CARDIOLOGY Rounds®

AS PRESENTED IN THE ROUNDS OF THE DIVISION OF CARDIOLOGY, ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO

Peripartum Cardiomyopathy

By MOHAMMAD I ZIA, MD, FRCPC, and GORDON MOE, MD, FRCPC

Peripartum cardiomyopathy (PPCM) is a rare cardiac condition associated with significant morbidity and mortality. It is an idiopathic form of dilated cardiomyopathy that presents in late pregnancy or post-delivery. The association between heart failure and pregnancy has been known for many years. It was first described in 1870 when Virchow and Porak reported autopsy evidence of myocardial degeneration in patients who died during the postpartum period. In 1937, Gouley et al further described the clinical and pathological features of 7 pregnant patients who had severe and often fatal heart failure.[1] These patients developed a dilated, nonischemic cardiomyopathy in the latter part of their pregnancy that persisted following delivery. Their autopsies revealed areas of widespread severe focal necrosis and fibrosis. This issue of *Cardiology Rounds* presents an overview of peripartum cardiomyopathy, focusing on its incidence, etiology, diagnosis, management, and prognosis.

Incidence and etiology

PPCM occurs in 1 of every 3,000 to 15,000 pregnancies.[2] There appears to be higher incidence among Africans, however, all races can be affected. One study identified a 6-fold excess risk of death from cardiomyopathy among Black women.[3] Women at particular risk are older, multiparous, have used tocolytic therapy, experienced preeclampsia, or had twin births.

One study revealed that the prevalence of myocarditis is as high as 62% (26 of 42 patients), based on histologic findings of endomyocardial biopsy.[4] The prevalence has been variable among different studies. This may be the result of differences in demographics, diagnostic criteria for PPCM or myocarditis, the selection of patients for endomyocardial biopsy, or the timing of the biopsy relative to symptom onset. It is generally recommended that endomyocardial biopsy be reserved for those patients who do not improve within 1 week of symptom onset.[5]

The etiology of PPCM is currently unknown. Early evidence suggested that nutritional deficiencies may play a role because some studies noted an increased incidence of PPCM in women who were malnourished. Recent studies, however, have not supported this relationship. Current evidence suggests that PPCM may represent a form of myocarditis arising from infectious, autoimmune, or as yet undefined processes.

Infectious

There are experimental data to support an infectious etiology for PPCM. Thus, pregnant mice appear to be more susceptible to viral infections such as coxsackieviruses and echoviruses than nonpregnant mice. In addition, pregnant mice were found to have higher viral concentrations in the myocardium when compared with levels found in nonpregnant mice.[6] This could be secondary to a blunted or muted immune response during pregnancy that, therefore, permits unregulated viral replication. Another study in Niamey, Africa, has shown a relationship between anti-*Chlamydia* pneumonia antibodies and PPCM.[7] However, this is the only known

St. Michael's Hospital
30 Bond St.,
Suite 7049, Queen Wing
Toronto, Ont. M5B 1W8
Fax: (416) 864-5941

clinical study suggesting a relationship between PPCM and *Chlamydia* pneumonia infection, suggesting that further investigations are needed to validate this possible relationship.

Immunologic

Many studies have demonstrated that chimerism occurs when hematopoietic lineage cells pass from the fetus to the mother during pregnancy.[6] The suggestion is that fetal cells escape into the maternal circulation and remain there without being rejected due to the weak immunogenecity of the paternal haplotype of the chimeric cells or the naturally-occurring immunosuppressive state of the mother, or both. For instance, chimeric hematopoietic cells infiltrate cardiac tissue during the immunosuppressed pregnancy state. Following the recovery of immune competence postpartum, they are recognized as foreign by the maternal immune system and a pathological autoimmune response may be triggered. The fact that there are high titers of autoantibodies against select cardiac tissue proteins (eg, adenine nucleotide translocator, branched chain alpha-keto acid dehydrogenase) associated with PPCM further support this hypothesis.[8]

Hemodynamic

Preload and cardiac output increase and afterload decreases during pregnancy. Geva et al, as well as others, have shown that there is a reversible decrease in left ventricular systolic function in the second and third trimesters that persists into the early postpartum period; however, it returns to baseline shortly thereafter.[9] PPCM may represent an exaggeration of this decrease in systolic function, although there are no data as yet to support such an hypothesis.

