"A PROSPECTIVE COHORT STUDY TO DETERMINE THE PREDICTORS OF PERIPARTUM CARDIOMYOPATHY IN HYPERTENSIVE DISORDERS OF PREGNANCY"

By

DR. SRIDEVI H S

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IN

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Under the guidance of

DR.NEELAMMA PATIL M.D, DNB

PROFESSOR

DEPARTMENT OF OBSTERITICS AND GYNAECOLOGY

BLDE (DEEMED TO BE UNIVERSITY)

SHRI B.M. PATIL MEDICAL COLLEGE, VIJAYAPURA

KARNATAKA

2020

B.L.D.E. (Deemed to be University)

SHRI. B. M. PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE,VIJAYAPUR

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I here by declare that this dissertation/thesis entitled

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& Research Center, Vijayapur.

Date:28-09-2020

Sridevi

Place: Vijayapur

Dr Sridevi H S

B.L.D.E. (Deemed to be University)

SHRI. B. M. PATIL MEDICAL COLLEGE HOSPITAL &

RESEARCH CENTRE, VIJAYAPUR

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Place: Vijayapur

Date: 28-09-2020

DR.(prof.) NEELAMMA PATILMD ,DNB
Professor
Department of Obstetrics & Gynaecology
BLDE (Deemed to be University)
Shri. B. M. Patil Medical College,
Hospital & Research Centre,
VIJAYAPUR.

B.L.D.E. (Deemed to be University)

SHRI. B. M. PATIL MEDICAL COLLEGE HOSPITAL &

RESEARCH CENTRE, VIJAYAPUR

CERTIFICATE BY THE CO-GUIDE

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Dr. Deepa Sajjanar

Place: Vijayapur

Date: 28-09-2020

DR.DEEPA SAJJANAR$_{MD}$
Associate Professor
Department of Biochemistry
BLDE (Deemed to be University)
Shri. B. M. Patil Medical College,
Hospital & Research Centre,
VIJAYAPUR

B.L.D.E. (Deemed to be University)

SHRI. B. M. PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE, VIJAYAPUR

ENDORSERSEMENT BY THE HEAD OF DEPARTMENT

This is to certify that the dissertation entitled —" **A PROSPECTIVE COHORT STUDY TO DETERMINE THE PREDICTORS OF PERIPARTUM CARDIOMYOPATHY IN HYPERTENSIVE DISORDERS OF PREGNANCY i**s a bonafide research work done by **Dr. Sridevi HS** under the guidance of **DR.(Prof)NEELAMMA PATIL**, Professor, Department of Obstetrics and Gynaecology, Shri. B.M. Patil Medical College, Vijayapur.

Place: Vijayapur

Date : 28-09-2020

Seal and signature of

HOD of Obstetrics and Gynaecology

Dr. S R MUDANUR M.D,DGO,FIGO

BLDE (Deemed to be University)

Shri. B. M. Patil Medical College,

Hospital & Research Centre,

VIJAYAPUR

B.L.D.E. (Deemed to be University)

SHRI. B. M. PATIL MEDICAL COLLEGE HOSPITAL &

RESEARCH CENTRE, VIJAYAPUR

ENDORSEMENT BY THE PRINCIPAL

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Place : Vijayapura

Date: 28-09-2020

Seal and signature of principal

DR . ARAVIND .A. PATIL **M.S**

BLDE (DEEMED to be University)

Shri B.M.Patil Medical College,

Hosiptal & Research Centre ,

VIJAYAPUR

B.L.D.E. (Deemed to be University)

SHRI. B. M. PATIL MEDICAL COLLEGE HOSPITAL &

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Sridevi

Date: 28-09-2020 **Dr. Sridevi H S**

Place: Vijayapur.

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Sridevi

Place: Vijayapur DR SRIDEVI HS

Date

ABSTRACT

BACKGROUND: Peripartum cardiomyopathy is one of the lately recognised causes of maternal mortality worldwide, but the exact cause of PPCM is still unknown. PPCM is often associated with many risk factors, especially hypertension in pregnancy, but its difficult to predict who among them will go for PPCM. So we wanted to study whether some of the markers which are raised in PPCM and hypertensive disorders of pregnancy can be used as predictors of PPCM.

OBJECTIVE: To evaluate whether total leucocyte count, troponin i, serum prolactin levels in hypertensive disorders of pregnancy can be used as predictors of peripartum cardiomyopathy

MATERIALS AND METHOD:A hospital based prospective cohort study was conducted among 265 study hypertensive patients . A blood sample was collected from pre eclampsia and eclampsia patients to see the level of biomarkers. These patients were further followed up up to 5 months postpartum to see whether they develop PPCM.

RESULTS:A total of 265 hypertensive patients were studied. All patients were followed upto 5 months after delivery for clinical features of PPCM. A level of >0.64 +/- 0.2 of Troponin I was significantly associated with developing PPCM (p value = 0.04). Serum Prolactin level of >171.30+/-72.07 (p value=0.007) was associated with PPCM similarly Total Leucocyte count >17166+/-9105.3 (p value = 0.05) was also significantly associated with developing PPCM in Hypertensive disorders of pregnancy

CONCLUSION: From the present study we conclude that PPCM is common in young hypertensive pregnant patients and markers like Total leucocyte count, serum prolactin and Troponin I can be used for early diagnosis of the disease so as to prevent further complications

Keywords: Hypertensive disorders of pregnancy , Peripartum cardiomyopathy.

LIST OF ABBREVATIONS

PPCM : Peripartum cardiomyopathy

PH : Pulmonary Artery Hypertension

HDP :Hypertension disorders of pregnancy

NACE : Neonatal adverse outcome effects

LV : Left ventricle

s FAS : Soluble factor receptor superfamily

HF : Heart failure

LVEF : Left ventricular ejection fraction

Hs-CRP : High sensitive C reactive protein

cTNI : Troponin I

BNP : Brain natriuretic peptide

PE : Pre eclampsia

AFLP : Acute fatty liver of pregnancy

AKI : Acute Kidney Injury

IUD : Intrauterine fetal demise

IUGR :Intrauterine growth restriction

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INTRODUCTION

Cardiomyopathy is a group of disorders in which the heart muscle is structurally and functionally abnormal in the absence of other diseases that could cause observed myocardial abnormality. (1) Cardiomyopathy either causes a decrease in preload or pumping capacity of the heart, which results in decreased ejection fraction of the heart.

It is a myocardial disorder in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular disease, and congenital heart disease sufficient to explain the observed myocardial abnormality. They are classified mainly into three types – Dilated, Hypertrophic and restrictive cardiomyopathy.

1) Dilated cardiomyopathy- In this type, the left ventricle of the heart becomes enlarged, which results in the inability of the heart to pump blood adequately. This occurs in middle age and is the most common cause of coronary artery disease or heart failure.

2) Hypertrophic cardiomyopathy- In this type, the heart muscle becomes abnormally thickened, which results in a decrease in the volume of the chambers of the heart, causing defective filling and in turn reduced ejection of blood.

