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PERIPARTUM CARDIOMYOPATHY: A CONTEMPORARY REVIEW

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Abstract

Peripartum cardiomyopathy is a rare and potentially fatal disease. Though approximately half of the patients recover, the clinical course is highly variable and some patients develop refractory heart failure and persistent left ventricular systolic dysfunction. It is diagnosed when women present with heart failure secondary to left ventricular systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. Etiology remains unclear, and treatment is similar to other cardiomyopathies and includes evidence-based standard heart failure management strategies. Experimental strategies such as intravenous immunoglobulin and bromocriptine await further clinical validation.

Introduction

Peripartum cardiomyopathy (PPCM) is a rare and potentially fatal disease.[1] Although phenotypically it resembles nonischemic dilated cardiomyopathy (DCM), the clinical course is highly variable and differs significantly from other forms of cardiomyopathies.[1] Its clinical course is highly unpredictable — it may vary from rapid progression to end-stage heart failure within a few days[2] to spontaneous resolution and complete recovery in a few weeks to months.[3-5]

Definition and Incidence

The initial definition of PPCM was established according to the four criteria adapted from the study by Demakis et al.[1] and recommended by a workshop convened in 1997 by the National Heart, Lung and Blood Institute and the Office of Rare Diseases of the National Institutes of Health.[2] The four criteria are as follows: (1) development of cardiac failure in the last month of pregnancy or within 5 months of delivery; (2) absence of an identifiable cause for the cardiac failure other than pregnancy; (3) absence of recognizable heart disease before the last month of pregnancy; and (4) left ventricular systolic dysfunction (LVSD) with left ventricular ejection fraction (LVEF) <45% by echocardiography, fractional shortening <30%, or both.[2] PPCM remains a diagnosis of exclusion; all other causes of DCM with heart failure must be systematically excluded before establishing the diagnosis of PPCM.[6] Since 1997, the definition of PPCM has varied slightly. The European Society of Cardiology on the classification of cardiomyopathies has defined it as "a non-familial, non-genetic form of dilated cardiomyopathy associated with pregnancy."[7] The AHA Scientific Statement on contemporary definitions and classifications of the cardiomyopathies has defined it as "a rare and dilated acquired primary cardiomyopathy-associated LV dysfunction and heart failure."[8] The restriction of the time frame to last month of pregnancy or first 5 months postpartum for diagnosis has been challenged. In a study by Elkayam et al., almost 20% of the patients developed symptoms of heart failure and were diagnosed with PPCM earlier than the last gestational month.[9] A comparison between patients with early presentation and those with traditional criteria of PPCM revealed no significant differences in age, ethnic background, obstetrical history, and rate of gestational hypertension. Furthermore, maternal outcome, LVEF at the time of diagnosis, and its recovery over time were strikingly similar between the two groups.[9] Hence, a slightly different definition was proposed in the position statement from the Heart Failure Association of the European Society of Cardiology Working Group on PPCM.[2] The authors believed that the time frame and echocardiographic cut-offs were arbitrary and could lead to underdiagnosis of PPCM. They eliminated the strict time limit to the diagnosis and proposed the following definition: "Peripartum cardiomyopathy is an idiopathic cardiomyopathy presenting with HF secondary to left ventricular (LV) systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of HF is found." Again, it is a diagnosis of exclusion. The left ventricle may not be dilated but the ejection fraction (EF) is nearly always reduced below 45%.

The incidence varies geographically. Based on available literature, the incidence of PPCM appears to be 1 in 1,000 in South Africa and 1 in 300 in Haiti.[2-4] Whereas, a detailed retrospective review of the National Hospital Discharge Survey database (1990–2002) reported an estimated lower incidence of 1 case per 3,189 live births in the United States.[3] The study also reported that patients with PPCM 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. A similar study examined ICD-9 codes within the database of the Kaiser Permanent health system in southern California from 1996–2005 and estimated a PPCM incidence of 1 case per 4,025 live births, again reporting the highest incidence in African-American women.[4] This study, however, had a high percentage of Hispanic women, the ethnicity with the lowest incidence of PPCM.

