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A study of clinical and investigative profile of peripartum cardiomyopathy

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Abstract
Introduction: Peripartum Cardiomyopathy is a rare distinct type of cardiomyopathy presenting in women in their late trimester of pregnancy and early puerperium. It is characterized by rapid onset of heart failure with propensity for spontaneous recovery but is associated with higher morbidities and mortalities if not diagnosed and treated promptly. Despite adequate literature available regarding its etiology, pathophysiology, clinical profile, treatment options and prognosis, scarce data is available regarding its clinical spectrum and outcome of patients in India. This study shall emphasize on various epidemiological, clinical and investigative parameters of peripartum cardiomyopathy that aids in the early diagnosis and treatment of patients with PPCM.
Aim: To study the clinical and investigative profile of patients with PPCM with reference to Echocardiography, BNP and Prolactin levels and its correlation with clinical features and future outcomes.
Materials and Methods: This was an observational longitudinal study conducted in patients visiting the indoor or outdoor sections of medicine or obstetrics and gynecology department of SSG hospital, Vadodara. A total of 30 patients of PPCM in study duration of 18 months who fulfilled the inclusion criteria were subjected to standardized interview. Complete medical and obstetric histories along with general and systemic examination was done. They were subjected for various laboratory and radiological investigations at presentations and repeated as required with follow up for 2D-Echo and Doppler examination. All data were analyzed using appropriate statistical tests by using MedCalc version 12.5 and a p value < 0.05 is to be considered statistically significant.
Results: Mean prolactin level was 78.72ng/ml and mean N-Pro-BNP level was 7920.4pg/ml. Mean Ejection fraction and Fractional Shortening were 29.6+ 8.3% and 16+4.9%. Patients who had higher Prolactin levels, higher N-Pro-BNP levels, high LVEDD, high LVESD, significant pulmonary hypertension, low EF and low FS at baseline have poor long-term prognosis.
Conclusion: Symptoms improved over time in significant number of patients which is corroborated by improvement of LV function seen by echocardiography thus ensuring PPCM as a form of reversible cardiomyopathy. Baseline echocardiographic parameters, Serum Prolactin and N-Pro-BNP were correlated with long term prognosis and as a marker of risk stratification of patients with PPCM.