3) Restrictive cardiomyopathy- In this type, the heart muscle becomes rigid and inelastic and is unable to pump blood resulting in a reduction of ejection fraction. This is the least common type of cardiomyopathy

Heart diseases contribute substantially to the burden of maternal mortality worldwide. (2)(3) In a study on neonatal and maternal outcomes among pregnant women with heart disease, it was found that 676 (17%) had cardiomyopathy, 1528 (40%) had valvular heart disease, 1367 (35%) had

adult congenital HD, and 300 (8%) had PH. Major adverse cardiac events occurred in 16.1% of women with HD, with most in the cardiomyopathy (45.9%) group. (4) Also, it was found that neonatal adverse clinical outcome (NACE) was more common among women with heart disease. Increased risk of NACE was noted for women with HD (odds ratio [OR]: 2.8; 95% confidence interval [CI], 2.5-3.0), with the highest risk for those with cardiomyopathy (OR: 5.9; 95% CI, 5.0-7.0)(4) One of the life-threatening forms of cardiomyopathy seen during pregnancy is peripartum cardiomyopathy (PPCM). Incidence of PPCM ranges from 1 in 1300 to 1 in 15,000 pregnancies. (5) The incidence varies widely depending on geographical region and ethnic background, A recent study using the US Nationwide Inpatient Sample found that its incidence increased from one in 1181 live births in 2004 to one in 849 live births in 2011(6)

Definition

Peripartum cardiomyopathy (PPCM) is a rare, idiopathic, and often dilated cardiomyopathy that is marked by systolic dysfunction that presents in late pregnancy or the early postpartum period. (6) A position statement from the heart failure association of the European society of cardiology working group on peripartum cardiomyopathy defines PPCM is an idiopathic form of cardiomyopathy, presenting with heart failure secondary to LV dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is identified(7)

Hemodynamic changes during pregnancy

Pregnancy is associated with vasodilation of the systemic vasculature and the maternal kidneys. The systemic vasodilation of pregnancy occurs as

early as at 5 weeks and therefore precedes full placentation and the complete development of the utero placental circulation. In the first trimester, there is a substantial decrease in peripheral vascular resistance, which decreases to a nadir during the middle of the second trimester with a subsequent plateau or slight increase for the remainder of the pregnancy. Cardiac output increases throughout pregnancy, the sharpest rise in cardiac output occurs by the beginning of the first trimester, and there is a continued increase into the second trimester. This is due to substantial activation of the renin-angiotensin-aldosterone system. The enhanced activity of the renin-angiotensin and aldosterone systems occurs early in pregnancy, with increases in plasma volume starting at 6 to 8 weeks There is a decrease in arterial pressures, including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure, and central SBP during pregnancy. DBP and mean arterial pressure decrease more than SBP during the pregnancy. Arterial pressures decrease to a nadir during the second trimester (dropping 5–10 mm Hg below baseline), but the majority of the decrease occurs early in pregnancy (6- to 8-week gestational age) compared with preconception values. Left ventricular wall thickness and left ventricular wall mass increase by 28% and 52% above pre-pregnancy values, respectively, throughout pregnancy. Volume overload and ventricular hypertrophy is accompanied by up regulation of vascular endothelial growth factor and increased myocardial angiogenesis with no increase in cardiac fibrosis.

Pathophysiology

The aetiology of PPCM is uncertain. A combined ‘two-hit’ model, including systemic angiogenic imbalance and host susceptibility, is thought to be crucial in the pathophysiology of PPCM. Significant hemodynamic changes occur during pregnancy. There is an increase in

preload secondary to the increase in red cell mass and blood volume. This also increases the cardiac output by 20% to 30% due to an increase in heart rate and stroke volume by 15% to 25%.This causes increase in strain on the heart muscle. If there is pre-existing weakness of the cardiac muscles due to the second hit it results in an inability of the heart to pump blood with full force causing reduction in ejection of blood from the left ventricle, i.e. the ejection fraction of the heart decreases. As ejection fraction goes below 45% blood supply to various organs decreases which result in activation of counter-regulatory mechanisms to increase the pumping capacity of the heart which ultimately causes increased workload on the heart resulting in heart failure. In a study based on initial echocardiogram among PPCM patients, a trend toward residual LV dysfunction was noted in patients with a dilated left ventricle as compared to those with a non-dilated left ventricle (18.8% versus 6.7%, P=0.32). A hypokinetic right ventricle was found in 15.2% of the women who suffered from PPCM.(8)

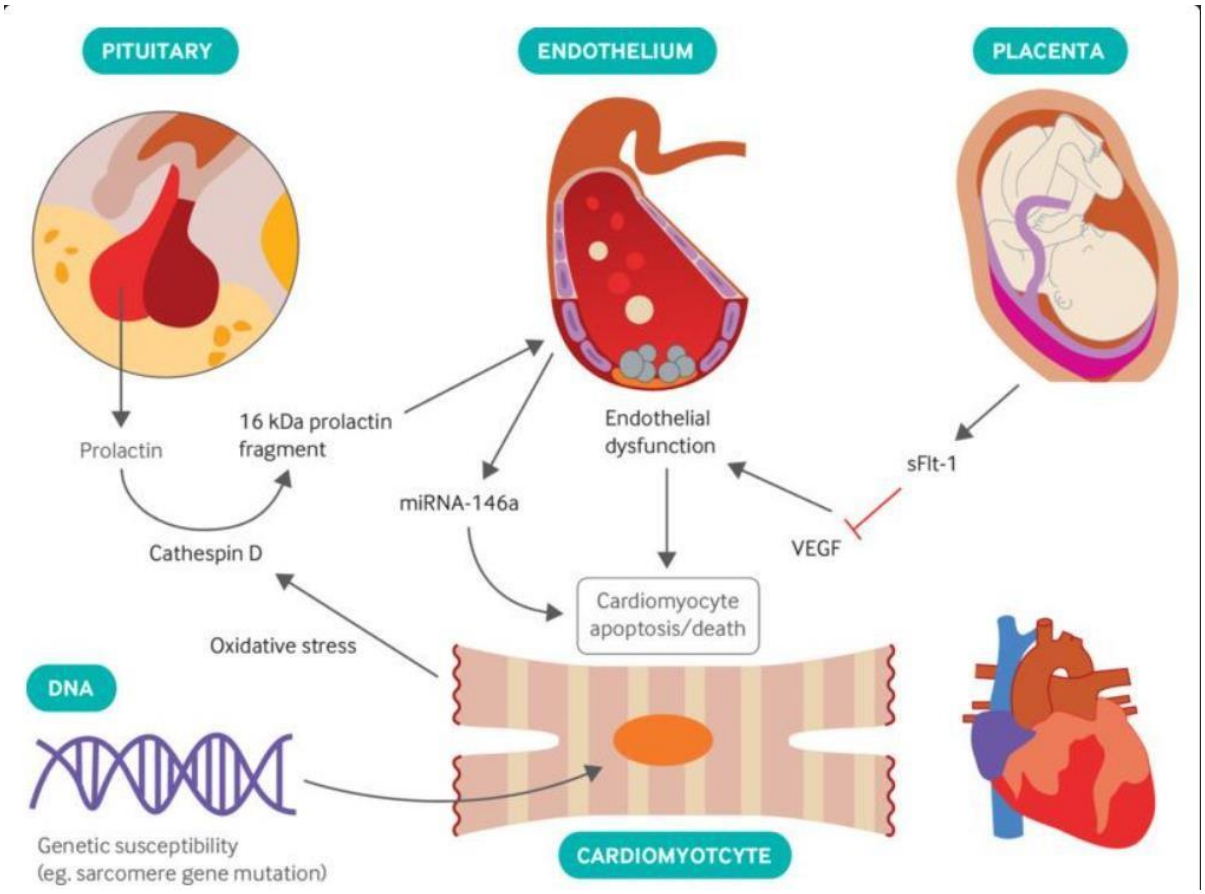


Figure 1.Pathophysiology of PPCM

Other aetiologies such as myocarditis have been hypothesized due to the presence of viral genomes in biopsy of patients with PPCM as echovirus, Coxsackie, and parvovirus B19 which can be further related to the increase inflammatory markers seen in cases of PPCM.

Another hypothesis says due to hormonal changes occurring at the end of pregnancy prolactin levels increase during late pregnancy and in the puerperium stage. This enzyme protects the heart from reactive oxygen species that, when increased, generates by a mechanism not known the secretion of a peptidase known as cathepsin D that cleavage prolactin into an angiostatic N-terminal 16 kDA prolactin fragment that promotes

apoptosis in endothelial cells and cardiomyocytes apoptosis. Thus resulting in damage to the heart and causing an inflammatory reaction.

