LEFT VENTRICULAR FUNCTION AND CLINICAL OUTCOME OF TANZANIANS WITH PERIPARTUM CARDIOMYOPATHY

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Abstract

Background: Peripartum cardiomyopathies are endemic in Sub-Sahara Africa, causing a high morbidity and mortality. The effect of the recent introduction of Angiotensin converting enzyme inhibitors [ACEI] and beta-adrenergic blockers in the treatment of heart failure is not well known in patients with peripartum cardiomyopathy in our set up.

Objective: To determine the left ventricular function and clinical outcome of patients with peripartum cardiomyopathy after treating them with ACEI ,beta-adrenergic blockers and diuretics.

Study Design: A descriptive prospective hospital based study

Study Setting: Hindu Mandal Hospital in Dar es Salaam ,Tanzania

Main OutCome Measures: Echocardiographic features useful in assessing patients with peripartum cardiomyopathy; clinical outcome as well as mortality after treatment with the current therapy of heart failure

Subjects: Sixty four consecutive patients with provisional diagnosis of peripartum cardiomyopathy who were referred to a cardiac clinic at Hindu Mandal Hospital.

Interventions: A detailed past and present medical history, clinical examination as well as echocardiographic evaluation were performed. After initiating treatment, patients were followed up for twelve months.

Results: Using echocardiography the left ventricular end-diastolic diameter at baseline was 65 ± 6mm (range 55 to 78 mm) and the left ventricular fractional shortening was 17. 0 ± 5.0% (range 7.0-31.0%). At 12 months ejection fraction improved from 30 ± 12 to 45 ± 15% (p=0.0001). Five types of outcome were observed after taking the current medical treatment for heart failure for one year :(a) Complete remission in 35 (54.7%) patients (b) Incomplete remission in 13 (20.3%) patients (c)Absence of remission in 4 (6.3%) patients (d) Lost during follow up in 7 (10.9%) patients and (e) Death in 5 (7.8%) patients. An initial ejection fraction below 30% and left ventricular end-diastolic dimension 6.0cm or greater, at the time of diagnosis were associated with more than 2 fold increased risk of incomplete/absence of remission when compared with those who had complete remission.

Conclusion: The addition of ACE inhibitors and B-adrenergic blockers to the therapy of peripartum cardiomyopathy led to a better clinical outcome compared with earlier reports. Left ventricular echocardiographic parameters provide significant prognostic information regarding recovery of cardiac function in patients with peripartum cardiomyopathy.

Key words: Left ventricular function, Per partum Cardiomyopathy

Introduction

Peripartum cardiomyopathy (PPCM) is a dilated cardiomyopathy in which left ventricular dysfunction and symptoms of heart failure occur between the last trimester of pregnancy and up to the first six months postpartum. Despite its original description in the medical literature during the nineteenth century by Ritchie and Virchow, the aetiology of peripartum cardiomyopathy remains unknown[1] Estimates of incidence range from 1:300 live births in Haiti to 1:15,000 in USA [2,3]. In Africa, it ranges from 1:100 live births in Zaria, Nigeria to 1:1,000 live births in Durban, South Africa[4,5]. The mortality rate of peripartum cardiomyopathy has historically been 25—50%, a rate that may still persist at some centers, with nearly one half of all related deaths occurring within the first 3 months after delivery[6]. These data of high mortality are derived from studies that included a small number of patients and in many of them there was no echocardiographic data [6].

Echocardiography is now the standard non-invasive tool for measuring cardiac function, quantifying left ventricular performance and providing a definitive diagnosis of left ventricular dysfunction. With the recent introduction of angiotensin converting enzyme (ACE) inhibitors and beta-adrenergic blocking drugs in the routine treatment of heart failure, the outcome of these patients is not well documented.

There has been no reported series of peripartum cardiomyopathy (PPCM) in the Tanzanian population. We have undertaken the current work to: (a) Study the clinical profile of peripartum cardiomyopathy as seen in our patient population in Dar es Salaam, Tanzania (b) Evaluate the left ventricular function and the clinical outcome of patients with peripartum Cadiomyopathy on current treatment of heart failure.

