PERIPARTUM CARDIOMYOPATHY: PREDICTORS OF RECOVERY

BY

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Abstract

Introduction: Peripartum Cardiomyopathy (PPCM) is a rare, poorly understood disease process with significant clinical implications in pregnant women during and after delivery. Improvement in left ventricular (LV) ejection fraction (EF) varies widely and few studies exist that define predictors of improvement in LV function in this sub population. The use of implantable cardioverter defibrillator (ICD) has also not been clearly understood in this population.

Methods: A retrospective study was conducted at 2 academic centers between January 1st 1999 and December 31st 2010. Clinical and demographic variables and delivery records of patients with a discharge or outpatient diagnosis of PPCM (ICD9 -674.5) were reviewed. Patients were followed over time until December 31st 2012 to assess improvement in LV function.

Results: The total sample comprised 100 patients of whom 55% were African Americans, 39% were Caucasians and 6% were Hispanic with mean age of 30±6 years. The mean time to diagnosis after delivery was 1.1±4 weeks. Mean EF at diagnosis was 28±9%. Forty two percent of patients showed some improvement in LVEF over a mean duration of 33±21 months. Postpartum diagnosis (HR 3, p=0.01) and Caucasian/Hispanic race (HR 2.2, p=0.01) were predictors of LVEF improvement. Only 7 of the 58 patients (12%) who did not improve their EF, had ICD implanted. There were 11 deaths with a trend towards higher mortality in those that did not display improved LV function (15% vs. 5%, p=0.1).

Conclusions: More than one-third of the women with PPCM improve LV function with delayed recovery noted in the majority of these women. Caucasians and those diagnosed postpartum seem to be most likely to recover. ICDs were underutilized for primary prevention of sudden cardiac death in this population.

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Introduction:

Peripartum cardiomyopathy (PPCM) is a rare, life threatening disease characterized by the development of heart failure in the last month of pregnancy or within 5 months of delivery (1, 2). The reported incidence shows significant geo-demographic variation from 1 in 500 live births in Haiti to 1 in 4000 live births in the USA (3 -6). Identified risk factors for PPCM include multiparity, advanced maternal age, twins, preeclampsia, gestational hypertension and African-American race (7-10).

Despite the recognition of this disease as a separate entity in 1937 (1), the mortality rates are still not well characterized (8-19) ranging from 4 % to 50% (2, 8-19). At least a quarter of deaths in PPCM are caused by ventricular tachyarrhythmias (16). Sudden cardiac death in these young women could potentially be averted by implantation of a cardioverter-defibrillator (ICD) and cardiac resynchronization (CRT) devices may reduce progression to end stage myocardial dysfunction. ACC/AHA/ESC 2009 guidelines recommend implantation of an ICD for primary prevention of sudden cardiac death in all patients with EF≤ 35% (20).To date, there are no studies that report the use of ICD or CRTD for primary prevention in this population. PPCM is also reported to be associated with a higher likelihood of recovery of left ventricular (LV) function than cardiomyopathy from other causes (2,10,17,19,21). Thus, predicting who recovers from the disease helps determine who might best benefit from an ICD implantation. Previous studies have shown that baseline LV ejection fraction (EF) >30%, LVEDD < 5.5cm, older age and Caucasian race predicted recovery of LV function (22-29). However these are single center studies with small sample sizes of ≤ 55 patients or the information was obtained from other countries and surveys that are subject to ascertainment, recall and selection bias.

We thus wanted to study the mortality and LV recovery rates and examine the ICD implantation rates at tertiary academic centers that offer a good mix of patients of different ethnicities. We sought to identify the predictors for LV recovery and the current rates of ICD use.

Methods:

This is a retrospective study conducted at two large tertiary care academic centers, University of Kansas, Kansas City and Detroit Medical Center, Detroit where cardiovascular and high risk pregnancy services are available. IRB approval was obtained from both institutions.

Patients: All patients > 18 years of age who were diagnosed with postpartum/peripartum cardiomyopathy at the 2 centers were studied. The medical records of these patients were identified by using ICD-9 diagnostic codes for PPCM (674.50. 674.51, 674.52, 674.53, 674.54) that were used for discharge diagnoses from the hospital and/or ambulatory clinic visits. At University of Kansas, medical records were obtained for patients diagnosed between January 1st 2004 and August 31st 2010. At the Detroit Medical Center, records were obtained for patients that were diagnosed with PPCM between January 1st 1999 and December 31st 2010. All delivery records and follow-up encounters were reviewed for clinical and demographic information. Patients with a history of prior cardiomyopathy from other causes or structural heart disease were excluded. Each patient was followed until December 2012 for any improvement in EF. The date of the last echo was considered as the last follow-up date for those without any improvement in EF. Time to recovery was noted for patients who had improvement in LV function. ICD implantation was also noted. All-cause mortality was obtained from the social security death index and confirmed by chart review when available.