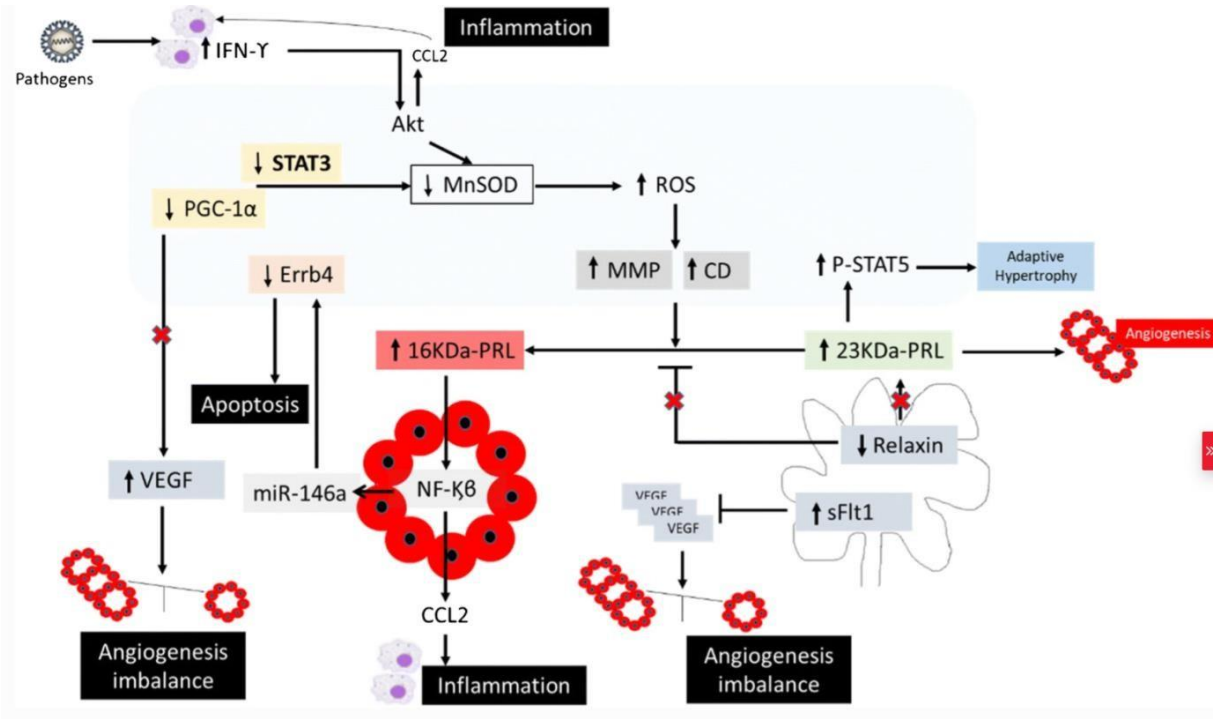


Figure 2. Angiogenic imbalance causing peripartum cardiomyopathy

Risk factors

The aetiology of PPCM is unknown, but viral, autoimmune, and idiopathic causes may contribute. Risk factors for PPCM include advanced maternal age, multiparity, African race, twinning, gestational hypertension, and long-term tocolysis. (5,9) Pre-existing cardiovascular disease (such as hypertension, diabetes, and smoking) also has been found to increase the risk. (10) Alterations in oestrogen, progesterone and prolactin levels are associated with changes in the cardiovascular system to support the growing foetus and counteract pregnancy stresses have also been linked to numerous pathophysiological outcomes on the cardiovascular system. (11)

Presentation:

The clinical presentation of patients with PPCM is similar to that of patients with dilated cardiomyopathy. (5,9) The symptoms include shortness of breath, swelling of the legs, fatigue, weight gain, fainting, palpitations, dizziness or light-headedness. Majority of the symptoms occur in a healthy pregnancy, and thus the diagnosis of PPCM becomes difficult.

Diagnosis

The diagnosis of peripartum cardiomyopathy is one of exclusion, National Heart, Lung, and Blood proposes that the new guidelines which include (12):-

- Heart failure within the last month of pregnancy or five months postpartum;
- Absence of pre-existing heart disease of no determinable aetiology,
- Absence of an identifiable cause for cardiac failure
- Strict echocardiographic criteria of left ventricular dysfunction: ejection fraction, or m-mode fractional shortening less than 45%, or both, and end-diastolic dimension more than 2.7 cm/m2.

Till date, there is no definitive test for diagnoses of PPCM though various markers have been proposed which guide diagnosis of the condition. As inflammation may play a role in the pathophysiology of PPCM. Serum markers of inflammation sFas/Apo-1, C-reactive protein, interferon-gamma (IFN-γ), and IL-6 are found to be elevated in patients with PPCM.(7,10,13–15) A study conducted in 100 patients with newly diagnosed PPCM reported Baseline levels of C-reactive protein correlated

positively with baseline LV end-diastolic (rs=0.33, P=0.0026) and end-systolic (rs=0.35, P=0.0012) diameters and inversely with LVEF (rs=-0.27, P=0.015).(15)

In another study, serum markers related to cardiac function, apoptosis, oxidative stress, remodelling, inflammation and the nursing hormone prolactin were analyzed among patients of PPCM and healthy controls. In a follow up after six months, a decrease in prolactin levels was significant in patients with cardiac function improvement but not in those without cardiac function improvement. (13) Various studies have also shown that Troponin-I is increased in pregnancy-induced hypertensive patients along with PPCM patients (16) Similarly high sensitive C reactive protein, TLC, prolactin levels are increased in PPCM patients(15).

Prognosis:

About half the patients of PPCM recover without complications, although outcomes, if not controlled early, can result in variable fates, including persistent heart failure, arrhythmias, thromboembolic events, and death. (19). The prognosis is reduced in patients with persistent cardiomyopathy or with pre-existing heart disease or pre-eclampsia. Persistence of disease beyond six months indicates irreversible cardiomyopathy and portends worse survival. (5,9) Rate of recovery ranged between 61-76% in studies from Europe, Japan, and the USA, compared with 27.6% for a Haitian cohort, and 23% for a predominantly African-American USA cohort. At six months, 53% of a South African cohort had died, LVEF <35%, or severe heart failure. Recovery to explantation in Left ventricular assist device recipients was 4% at 36 months. (21). A nationwide Danish cohort study was conducted on

women diagnosed with PPCM from 2005 to 2014 over 91 months which concluded that women with PPCM generally recovered left ventricular ejection fraction and were asymptomatic 7 years after , but had subtle diastolic dysfunction on cardiac magnetic resonance imaging and reduced peak VO 2.(23) In another study Clinical follow-up was available for 32 women with PPCM. In time to event analysis, patients with pre-eclampsia had worse event-free survival during 1-year follow-up (P=0.047). Echocardiographic follow-up was available in 10 survivors with and 16 without pre-eclampsia. LV ejection fraction recovered in 80% of survivors with versus 25% without pre-eclampsia (P=0.014). (18)

Treatment

The objective of peripartum cardiomyopathy treatment is to keep extra fluid from collecting in the lungs and to help the heart recover as completely as possible. Medicines such as Beta-blockers, diuretics are prescribed after considering the teratogenic potential of the drugs and month of pregnancy. Also, medications are prescribed to alleviate complications such as heart failure and thrombosis.