Risk Factors

The strongest risk factor for PPCM appears to be African-American ethnicity (OR 15.7; CI 3.5–70.6).[5] Other reported risk factors include age, pregnancy-induced hypertension or preeclampsia,[3] multiparity, multiple gestations, obesity, chronic hypertension, and the prolonged use of tocolytics (Table 1).[10]

PPCM Risk Factors
Ethnicity
• Highest incidence in certain ethnic groups in Africa
• African-American ethnicity is the strongest risk factor in the United States
Age
Pregnancy induced hypertension or preeclampsia
Multiparity
Multiple gestations
Obesity
Chronic hypertension
Prolonged use of tocolytics

Table 1. Risk factors for peripartum cardiomyopathy.

Pathophysiology

The cause of PPCM remains unclear, but several mechanisms have been proposed, which indicates a potentially multi-factorial etiology (Table 2).

PPCM Pathophysiology
Prolactin, 16-kDa Prolactin, and Cathepsin D Cascade
Defective antioxidant mechanism • Increased cleavage of prolactin into an antiangiogenic and proapoptotic isoform
Autoimmune Mechanism
Class G and all subclass immunoglobulins against cardiac myosin heavy chain shown to be raised in PPCM • Fetal microchimerism (fetal cells in maternal blood) in patients with PPCM
Inflammation
Elevated serum markers of inflammation such as C-reactive protein, soluble death marker SFAS/Apo 1, interferon-gamma, interleukin (IL)-6, and TNF
Viral Infection
Role of viral infection less established
Genetic Susceptibility
Family clustering seen

Table 2. Pathophysiology of peripartum cardiomyopathy.

Prolactin, 16-kDa Prolactin, and Cathepsin D Cascade

There appears to be a cascade involving oxidative stress, the prolactin-cleaving protease cathepsin D, and prolactin in the pathophysiology of PPCM.[9] Markers of cellular oxidation rise during pregnancy and hence an efficient antioxidant defense mechanism in the maternal heart is crucial, especially late in pregnancy and in the postpartum period. Experimental data in a mouse model of PPCM (mice with cardiomyocyte-restricted deletion of STAT3, signal transducer and activator of transcription-3) suggest that defective antioxidant mechanism may be responsible for the development of PPCM. Reduction in STAT3 appears to be a trigger that leads to activation of cathepsin D in the cardiomyocytes, which subsequently causes increased cleavage of prolactin into an antiangiogenic and proapoptotic 16-kDa isoform.[9] The 16-kDa prolactin fragment has potentially detrimental cardiovascular actions that could play a role in the pathophysiology of PPCM. It has been shown to inhibit endothelial cell proliferation and migration, induce endothelial apoptosis and disrupt already formed capillary structures, promote vasoconstriction, and impair cardiomyocyte function. The functional role of an activated oxidative stress-cathepsin D-16-kDa prolactin cascade is supported by the observation that in mice, treatment with bromocriptine, an inhibitor of prolactin secretion, prevented the development of PPCM. Also, patients with PPCM have increased serum levels of activated cathepsin D, total prolactin, and cleaved 16-kDa prolactin fragment.[11]

Autoimmune Mechanism

High titers of auto-antibodies against selected cardiac tissue proteins have been found in the majority of women with PPCM.[12] Warraich et al. investigated the role of humoral immunity and showed that unlike the selective upregulation of immunoglobulins of the G3 subclass (IgG3s) in DCM, class G and all subclass immunoglobulins against cardiac myosin heavy chain were raised in PPCM.[13] Of the serological variables, IgG3s (immunoglobulins with proinflammatory characteristics) discriminated NYHA functional status at diagnosis. IgG3-positive patients were in a higher NYHA class at initial presentation. Similarly, Ansari et al. investigated the role of fetal microchimerism (fetal cells in maternal blood) in patients with PPCM. In a small sample of patients, the amount of male chromosomal DNA in maternal plasma was significantly greater in patients with PPCM than in control mothers without PPCM during the third trimester of pregnancy, which could theoretically lead to the initiation of an autoimmune myocarditis.[14]