Keywords: NT-proBNP, peripartum cardiomyopathy, pregnancy, prolactin

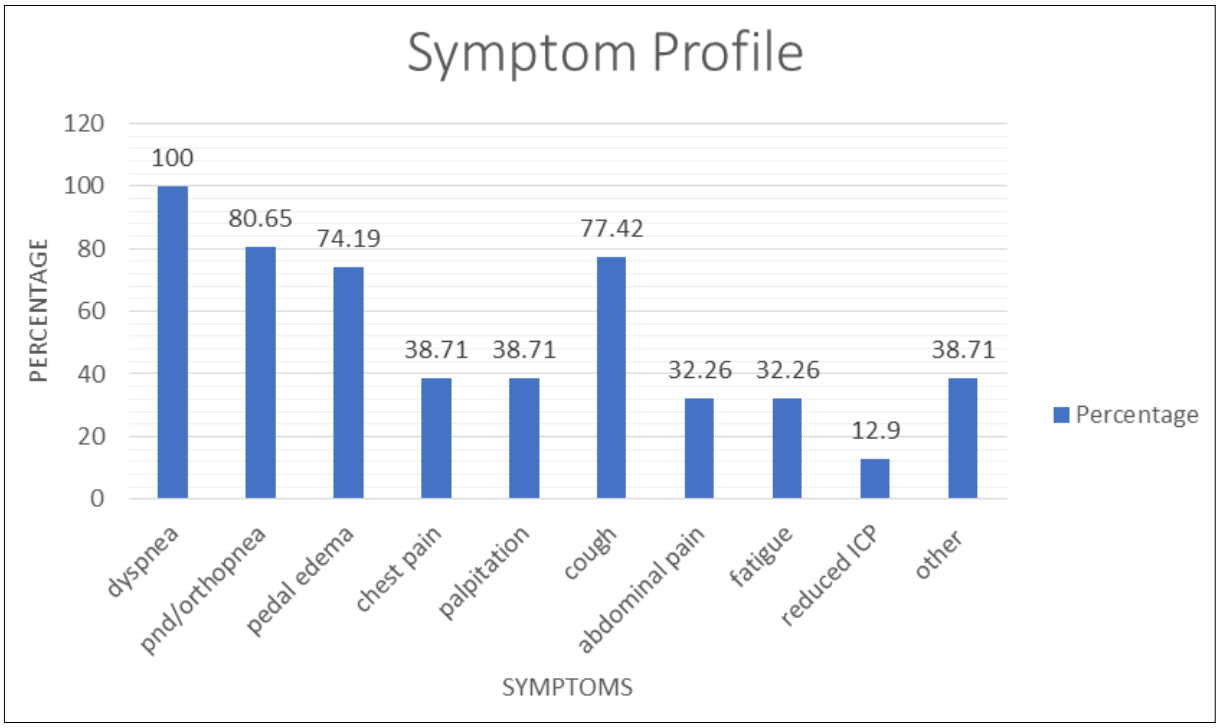
Introduction

Peripartum cardiomyopathy is an uncommon idiopathic form of specific cardiomyopathy that affects women in their last trimester of pregnancy or within first five months after delivery. Its occurrence is highest in African Americans with an incidence rate of one case per 102 live births in Nigeria to 1 in 350 live births in Haiti [1].

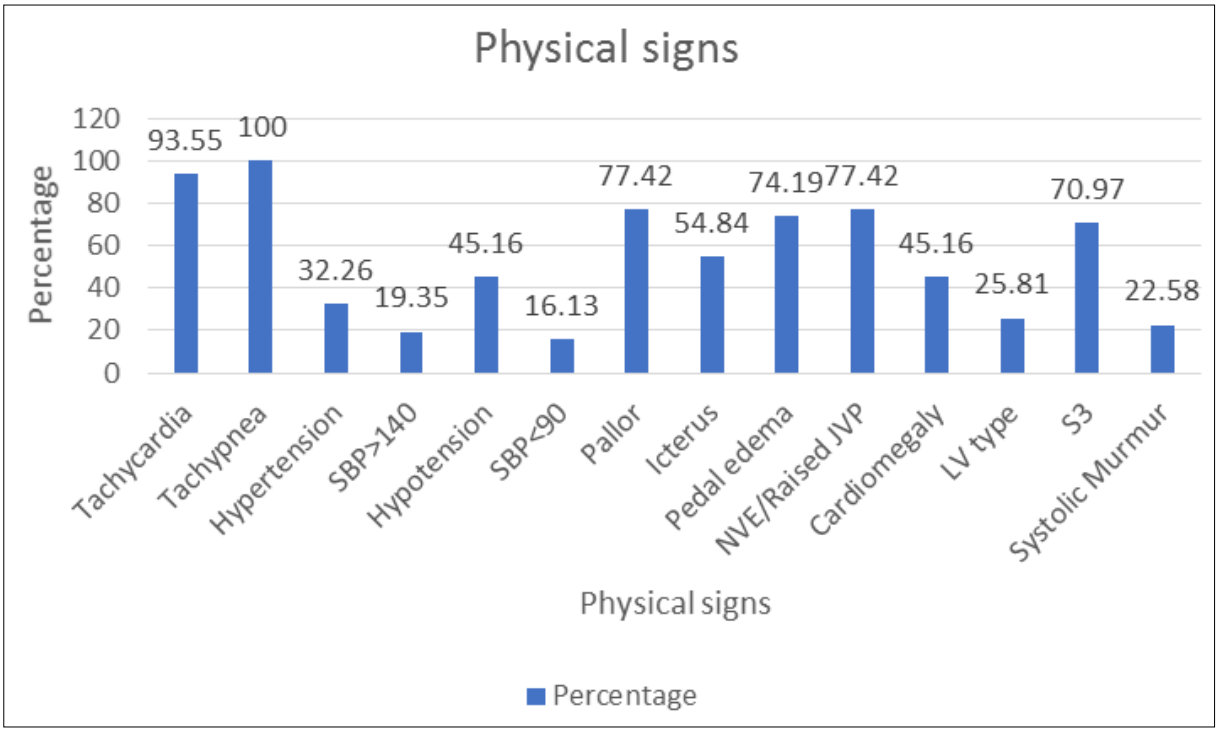
Patients usually presents with signs and symptoms of left ventricular failure like fatigue, dyspnoea, orthopnoea, cough, pedal oedema, chest pain and recent weight gain. The diagnostic criteria as described by the European Society of Cardiology states PPCM as development of heart failure towards the end of pregnancy or in postpartum period with absence of other identifiable cause of heart failure and presence of left ventricular systolic impairment with an ejection fraction (EF)< 45% and fractional shortening <30%. It is not imperative for the left ventricle to be found dilated in every case of PPCM. The diagnostic workup includes clinical exam of the patient where constant sinus tachycardia, basal pulmonary crackles and elevated jugular venous pressure if present are considered abnormal for pregnancy state. Other investigations include complete blood count and biochemical parameters, cardiac biomarkers, electrocardiogram, chest X-ray, echocardiography, and rarely cardiac MRI.