Assessment of Ejection fraction (EF): EFs at the time of diagnosis of PPCM were recorded and termed as baseline EF. Each patient was followed over time to assess EF and the EF from the last echocardiogram report was noted for those without LV improvement. For patients who had an improvement in EF, the EF and the time to improvement in EF were noted.

Definition of improvement: An EF > 50% at follow-up was considered as complete recovery. If the EF remained < 35%, it was considered as no improvement. If the follow-up EF was between 35% and 50% the improvement was considered partial provided that there was > 10% positive change from baseline.

If patients had either partial or complete improvement they were included in the 'any' improvement category used for the analysis.

Statistical analysis: Statistical analysis of the data was performed using SAS version 9.3 (SAS Inc, North Carolina, USA). Chi square was used for comparisons of categorical data and Student's t-test for continuous parameters. A Cox proportional hazards model was used to assess the predictors for any improvement in EF after adjusting for significant covariates. Univariate predictors were initially obtained and if $p<0.1$, they were included in the multivariate analysis. Baseline EF was tested both as a continuous variable as well as a categorical variable (EF < 30% and > 30%) to see if it predicted recovery or mortality. Statistical significance was considered present when $p < 0.05$ in the multivariate analysis. The model fit was tested using the test for proportionality. Kaplan Meier curves for improvement in EF and mortality were constructed for the entire population.

Results:

The flowchart of cohort assembly is illustrated in figure 1. The final cohort consisted of 100 patients with a mean age of 30±6.5 years. Mean duration of follow-up was 35±21 months. African-Americans predominated in the sample (55%) with 39% Caucasians and 6% Hispanics.