Inflammation

Serum markers of inflammation like C-reactive protein, soluble death marker SFAS/Apo 1, interferon-gamma, interleukin (IL)-6, and TNF all have shown to be elevated in PPCM.[11] In a study of 29 black women, IL-6 levels in patients with left ventricular thrombus were significantly higher compared with the rest of the study population.[15] Pentoxifylline, an anti-inflammatory agent, was shown to improve clinical outcomes when added to conventional therapy in a small nonrandomized study of 59 patients.[16]

Viral Infection

The definitive role of viral infection in PPCM has not been well established. A study by Bultmann et al. identified viral genomes in cardiac tissue of PPCM patients by polymerase chain reaction (PCR) testing.[17] PPCM patients who were viral-positive had histological evidence of a cardiac interstitial inflammatory process, while control patients who were viral positive did not. Viruses identified in 8 out of 26 PPCM patients (30.8%) included Epstein-Barr virus, human cytomegalovirus, human herpes virus 6, and parvovirus.[17, 18] However, a study by Lamparter et al. reported no evidence of viral infection in snap-frozen tissue from 7 PPCM patients undergoing left ventricular endomyocardial biopsy within 48 hours of diagnosis, questioning the role of viral infections in PPCM.[18, 19]

Genetic Susceptibility

Familial clustering of PPCM has been systematically evaluated in the two studies.[20, 21] A study by van Spaendonck-Zwarts et al. suggested that a subset of PPCM may be a part of the spectrum of

familial DCM, presenting in the peripartum period.[20] In this study, the authors identified a substantial number of DCM families with PPCM (5 of 90, 6%). Also, undiagnosed DCM was identified in all three families of PPCM patients who did not show full recovery. Finally, the authors identified a mutation in a DCM family with one PPCM patient and another family member who had died suddenly soon after delivery. Hence the authors believe that it is justifiable to offer cardiological screening to first-degree relatives of recovered and unrecovered PPCM patients. A study of 520 pedigrees in the Familial Dilated Cardiomyopathy Research Project database found 45 cases of PPCM or pregnancy-associated cardiomyopathy (PACM) among 4,110 women.[21] Evidence of familial clustering of dilated cardiomyopathy was noted in 23 of 42 unrelated cases. However, based on current levels of evidence, genetic testing is not recommended as routine but is currently being done as part of research projects.[22]

Clinical Presentation and Diagnosis

Clinical presentation of patients with PPCM may be highly variable, but patients usually present with symptoms similar to those in patients presenting with systolic heart failure due to other causes. The signs and symptoms may be similar to normal physiological findings of pregnancy like edema of the legs, dyspnea on exertion, cough, paroxysmal nocturnal dyspnea, and orthopnea. Other symptoms may include abdominal discomfort, palpitations, dizziness, and chest pain.[22] Most frequent initial presentation is NYHA class III or IV symptoms.[23] The majority of patients present with symptoms in the first 4 months after delivery (78%), and only 9% present in the last month of pregnancy.[22] The remaining 13% present either before the last month of delivery or more than 4 months postpartum.[24] LV thrombus is common in PPCM patients, and some patients presenting with peripheral embolic episodes including cerebral and coronary embolism have been described in the literature.[25, 26] The diagnosis of PPCM involves a high index of suspicion as symptoms may be similar to those of physiological changes that occur during pregnancy. It also is a diagnosis of exclusion, and a thorough investigation must be done to rule out an alternative etiology of heart failure.[22]