The traditional risk factors identified to the development of PPCM are included in figure 1 (2) (3). Experimental data in a mouse model of PPCM suggests that a defect in neutralising the oxidants in the body can cause vasculotoxic injury playing an integral role in the pathogenesis of PPCM. (4) Additionally this model showed, prolactin which peaked during the third trimester of pregnancy is cleaved into pro-apoptotic and antiangiogenic forms by a cardiac oxidant cathepsin, producing PPCM which is easily reversed by a prolactin inhibitor

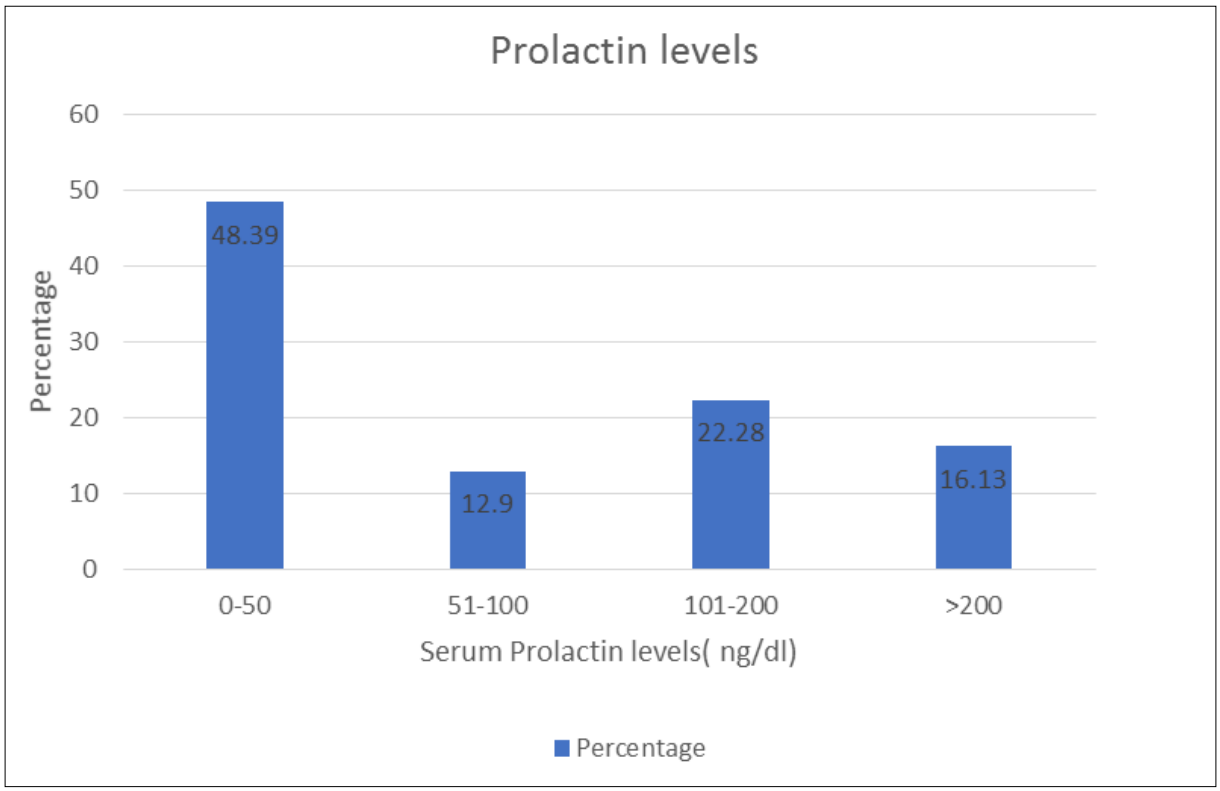
bromocriptine. (5) The natural clinical course of the disease is highly variable with some forms rapidly progressing to end-stage heart failure alternating with resolution of the symptoms and spontaneous recovery of cardiac function being relatively a more common form. Intracardiac thrombus particularly in patients with low ejection fraction can potentially embolize resulting in stroke, acute myocardial infarction, mesenteric infarction, lower extremity ischemia and pulmonary embolism. Ventricular arrhythmias at times leading to sudden cardiac death have been reported in up to 20% of patients with PPCM with latter occurring during both the acute and chronic stage. (6) Medical treatment of peripartum cardiomyopathy is similar to treatment of congestive heart failure with special concern regarding the safety profile during pregnant state. Immunosuppressive therapy can be considered for women with myocarditis. With scarce literature available regarding peripartum cardiomyopathy in India, the main goal of this study is to expand the existing data regarding clinical spectrum and outcome of patients with PPCM and fill in the voids of inconsistency of knowledge by assessing the role of prolactin and BNP as markers for prognosis of the disease.