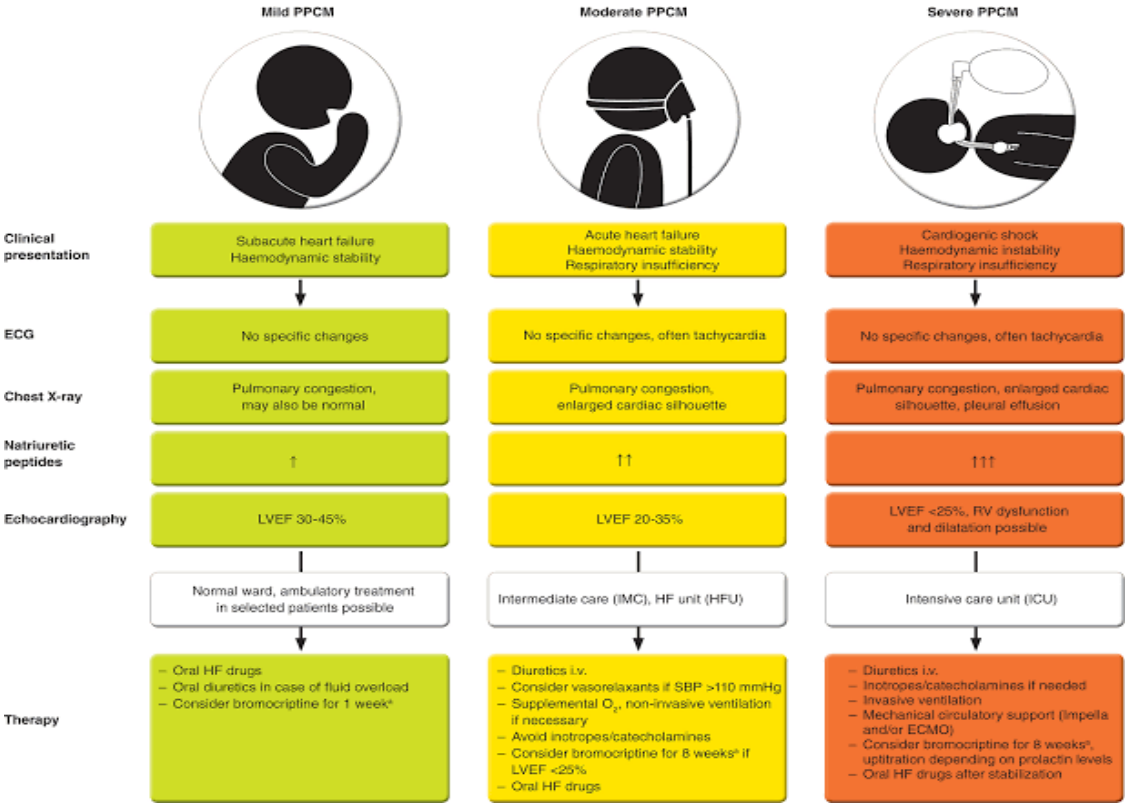


Figure 3. Overview of different clinical scenarios in patients with PPCM

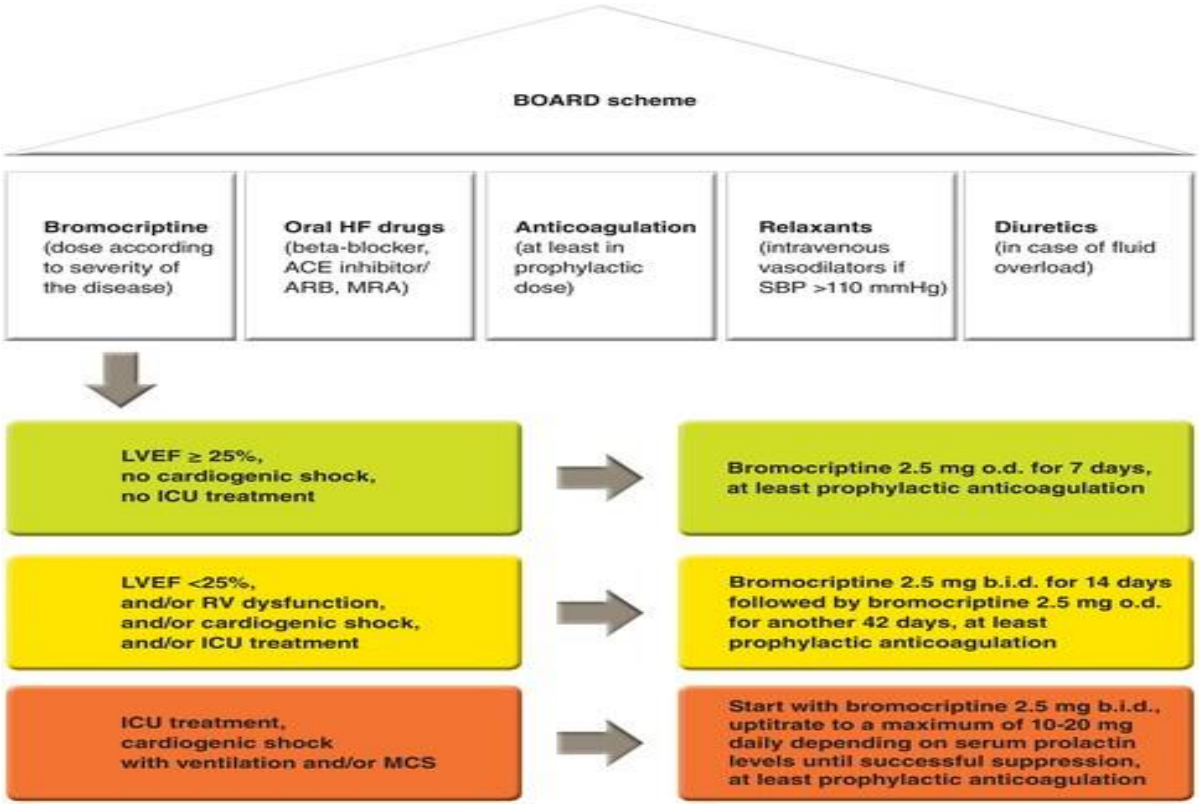


Figure 4 . BOARD scheme for the therapy of patients with acute peripartum cardiomyopathy

Rationale of the Study:

Early diagnosis and initiation of treatment are essential to optimize pregnancy outcome. Symptoms of heart failure mimic those of healthy pregnancy, often resulting in a delay in diagnosis and preventable complications of PPCM. Although various markers for diagnosis have been studied. None of the studies have seen whether these markers can be used as predictors in high risk patients. Since the commonest high risk factor of PPCM is hypertension in pregnancy, we decided to study these markers in such patients as predictors of PPCM.

Various studies have shown that troponin I , serum prolactin and total leucocyte count are increased in PIH patient and also in PPCM patients. But none of the studies have seen whether these patients with increased markers actually develop PPCM or not. So our study aims to see the correlation by following up these patients in postpartum period to look for the development of PPCM.

AIMS AND OBJECTIVES

To Evaluate Whether Total Leucocyte Count, Troponin I, Serum Prolactin Levels In Hypertensive Disorders Of Pregnancy Can Be The Predictors Of Peripartum Cardiomyopathy

Objectives.

1) To study socio demographic profile and clinical history of the study participants.

2) To evaluate Total Leucocyte Count, Troponin I, Serum Prolactin Levels In Hypertensive Disorders Of Pregnancy.

3) To find association of Total Leucocyte Count, Troponin I, Serum Prolactin Levels in Hypertensive disorders of pregnancy with PPCM.

REVIEW OF LITERATURE

Cardiomyopathy is a myocardial disorder in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular disease, and congenital heart disease sufficient to explain the observed myocardial abnormality.

PPCM is a rare form of dilated cardiomyopathy occurring during the late month of pregnancy or even postpartum.