Methodology

Between January 2000 and December 2004, sixty four consecutive patients were referred to our cardiac clinic with a provisional diagnosis of peripartum cardiomyopathy for further evaluation. These patients who had already delivered were recruited from Hindu Mandal Hospital, which is one of the big private hospitals in Dar-es-Salaam, situated at the centre of the city. Informed consent was obtained from the patients. Demographic data, including age, race and parity were recorded as well as information on timing of presentation in relation to gestation, presenting symptoms, signs and risk factors. Some of the information was obtained from their antenatal clinic cards. The study population fulfilled the following inclusion criteria**:**

a) Age ≥ 15 years
b) Symptoms of congestive heart failure [New York Heart Association {NYHA} functional class 11—1V] that developed in the last trimester of pregnancy or in the first six months postpartum
c) Roentgenographic cardiomegaly (cardiothoracic ration > 0.50)
d) No other identifiable cause of heart failure and no demonstrable cardiac disease in the last three months of pregnancy.
e) Eligible patients in whom good quality echocardiographic images could be obtained.

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Exclusion criteria were

(a) Severe anaemia [Hb < 8.0 g/dl
(b) Coronary heart disease
(c) Significant organic valvular heart disease
(d) Systemic hypertension
(e) Cor-pulmonale
(f) Congenital heart disease
(g) Systemic diseases including HIV infection, diabetes mellitus and alcoholism.

In all patients, the following baseline evaluations were performed at entry into the study: history, physical examination, chest x-ray, electrocardiogram, full blood picture, blood biochemistry, HIV test and echocardiography.

All patients received treatment with frusemide, digoxin and captopril or enalapril. Carvedilol or metoprolol was added after resolution of overt heart failure and the dose was slowly titrated up as tolerated. Patients with an ejection fraction $\leq$ 25% or left ventricular thrombus received anticoagulation therapy.

Echocardiographic Studies

Two-dimensional targeted M-Mode echocardiography with Doppler colour flow mapping was performed using a Hewlett – Packard Sonos 1000 echocardiography attached to a 2.5 or 3.5 Mhz transducer. All studies were recorded on videotape and were done by the same operator. Left ventricular dimensions were measured according to the American Society of Echocardiography guidelines.[7] For left ventricular measurements, an average of $\geq$ 3 beats were obtained. Diastolic mitral flow was assessed by pulsed-wave Doppler echocardiography from the apical four-chamber view. The E-wave deceleration time was measured as the interval between the peak early diastolic velocity and the point at which the steepest deceleration slope was extrapolated to the zero line. A diastolic restrictive pattern was defined, if the trans-mitral E/A ratio was $\geq$ 2 or if it was 1 to 2 with an E-wave deceleration time $\leq$ 140 ms. Patients were defined as improvers if they fulfilled both of the following criteria at the end of the study:

(1) Left ventricular ejection fraction $\geq$ 30% .
(2) A relative increment in ejection fraction $\geq$ 20% from baseline.

All patients underwent an echocardiogram at the entry of the study and at follow up.

Follow up

Follow up was done at two monthly intervals in our cardiac clinic. Patients were however seen at shorter intervals where indicated. Counselling on compliance with medications and clinic appointment was given. The end points of the study were: Completed 12 calendar months of follow up. Death or lost to follow-up.

Statistical Analysis

Data was analysed using EPI info version 6 software. Students t-test was used for numerical variables and chi-square test was applied for the categorical variables. Significance was assumed at a two-tailed value $p<0.05$.

Results

The study included 64 consecutive patients with peripartum cardiomyopathy. They had no cardiovascular antecedent or any pathology which could explain the heart failure. Antenatal records of 53 of the 64 study patients were available for analysis. In the remaining patients, there was no antenatal records and from the medical history, it appeared that none of these patients had family history or symptoms to suggest either hypertension or cardiac failure. Majority of the patients (75%) had poor socio-economic background and their age was between 17 to 44 years (mean 31$\pm$8 years]. Their parity in the index pregnancy ranged 1 to 8 (mean 3.2 $\pm$ 1.4). The mode of delivery was 89.1% vaginal and 10.9% by caesarean. In each case, the clinical picture was the same: idiopathic congestive heart failure occurred between the 2nd and 20th week postpartum; 48 (75%) patients within 12 weeks after delivery and 16 (25%) patients between 13 and 20 weeks after delivery. At baseline 23 (35.9%) patients were in NYHA FCII, 33 (51.6%) in FCIII and 8 (12.5%) in FC IV (See table 1). Functional mitral and tricuspid incompetence were detected in all patients.

All patients received furosemide (mean dose 100 $\pm$ 20mg), digitalis 0.25mg daily captopril 25mg twice a day or enalapril 10 mg daily. The mean dose of carvedilol was 12.5 $\pm$ 6.25mg and for metoprolol 50 $\pm$ 25mg daily.