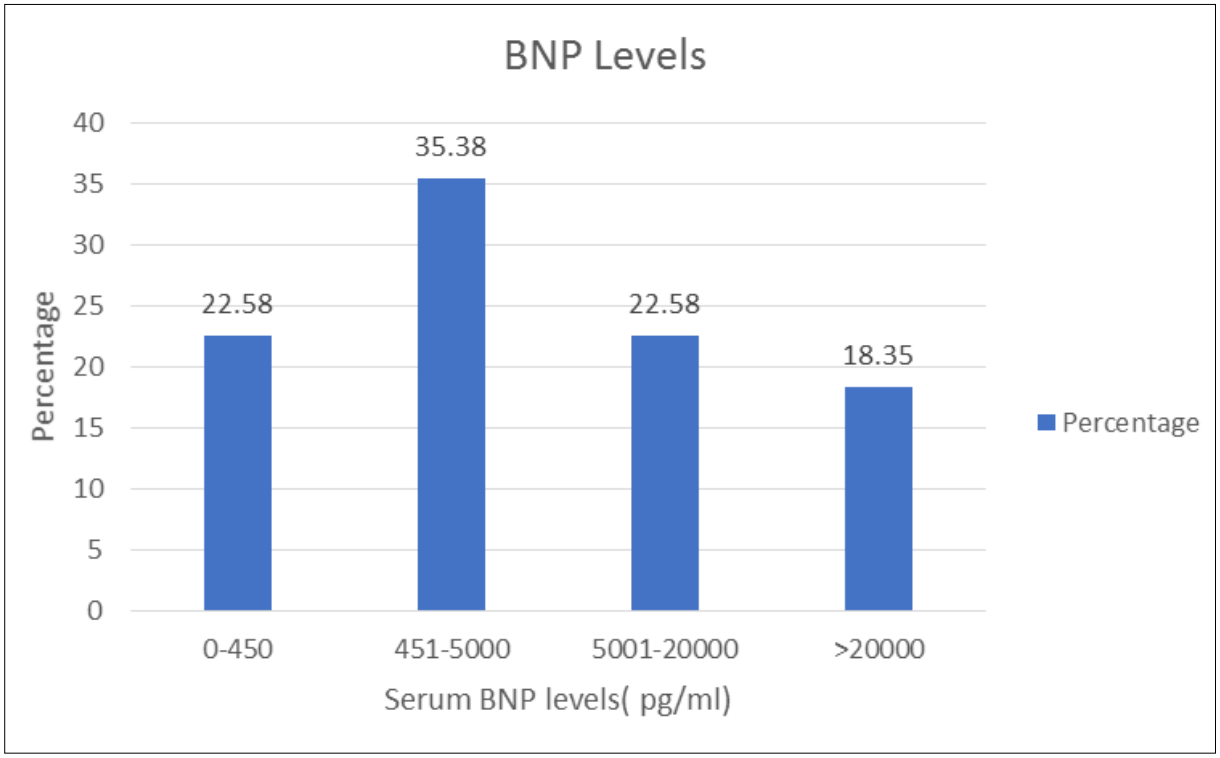
Graph I: symptom profile of patients with peripartum cardiomyopathy



Graph II: Physical Signs profile of patients with peripartum cardiomyopathy



Graph IIII: Serum prolactin levels of patients with peripartum cardiomyopathy



Graph IV: Serum BNP levels of patients with peripartum cardiomyopathy.

Materials and Methods

This is an observational longitudinal study conducted in the patients who came to Indoor or Outdoor sections of Medicine or Obstetrics and Gynaecology department of SSG hospital, Vadodara who had signs and symptoms of heart failure in the last trimester of pregnancy or within first five months post-partum. After obtaining consent from the ethics committee of SSG hospital, the study was conducted.

As PPCM is rare and there is little data available regarding incidence of PPCM in India, it was not possible to estimate an exact sample size and hence sample size was decided on the basis of achievability.

According to past medical data in Medicine department, SSG hospital there were approximately 10 patients of PPCM diagnosed during 6-8 months prior to beginning of the study. Hence, we were expecting around 30 patients of PPCM in study duration of about 18 months.

Inclusion Criteria

- Development of cardiac failure in the last trimester of Pregnancy or within 5 months after delivery.
- Absence of other demonstrable cause for the cardiac failure.
- Absence of a demonstrable heart disease before the last trimester of pregnancy.
- Documented systolic dysfunction by echocardiography with Ejection fraction of < 45%, fractional shortening of <30% or both and end diastolic dimension of >2.7cm/m2 body surface area.

Exclusion Criteria

- Pre-existing Structural or Functional heart disease.
- Patient having dilated cardiomyopathy due to Ischemic, Hypertensive, Valvular heart disease, and other causes of dilated cardiomyopathy like nutritional, metabolic, endocrinal, autoimmune, toxic(alcohol) and drugs (Cocaine, Amphetamine, Trastuzumab, Adriamycin, Rosiglitazone)

Methodology

After obtaining written and informed consent about enrolment in the observational study and maintaining adequate privacy and confidentiality, all patients were subjected to standardized interview. Complete medical and obstetric histories were obtained and complete General and Systemic examination along with laboratory investigations were done. Patients were asked to come for follow up and were examined clinically at regular intervals of 15 days. After 2 months Echocardiography was repeated along with other laboratory investigations.
Investigations which were done were complete blood count, Urine analysis, Renal function tests, Liver function tests, Random blood glucose, Electrolytes, CK-MB, BNP, PROLACTIN, ECG, Chest X-ray, Chest Ultrasonography, Antenatal sonography, 2D Echocardiography and Doppler. These were done at presentations and repeated as required according to the clinical status of the patient.
All data were analysed using appropriate statistical tests by using MedCalc version 12.5 and a P value< 0.05 will be considered statistically significant.