Incidence and prevalence

The Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project(24) was a cross-sectional study of 14,323,731 hospitalizations for pregnancy in the USA between 2004 and 2006. They reported among all pregnancy hospitalizations, the overall prevalence of hospitalizations with myocardial disorders was 1.33 per 1,000 deliveries. The rate of pregnancy hospitalizations with cardiomyopathy was 0.46 per 1,000 births (0.18 for apparent peripartum cardiomyopathy and 0.28 for other cardiomyopathies). The rate of pregnancy hospitalizations with other myocardial disorders was 0.87 per 1,000 deliveries. Myocardial disorders were rare during delivery hospitalizations (0.01%) but not uncommon among postpartum hospitalizations (4.2%).

Fett et al. (25) conducted a hospital-based study on 25 pregnant women with heart disease and 25 pregnant women without heart disease who had no evidence of heart disease to find out the incidence of PPCM among Haitian women. They used echocardiographic criteria along with biomarkers for diagnosis of PPCM. They reported an incidence of PPCM in 1 per 299 live births in Haiti.

Brar et al. (26) conducted a study among 241,497 deliveries within the Southern California Kaiser healthcare system to find out the incidence of PPCM. They used the following criteria for the diagnosis of PPCM- (1) left ventricular ejection fraction <0.50, (2) met the Framingham criteria for HF, (3) new symptoms of HF or initial echocardiographic diagnosis of left ventricular dysfunction occurred in the month before or in the five months after delivery, and (4) no alternative cause of HF could be identified. They reported that the overall incidence of PPCM was 1 in 4,025 deliveries. The incidence in whites, African-Americans, Hispanics, and Asians was 1 of 4,075, 1 of 1,421, 1 of 9,861, and 1 of 2,675 deliveries, respectively. The incidence of PC was most significant in African-Americans, which was 2.9-fold higher compared with whites ($p = 0.03$) and 7-fold that of Hispanics ($p <0.001$).

Thus significant variation in incidence among various regions and races was reported in multiple studies. However, there are no studies which indicate the incidence of PPCM in Asia, Australia, and Europe.

Risk factors

Dhaval Kolte et al. (27) conducted a study to find out the temporal trends of PPCM among all women aged 15-45 years in Nationwide Inpatient Sample databases at the United States. The identified 34 219 women aged 15 to 54 years with PPCM. They reported women with chronic hypertension had the highest incidence of PPCM (267.5 [95% CI 262.3 to 272.7] per 10 000 live births). Similarly, the presence of eclampsia and diabetes mellitus were associated with a higher incidence of PPCM than their absence PPCM rates were similar in women with or without pregnancy-associated hypertension (10.1 [95% CI 9.5 to 10.6] and 10.4 [95% CI 10.3 to 10.5] per 10 000 live births, respectively). Interestingly,

PPCM rates were higher in women who were non-smokers, primipara, or had single gestation pregnancy.

Gunderson et al. (28) conducted a study on all women who were diagnosed with heart failure within one month before to 5 months after delivery of a liveborn neonate between 1995 and 2004 at California. Among 227,224 eligible women, they confirmed 110 recognized peripartum cardiomyopathy. They reported, independent predictors of PPCM included maternal age of 25 years or older, non-Hispanic African American and Filipino groups, parity of 4 or higher, multiple gestation, severe anaemia, pre-existing and pregnancy-related hypertensive disorders, and hemolysis, elevated liver enzymes, low platelets syndrome. Maternal death rate (per 1,000 person-years) was higher among cases (6.12) than noncases (0.23; P<.001).

Haghikia et al. (29) conducted a study among 115 patients with confirmed PPCM at time of diagnosis and control collectively consisted of healthy postpartum women with established normal cardiac function (echocardiography, LVEF > 55 %, n = 19) in the first postpartum week in USA. They reported 16.5 % of PPCM patients in their registry reported a positive family history of cardiomyopathy, supporting the idea that genetic factors may be involved in some PPCM patients. They observed that the number of HTN was more than three times higher in these patients, albeit not significant but suggesting that they may be more refractory to medical therapy and tend to have a more severe course of the disease. They concluded that peripartum stress might demask genetic predispose PPCM. Thus phenotype, as well as family history, may be considered as risk factors.

Patten et al. (30) conducted a study to see the effect of anti-angiogenic factors and oxidative stress on the pathophysiology of PPCM. They reported that PPCM is in part a two-hit vascular disease due to imbalances in angiogenic signalling and that anti-angiogenic states such as pre-eclampsia or multiple gestations significantly worsen the process. Our data may explain why pregnancy triggers PPCM, and also explain the longstanding epidemiological observation that pre-eclampsia is a risk factor for developing PPCM. Thus they concluded when the balance between oxidants and antioxidants is disturbed, it may predispose to PPCM.

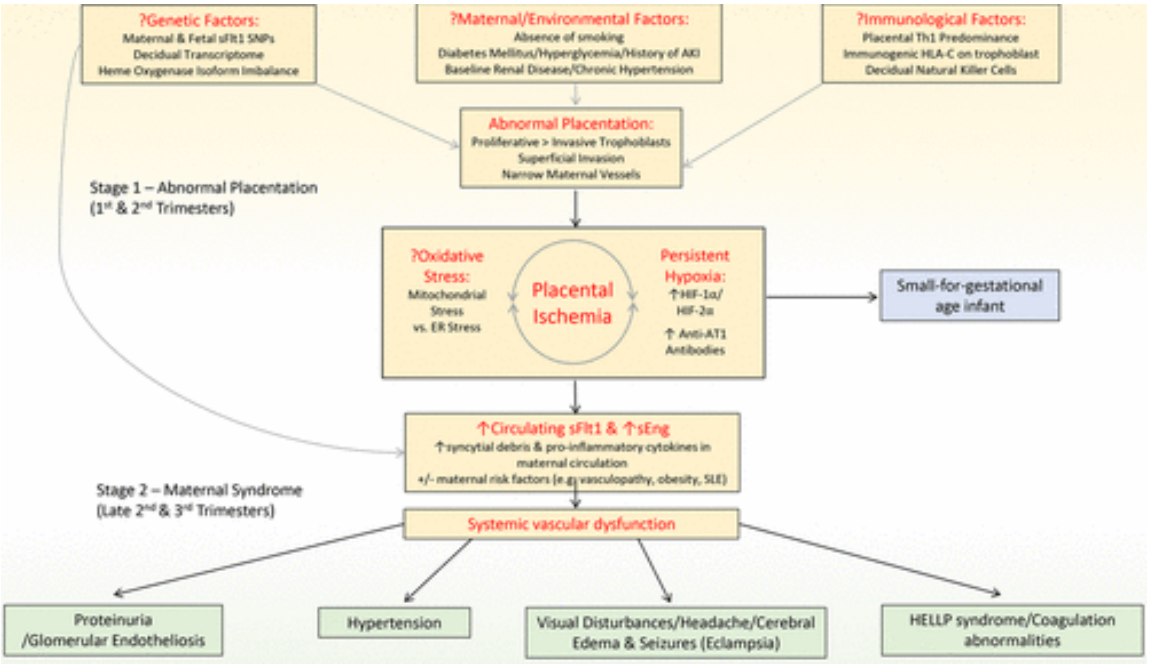


Figure 5. **Schematic of the pathogenesis of preeclampsia**. Genetic factors, immunologic factors, other maternal factors cause placental dysfunction which in turn leads to the release of antiangiogenic factors (such as sFLT1 [soluble fms-like tyrosine kinase 1] and sENG [soluble endoglin]) and other inflammatory mediators to induce preeclampsia.

Clinical features

Honigberg et al. (6) published a review on peripartum cardiomyopathy in which they enumerate PPCM typically present with symptoms of congestion, including dyspnoea on exertion, orthopnoea, paroxysmal nocturnal dyspnoea, and oedema of the lower extremities. At the same time, uncommon presentations are cardiogenic shock, thromboembolism and unstable arrhythmias.