Initial investigation usually involves routine blood tests to rule out anemia, electrolyte disturbances, and liver, renal, and thyroid dysfunction. Serum B-natriuretic peptide (BNP) or NT-BNP are also commonly elevated in PPCM patients. Electrocardiogram (EKG) findings may be nonspecific. Sinus tachycardia, atrial fibrillation, atrial flutter, and ventricular tachycardia have been reported in patients with PPCM. An EKG QRS time of ≥120 ms has been identified as a predictor for mortality, indicating a potential impact of QRS time on the mortality of patients with PPCM.[27] Echocardiogram is used to rule out other causes of heart failure such as valve disease and to establish reduced ejection fraction. Among patients with LVEF >30% at diagnosis, restoration of normal LVEF is more likely. The left ventricle may not always be dilated; however, an initial left ventricular end-systolic diameter of ≤5.5 cm has been shown to predict recovery of left ventricle function.[27] LV thrombus has been found on initial echocardiography in 10–17% of patients.[28,29] PPCM also is associated with an increased incidence of thromboembolism compared with DCM from other etiologies. Other imaging modalities such as cardiac MRI do not show any specific pattern in PPCM to help differentiate from other causes of cardiomyopathy, although it can give a more accurate measurement of chamber volumes and ventricular function than echocardiography.[30] The role of cardiac MRI in PPCM is being further investigated in the Investigation in Pregnancy Associated Cardiomyopathy (IPAC) study. One of the study's objectives is to investigate the frequency of myocardial injury or inflammation on cardiac MRI and the ability of tissue characteristics to predict subsequent recovery of LVEF.[31] Endomyocardial biopsy is not routinely recommended or a part of the typical diagnostic work up of PPCM. If a biopsy seems warranted based on suspicion of other infiltrative cardiomyopathies or treatable causes, it should be undertaken with caution. A variable proportion of patients with PPCM may have evidence of myocarditis, and since there are no pathognomonic findings in PPCM, there is an inherent risk in performing a biopsy of a dilated right ventricle.

Management

A multidisciplinary approach involving a cardiologist, obstetrician, intensivist, anesthesiologist, and pediatrician is essential and should be engaged as early as possible. Initial management is similar to that of other forms of nonischemic cardiomyopathy and includes oxygen, fluid restriction, loop-diuretics and/or other diuretics, nitrates, and hydralazine (safe to use during pregnancy), especially for hypertension. Angiotensin converting enzyme inhibitors should be avoided in the second and third trimester but are safe to use postpartum. Beta-blockers can be used when not contraindicated during pregnancy, and they can be used postpartum. During pregnancy, β-1 selective agents are preferred because β-2 receptor blockade may have an antitocolytic effect. Inotropic agents should be used in patients with signs of low cardiac output or with persistent congestion despite diuretics/afterload-reducing agents. Anticoagulation is recommended in patients with PPCM as these patients have a high incidence of LV thrombus, especially patients with an LVEF <35%. Heparin (unfractionated and low-molecular-weight) is favored in pregnancy since, unlike warfarin, it doesn't cross the placenta. Warfarin should be avoided as it is teratogenic in early pregnancy and has a risk of causing fetal cerebral hemorrhage in the second and third trimester. After delivery, PPCM should be treated according to current guidelines for heart failure.[22]

Specific Experimental Treatment Strategies Awaiting Further Validation

Immunosuppressive agents: The prevalence of myocarditis in PPCM varies from 9–78%.[32, 33] A single nonrandomized study suggested that immunosuppression may benefit women with biopsy-proven myocarditis.[34] However, the Myocarditis Treatment Trial did not show any benefit of immunosuppressive medications and, given the risks of immunosuppressive therapy, they are currently not widely utilized.[33, 35]

Intravenous immune globulin (IVIG): The role of IVIG in PPCM was evaluated in a retrospective study of six women treated with IVIG and 11 controls treated conventionally.[36] After a 6-month follow-up, the absolute increase in LVEF was greater in those treated with IVIG compared to controls (26% vs. 13%). However, the IMAC trial (Controlled Trial of Intravenous Immune Globulin in Recent-Onset Dilated Cardiomyopathy) showed that despite the potential therapeutic efficacy suggested by previous uncontrolled studies, immune globulin treatment of adult patients with recent-onset cardiomyopathy in this placebo-controlled trial did not affect improvements in LVEF or functional capacity during follow-up.[36]