Results

Thirty-one patients fulfilled criteria for peripartum cardiomyopathy in Shri Sayaji General hospital, Baroda with mean age of 24.7±4.4 years. Majority of the patients (70.97%) were below 25 years of age with 12.9% of the patients more than 30 years of age. Graph I and graph II elaborate the symptom and physical signs of patients with PPCM. Out of the total population, 35.4% of the patients were Primi gravida, 35.48% were second gravida and 45.16% of patients were primi para. Majority of the patients (77.42%) presented with NYHA Class 4. Table I show mean of all baseline blood investigations that were done in patients with PPCM which showed 83.87% of the patients having Hb level 8gm/dl or above. Investigating further for the abnormal renal and liver function tests, 64.52% of patients had raised blood urea levels while 29.03% had raised serum creatinine levels and 35.48% of patients had raised serum bilirubin level >1.2 mg/dl and 51.61% of patients had raised SGPT levels >40U/L. Considering the systolic cardiac failure, cardiac markers were also calculated which showed only 12.9% patients had normal levels, 77.42% of patients had up to twice high CK-MB levels and 12.9% had CK-MB levels more than 3 times upper normal limit. Serum prolactin and serum BNP levels of the patients are shown in graph III and graph IV respectively.

Table 1: Investigate biochemical profile of patients with peripartum cardiomyopathy

Sr. No.	Investigations	Mean± SD (n= 31)
1	Haemoglobin(gm/dl)	9.5±1.8
2	Total count (per cumm)	16278±7373
3	ESR (mm)	57±34
4	Blood Glucose (mg/dl)	104±19
5	Blood urea(mg/dl)	62±43
6	Serum creatinine(mg/dl)	2±1.1
7	Serum Bilirubin(mg/dl)	1.4±0.9
8	SGPT(U/L)	95±76
9	Total protein(gm/dl)	5.5±0.7
10	Serum albumin(gm/dl)	2.9±0.4
11	Serum sodium(mEq/dl)	136±7.4
12	Serum potassium (mEq/dl)	4.8±1
13	CK-MB(U/L)	54±41
14	Serum Prolactin(ng/ml)	78.72
15	N-Pro-BNP (pg/ml)	7920.4

Electrographic characteristics of patients with PPCM predominantly showed Sinus tachycardia (93.55%) and ST-T abnormalities (70.97%). Other abnormalities included Left axis deviation (16.13%), Left atrial enlargement (9.68%), Poor R wage progression (9.68%), Low voltage complexes (6.45%) and left ventricular hypertrophy (3.23%). Chest X-ray findings of patients with PPCM showed cardiomegaly in 93.55% along with pulmonary oedema (41.94%) and Pleural effusion (61.29%). Chest Ultrasonography of patients exhibited bilateral pleural effusions (51.61%) and right sided pleural effusion (16.13%) with none having left sided pleural effusion. Echocardiographic characteristic changes are given in table II. 90.32% patients had functional mitral regurgitation among which 6.45% of patients had severe MR, 87.1% of patients had functional tricuspid regurgitation, among which 9.68% of patients had severe TR. 70.97% of patients had RV dysfunction and pulmonary hypertension with mean pulmonary arterial pressure being 50.7±9. 22.58% of patients had Pericardial effusion that was not compromising cardiac filling.