Nutritional

Earlier studies demonstrated an increased incidence of PPCM in malnourished women;[10] however, no definitive epidemiological studies have validated such observations. The increased incidence of PPCM in Africa may be explained by nutritional differences in salt intake. Low selenium levels have also been reported to be a possible risk factor for PPCM and studies have found lower levels of selenium in patients with PPCM. However, in one large study that compared selenium and other micronutrient levels in mothers with PPCM with those in parity-matched control mothers,[11] the mean selenium plasma levels of the PPCM patients were similar to the control group. Selenium may play a role in the pathogenesis of PPCM via several mechanisms. Low levels of selenium cause increased susceptibility to damage from viral infection or hypertension. However, there is no direct evidence that a selenium deficiency is a cause or risk factor for PPCM.

Drug-induced

Prolonged terbutaline therapy has been associated with PPCM. In one case study in 15 women with PPCM, 4 had received prolonged terbutaline therapy.[12] It is unclear, however, whether this agent induces cardiomyopathy or simply unmasks subclinical heart disease.

Familial

Familial PPCM has been previously documented, suggesting that it may be a type of familial dilated cardiomyopathy unmasked by the stress factors associated with pregnancy.[13-15]

Diagnosis

The diagnosis of PPCM depends mainly on the echocardiographic identification of new left ventricular systolic dysfunction during a limited period surrounding parturition. This poses a challenge since, during in the last month of a normal pregnancy, many women experience dyspnea, fatigue, and pedal edema, symptoms that are identical to congestive heart failure. As a result, PPCM may go unrecognized, thus leading to underestimation of incidence. Clinical features of heart failure (eg, paroxysmal nocturnal dyspnea, chest pain, cough, neck vein distension, new murmurs consistent with atrioventricular valve regurgitation, and pulmonary crackles) raise the suspicion of PPCM.

The diagnosis of PPCM requires the exclusion of other causes of cardiomyopathy and is confirmed by standard echocardiographic assessment of left ventricular systolic dysfunction, including depressed fractional shortening and ejection fraction.[6]

PPCM is defined on the basis of 4 criteria, adapted from work by Demakis et al. and summarized in Table 1.[16] The reason for the emphasis on adhering to the interval from 1 month before delivery to 5 months postpartum is to exclude pre-existing causes of cardiomyopathy that may be exacerbated by pregnancy, rather than arising as a result of pregnancy. For instance, heart failure occurring earlier in pregnancy may be caused by previously unsuspected dilated cardiomyopathy that is unmasked by the hemodynamic or hormonal stress of pregnancy. PPCM is strictly defined as occurring only in those patients with no prior history of recognizable heart disease and may be diagnosed only in the absence of an alternative explanation for the cardiomyopathy.[6]

Table 1: Definition of peripartum cardiomyopathy

Classic

- Development of cardiac failure during the last month of pregnancy or within 5 months of delivery
- Absence of an identifiable cause for the cardiac failure
- Absence of recognizable heart disease before the last month of pregnancy

Additional

- Left ventricular systolic dysfunction demonstrated by classic echocardiographic criteria
  - Ejection fraction <45%
  - Fractional shortening <30%
  - End-diastolic dimension >2.7 cm/m^2 body surface area

Treatment

The treatment for PPCM is similar to that for other nonischemic dilated cardiomyopathies as summarized in Table 2, except that consideration is given to the wellbeing of the fetus.[17] The general goal is to reduce the amount of volume returning to the heart (preload reduction), decrease the resistance against which the heart must pump (afterload reduction), and increase the contractile force of the heart (inotropy).