Bromocriptine: This treatment strategy is based on an experimental observation of preventing PPCM in mice via prolactin blockade with bromocriptine.[11] In a randomized open-label study performed in South Africa, 20 women with newly diagnosed PPCM were randomly assigned to receive either

standard care plus bromocriptine or standard care alone.[37] The 10 women receiving bromocriptine demonstrated significantly greater improvement in LVEF compared to the 10 women receiving standard care only (27% to 58% vs. 27% to 36%). One patient in the bromocriptine group died compared to four in the standard care group. Fewer patients in the bromocriptine group reached the composite endpoint of death, NYHA functional class III or IV heart failure, or LVEF <35% at 6 months as compared to patients in the standard care group (1 vs. 8). The generalizability of these results is unclear given the small sample size, the higher than expected mortality rate in the standard care group, and differences in PPCM characteristics in patients in Africa as compared to those elsewhere. Further studies aimed at clearly establishing the efficacy and safety of bromocriptine are needed before it can be recommended for the treatment of PPCM.

Pentoxifylline: In a single center study involving 59 patients with PPCM, Sliwa et al. sought to evaluate the effects of pentoxifylline, a drug known to inhibit the production of TNF-α, on clinical status, LV function, and circulating plasma levels of TNF-α.[16] One group was treated with diuretics, digoxin, enalapril, and carvedilol, and the other group received pentoxifylline 400 mg three times daily in addition to the previous therapy. Treatment with pentoxifylline was an independent predictor of favorable outcome with better LVEF, NYHA class, and survival. The promising role of pentoxifylline remains experimental until it is validated by a larger scale, placebo-controlled, randomized clinical trial.[16]

Advanced Care and Device Therapy

Decisions about both the necessity and timing of CRT or ICD implantation in PPCM patients are extremely difficult and require careful consideration of the risks and benefits and the natural history of PPCM. However, if a patient has persistently depressed LV dysfunction 6 months following presentation despite optimal medical therapy, implantation of an ICD is advised. CRT should be considered if the patient has NYHA class III or IV symptoms and a QRS >120 msec. For patients who are dependent on inotropes or intra-aortic balloon pump despite optimal medical therapy, implantation of a mechanical assist device or cardiac transplantation may be considered.[22, 38]

Prognosis

Factors associated with favorable prognosis include small LV diastolic dimension (<5.5–6.0 cm) and elevated systolic function (LVEF >30–35% and fractional shortening >20%) at the time of diagnosis,[39, 40] absence of troponin elevation,[41] absence of LV thrombus,[29] and non-African American ethnicity.[42] Recent multivariate analysis by Goland et al. in 187 patients with PPCM found LVEF <30% and LV end-diastolic dimension <55 mm to be significantly related to LV recovery, suggesting a relationship between the degree of initial myocardial insult and recovery.[42] These parameters, however, have limited sensitivity in predicting recovery in individual patients. Despite the strong association between LVEF at time of diagnosis and rate of recovery, 70% of patients in group I (LVEF 10–19%) and 87% of patients in group II (LVEF 20–29%) recovered almost beyond the "device threshold" at ≥6 months. Hence the authors suggest that baseline parameters of LV function should not be used alone as an indication for the premature use of devices or heart transplantation.

Subsequent Pregnancies

PPCM is associated with a high risk of recurrence in subsequent pregnancies both in patients who have recovery of LV function and in those with persistent LV dysfunction.[43-46] Patients with PPCM who recover their LV function have a lesser chance of recurrence compared to those with persistent LV dysfunction.[46] The increased deterioration of LV function in subsequent pregnancy in patients with persistent LV dysfunction leads to a worse prognosis (20–30% mortality in subsequent pregnancy), whereas patients with a full recovery of LV function have negligible mortality in subsequent pregnancies.[46, 47] Appropriate counseling regarding subsequent pregnancies and contraception is important.[48] Every woman with PPCM should be informed about detrimental effects of a subsequent pregnancy on cardiac function, and women with LVEF of <25% at diagnosis of PPCM or persistent LV dysfunction should be advised against a subsequent pregnancy.[48] The safety of contraceptive use among women with PPCM has not been well studied.[49, 50] Counseling to women with recovered ventricular function is challenging. LV systolic function is considered a major prognostic factor for subsequent pregnancies in patients with PPCM.[51, 52] If a woman plans to become pregnant, echocardiography should be performed, and dobutamine stress echocardiography may be helpful.[51] Dobutamine stress echocardiography can be used to determine the contractile reserve in patients with recovered LV function.[53, 54] Women with recovered LV function on both echocardiography and dobutamine stress test have approximately 35% risk of recurrence of PPCM during subsequent pregnancies.[51] Still, every subsequent pregnancy in women with PPCM should be managed in high-risk perinatal centers, as subsequent pregnancies are associated with a high risk of recurrence despite recovered LV function.[44, 54, 2]

