among medical specialists, including obstetricians, cardiologists, perinatologists, and neonatologists, is essential. The discussion that follows should be considered a general guide, rather than a specific algorithm.

Angiotensin-converting enzyme inhibitors are contraindicated during pregnancy because of teratogenicity, but should be considered a mainstay of treatment for PPCM after delivery. Safe alternatives during pregnancy include hydralazine and nitrates. Calcium channel blockers can be used during pregnancy to control blood pressure (and decrease uterine contractility), but most have negative inotropic properties that may make them unacceptable for use in this situation. Amlodipine, a dihydropyridine calcium channel blocker, has been shown to improve survival in nonischemic cardiomyopathy patients and may have a role in management of PPCM. Plasma levels of interleukin 6, a proinflammatory cytokine, were reduced among amlodipine recipients in the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial, providing an additional potential rationale for its use in PPCM.

Second-generation β-adrenoceptor antagonists have beneficial effects in selected patients with dilated cardiomyopathy. Studies of β-adrenoceptor antagonists in patients with congestive heart failure have demonstrated safety and modest clinical benefit, but conflicting results regarding survival. Vasodilating β-blockers such as carvedilol also reduce afterload through α-adrenergic blockade. Data from the US Carvedilol Heart Failure Program suggest a potential clinical benefit, including mortality reduction, in dilated cardiomyopathy. These drugs are not contraindicated in pregnancy, but as with other agents, there are no data evaluating their use in PPCM. A reasonable approach would be to use β-adrenoceptor antagonists in the peripartum period in patients who continue to have symptoms and echocardiographic evidence of left ventricular compromise despite more than 2 weeks of standard heart failure management.

With mild left ventricular dysfunction, therapy can be initiated in the outpatient setting. Patients with severe heart failure may require hospitalization and more aggressive support, including intravenous inotropic agents, oxygen, and invasive monitoring. Patients with significantly depressed left ventricular function (ejection fraction ≤35%) may benefit from anticoagulation therapy (heparin before delivery, warfarin afterward) to prevent thrombosis and emboli. Arrhythmias should be treated according to standard protocols. Immunosuppressive therapy may be considered in patients with myocarditis documented by endomyocardial biopsy who fail to improve spontaneously within 2 weeks of initiation of standard heart failure therapy. The Myocarditis Treatment Trial failed to demonstrate an overall advantage for immunosuppressive therapy, but did not evaluate its merits in women with PPCM. A more recent retrospective study suggested that women with PPCM treated with intravenous immune globulin had a greater improvement in ejection fraction during early follow-up than patients treated conventionally. Women who fail maximal medical management may be candidates for cardiac transplantation. One study of 10 PPCM patients who underwent heart transplantation reported survival comparable to age-matched women undergoing heart transplantation for other indications, but noted a marginally higher rate (P = .05) of biopsy-proven early rejection, necessitating increased cytolytic therapy.

Salt and water restriction are important in patient management, particularly in women with symptoms and signs of heart failure. Once heart failure symptoms have been controlled, modest exercise may improve symptoms as well as peripheral muscular and arterial tone. The need for early delivery and the mode of delivery should be assessed through collaboration with cardiologists and anesthesiologists. There is little systematic evidence that infants born to women with PPCM are adversely affected, although one study did report a premature delivery rate of 21% in 14 women.

PROGNOSIS FOR WOMEN WITH PPCM

The prognosis for women with PPCM appears to depend on the normalization of left ventricular size and function within 6 months after delivery. In one study, approximately half of 27 women studied had persistent left ventricular dysfunction. In this group, the cardiac mortality rate was 85% over 5 years, compared with the group in whom cardiac size returned to nor-
mal, who experienced no reported cardiac mortality in the same time interval. A more recent study corroborates these results: 50% (7/14) of patients had dramatic improvement soon after delivery, but 6 of the 7 remaining patients died. Survivors were found to have a higher mean ejection fraction (23% vs 11%) and smaller mean left ventricular cavity size (5.8 vs 6.9 cm) at diagnosis.