Nonpharmacologic options for patients with PPCM include sodium restriction to <4 g per day, fluid restriction to <2 litres per day, and a regimen of modest exercise once the symptoms of heart failure are controlled.[6]

Diuretics, vasodilators, and dioxin comprise standard heart failure therapy. Angiotensin-converting enzyme (ACE) inhibitors are contraindicated during pregnancy, due to their potential teratogenic effects; however, they should be included in the postpartum management of PPCM. Afterload reduction and vasodilation can be achieved using hydralazine and nitrates. Calcium channel blockers can be used for blood pressure regulation, if needed, with the potential added benefit of decreasing uterine contractility. Preload reduction can be achieved with diuretics and nitrates; however, caution must be used to prevent dehydration, which can cause uterine hypoperfusion and fetal distress.[6]

Breastfeeding with the concurrent use of loop diuretics, digoxin, warfarin, or heparin is considered safe. ACE inhibition using enalapril and captopril also appear to be safe.[10]

Table 2: Treatment of peripartum cardiomyopathy

Nonpharmaceutical therapy

- Low sodium diet (<4 g/d)
- Fluid restriction (<2 L/d)
- Modest daily exercise (ie, walking)

Oral pharmaceutical therapy

Prepartum

- Amlodipine, hydralazine/nitrates
- Digoxin
- Diuretics
- α-blockers

Postpartum

- Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker
- Digoxin
- Diuretics
- ß-blockers (low dose)
- Amlodipine
- Hydralazine/nitrates
- α-blockers

Intravenous pharmaceutical therapy for patients with severe symptoms

Unresponsive to above oral therapy

- Dobutamine
- Dopamine
- Milrinone
- Nitroprusside

Reprinted from Brown CS. Peripartum cardiomyopathy: a comprehensive review. *Am J Obstet Gynecol* 1998;178:411.

Patients who are acutely ill may require parenteral agents such as nitroprusside or nitroglycerin. Inotropic agents (eg, dopamine, dobutamine, and milrinone) may also be used. The goal is to maintain maternal tissue perfusion and euvolemia. Nitroprusside, if used, requires extreme caution to avoid fetal thiocyanate and cyanide accumulation. Beta-blockers have been shown to provide a mortality benefit in patients with congestive heart failure; however, such effects have not been evaluated in the setting of PPCM. Although beta-blockers are not contraindicated in pregnancy, this class of drugs has been associated with some long-term adverse effects, such as low-birth-weight babies.[5,17]

Anticoagulation

The Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombo-

lytic therapy stated that anticoagulant therapy is indicated during pregnancy for the prevention and treatment of venous thromboembolism (VTE).[18] However, these recommendations are based on data from non-pregnant patients, case reports and, case series of pregnant patients. Heparin-related compounds such as low-molecular weight heparin (LMWH) or unfractionated heparin (UFH) are the anticoagulants of choice during pregnancy. Potential fetal complications of anticoagulation during pregnancy include teratogenicity and bleeding.

Arrhythmias

Patients with PPCM may present with arrhythmias.[19] These arrhythmias should be treated according to the standard practice for management of arrhythmias in the context of heart failure. However, class 3 (amiodarone) and class 4 (verapamil) antiarrhythmics should be avoided because of potential adverse effects on the fetus, including fetal hypothyroidism, premature delivery, fetal bradycardia, heart block, and hypotension.[20]

Immunosuppresion

Given that PPCM may be due to myocarditis, immunosuppressive therapy has a potential role. Pentoxifylline has been demonstrated to inhibit pro-inflammatory cytokines and may have beneficial effects on New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), and markers of apoptosis in patients with idiopathic dilated cardiomyopathy. In a recent study of 59 consecutive women with PPCM, the first 29 women received standard therapy, while the next 30 consecutive patients received pentoxifylline 400 mg three times daily, in addition to standard therapy. The composite endpoint, death, failure to improve LVEF by >10 absolute points or NYHA class III or IV at the latest follow-up, occurred in 27% of the patients treated with pentoxifylline and in 52% of those on usual therapy.[21] In patients with heart failure resulting from ischemic left ventricular dysfunction, treatment with pentoxifylline improved LVEF and reduced plasma markers of inflammation including TNF-α, C-reactive protein (CRP), and Fas/Apo-1. The results of this study suggest that the addition of pentoxifylline to conventional treatment may improve outcome in patients with PPCM. The use of intravenous immune globulin has also been shown to improve the LVEF in women with PPCM.[22]