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References

1. Demakis JG, Rahimtoola SH, Sutton GC, Meadows WR, Szanto PB, Tobin JR, et al. Natural course of peripartum cardiomyopathy. Circulation. 1971;44(6):1053-61.
2. Pearson GD, Veille JC, Rahimtoola S, Hsia J, Oakley CM, Hosenpud JD, 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 Mar 1;283(9):1183-8.
3. Mielniczuk LM, Williams K, Davis DR, Tang AS, Lemery R, Green MS, et al. Frequency of peripartum cardiomyopathy. Am J Cardiol. 2006 Jun 15;97(12):1765-8.
4. Brar SS, Khan SS, Sandhu GK, Jorgensen MB, Parikh N, Hsu JW, et al. Incidence, mortality, and racial differences in peripartum cardiomyopathy. Am J Cardiol. 2007;100(2):302-4.
5. Gentry MB, Dias JK, Luis A, Patel R, Thornton J, Reed GL. African-American women have a higher risk for developing peripartum cardiomyopathy. J Am Coll Cardiol. 2010;55(7):654-9.
6. Sliwa K, Fett J, Elkayam U. Peripartum cardiomyopathy. Lancet. 2006;368(9536):687-93.

7. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008 Oct;29(19):2388-442.
8. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation. 2006 Apr 11;113(14):1807-16.
9. Elkayam U, Akhter MW, Singh H, Khan S, Bitar F, Hameed A, et al. Pregnancy-associated cardiomyopathy: clinical characteristics and a comparison between early and late presentation. Circulation. 2005;111(16):2050-5.
10. Heider AL, Kuller JA, Strauss RA, Wells SR. Peripartum cardiomyopathy: a review of the literature. Obstet Gyncol Surv. 1999;54(8):526-31.
11. Hilfiker-Kleiner D, Kaminski K, Podewski E, Bonda T, Schaefer A, Sliwa K, et al. A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. Cell. 2007 Feb 9;128(3):589-600.
12. Selle T, Renger I, Labidi S, Bultmann I, Hilfiker-Kleiner D. Reviewing peripartum cardiomyopathy: current state of knowledge. Future Cardiol. 2009 Mar;5(2):175-89.
13. Warraich RS, Sliwa K, Damasceno A, Carraway R, Sundrom B, Arif G, et al. Impact of pregnancy-related heart failure on humoral immunity: clinical relevance of G3-subclass immunoglobulins in peripartum cardiomyopathy. Am Heart J. 2005 Aug;150(2):263-9.
14. Ansari AA, Fett JD, Carraway RE, Mayne AE, Onlamoon N, Sundstrom JB. Autoimmune mechanisms as the basis for human peripartum cardiomyopathy. Clin Rev Allergy Immunol. 2002 Dec;23(3):301-24.
15. Sliwa K, Skudicky D, Bergemann A, Candy G, Puren A, Sareli P. Peripartum cardiomyopathy: analysis of clinical outcome, left ventricular function, plasma levels of cytokines and Fas/APO-1. J Am Coll Cardiol. 2000 Mar;35(3):701-5.
16. Sliwa K, Skudicky D, Candy G, Bergemann A, Hopley M, Sareli P. The addition of pentoxifylline to conventional therapy improves outcome in patients with peripartum cardiomyopathy. Eur J Heart Fail. 2002 Jun;4(3):305-9.
17. Bultmann BD, Klingel K, Nabauer M, Wallwiener D, Kandolf R. High prevalence of viral genomes and inflammation in peripartum cardiomyopathy. Am J Obstet Gyncol. 2005 Aug;193(2):363-5.
18. Fett JD. Viral infection as a possible trigger for the development of peripartum cardiomyopathy. Int J Gynaecol Obstet. 2007 Mar 21;97(2):149-50.
19. Lamparter S, Pankuweit S, Maisch B. Clinical and immunologic characteristics in peripartum cardiomyopathy. Int J Cardiol. 2007 May16;118(1):14-20.