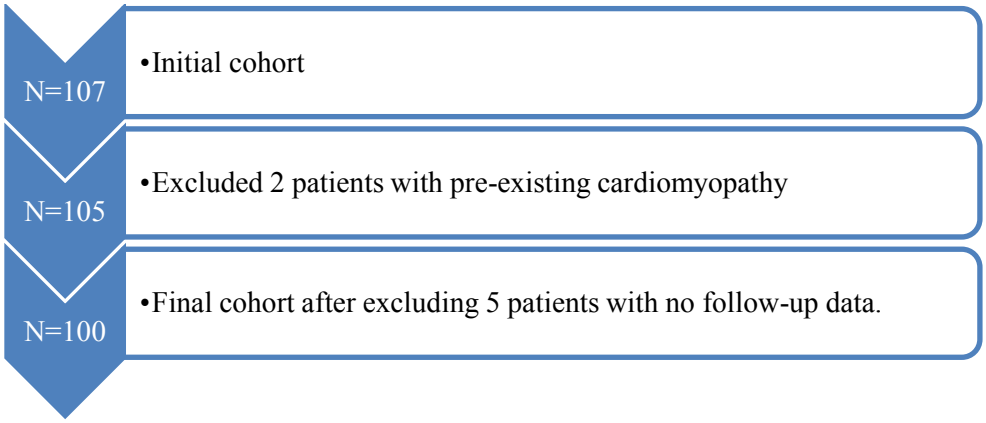

Figure 1: Flow chart of patients

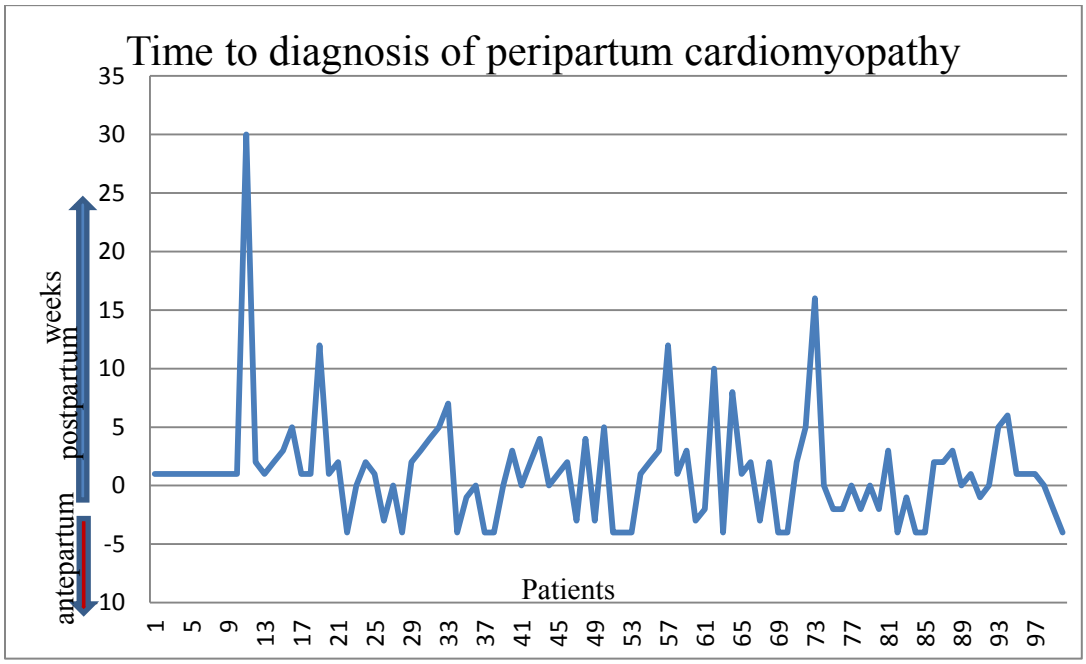

Figure 2: Time of Diagnosis (in weeks) of PPCM for each patient

Maternal and Fetal Characteristics: Preeclampsia was diagnosed in 36%; 61% were multiparous. The majority of patients were diagnosed after delivery (71%). The mean time to diagnosis of PPCM was 1.1±4 weeks. Figure 2 shows the time to diagnosis for each patient. Forty patients had preterm delivery prior to 37 weeks and tocolytic agents were used in 9. The cesarean section rate was 56%. Three women had stillbirths. The mean birth weight of the neonates was 3±0.92kg. Thirty five women had subsequent pregnancies. Mean NYHA class was 2±1.2. Thirty percent (30%) of patients were in NYHA class 1, 15% in class II, 45% in class III and 8% in class IV. There were 4 patients with QRS duration > 120ms at baseline. Among patients who did not recover LV function, one woman had a ventricular assist device implanted. Two women were listed for heart transplantation.

Table1: Baseline characteristics of all patients

Variables	Total (N=100)	Improvement (N=42)	No improvement (N=58)	p value
Age (years)	30±6.5	30±7	30±6.2	0.7
Race (%) (African-American)	55	48	65	0.09
Baseline EF (%)	28±9.9	29±9	28±10	0.9
Diabetes (%)	29	23	32	0.3
Hypertension(%)	33	35	31	0.8
Gestational hypertension(%)	33	33	32	0.9
Preeclampsia (%)	36	40	32	0.4
Hyperlipidemia (%)	9	7	10	0.6
Multiparity (%)	61	52	67	0.12
Tobacco abuse (%)	30	39	24	0.12
Alcohol (%)	11	14	8	0.3
Cesarean section (%)	56	59	54	0.46
Family history of cardiomyopathy(%)	13	14	12	0.7
Left atrium enlarged (%)	64	64	63	0.9
postpartum diagnosis (%)	71	83	62	0.02
QRS duration (ms)	85±18	83±21	86±16	0.4
Creatinine (mg/dl)	0.8±0.7	0.82±0.2	0.9±0.9	0.6
Hemoglobin (mg/dl)	10.7±1.7	10.7±1.5	10.8±1.8	0.6
Betablocker (%)	82	89	78	0.2
ACEI/ARB (%)	85	83	86	0.7

Table 2: Distribution of baseline Ejection Fraction against follow-up Ejection Fraction

Baseline Ejection Fraction	Follow-up EF <20%	Follow-up EF 20%-30%	Follow-up EF 31%-50%	Follow-up EF >50%	Percent improved (per study definition)
<20%	n=8	n=2	n=2	n=1	n=3/13 (23%)
20%-30%	n=10	n=7	n=12	n=13	n=22/42 (52%)
31%-50%	n=7	n=13	n=16	n=9	n=17/45 (38%)

LV recovery: Forty two of 100 patients (42%) had 'any' improvement in EF over a mean duration of 33±21 months. Of these patients, 23 women had complete improvement while 19 had partial recovery of LV function. Baseline characteristics of patients with and without improvement in EF are shown in table 1. The distribution of baseline EF versus follow-up EF is shown in table 2. The mean baseline EF was 28±9.9%. The mean EF at follow-up for the entire group was 34±18% during a mean follow-up duration of 35±21 months. Figure 3 demonstrates the range of improvement in EF that occurred with different baseline EFs of < 20%, 20 to 30% and >30%.