Other treatment options

For those who fail to show improvement or who clinically deteriorate despite medical management, cardiac transplant is needed. Intraaortic balloon pump or ventricular assist devices can be used as a bridge to cardiac transplant.[6]

Delivery

Early delivery is not required in patients with PPCM. On the other hand, if medical management is unsuccessful and there is evidence of clinical deterioration, then early delivery may be imperative. The mode of delivery should be assessed in collaboration with an obstetrician, cardiologist, and anesthesiologist. Although vaginal deliveries are preferable to cesarean deliveries as a result of the reduced risk of endometritis, pulmonary embolism, and postoperative complications associated with cesarean delivery, the cardiovascular benefit from prompt delivery is the most important issue.[23]

Postpartum management

The postpartum management of patients with PPCM should continue with the standard therapy for heart failure: diuretics, vasodilators, and digoxin. Patients previously on hydralazine and nitrates can safely be placed on ACE inhibitors in the postpartum period. Patients with persistent systolic dysfunction should be maintained on vasodilators, nitrates, and diuretics, as indicated.[23]

Prognosis

The prognosis of PPCM is dependent on normalization of ventricular function 6 months after delivery. Failure to regain normal left ventricular function and size by this time is an indication of permanent dysfunction. In one study, 50% of women regained normal left ventricular function and had no excess cardiac mortality in a 5-year follow-up period. This is in comparison to a cardiac mortality of 85% in women who had ventricular impairment.[24]

Future pregnancies

The risk of recurrence of PPCM in a subsequent pregnancy is related to the degree of underlying left ventricular impairment. However, even if left ventricular function has normalized by 6 months postpartum, there is still a risk of heart failure in a future pregnancy. There is an approximately 20% risk of developing heart failure if ventricular function is

normal before conception, but this increases to almost 50% in those women with pre-existing left ventricular impairment.[24] Women who fail to recover ventricular function should be counselled to avoid a further pregnancy.[6] Patients who have normalized their ventricular function remain at significant risk during a future pregnancy and warrant close monitoring throughout the pregnancy.

One study, reporting an abnormal response to low-dose dobutamine in women with normal ventricular function at rest, provides an explanation as to why 20% of women with normal function may deteriorate during a future pregnancy.[25] Failure to mount a normal inotropic response to low-dose dobutamine is an indication of abnormal contractile reserve. In women with previous PPCM, this may lead to an inability to meet the increased hemodynamic burden encountered in a future pregnancy.

Conclusion

PPCM is a rare form of cardiomyopathy of unknown etiology. It is associated with significant morbidity and mortality and characterized by the presence of heart failure within a month of delivery and up to 5 months postpartum. Other causes of heart failure have to be excluded to make a diagnosis of PPCM. Future pregnancies carry a risk of recurrence, which correlates with the degree of recovery of left ventricular function.