Elkayam et al. (31) conducted a review of the literature on the clinical characteristic of patients with PPCM. They reported mostly patients present with dyspnea and orthopnea, in addition, cough, chest pain, and abdominal pain are frequently encountered and tend to confuse the initial clinical evaluation. Physical examination often reveals tachycardia and tachypnea, blood pressure may be elevated or reduced, and patients are often not able to lie down flat because of shortness of breath. There is usually increased jugular venous pressure, displaced apical impulse, right ventricular heave, murmurs of mitral and tricuspid regurgitation, third heart sound, pulmonary rales, and peripheral oedema.

Goland et al. (32) conducted a retrospective review and analysis of clinical data of 182 patients with PPCM. They reported 25% of patients had severe left ventricular dysfunction with a mean LVEF of 24. Cardiopulmonary arrest was reported in 6 women, one due to ventricular tachycardia, and five due to acute respiratory failure. All events occurred early, either during the delivery (3 patients) or within the first six days postpartum (3 patients). Anoxic brain damage and slow recovery were reported in 5 patients. Severe pulmonary oedema requiring intensive care occurred in 17 patients: between 1 day before and seven days after delivery in 16 and at three months postpartum in 1 patient.

Thromboembolic events were reported in 4 patients between 5 days and three months postpartum. All of them developed left ventricular thrombus, three presented with cerebrovascular accident (plus pulmonary embolism in 1), and 2 with leg ischemia requiring amputation in one.

Arany et al. (17) wrote a review from published literature on PPCM. They reported most women with PPCM present with signs and symptoms of heart failure, including orthopnea and paroxysmal nocturnal dyspnea. These symptoms are often confused with those of healthy pregnancy, especially of late gestation, a fact that often leads to missed or delayed diagnosis of PPCM and underestimation of the incidence of this condition. Physical examination usually reveals signs of heart failure, including tachycardia, elevated jugular venous pressure, pulmonary rales, and peripheral oedema

Diagnosis

Demakis et al. (33) conducted a study to find out the natural coarse of disease in Peripartum cardiomyopathy among 27 patient who was followed up for 21 years. They reported that Cardiomegaly on x-ray was present in all cases, and many had pulmonary venous congestion on the chest X-ray. The initial ECG was abnormal in each patient. One patient had Q-waves in V1-V3 that could be read as the pattern of an anteroseptal myocardial infarct.

Uri Elkayam et al. (34) compared the clinical outcomes of patients presenting with ppcm in early pregnancy with patients presenting later in pregnancy or postpartum among 127 subjects diagnosed with PPCM. They reported that in echocardiogram left ventricular ejection fraction at the time of diagnosis was 29±11% and improved to 46±14% ($P \leq 0.0001$) at follow-up. Normalization of left ventricular ejection fraction occurred

in 54% and was more likely in patients with left ventricular ejection fraction >30% at diagnosis. They found that a comparison between the peripartum cardiomyopathy and early pregnancy-associated cardiomyopathy groups revealed no differences in age, race, associated conditions, left ventricular ejection fraction at diagnosis, its rate and time of recovery, and maternal outcome.

Bhattacharya et al. (35) in his review on peripartum cardiomyopathy mentioned diagnosis requires a high degree of suspicion because symptoms of peripartum cardiomyopathy can be confused with physiologic changes associated with advanced pregnancy. Common signs of peripartum cardiomyopathy include displacement of the apical impulse, presence of S3, and evidence of mitral or tricuspid regurgitation. Engorgement of the neck veins, pulmonary crepitations, hepatomegaly, and pedal oedema may also be present. Peripartum cardiomyopathy is diagnosed only when the following criteria are met: left ventricular ejection fraction (LVEF) <0.45 or M-mode fractional shortening <30% (or both) and end-diastolic dimension >2.7 cm/m. They said The most commonly seen electrocardiographic changes are left ventricular (LV) hypertrophy and ST-T wave abnormalities.

Lampert et al. (36) conducted a review on PPCM in which they found the echocardiographic featured of patients with PPCM. They reported that the echocardiogram usually shows a dilated left ventricle with marked impairment of overall systolic performance. Besides, regional heterogeneities in systolic wall thickening, a B notch on the M-mode tracing, mitral regurgitation, atrial enlargement, and a small hemodynamically insignificant pericardial effusion may be noted.

Markers of PPCM

1) Prolactin

Hilfiker et al. (14) conducted a study to see for the role of prolactin(PRL) in cardiac remodelling during pregnancy in mouse model. They inferred that pregnancy-related adaptive hypertrophy is associated with enhanced cardiac angiogenesis and that maintenance of the latter in the postpartum phase critically depends on STAT3 gene. The absence of cardiomyocyte STAT3 gene(Signal transducer and activator of transcription 3) in the postpartum heart causes increased oxidative stress due to blunted induction of the antioxidant enzyme MnSOD(Manganese superoxide dismutase)enzyme. As a consequence, expression and proteolytic activity of CD(Cluster of differentiation) are increased, which in turn, induces a detrimental conversion of the nursing hormone PRL into its anti-angiogenic 16 kDa derivative. The generation of 16 kDa PRL greatly accelerates the adverse effects of oxidative stress and activated CD. Its detrimental effects on the coronary microvasculature promote myocardial hypoxia and apoptosis, thereby contributing to the development of PPCM. Thus, we provide evidence that enhanced activity and release of CD mechanistically connects the increased oxidative stress in STAT3-deficient cardiomyocytes to the development of PPCM.

Denise et al.(37) published a review to investigate the role of prolactin in PPCM and its implication in treatment. They wrote recent experimental and clinical studies suggest a causal role for the angiostatic and proapoptotic 16-kDa PRL for the initiation and progression of PPCM because the suppression of PRL release by the dopamine D2-receptor agonist, bromocriptine, could prevent the onset of disease in an animal model of PPCM (PPCM due to a cardiomyocyte-restricted knockout of

signal transducer and activator of transcription 3 [STAT3; STAT3-KO]). This notion is further supported by initial clinical data sets from case reports and small studies showing that the addition of bromocriptine to standard heart failure therapy was associated with improved LV function and a composite clinical outcome in women with acute severe PPCM

Olaf foster (38) conducted a study in which they obtained data of pregnant patients with heart disease ,the patients satisfied the inclusion criteria and were followed up after six months to see for the variation in biomarkers regarding their cardiac status. For each patient at baseline and at the 6-month follow-up visit, blood samples (12 ml) were withdrawn from an anterior cubital vein between 10 a.m. and 12 noon. During assessment after six months of standard cardiac failure therapy, 25 patients were classified as cardiac function improvers (IMP) and 13 as non-improvers (NIMP). Patients were classified as cardiac function improvers if their LVEF determined by echocardiography improved by at least ten units (i.e. 25 to 35%) and their NYHA class improved by at least one grade They revealed there was a striking difference in prolactin serum levels between PPCM patients and controls., PPCM patients (NIMPs and IMPs) displayed 3-fold higher median prolactin serum levels at baseline compared with age and gravida matched peripartum controls.

Janes et al.(39) published a case report of a woman who had developed HELLP syndrome and had an uneventful delivery by ceasearan section but one day after discharge she developed dyspnea and orthopnea and was readmitted. Despite appropriate therapy, the left ventricular (LV) contractility deteriorated considerably, and the ejection fraction dropped to 30% within the next four days. The coronary angiography was normal. The myocardial biopsy revealed a histopathological picture of cardiomyopathy. The prolactin cleaving protease Cathepsin D gave a

strong and specific signal on biopsy section. The patient responded very well to medically induced diuresis. She received angiotensin-converting enzyme (ACE)-inhibitor, digoxin, and beta-blockers, to treat cardiac failure, and was also given Bromocriptine 2.5 mg/QD after written consent. On discharge 16 days after the second admission, the left ventricular contractility had improved with an ejection fraction of 43%. At follow-up examinations, the ejection fraction of the left ventricle had improved further (after six months: ejection fraction 50%). Bromocriptine was discontinued after 3 months. They concluded we report that bromocriptine in addition to standard therapy, improved the symptoms of PPCM. Based on experimental and initial clinical findings, bromocriptine may serve as a causative therapeutic option.