Table 2: echocardiographic changes in patients with peripartum cardiomyopathy

Parameters	Range	Mean	Number (n=31)	Percentage (%)
Ejection Fraction	40-45%	29.6±8.3	7	22.58
	30-39%		8	25.81
	20-29%		16	51.60
	<20%		0	0
Fractional Shortening	20-30%	16±4.9	8	25.81
	15-19%		7	22.58
	10-14%		16	51.61
	<10		0	0
LVEDD	40-49mm	54±4.4	6	19.35
	50-55mm		10	32.26
	56-60mm		14	45.16
	>60mm		1	3.23
LVESD	25-50mm	43±6.1	9	29.03
	41-45mm		10	32.26
	46-50mm		9	29.03
	>50mm		3	9.68
Left atrium	<30mm	36±5.3	2	6.45
	30-40mm		21	67.74
	<40mm		8	25.81
RVEDD	<20mm	25±4.3	6	19.35
	20-24mm		11	35.48
	>24mm		14	45.16
Hypokinesia	Global	-	30	96.77
	Regional		1	3.23

77.42% of patients had normal vaginal delivery while 12.9% required LSCS and 45.16% of the patients in total had adverse fetal outcome. Maternal Outcome as recorded showed 19.31% of patients died due to pulmonary causes. 25.81% of the patients not recovering and 54.84% of patients recovering fully without any functional impairment.

Results of the conducted follow up for the patients produced significant improvement in Ejection fraction (P=<0.0001), LV end diastolic dimension (P=<0.0001), LV end systolic dimension(P=<0.0001), LA size(P=0.0001), RV end diastolic dimension(P=0.0008), Pulmonary arterial pressure(P=0.018). On follow up examination there was significant reduction of RV dysfunction (P=0.008), Mitral regurgitation(P=<0.0001) and tricuspid regurgitation (P=0.0005). Comparing the baseline investigations between patients who recovered with those who did not, revealed higher total count in recovered group (19183) with P=0.002 and markedly elevated N-Pro-BNP levels in those not recovered group with P= 0.038. Ejection fraction and Fractional shortening were also markedly reduced in Not recovered group (23.1, 12.1) as compared to Recovered group (35.12, 18.8) with P= 0.0001, 0.0004. Left ventricular end diastolic and end systolic dimension were also markedly increased in Not recovered group (56.9, 48.4) as compared to Recovered group (52, 40) with P=0.01, 0.0009. Patients who did not recover had higher mean Pulmonary arterial pressure at baseline (57.4mm Hg) than those who recovered (45.7 mmHg) with P=0.005. There was no statistically significant difference in baseline parameters like Age, Hb level, Prolactin level, parity distribution, presence of RV dysfunction and adverse fetal outcome in patients who recovered and who did not. Serum Prolactin level was markedly raised in Expired group (159.1) as compared to Recovered group (46.8) with P=0.0005. N-Pro-BNP level was markedly raised in Expired group (19851.3) as compared to Recovered group (3033) with P=<0.0001. Left ventricular end diastolic and end systolic dimension were also markedly increased in Expired group (56.3, 45.5) as compared to Recovered group (52, 40) with P= 0.03, 0.048. There was no statistically significant difference in baseline parameters like age, Hb level, Total count, pulmonary arterial pressure, parity distribution, presence of RV dysfunction and presence of adverse

foetal outcome in patients who recovered and who expired. Comparing the baseline investigations between patients who did not recover and with those who expired displayed markedly elevated N-Pro-BNP levels in Expired group (19851.30) as compared to Not recovered group (9560.6) with P=0.04. There was no statistically significant difference in all other baseline investigations in patients who did not recover and those who expired.