References

1. Gouley BA, McMillan TM, Bellet S. Idiopathic myocardial degeneration associated with pregnancy and especially the peurperium. *Am J Med Sci* 1937;19:185-99.
2. Mehta NJ, Mehta RN, Khan IA. Peripartum cardiomyopathy: clinical and therapeutic aspects. *Angiology* 2001;52: 759-62.
3. Whitehead SJ, Berg CJ, Chang J. Pregnancy-related mortality due to cardiomyopathy: United States 1991-1997. *Obstet Gynecol* 2003;102:1326-31.
4. Felker GM, Jaeger CJ, Klodas E, et al. Myocarditis and long-term survival in peripartum cardiomyopathy. *Am Heart J* 2000;140:785-91.
5. Brown CS, Bertolet BD. Peripartum cardiomyopathy: a comprehensive review. *Am J Obstet Gynecol* 1998;178:409-14.
6. Pearson GD, Veille JC, Rahimtoola S, et al. Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. *JAMA* 2000;283: 1183-88.
7. Cenac A, Djibo A, Chaigneau C, et al. Are anti-Chlamydia penumoniae antibodies prognosis indicators for peripartum cardiomyopathy? *J Cardiovasc Risk* 2003;10:195-99.
8. Ansari AA, Neckelmann N, Wang YC, et al. Immunologic dialogue between cardiac myocytes, endothelial cells, and mononuclear cells. *Clin Immunol Immunopathol* 1993;68:208-14.
9. Geva T, Mauer MB, Striker L, et al. Effects of physiologic load of pregnancy on left ventricular contractility and remodeling. *Am Heart J* 1997;133:53-9.
10. James PR. A review of peripartum cardiomyopathy. *Intern J Clin Pract* 2004;58:363-65.
11. Fett JD, Ansari AA, Sundstrom JB, et al. Peripartum cardiomyopathy: a selenium disconnection and an autoimmune connection. *Intern J Card* 2002;86:311-16.
12. Lampert MB, Hibbard J, Weinart L, et al. Peripartum heart failure associated with prolonged tocolytic therapy. *Am J Obstet Gynecol* 1993;168:493-95.
13. Pierce JA. Familial occurrence of post partal heart failure. *Arch Intern Med* 1963;111:163-66.
14. Massad LS, Reiss CK, Mutch DG, et al. Familial peripartum cardiomyopathy after molar pregnancy. *Obstet Gynecol* 1993; 81:886-88.
15. Pearl W. Familial occurrence of peripartum cardiomyopathy. *Am Heart J* 1995;129:421-22.
16. Demakis JG, Rahimtoola SLI, Sutton GC, et al. Natural course of peripartum cardiomyopathy. *Circulation* 1971;44: 1053-61.
17. Qasqas SA, McPherson C, Frishman WH et al. Cardiovascular pharmacotherapeutic consideration during pregnancy and lactation. *Cardiol Review* 2004;12:201-21.
18. Bates SM, Greer IA, Hirsh J, et al. Use of antithrombotic agents during pregnancy: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126:627S-644S.
19. Gemici G, Tezcan H, Fak AS, et al. Peripartum cardiomyopathy presenting with repetitive monomorphic ventricular tachycardia. *Pacing Clin Electrophysiol* 2004;27:557-58.
20. Ray P, Murphy GJ, Shutt LE. Recognition and management of maternal cardiac disease in pregnancy. *Brit J Anesth* 2004; 93:428-39.
21. Sliwa K, Skudicky D, Candy G, et al. The addition of pentoxifylline to conventional therapy improves outcome in patients with peripartum cardiomyopathy. *Europ J Heart Fail* 2002;4:305-9.
22. Bozkurt B, Villaneuva FS, Holubkov R, et al. Intravenous immune globulin in the therapy of peripartum cardiomyopathy. *J Am Coll Card* 1999;34:177-80.
23. Ro A, Frishman W. Peripartum cardiomyopathy. *Cardiol Review* 2006;14:35-42.
24. James PR. A review of peripartum cardiomyopathy. *Intern J Clin Pract* 2004;58:363-5.
25. Lampert MB, Weinert L, Hibbard J, et al. Contractile reserve in patients with peripartum cardiomyopathy and recovered left ventricular function. *Am J Obstet Gynecol* 1997;176:189-95.

Abstracts of Interest

A review of peripartum cardiomyopathy

JAMES PR. LONDON, UK.