20. van Spaendonck-Zwarts KY, van Tintelen JP, van Veldhuisen DJ, van der Werf R, Jongbloed JD, Paulus WJ, et al. Peripartum cardiomyopathy as a part of familial dilated cardiomyopathy. Circulation. 2010 May 25;121(20):2169-75.
21. Morales A, Painter T, Li R, Siegfried JD, Li D, Norton N, et al. Rare variant mutations in pregnancy-associated or peripartum cardiomyopathy. Circulation. 2010 May 25;121(20): 2176-82.
22. Sliwa K, Hilfiker-Kleiner D, Petrie MC, Mebazaa A, Pieske B, Buchmann E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. Eur J Heart Fail. 2010 Aug;12(8):767-78.
23. Desai D, Moodley J, Naidoo D. Peripartum cardiomyopathy: experiences at King Edward VIII Hospital, Durban, South Africa and a review of the literature. Tropical Doctor. 1995;25(3):118-23.
24. Lampert MB, Lang RM. Peripartum cardiomyopathy. Am Heart J. 1995 Oct;130(4):860-70.
25. Helms AK, Kittner SJ. Pregnancy and stroke. CNS Spect. 2005 Jul;10(7):580-7.
26. Box LC, Hanak V, Arciniegas JG. Dual coronary emboli in peripartum cardiomyopathy. Tex Heart Inst J. 2004;31(4):442-4.
27. Duran N, Gunes H, Duran I, Biteker M, Ozkan M. Predictors of prognosis in patients with peripartum cardiomyopathy. Int J Gynaecol Obstet. 2008 May;101(2):137-40.
28. Napporn AG, Kane A, Damorou JM, Dia AA, Diop IB, Sarr M, et al. [Intraventricular thrombosis complicating peripartum idiopathic myocardiopathy]. Annales de cardiologie et d'angeiologie. 2000 Aug;49(5):309-14.
29. Amos AM, Jaber WA, Russell SD. Improved outcomes in peripartum cardiomyopathy with contemporary. Am Heart J. 2006;152(3):509-13.
30. Mouquet F, Lions C, de Groote P, Bouabdallaoui N, Willoteaux S, Dagorn J, et al. Characterisation of peripartum cardiomyopathy by cardiac magnetic resonance imaging. Eur Radiol. 2008 Dec;18(12):2765-9.
31. Clinical Trials [Internet]. Bethesda, MD: National Institutes of Health; c2012. Investigation in Pregnancy Associate Cardiomyopathy (IPAC); 2012 Oct 24 [cited 2013 Jan 9]. Available from: http://clinicaltrials.gov/ct2/show/NCT01085955.
32. Rizeq MN, Rickenbacher PR, Fowler MB, Billingham ME. Incidence of myocarditis in peripartum cardiomyopathy. Am J Cardiol. 1994 Sept 1;74(5):474-7.
33. Mason JW, O'Connell JB, Herskowitz A, Rose NR, McManus BM, Billingham ME, et al. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. New Engl J Med. 1995 Aug 3;333(5):269-75.
34. Midei MG, DeMent SH, Feldman AM, Hutchins GM, Baughman KL. Peripartum myocarditis and cardiomyopathy. Circulation. 1990 Mar;81(3):922-8.
35. Biteker M, Duran NE, Kaya H, Gunduz S, Tanboga HI, Gokdeniz T, et al. Effect of levosimendan and predictors of recovery in patients with peripartum cardiomyopathy, a randomized clinical trial. Clin Res Cardiol. 2011 Jul;100(7):571-7.
36. Bozkurt B, Villaneuva FS, Holubkov R, Tokarczyk T, Alvarez RJ Jr, MacGowan GA, et al. Intravenous immune globulin in the therapy of peripartum cardiomyopathy. J Am Coll Cardiol. 1999 Jul;34(1):177-80.
37. Sliwa K, Blauwet L, Tibazarwa K, Libhaber E, Smedema JP, Becker A, et al. Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: a proof-of-concept pilot study. Circulation. 2010 Apr 6;121(13):1465-73.