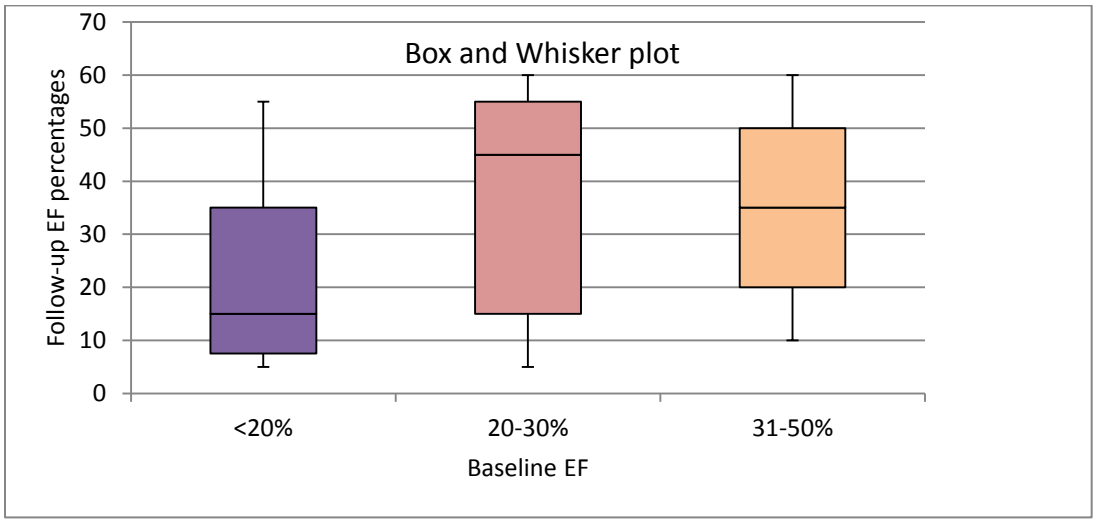

Figure 3: Box and Whisker plot of follow-up EF against baseline EF

Table 3: Multivariate predictors of LV recovery

Predictors	**Hazard Ratio**	**95% Confidence interval**	**p value**
Race (African-American vs other)	0.45	0.2-0.8	0.01
Postpartum Diagnosis	3	1.2-7	0.01
Diabetes	0.4	0.2-1	0.06

In women who had any improvement (partial and complete) in LV function, the mean baseline EF was 29±8% and the mean follow up EF was 52%±5%. The mean baseline EF in patients with complete recovery was 30 ±9% and the mean follow-up EF was 56% over a mean of 26 ±22 months. Of these, only 4 women had complete improvement within 6 months. Delayed complete recovery beyond 6 months was noted in 83% (n=19/23) of patients. The mean baseline EF in patients with partial improvement was 30±9% and the mean follow-up EF was 48% and was achieved after a mean of 40±17 months. Univariate and multivariate analysis of predictors of LV recovery (any improvement) revealed that race (Caucasians and Hispanics) and postpartum diagnosis were the predictors of LV recovery while there was a trend for no improvement in LV function in patients with diabetes (See table 3). A Kaplan-Meier curve for recovery of LV function is shown in figure 4.

Mortality: The majority of the women were treated with optimal therapy for heart failure (beta-blockers and angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARBs)). There was no difference in the use of beta-blockers and ACEI/ ARBs in patients with and without recovery of LV function (see table 1). Eleven women died (n=11) during an average follow-up of 29±29 months. Nine were in the group that did not recover. There was a trend towards higher mortality in the group that did not recover their LV function (15% vs 5%, p=0.09). Only 1 had an ICD and died from intractable heart failure. Two other women died from arrhythmic causes while the cause of death is not known in 8 other patients. A Kaplan Meier survival curve for the entire group is shown in figure 5.

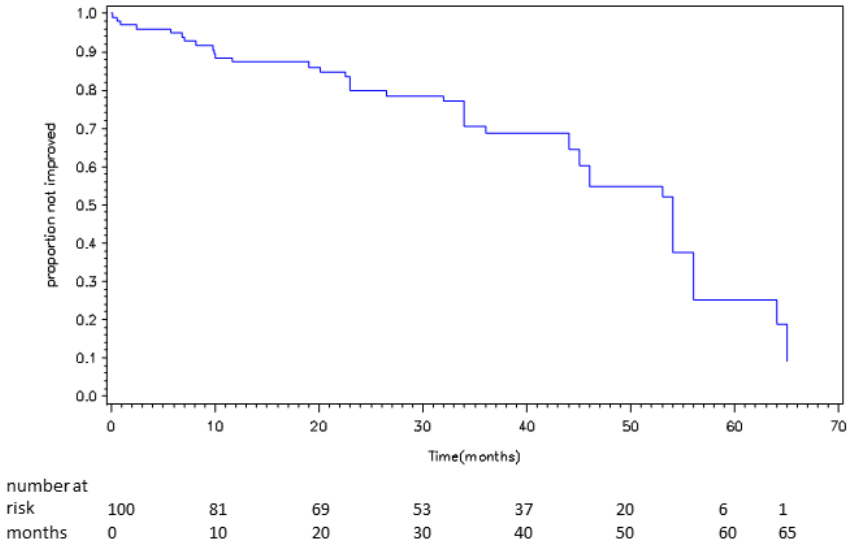

Figure 4: Kaplan-Meier curve showing proportion of patients not-improved over time.