Peripartum cardiomyopathy is a rare form of cardiomyopathy, of unknown aetiology, which is associated with a significant morbidity and mortality. It is characterised by the presentation of heart failure, within a month of delivery and up to 5 months post-partum, secondary to left ventricular impairment. It is essentially a diagnosis of exclusion and can only be made in the absence of any other demonstrable cause. One of the most challenging areas is in pre-natal counselling, when a woman wishes to undertake a further

pregnancy, because recovery of left ventricular function gives no guarantee of safety.
Int J Clin Pract 2004;58(4):363-5

Peripartum cardiomyopathy

RO A, FRISHMAN WH. NEW YORK, NY
Peripartum cardiomyopathy (PPCM) is a rare cardiac disorder associated with high rates of mortality that occurs during the peripartum period. PPCM is recognized as a distinct entity, separate from preexisting cardiomyopathies that are worsened by the stressors of pregnancy. To date, its etiology is unknown, although several theories are under investigation in an effort to provide more information regarding available treatment options. A multidisciplinary review of PPCM held by the National Heart, Lung, and Blood Institute, in conjunction with the Office of Rare Disease of the National Institutes of Health, in April 1997 reviewed the current knowledge and developed recommendations for areas of further research and education about PPCM. Since then, there have been some promising research testing hypotheses regarding the etiology of PPCM and advancements in possible treatment options. However, despite these efforts, knowledge and treatment recommendations about PPCM are still generally unchanged, whereas mortality rates remain high. This article attempts to provide an updated, comprehensive review about PPCM and draw attention to areas in need of further research.
Cardiol Rev 2006;14(1):35-42.

Frequency of peripartum cardiomyopathy

MIELNICZUK LM, WILLIAMS K, DAVIS DR, ET AL.
BOSTON, MASSACHUSETTS
Reports from case series have estimated the incidence of peripartum cardiomyopathy (PC) at 1 case/1,485 live births to 1 case/15,000 live births and probable mortality rates of 7% to 60%. The objective of this study was to produce the first population-based study of the incidence, mortality, and risk factors for PC. The National Hospital Discharge Survey was used. Discharge information was available for 3.6 million patient discharges from 1990 to 2002. There were an estimated 16,296 cases of PC from 1990 to 2002. During this period, there were 51,966,560 live births in the United States. Thus, the incidence of PC was 1 case/3,189 live births. There was a trend toward an increase in PC incidence during the study period, with an estimate for the years 2000 to 2002 of 1 case/2,289 live births. The in-hospital mortality rate was 1.36% (95% confidence interval 0% to 10.2%). The total mortality rate was 2.05% (95% confidence interval 0.29% to 10.8%). Patients with PC were older (mean age 29.7 vs 26.9 years), were more likely to be black (32.2% vs 15.7%), and had a higher incidence of pregnancy associated hypertensive disorders (22.5% vs 5.87%) compared with national data. In conclusion, the incidence of PC is relatively uncommon, occurring at an average frequency of 1 case/3,189 live births from 1990 to 2002. The estimated mortality of 1.36% to 2.05% (95% confidence interval 0.29% to 10.8%) is less than previously reported from most case series.
Am J Cardiol 2006;97(12):1765-8

Upcoming meetings

10-13 September 2006
Heart Failure Society of America
Annual Scientific Meeting
Seattle, Washington
Contact: www.hfsa.org

21-26 October 2006
Canadian Cardiovascular Society
CCC 2006
Vancouver, British Columbia
Contact: www.ccs.ca

12-15 November 2006
American Heart Association Scientific Sessions 2006
Chicago, Illinois
Contact: www.scientificsessions.org

11-15 March 2007
23rd Annual Cardiovascular Conference Lake Louise
Fairmont Chateau Lake Louise Hotel,
Lake Louise, Alberta, Canada
Contact: www.acclakelouise.com

Disclosure Statement: *Dr. Zia and Dr. Moe have no disclosures to declare in association with the contents of this issue.*

Change of address notices and requests for subscriptions to *Cardiology Rounds* are to be sent by mail to P.O. Box 310, Station H, Montreal, Quebec H3G 2K8 or by fax to (514) 932-5114 or by e-mail to info@snellmedical.com. Please reference *Cardiology Rounds* in your correspondence. Undeliverable copies are to be sent to the address above. Publications Post #40032303

This publication is made possible by an educational grant from

Novartis Pharmaceuticals Canada Inc.