2. C-Reactive protein

Silwa et al. (40) conducted a study to find the relationship between inflammatory markers and PPCM. One hundred patients with newly diagnosed PPCM was single-centred, prospective, and longitudinal. Clinical assessment, echocardiography, and blood analysis were done at baseline and after six months of standard therapy. Inflammatory markers were measured at baseline only. They reported the median plasma level of C-reactive protein for the 100 PPCM patients was 10.0 mg/L (range 1–90) with 45% of patients having values of >10 mg/L . Only ten patients had a C-reactive protein level of <3 mg/L. Baseline plasma levels of C-reactive protein correlated positively with LV end-diastolic (rs=0.33, P=0.0026) and end-systolic dimensions (rs=0.35, P=0.0012), whereas the correlation with LVEF (rs=−0.27, P=0.015) was inverse. Baseline plasma levels of C-reactive protein, TNF-alpha, and Fas/Apo-1 were elevated in patients with PPCM when compared with age, sex, body mass index, and parity comparable healthy volunteers.

Huang et al.(41) conducted a study in which 52 PPCM patients and 52 normal delivery subjects (control group) were followed up for one year. Blood samples patients were collected during admission, discharge and at follow up visit. Compared with the control group, PPCM patients were older, with a higher level of blood pressure, and a higher rate of suspected respiratory infection. The level of leucocytes, hs-CRP, cTNI and NT-proBNP in PPCM patients were higher than in control. Multivariate logistic regression analysis showed that elevated plasma hs-CRP (OR =1.86, $p<0.05$), respiratory infection (OR = 2.87, $p<0.01$), and hypertension (OR =1.68, $p < 0.05$) were independent risk factors for PPCM. They concluded that hypertension and inflammation might play a role in the pathogenesis of peripartum cardiomyopathy.

Sarojini et al.(42) conducted a prospective case-control study in which a total of 86 subjects were enrolled [patients (n = 46) and controls (n = 40)]. The details of the history of pre-eclampsia and mode of delivery were obtained from the patients. The history of onset of symptoms and signs was recorded at the first presentation and six months. Clinical assessment, echocardiography, and blood analysis were done at baseline and after six months of standard therapy. The reported C-reactive protein (22 vs 08 mg/dl, $p < 0.05$), TNF-α (9.6 vs 3.2 pg/dl, $p < 001$), and IL-6 (73.19 ± 34.4 vs 31.52 ± 8.83 pg/dl, $p < 0.005$) were significantly abnormal. These patients showed significantly higher LV dimensions, LV EDD (61.6 ± 7.1 vs 46 ± 9 mm $p < 0.004$) LV ESD ($53.1 \pm$ seven vs 32 ± 8, $p < 0.005$), and significantly lower echocardiographic left ventricular ejection fraction (LVEF) (25.9 ± 8.2 vs 55 ± 12 $p < 0.001$) and correlate well with NYHA FC and death. LVEF improved from 25.9 ± 8.2 to 42.9 + 13.6 % at six months ($p < 0.0001$). They concluded that plasma markers of inflammation were significantly elevated in PPCM patients

and correlated with increased LV dimensions and lower EF at presentation. Baseline CRP, IL-6, TNF-α, and higher NYHA FUNCTIONAL CLASSIFICATION were the only predictors of mortality. These results contribute to inflammation which may contribute to the pathogenesis of PPCM and its complications and predictors of mortality.

Bitekar et al.(43) conducted a study to find out the predictors of early and late recovery of cases of PPCM. Fifty-two consecutive women with PPCM were enrolled in this prospective study. Each patient underwent transthoracic echocardiography, B-type natriuretic peptide (BNP) and C-reactive protein (CRP) measurement at admission, and every three months. Early recovery was defined as resolution of heart failure at six months postdiagnosis, delayed recovery was defined if the length of time required for recovery of left ventricular function was longer than six months, and persistent left ventricular dysfunction (PLVD) was defined as an ejection fraction of less than 50% at the end of follow-up. They reported patients with complete recovery were more likely to have a higher left ventricular ejection fraction, smaller left ventricle end-systolic dimensions at baseline, and lower CRP and BNP levels at follow-up. Elevated levels of BNP and CRP on follow up at 3 and 6 months were associated with nonrecovery. Third and sixth month BNP values were significantly lower in patients with rapid recovery, compared to patients with delayed recovery. Thus the persistent elevation of plasma CRP and BNP levels at follow-up portend a slower response or nonrecovery in patients with PPCM.

Marino et al. (44) reported in their study that Proinflammatory cytokines IL-17 and sIL2R were associated with adverse events and less myocardial recovery. In contrast, higher levels of inhibitory IL-2 and IL-4

corresponded with higher subsequent LVEF. A pro-inflammatory environment in PPCM is linked to more severe disease and worse outcomes, while an anti-inflammatory milieu may be protective.

3. Troponin-I

Haghikia et al.(45) conducted a case-control study, 70 patients diagnosed with PPCM and 50 pregnancy-matched healthy women with normal cardiac function were enrolled. Clinical assessment, echocardiography and blood tests were performed at baseline and six ± two months follow-up. The presence of serum AABs(auto antibodies) against MHC (anti-MHC)Major Histocompatibility complex and TnI (anti-TnI) was determined with a custom-made enzyme-linked immunosorbent assay (ELISA). The seropositivity for these AABs was correlated with the severity of LV dysfunction and the occurrence of pericardial effusion indicative of per myocardial inflammation at baseline. They concluded in PPCM the presence of either one of these AABs was associated with significantly lower baseline LVEF and a lower rate of full cardiac recovery at follow-up. Patients who were seropositive for anti-TnI AABs showed more frequently pericardial effusion indicative of a more pronounced immune response of the peri myocardium in these patients. Thus troponin I and PPCM had a relation which needs to be evaluated.

Neutrophil and Hypertension in pregnancy

Greer et al. (46) conducted a study in which they included 30 normal non-pregnant women, 32 women with healthy pregnancies, 19 with mild/moderate PIH and 16 with severe PIH between 28 and 39 weeks gestation to see the relation of human neutrophil elastase with hypertension in pregnancy. They reported that there was a significantly higher concentration of plasma neutrophil elastase in both mild/moderate

and severe PIH than in normotensive pregnancies, and this may contribute to the vascular lesion associated with PIH. Levels were also significantly higher in healthy pregnancy than in non-pregnant women which suggest that neutrophil activation and degranulation are increased in a healthy pregnancy.

Canzoneri et al. (47) conducted a retrospective study on 240 women who were delivered at from January 1, 2002, to July 31, 2003. A total of 80 patients were studied in each group: normal pregnancy, mild PE, or severe PE. Leukocyte total and neutrophil, lymphocyte, monocyte, eosinophil, basophil, haemoglobin, and platelet counts were analyzed by analysis of variance and pairwise comparison. The total leukocyte count was significantly increased in women with severe PE compared with women with mild PE and normal pregnant controls: 10.66±3.70 ($p<0.0001$) versus 9.47±2.59 and 8.55±1.93 ($1\times103/\mu L$), respectively. The increased total leukocyte count was mainly due to the increase in neutrophil numbers: 8.05±4.01 (severe; $p<0.0001$) versus 6.69±2.23 (mild) and 5.90±1.79 (controls), respectively. The total neutrophil count was further increased 48 hours after delivery in the group with severe PE.