ICD use: Thirteen women (n=13) had ICDs implanted at some point including 2 with cardiac resynchronization therapy devices (CRTD). Six women among the 41 who had complete recovery of PPCM received an ICD early in their follow-up (n=6/42, 14%) while 7 (n=7/58, 12%) patients without any EF improvement received ICDs. Fifty four of the 59 patients who did not recover had EF ≤35% and qualified for an ICD device for primary prevention of sudden cardiac death; only 7 (13%) had a device implanted. ICD implantation was for primary prevention in 12 patients and secondary prevention in 1 patient.

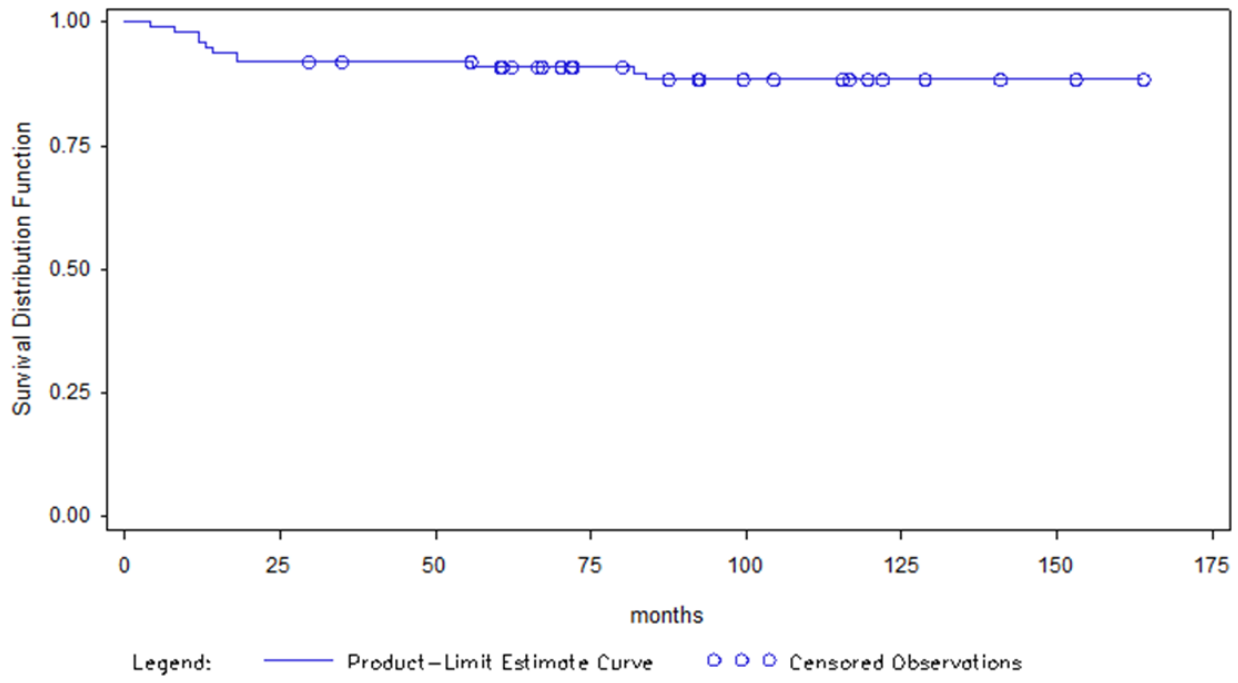

Figure 5: Kaplan –Meier survival curve for the entire population

Discussion:

We found that a substantial proportion of patients with PPCM recover LV function (42%), complete recovery occurred in 23%. Our follow-up duration was long enough to note delayed complete recovery of EF beyond 6 months in majority of the patients in both Caucasians and African-Americans (83%). This study underlines the high mortality rate (11%) in these young women. This is the one of the first studies to address ICD use and suggests their underutilization according to guidelines.

PPCM is distinct from other types of heart failure, although the symptoms resemble that of dilated cardiomyopathies. Oxidative stress, genetic susceptibility, auto-immunity and