The echocardiographic studies at baseline revealed a dilated and poorly contracting heart; left ventricular –end-diastolic diameter 65 $\pm$ 6mm (range 55 to 78mm); left ventricular fractional shortening 17.0 $\pm$ 5.0% (range 7.0 to 31.0%). The left ventricular ejection fraction improved from 30 $\pm$ 12% to 45 $\pm$ 15% at one year (p=0.0001). An increment of 10 or more units of ejection fraction occurred in 23 (35.9%) patients (26 $\pm$ 8% to 53 $\pm$ 4%, p=0.001). Normalization of the left ventricular ejection fraction (> 50%) was observed in 54.7% of the patients. This occurred mostly within the first six months and was more likely in older patients (> 30 years) and those with LVEF > 30% at diagnosis. A diastolic restrictive pattern was present in 56 (87.5%) patients at baseline. From the 52 patients who completed the study 40 (76.9%) patients had a restrictive pattern at baseline, but only 12 (23,1%) patients after one year of treatment. Left ventricular thrombi were detected on echocardiography in 7 patients.
Five types of outcome were observed after a 12 months follow-up of the 64 patients:

(a) Complete remission (clinical and echocardiography) in 35 (54.7%) patients.
(b) Incomplete remission, defined by the cardiomegaly and/or echocardiographically left ventricular dilatation observed in 13 (20.3%) patients
(c) Absence of remission, defined by relapse of clinical signs of heart failure occurred in 4 (6.3) patients

(d) Lost to follow-up or moved to another district 7 (10.9%) patients and
(e) Death in 5 (7.8%) patients.

Table 1: Baseline characteristics of Peripartum Cardiomyopathy patients (n=64)

Age (yrs) (range)	**31 ± 8 (17--44)**
Party (range)	3.2 ± 1.4 (1---8)
Duration of symptoms of CHF (months)	2.4 ± 1.6
NYHA functional class (n,%):	
II	23 (35.9)
III	33 (51,6)
IV	8 (12.5)
Blood Pressure (mmHg: SystolicDiastolic	111 ± 17
	70 ± 14
Heart rate (beats/min)	94 ± 18
Chest X-ray findings	
Cardiothoracic ratio	0.57 + 0.10
Pulmonary Congestion (n.%)	31 (48.4%)
ECG Findings: (n,%)	
Atrio - Ventricular (AV) Block	8 (12.5%)
Left bundle branch block (LBBB)	15 (23.4%)
Right bundle branch block (RBBB)	4 (6.3%)
Atrial fibrillation (AF)	14 (21.9%)
ST-Twave abnormalities	40 (62.52%)
Left ventricular hypertrophy (LVH)	18 (28.12%)
Sinus tachycardia (100 beats/min)	31 (48.4%)
Echocardiographic data:	
Left atrial diameter (range) (mm)	44 ± 12 (32-61)
Left ventricular end-diastolic diameter (mm) range)	65 ± 6 (55.78)
Left ventricular end-systolic diameter (mm) (range)	53 ± 11 (40-68)
LV ejection fraction (%) (range)	30 ± 12(15-39)
Left ventricular fractional shortening (%) (range)	17 ± 5 (7-31)
Deceleration time (ms)	108 ± 24
E-wave	70 ± 26
A-wave	42 ± 16
E/A ratio	1.2 ± 0.9
Restrictive mitral pattern (%)	56 (87.5%)
Left Ventricular thrombus (n,%)	7 (10.9)

NYHA =New York Heart Association

Deaths were attributed to progressive failure in 2 patients; pulmonary emboli in 2 patients and indeterminate cause in 1 patient. Four of the 5 deaths occurred during the first six months after the onset of symptoms [none of them was on anticoagulant]. Left ventricular ejection fraction and left ventricular-end diastolic dimension were significantly different between the group that had complete remission and the group with incomplete and absence of remission. An initial ejection fraction below a threshold of 30% at the time of diagnosis was associated with a 2 fold increased risk of incomplete/absence of remission at follow up. Furthermore, a left ventricular end diastolic dimension of 6.0 cm or greater at the time of initial diagnosis was associated with more than 3 times increased risk of incomplete/ absence of remission compared with those who had complete remission [Table 3].

Table 2: Clinical variables, left ventricular dimensions and functional class from the 52 patients who completed the 12 months study.