38. Rasmusson K, Brunisholz K, Budge D, Horne BD, Alharethi R, Folsom J, et al. Peripartum cardiomyopathy: post-transplant outcomes from the United Network for Organ Sharing Database. J Heart Lung Transplant. 2012 Feb;31(2):180-6.

39. Chapa JB, Heiberger HB, Weinert L, Decara J, Lang RM, Hibbard JU. Prognostic value of echocardiography in peripartum cardiomyopathy. Obstet Gynecol. 2005 Jun;105(6):1303-8.

40. Hu CL, Li YB, Zou YG, Zhang JM, Chen JB, Liu J, et al. Troponin T measurement can predict persistent left ventricular dysfunction in peripartum cardiomyopathy. Heart. 2007 Apr;93(4):488-90.

41. Goland S, Bitar F, Modi K, Safirstein J, Ro A, Mirocha J, et al. Evaluation of the clinical relevance of baseline left ventricular ejection fraction as a predictor of recovery or persistence of severe dysfunction in women in the United States with peripartum cardiomyopathy. J Car Fail. 2011 May;17(5):426-30.

42. Fett JD, Fristoe KL, Welsh SN. Risk of heart failure relapse in subsequent pregnancy among peripartum cardiomyopathy mothers. Inter J Gynaecol Obstet. 2010 Apr;109(1):34-6.

43. Habli M, O'Brien T, Nowack E, Khoury S, Barton JR, Sibai B. Peripartum cardiomyopathy: prognostic factors for long-term maternal outcome. Am J Obstet Gynecol. 2008 Oct;199(4):415.

44. Mandal D, Mandal S, Mukherjee D, Biswas SC, Maiti TK, Chattopadhaya N, et al. Pregnancy and subsequent pregnancy outcomes in peripartum cardiomyopathy. J Obstet Gynaecol Res. 2011 Mar;37(3):222-7.

45. Elkayam U, Tummala PP, Rao K, Akhter MW, Karaalp IS, Wani OR, et al. Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. N Engl J Med. 2001 May 24;344(21):1567-71.

46. Sliwa K, Forster O, Zhanje F, Candy G, Kachope J, Essop R. Outcome of subsequent pregnancy in patients with documented peripartum cardiomyopathy. Am J Cardiol. 2004 Jun 1;93(11):1441-3.

47. Sliwa K, Hilfiker-Kleiner D, Petrie MC, Mebazaa A, Pieske B, Buchmann E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. Eur J Heart Fail. 2010; 12(8):767-78.

48. Tepper NK, Paulen ME, Marchbanks PA, Curtis KM. Safety of contraceptive use among women with peripartum cardiomyopathy: a systematic review. Contraception. 2010 Jul 82(1):95-101.

49. Thorne S, MacGregor A, Nelson-Piercy C. Risks of contraception and pregnancy in heart disease. Heart. 2006; 92(10):1520-25.

50. Pyatt JR, Dubey G. Peripartum cardiomyopathy: current understanding, comprehensive management review and new developments. Postgrad Med J. 2011 Jan;87(1023):34-9.

51. Moioli M, Valenzano Menada M, Bentivoglio G, Ferrero S. Peripartum cardiomyopathy. Arch Gynecol Obstet. 2010 Feb;281(2):183-8.

52. Lampert MB, Weinert L, Hibbard J, Korcarz C, Lindheimer M, Lang RM. Contractile reserve in patients with peripartum cardiomyopathy and recovered left ventricular function. Am J Obstet Gynecol. 1997 Jan;176(1Pt 1):189-95.

53. Twomley KM, Wells GL. Peripartum cardiomyopathy: a current review. J Pregnancy. 2010:2010:149127.

54. Tomlinson M. High Risk Pregnancy Management Options. In: James D, Steer P, Weiner C, Gonik B, editors. Cardiac diseases. 3rd ed. Philadelphia: Elsevier Saunders; 1999. p. 798–827.