myocarditis have all been implicated in the pathogenesis (2, 30). Complete recovery of ventricular function occurs in substantial proportion of women which is unusual in other forms of cardiomyopathy (6). Complete recovery was seen in 23% of patients in our study and partial recovery in 19%. Other studies have reported rates complete recovery rates between 20 and 60% (22-30). Factors predictive of recovery suggested in prior studies included baseline ejection fraction ≥30%, LV end diastolic diameter<5.5cm (22-26). All these studies were from single centers that involved less than 55 patients with limited follow- up and none of these studies were controlled for other covariates. The present study is one of the largest studies in the United States with clinical and echocardiographic variables that were included in the model unlike the study by Goland et al that primarily assessed echocardiographic predictors (26). A recent report of 176 South African peripartum cardiomyopathy patients followed only for 6 months concluded that older age and lower LV end systolic diameter but not the EF, predicted recovery (27). However, this may not be applicable to our population given the racial and genetic differences. We did not find age to be a predictor, but did find confirm that race and postpartum diagnosis were predictors. The differences may also be explained by our longer follow-up duration as delayed recovery of EF beyond 6 months has been reported in 3 other recent studies. (18,31,32). Biteker et al (31) noted that only 14% of Turkish women recovered their EF in the first 6 months while another 33% of women recovered beyond 6 months. Modi et al reported a median time to recovery of 54 months in African-American women in the United States (18) while Fett followed 32 PPCM patients in Haiti and found that the mean duration to LV recovery was 35 months (32). This is important to note as some have concluded that EF recovery occurs in the first 6 months and persistence of LV dysfunction beyond 6 months is a marker of worse survival (2). In the present study, complete recovery of EF within 6 months was seen in only 4 patients (17%) while

delayed recovery occurred in 83% of patients. To our knowledge our study is the first to note delayed recovery of EF in Caucasian women with PPCM. The Kaplan-Meier curve in figure 4 shows 10% non-recovery rates after 5 years. Long term follow-up of these patients is thus needed and serial clinical and echocardiographic assessments of LV function recovery should be made.

Predictors of LV recovery in our study were race and postpartum diagnosis as was previously suggested in other studies (23, 33). There are several possibilities why an antepartum diagnosis could represent a worse outcome. Early presentation could represent more severe disease. Treatment with optimal heart failure medications is limited during pregnancy at a stage when therapy is needed the most. It is also possible that these women had subclinical PPCM with a prior pregnancy that remained undiagnosed and has now progressed to become clinically manifest in the ante-partum stage of the subsequent pregnancy. There was a trend for worse outcomes in patients with diabetes. This association was not reported earlier with PPCM but is true in case of structural heart disease. Prior studies were small and few included clinical variables. With the rising incidence of diabetes in the young population, this association may have now become evident.

Therapy for heart failure consists of optimal medical management and ICD/CRTD for primary prevention of sudden cardiac death (20). More than 80% of the population in our study was on beta-blockers and ACEI/ARBs. Small studies that predated guideline driven heart failure therapy have reported higher mortality rates. Recent studies in the current era including the present study show better outcomes (10, 12, 22). Some new therapies currently under investigation are pentoxiphylline and bromocriptine (34, 35, 36). A very recent prospective study

evaluated treatment with bromocriptine and suggests potential benefit in the European population (36). Cardiac resynchronization therapy has also been shown to be effective in this population (37).

Device therapy for primary prevention of sudden cardiac death in PPCM patients is not specifically addressed in the 2008 device therapy guidelines (38). The present study suggests that devices are underutilized in this population. Another study reported that 7 of 182 patients with PPCM had ventricular arrhythmias and underwent ICD implantation in a tertiary hospital in California, 3 of the ICDs were CRTDs (39). Similarly 3 of 14 patients without improvement underwent ICD implantation in a recent prospective study in Europe (36). Reasons for underutilization of ICDs in the present study are not too clear but possible reasons include lack of specific guidelines on the use of ICDs in PPCM patients, socio-economic factors, patient compliance, access to long term follow-up care and possible follow-up by physicians other than cardiologists who are probably not very familiar with the device indications for primary prevention of sudden cardiac death.

The need and the optimal time for device implantation in women with PPCM is difficult to state since even though delayed EF recovery may occur, risk for sudden death prior to recovery remains a concern. Baseline EF was not shown to be a predictor of recovery of LV function in our study and a few others (4, 18). Although EF was a predictor of improvement in a study by Goland et al, they concluded that baseline EF would not be useful as a marker for early implantation of ICDs since it had limited sensitivity in predicting a lack of EF improvement (29). The largest epidemiological study to date of 680 PPCM patients in North Carolina reported a high mortality rate of 16% (40) in these young women. Sudden death due to ventricular

arrhythmias occurred in 38% of women while 46% died of progressive heart failure and 15% from unknown causes in a study describing complications of PPCM (39).We thus suggest that patients with PPCM should undergo ICD implantation if no improvement is detected within the first 3-6 months, especially in African- American patients who are diagnosed with the disease antepartum to prevent sudden cardiac death. Subcutaneous ICDs may have a role in this population with the added advantage of not having an endovascular system and the subsequent issues related to device extraction especially in those with clinical improvement where a continued indication for primary prevention ceases to exist (41, 42).

Limitations: This is a retrospective study with a reasonable size. We reported all-cause mortality and complete data on causes of death was not available in all patients.

Conclusions:

In our study 42% of the women with PPCM improved their LV function with delayed recovery (>6 months) noted in the majority. Caucasians/Hispanics and those diagnosed postpartum seem to have the highest recovery rates. ICDs are underutilized for primary prevention of sudden cardiac death in this population. Future studies should address the application of ICD and CRT in these women.