Discussion

Peripartum cardiomyopathy can present as left ventricular systolic failure or biventricular failure in severe cases. The mean age of patients presenting with PPCM as mentioned in one study conducted in India, Mishra *et al* was 31±5 years while that conducted by Sliwa *et al* ranges from 29±7 years to 33±5 years (2)(7). However, in this study the mean age (24.7±4.4 years) was markedly lower than that seen with other studies done in India and worldwide which could be due to regional or genetic variations in the study population. However, younger age should not preclude the diagnosis of PPCM. Most of the study report that majority of patients were having NYHA III or IV with more percentage of symptoms of orthopnoea /PND and oedema reflecting severe disease extent in the current study. Anaemia is a contributing factor for development of heart failure, however, majority of the patients in this study had Hb levels >8gm/dL (83.87%) and none had levels <6gm/dL supporting in making peripartum cardiomyopathy a diagnosis of exclusion. Increased awareness about antenatal care and regular supplementation of iron, folic acid and vitamin B12 has probably resulted into better Hb levels. Abnormal renal function tests such as high serum creatinine (29.03%) was probably because of low renal perfusion secondary to decreased cardiac output. 51.61% of patients were having high SGPT levels reflecting liver injury secondary to congestive hepatopathy. PPCM is a myocardial disease and increased levels of CK-MB observed in this study concurs with the myocardial injury.

Mean serum prolactin level in this study was 78.72ng/ml which is markedly raised as compared to that seen in study by Forster. (8) However, in this study controls were not taken which can account for possible bias. Prolactin`s pro-inflammatory derivative, 16-kDa prolactin responsible for endothelial damage, is produced from the cleavage by proteases which are activated due to unbalanced oxidative stress (9).Total prolactin level could not reflect cleaved forms and hence more studies are required to clarify correlation of total prolactin level and PPCM.

NT-proBNP is considered a crucial marker of ventricular wall stress and heart failure. Possibly, kinetics of NT-proBNP in correlation with values of other specific markers like IFN-Y, prolactin may help to stratify patients with poor prognosis. In this study the mean serum N terminal Pro-BNP level was high (7920.4pg/ml) signifying that it can be used as an early marker for diagnosis and risk stratification of patients with PPCM.

There are no specific ECG findings however echocardiographic changes mostly showed global hypokinesia and only one patient had regional wall motion abnormality which is rare. Mean ejection fraction was 29.6±8.3 with decrease in fractional shortening. Mitral and tricuspid regurgitation is secondary to dilated cardiomyopathy. 9.68% of patients had Intracardiac clot also owing to dilatation of chambers and hypokinesia. However, on comparing the baseline and follow up echocardiographic characteristics showed people who recovered had statistically significant higher EF and FS and lower LVEDD, LVESD and Pulmonary arterial pressure as compared to patients who did not recover. Adverse Fetal outcomes of this study (45.16%) compared to a study by Hasan (15.6%) are given in table III. Maternal mortality rate was 19.35% and major morbidity was in form of persistent cardiomyopathy observed in 25.81%. Recovery is defined as regaining of ejection fraction >45% was observed in 54.84% in this study. 9.68% had intracardiac clots and two patients died because of pulmonary embolism.

Table 3: Adverse fetal outcomes

Foetal Outcome	**Current Study**	**Hasan *et al*** (10)
Alive	54.84%	84.83%
IUFD	9.68%	-
Still Birth	29.03%	9.37%
Neonatal death	6.45%	6.25%
Total adverse outcome	45.16%	15.6%

Diagnosis of PPCM is often delayed even in symptomatic patients leading to higher complications and hence increased awareness of PPCM among clinicians is requisite. Baseline echocardiographic parameters, serum prolactin and N-Pro-BNP levels were correlated with long term prognosis of patients with PPCM. There is also a strong correlation of NT-proBNP and Serum prolactin levels as a marker for risk stratification of patients with PPCM.

Conflict of Interest

There are no conflicts of interest to declare.

Abbreviations

BNP: Brain natriuretic peptide
EF: Ejection fraction

FS: Fractional shortening
Hb: Haemoglobin
LVEDD: Left ventricular end diastolic diameter
LVESD: Left ventricular end systolic diameter
PPCM: Postpartum Cardiomyopathy
RVEDD: Right ventricular end diastolic diameter

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