Currently, there is no consensus regarding recommendations for future pregnancy after PPCM. Patients whose left ventricular size or function does not return to normal should be counseled strongly to avoid subsequent pregnancy and treated accordingly, including adopting a heart-healthy diet and lifestyle. Patients whose cardiomyopathy apparently resolves completely are a more difficult group to counsel. In the long-term follow-up study reported by Demakis et al, of 14 patients whose heart size returned to normal after the first episode of PPCM had subsequent pregnancies. Of the 8 patients, 2 developed PPCM with subsequent pregnancies. Sutton and colleagues reported normal subsequent pregnancies and normal left ventricular function (by echocardiography) in 4 women whose heart size returned to normal after PPCM in a prior pregnancy. Because PPCM has been associated with multiparity in some studies, the risk of irreversible cardiac damage may increase with each subsequent pregnancy. In addition, even though the left ventricular size and function return to normal, there is evidence that contractile reserve is impaired, and recurrence of PPCM despite rapid return of heart size and function to normal in the prior affected pregnancy has been reported. Therefore, subsequent pregnancies, if they cannot be avoided, should be managed in collaboration with a high-risk perinatal center.

SUMMARY AND RECOMMENDATIONS

Peripartum cardiomyopathy is a rare disease of unknown cause that strikes women in the childbearing years, may recur, and is associated with a high mortality rate. Hypotheses about the cause center on interactions of peripartum physiology with infectious, inflammatory, genetic, hormonal, or metabolic factors. Diagnosis of PPCM is challenging and requires vigilance. Once PPCM is identified based on the workshop criteria, the primary goal of therapy is to alleviate symptoms of congestive heart failure. If left ventricular size returns to normal after pregnancy, the short-term prognosis is likely to be favorable, although long-term sequelae, particularly with repeat pregnancy, still are not known. Failure of heart size to return to normal is associated with excess morbidity and mortality.

Based on the information presented at the workshop and on the identified gaps in knowledge, participants made the following clinical and research recommendations:

- Adherence to the criteria in Table 1, especially the timing and the necessity for echocardiographic demonstration of left ventricular systolic dysfunction, is important in making the diagnosis of PPCM.
- Once the diagnosis is made, close collaboration between specialists in obstetrics, perinatology, and cardiology is essential. If the diagnosis is made before birth, the team should include anesthesiology and neonatology as well, and transfer to a high-risk perinatal center should be considered.
- For affected patients, family history may be revealing and should be elicited.
- Therapy should be initiated using standard heart failure protocols. Angiotensin-converting enzyme inhibitors should be avoided prenatally, but are a mainstay of therapy otherwise.
- Immunosuppressive therapy can be considered if an endomyocardial biopsy indicates myocarditis, and if there is no improvement after 2 weeks of standard heart failure therapy.
- Subsequent pregnancies remain controversial, but at the very least should be managed in a high-risk perinatal center if they cannot be avoided.

Workshop participants also made recommendations about the need for additional research and dissemination of information:

- An international registry should be established to capture prospectively all women with PPCM to facilitate the following: (1) development of better incidence and prevalence estimates, (2) determination of risk factors and prognostic variables, (3) ascertainment of cardiovascular risks for subsequent pregnancies, (4) establishment of a centralized serum and tissue bank to help facilitate identification of the cause of PPCM, and (5) evaluation of therapeutic interventions.

- A review of current knowledge about PPCM should be prepared for publication. This article fulfills that recommendation.

- Because PPCM is an under-recognized obstetrical problem, an educational brochure should be prepared for broad dissemination to individuals involved in the care of women of childbearing age.

Participants, Peripartum Cardiomyopathy Workshop, April 14, 1997: Judith Hsia, MD, Chair, George Washington University School of Medicine and Health Sciences, Washington, DC; Aftab Ansari, MD, Emory University School of Medicine, Atlanta, GA; Susanne L. Bathgate, MD, George Washington University School of Medicine and Health Sciences; Kenneth L. Baughman, MD, Johns Hopkins University School of Medicine, Baltimore, MD; Gautam Chaudhuri, MD, PhD, University of California, Los Angeles School of Medicine; Heidi M. Connolly, MD, Mayo Graduate School of Medicine, Rochester, Minn; Maria Rosa Catarozzo, MD, Rush-Presbyterian-St Luke’s Medical Center, Chicago, Ill; Judith Hibbard, MD, University of Chicago, Chicago, Ill; David Homans, MD, University of Minnesota Medical School, Minneapolis; Jeffrey D. Hong, MD, Medical College of Wisconsin, Milwaukee; Celia M. Oakley, MD, Imperial College Medical School, London, England; Shabudin Rahimtoola, MD, University of Southern California, Los Angeles; Jean-Claude Veille, MD, Bowman Gray School of Medicine, Winston-Salem, NC; and Renu Virmani, MD, Armed Forces Institute of Pathology, Washington, DC. National Heart, Lung, and Blood Institute Staff: Gail D. Pearson, MD, ScD, Constance Weinstein, PhD.

REFERENCES

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