		Baseline	**12 months**	**P/Value**
NYHA functional class (n%):	**1**	**0 (0)**	**33 (63.7%)**	**0.0006**
II		**23 (35.9)**	**16 (30.8%)**	**0.24**
III		**33 (51.6)**	**3 (5.8)**	**0.005**
IV		**8 (12.5)**	**0 (0)**	**0.03**
Blood pressure (mmHg): Systolic		**111 ± 17**	**104 ± 19**	**0.65**
Diastolic		**70 ± 14**	**65 ± 9**	**0.14**
Heart rate(beats min)		**94 ± 18**	**76 ± 12**	**0.006**
Echocardiographic data:				
Left atrial diameter (mm) (range		**44 ± 12**	**32± 8**	**0.30**
Left ventricular end-diastolic diameter (mm)		**65 ± 6**	**54 ± 8**	**0.001**
Left ventricular end-systolic diameter (mm)		**53 ± 11**	**40 ± 10**	**0.051**
Left ventricular ejection fraction (%)		**30 ± 12**	**45 ± 15**	**0.0001**
Left Ventricular fractional shortening (%)		**17 ± 5**	**32 ± 7**	**0.0003**
Deceleration time (ms)		**108 ± 24**	**175 ± 56**	**0.0002**

Data are presented as n[%] or mean ± SD, Abbreviations as in Table 1

Table 3 Risk for Incomplete/Absence of Remission Based on Echocardiographic Parameters at Time of Initial Diagnosis

	Relative Risk	**95% Confidence Interval**	**P value**
Ejection Fraction < 30%	**2.05**	**1.25---6.14**	**0.004**
Left Ventricular end-diastolic Dimension > 6.0cm.	**3.15**	**1.09----11.02**	**0.01**

Discussion

Peripartum cardiomyopathy (PPCM) is an uncommon, but sometimes fatal form of heart failure, whose aetiology remains obscure. Known risk factors related to this disease are multiparty, twin pregnancy, poverty black race and advanced age (older than 30 years) at conception[8]. Our study population confirms that peripartum cardiomyopathy occurs in older women, of poor socio-economic status but not of high parity. The mean parity of our patients was 3.2 ± 1.4. In another study, Connell reported that 57% of their patients were primiparous.[9] Twin pregnancies have been reported in 7-10% of published cases of peripartum cardiomyopathy.[1] Twin pregnancies were present in only 4 (6.3%) patients in our study and neither had hypertension in the antenatal period.

The pharmacological therapy for heart failure has evolved tremendously and is now based on sound therapeutic principles that include afterload reduction and increasing myocardial contractility. This can be attained effectively during gestation with fluid restriction, judicious use of diuretics, digoxin and a careful use of a potent vasodilator such as hydralazine. Angiotensin-converting enzyme [ACE] inhibitors and some beta-adrenergic blockers are also an excellent choice in the postpartum setting for afterload reduction, but these drugs can lead to embryopathy when used during pregnancy.[10] In our study, patients were analysed during postpartum period and the mortality rate was lower than that documented by other investigators.[6,11] Unlike previously published data, in this study, there was a higher [54%] percentage of patients who showed a remarkable improvement in left

ventricular function that could be attributed to the treatment with ACE inhibitors and beta-adrenergic blockers.[12] Ejection fraction increased from 30+-12% at baseline to 45±!5% after twelve months (=0.0001).

In this study, we have confirmed what other previously published data have shown, that the specific parameters of ejection fraction and left ventricular end-diastolic dimension at the time of diagnosis are predictive of the degree of recovery of cardiac function at follow up.[13,14] Those patients with an ejection fraction less than 30% or left ventricular end-diastolic diameter of 6.0 cm or greater on initial echocardiogram incurred more than a 2 times increased risk of not fully recovering their left ventricular function.

The reported incidence of thromboembolic complications in peripartum cardiomypathy is approximately 25%. Some authors believe that thromboembolism occurs more commonly in peripartum cardiomyopathy than any other cardiomyopathy unrelated to pregnancy.[15] In our study 7(10.9%) patients had left ventricular thrombus and 2 patients presented with severe massive haemoptysis due to pulmonary embolism. Previously, anticoagulant therapy was recommended in all patients with peripartum cardiomyopathy until the return of normal cardiac function as judged by imaging techniques.[5] Currently the only clear indications for anticoagulation in most patients with dilated cardiomyopathy including peripartum cardiomyopathy are: atrial fibrillation, a previous thromboembolic event or left ventricular thrombus and left ventricular ejection fraction less than 25%. Analysis of the SAVE database showed that low dose asprin may be quite useful in preventing thromboembolic and may be much less risky than warfarin.[16]

Conclusion

Echocardiography is valuable in diagnosing and following the course of peripartum cardiomyopathy. Specific echocardiographic parameters, including ejection fraction and left ventricular end-diastolic dimension at the time of diagnosis, may be predictive of long term cardiac dysfunction. The addition of ACE inhibitors and beta-adrenergic blockers to the therapy of peripartum cardiomayopathy, reduces the morbidity and mortality. Most of our patients who were alive one year after the initiation of therapy had improved left ventricular function significantly.

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