References:

1. Demakis JG, Rahimtoola SH, Sutton GC, Meadows WR, Szanto PB, Tobin JR, Gunnar RM. Natural course of peripartum cardiomyopathy. Circulation. 1971;44:1053-1061.
2. Pearson GD, Veille JC, Rahimtoola S, Hsia J, Oakley CM, Hosenpud JD, Ansari A, Baughman KL. Peripartum cardiomyopathy: national heart, lung and blood institute and office of rare diseases (national institutes of health) workshop recommendations and review. JAMA 2000;283:1183-1188
3. Mielniczuk LM, Williams K, Davis DR. Frequency of peripartum cardiomyopathy. Am j cardiol 2006;97:1765
4. Fett JD, Carraway RD, Dowell DL, king ME, Pierre R. Peripartum cardiomyopathy in the Hospital Albert Schweitzer District of Haiti. Am J Obstet Gynecol 2002;186:1005.
5. Sliwa K, Damasceno A, Mayosi BM. Epidemiology and etiology of cardiomyopathy in Africa. Circulation 2005;112:3577.
6. Fett JD, Christie LG, Carraway RD, Murphy JG. Five-year prospective study of the incidence and prognosis of peripartum cardiomyopathy at a single institution. Mayo Clin Proc 2005;80:1602.
7. Whitehead SJ, Berg CJ, Chang J. Pregnancy-related mortality due to cardiomyopathy: United States, 1991–97. Paediatr Perinat Epidemiol 2008;15:A36–7.
8. Witlin AG, Mabie WC, Sibai BM. Peripartum cardiomyopathy: an ominous diagnosis. Am J Obstet Gynecol 1997;176:182 -8.
9. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, Baughman KL, Kasper EK. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med 2000;342:1077-1084.

10. Lampert MB, Lang RM. Peripartum Cardiomyopathy. Am Heart J 1995;130(4):860–70.
11. Desai D, Moodley J, Naidoo D. Peripartum cardiomyopathy: experiences at King Edward VIII Hospital, Durban, South Africa and a review of the literature. Trop Doct 1995;25:118-123
12. Barr SS, Khan SS, Sandhu GK, Jorgensen MB, Parikh N, Hsu JW, Shen AY . Incidence, mortality, and racial differences in peripartum cardiomyopathy. Am J Cardiol 2007;100:302–4.
13. Cunningham FG, Pritchard JA, Hankins GD, Anderson PL, Lucas MJ, Armstrong KF. Peripartum heart failure: idiopathic cardiomyopathy or compounding cardiovascular events? Obstet Gynecol. 1986;67:157-168.
14. Ventura SJ, Peters KD, Martin JA, Maurer JD. Births and deaths: United States, 1996. Mon Vital Stat Rep. 1997;46(1 suppl 2):1-40.
15. Elkayam U, Tummala PP, Rao K, Akhter MW, Karaalp IS, Wani OR, Hameed A, Gviazda I, Shotan A. Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. N Engl J Med 2001;344: 1567–71.
16. Sliwa K, Forster O, Libhaber E, Fett JD, Sundstrom JB, Hilfiker-Kleiner D, Ansari AA. Peripartum cardiomyopathy: inflammatory markers as predictors of outcome in 100 prospectively studied patients. Eur Heart J 2006; 27:441-446.
17. Costanzo-Nordin MR, Subramanian R, Robinson JA, Wallis DE, Scanlon PJ, Gunnar RM. Peripartum cardiomyopathy: clinical, O'Connell JB hemodynamic, histologic and prognostic characteristics. J Am Coll Cardiol 1986;8:52-6

18. Modi KA, Illum S, Jariatul K, Caldito G, Reddy PC. Poor outcome of indigent patients with peripartum cardiomyopathy in the United States. Am J Obstet Gynecol. 2009;201(2):171.

19. Sutton MS, Cole P, Plappert M, Saltzman D, Goldhaber S. Effects of subsequent pregnancy on left ventricular function in peripartum cardiomyopathy. AmHeart J. 1991;121:1776-1778

20. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Developed in Collaboration With the International Society for Heart and Lung Transplantation. Circulation. 2009;119:1977-2016

21. Chee KH. Favourable outcome after peripartum cardiomyopathy: a ten-year study on peripartum cardiomyopathy in a university hospital. Singapore Med J. 2013 Jan;54(1):28-31

22. Amos AM, Jaber WA, Russell SD. Improved outcomes in peripartum cardiomyopathy with contemporary. Am Heart J. 2006;152(3):509-13

23. Safirstein JG, Ro AS, Grandhi S, Wang L, Fett JD, Staniloae C. Predictors of left ventricular recovery in a cohort of peripartum cardiomyopathy patients recruited via the internet. Int J Cardiol. 2012;154(1):27-31

24. Duran N, Günes H, Duran I, Biteker M, Ozkan M. Predictors of prognosis in patients with peripartum cardiomyopathy. Int J Gynaecol Obstet. 2008;101(2):137-40.

25. Elkayam U, Akhter MW, Singh H, Khan S, Bitar F, Hameed A, Shotan A. Pregnancy-associated cardiomyopathy: clinical characteristics and a comparison between early and late presentation. Circulation. 2005;111(16):2050-5

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

27. Blauwet LA, Libhaber E, Forster O, Tibazarwa K, Mebazaa A, Hilfiker-Kleiner D, Sliwa K. Predictors of outcome in 176 South African patients with peripartum cardiomyopathy. Heart. 2013;99(5):308-13.

28. Horgan SJ, Margey R, Brennan DJ, O'Herlihy C, Mahon NG. Natural history, management, and outcomes of peripartum cardiomyopathy: an Irish single-center cohort study. J Matern Fetal Neonatal Med. 2013;26(2):161-5

29. Goland S, Bitar F, Modi K, Safirstein J, Ro A, Mirocha J, Khatri N, Elkayam U. 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 Card Fail. 2011;17(5):426-30.

30. Sliwa K, Hilfiker-Kleiner D, Pieske B, Mebazaa A, Pieske B, Buchmann E, Regitz-Zagrosek V, Schaufelberger M, Tavazzi L, van Veldhuisen DJ, Watkins H, Shah AJ, Seferovic PM, Elkayam U, Pankuweit S, Papp Z, Mouquet F, McMurray JJ. 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;12:767.

31. Biteker M, Ilhan E, Biteker G, Duman D, Bozkurt B. Delayed recovery in peripartum cardiomyopathy: an indication for long-term follow-up and sustained therapy. Eur J Heart Fail. 2012;14(8):895-901
32. Fett JD, Sannon H, Thélisma E, Sprunger T, Suresh V . Recovery from severe heart failure following peripartum cardiomyopathy. Int J Gynaecol Obstet. 2009;104(2):125-7
33. Goland S, Modi K, Hatamizadeh P, Elkayam U. Differences in clinical profile of African-American women with peripartum cardiomyopathy in the United States. J Card Fail. 2013;19(4):214-8
34. Sliwa K, Skudicky D, Candy G, Bergmann A, Hopley M, Sareli P. The addition of Pentoxiphylline to conventional therapy improves outcome in patients with peripartum cardiomyopathy. Eur J Heart Fail 2002;4: 305.
35. Sliwa K, Blauwet L, Tibazarwa K, Libhaber E, Smedema JP, Becker A, McMurray J, Yamac H, Labidi S, Struman I, Hilfiker-Kleiner D. Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy. A proof of concept pilot study. Circulation 2010;121:1465.
36. Haghikia A, Podewski E, Libhaber E, Labidi S, Fischer D, Roentgen P, Tsikas D, Jordan J, Lichtinghagen R, von Kaisenberg CS, Struman I, Bovy N, Sliwa K, Bauersachs J, Hilfiker-Kleiner D. Phenotyping and outcome on contemporary management in a German cohort of patients with peripartum cardiomyopathy. Basic Res Cardiol. 2013;108(4):366
37. Mouquet F, Mostefa Kara M, Lamblin N, Coulon C, Langlois S, Marquie C, de Groote P. Unexpected and rapid recovery of left ventricular function in patients with peripartum

cardiomyopathy: impact of cardiac resynchronization therapy. Eur J Heart Fail. 2012;14(5):526-9

38. Epstein AE, Dimarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO. ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities. American College of Cardiology; American Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; Society of Thoracic Surgeons. Heart Rhythm. 2008;5(6):e1-62
39. Goland S, Modi K, Bitar F, Janmohamed M, Mirocha JM, Czer LS, Illum S, Hatamizadeh P, Elkayam U. Clinical profile and predictors of complications in peripartum cardiomyopathy. J Card Fail. 2009 Oct;15 (8):645-50.
40. Harper MA, Meyer RE, Berg CJ. Peripartum cardiomyopathy: population-based birth prevalence and 7-year mortality. Obstet Gynecol. 2012;120(5):1013-9.
41. Cappato R, Smith WM, Hood MA, Crozier IG, Jordaens L, Spitzer SG, Ardashev AV, Boersma L, Lupo P, Grace AA, Bardy GH. Subcutaneous chronic implantable defibrillation systems in humans. J Interv Card Electrophysiol. 2012 Sep;34(3):325-32
42. de Bie MK, Thijssen J, van Rees JB, Putter H, van der Velde ET, Schalij MJ, van Erven L. Suitability for subcutaneous defibrillator implantation: results based on data from routine clinical practice. Heart. 2013;99(14):1018-23