Association between the hypertensive disorder of pregnancy and PPCM

Kimura et al. (48) conducted a study in which they prospectively collected the data of 405 pregnant women who were treated at a Japanese general hospital between 2012 and 2013. They analyzed their laboratory data and echocardiographic findings during the third trimester (28–30 weeks' gestation) and within four days of delivery. They reported cTnI levels increased to over 0.015 ng/mL after delivery in 4.0% of pregnant women. In a multivariate analysis, PIH (OR: 18.71, P = 0.003), placental abnormality (OR: 26.78, P = 0.007), and decreased haemoglobin after

delivery (OR: 2.59, P <0.001) were the factors associated with elevated cTnI. They reported that subclinical myocardial injury might occur during the peripartum period if PIH, placental abnormality, and anaemia after delivery are present. This may be related to PPCM postpartum or in subsequent pregnancies.

Parameshwari et al. conducted a case-control study involving 96 patients with PPCM as the case group, and 96 healthy patients without PPCM as the control group with a 1:1 ratio to evaluate the most influential risk factor of PPCM. The multivariate analyses suggest lower socioeconomic status had 3.312 times (CI 1.383 to 7.932) increased the risk of having PPCM after consideration of other significant factors. Hypertension in current pregnancy raises the risk of PPCM 2.311 times (CI 1.164 to 4.590); while the history of hypertension in previous pregnancy suggests 4.862 times (CI 1.245 to 8.988) increased risk of PPCM. Multi-foetal pregnancies increase the risk of PPCM 7.057 times (CI 0.777 to 64.097). The results of this study, based on the multivariate analysis and confidence interval at the narrowest range, and other significant risk factors under consideration, indicate that the most influential risk factors for PPCM in Japanese ethnic patients are the history of hypertension in previous pregnancy and hypertension in current pregnancies. Most of the case groups (57.9%) in this study had pre-eclampsia as the type of hypertension in pregnancy.

Fleming et al.(16) Conducted a study to find the association of cardiac troponin with hypertension during pregnancy. Women with hypertension in pregnancy (at least two readings of systolic blood pressure > 140 mmHg and diastolic blood pressure > 90 mmHg) (n = 26) and normotensive women (n = 43) were included in the study. Serum cardiac troponin I was measured using Beckman Access immunoassay. The

median serum cardiac troponin I level in pregnancies complicated by hypertension was 0.118 ng/mL (n = 26) which was significantly greater than that measured in samples obtained from normotensive women in pregnancy (0.03 ng/mL; n = 43) (P < 0.0001). There were higher median serum cardiac troponin I levels in hypertensive women with significant proteinuria (0.155 ng/mL; n = 6), compared with those without proteinuria (0.089 ng/mL; n = 20; P = 0.03).They concluded that serum cardiac troponin I is elevated in women with hypertensive disorders of pregnancy indicating some degree of cardiac myo fibrillary damage in these disorders.

Behrens et al. (49) conducted a nationwide Danish cohort study among women diagnosed with PPCM from 2005 to 2014 (PPCM group) were invited to participate in a clinical follow-up study including maximal cardiopulmonary exercise testing and cardiac magnetic resonance imaging. Matched women with previous severe pre-eclampsia (pre-eclampsia group) and previous uncomplicated pregnancies (uncomplicated pregnancies group) served as comparison groups. A total of 84 women with 28 in each group participated. Median time to follow-up after PPCM was 91 months. Most women (85%) in the PPCM group reported no symptoms of heart failure. Mean left ventricular ejection fraction in the PPCM group was normal at 62%, but significantly lower than in the pre-eclampsia group and the uncomplicated pregnancies group where mean left ventricular ejection fraction was 69% and 67%, respectively (P<0.0001). Women in the PPCM group also had impaired diastolic function with reduced left ventricular peak filling rate, left atrial passive emptying volume, and left atrial passive emptying fraction. Maximal exercise capacity (peak VO 2) was also reduced in the PPCM group compared with the pre-eclampsia group and the uncomplicated

pregnancies group, and PPCM , high body mass index, and low left ventricular ejection fraction independently predicted reduced peak VO 2. They concluded although 70% of PPCM occurred in women with normotensive pregnancies, HDPs were associated with substantial increases in PPCM risk that depended on HDP severity. The heart's capacity to adapt to a normal pregnancy may be exceeded in some women already susceptible to cardiac insult, contributing to PPCM. HDPs, severe pre-eclampsia in particular, probably represent an additional cardiac stressor during pregnancy.

Bello et al. (50) conducted a meta analysis in 2013 on 22 studies on pregnancy induced HTN and PPCM.They reported the pooled prevalence of 22% (95% confidence interval [CI] 16 to 28) was more than quadruple the 5% average worldwide background rate of PE in pregnancy ($p < 0.001$). Thus they inferred the prevalence of PE, hypertensive disorders, and multiple gestations in women with PPCM is markedly higher than that in the general population. These findings support the concept of a shared pathogenesis between PE and PPCM and highlight the need for awareness of the overlap between these 2 diseases.

Lindey et al. conducted a study to access if pre-eclampsia is a risk factor for the development of peripartum cardiomyopathy (PPCM).They included This retrospective cohort study included women diagnosed with PPCM delivering at Barnes-Jewish Hospital between 2004 to 2014. The primary outcome was one-year event-free survival rate for the combined end point of death and hospital readmission. The secondary outcome was recovery of LV ejection fraction. They reported seventeen of 39 women (44%) with PPCM had pre-eclampsia. The groups had similar mean LV ejection fraction at diagnosis (29.6 with versus 27.3 without pre-eclampsia; P=0.5). Women with pre-eclampsia had smaller mean LV

end-diastolic diameters (5.2 versus 6.0 cm; P=0.001), greater relative wall thickness (0.41 versus 0.35 mm Hg; P=0.009), and lower incidence of eccentric remodeling (12% versus 48%; P=0.03). In time to event analysis, patients with pre-eclampsia had worse event-free survival during 1-year follow-up (P=0.047). They concluded PPCM with concomitant pre-eclampsia is associated with increased morbidity and mortality and different patterns of LV remodeling and recovery of LV function when compared with patients with PPCM that is not complicated by pre-eclampsia.

Pergialitos et al. (51) conducted a systemic review from the Medline (1966–2015), Scopus (2004–2015), Popline (1974–2015), ClinicalTrials.gov (2008–2015) and Cochrane Central Register of Controlled Trials (CENTRAL) (1999–2015) databases to see the relationship of Troponin I in cardiac patients who suffer from pre eclampsia. They reported that cTnI might be elevated in pre-eclamptic pregnant women, although this observation is not always reported. Thus hypertension may actually be a risk factor of development of future cardiac disease.

Prognosis

Felker et al. (52) conducted a study to evaluate the outcomes of 1230 patients with cardiomyopathy. They reported that Patients with peripartum cardiomyopathy appear to have a better prognosis than those with other forms of cardiomyopathy. Patients with cardiomyopathy due to infiltrative myocardial diseases, HIV infection, or doxorubicin therapy have an especially poor prognosis.

Raddino et al. (53) published a review on heart diseases during pregnancy in which they wrote about half the patients of PPCM recover without

complications. The prognosis is poor in patients with persistent cardiomyopathy. Persistence of disease after six months indicates irreversible cardiomyopathy and portends worse survival.

Gunderson et al. (28) conducted a retrospective study in which they included all cases of diagnosed heart failure that occurred among women within one month before to 5 months after delivery of a live born neonate in Kaiser Permanente Northern California delivery hospitals between 1995 and 2004. Among 227,224 eligible women, we confirmed 110 recognized peripartum cardiomyopathy cases. They reported maternal death rate (per 1,000 person-years) was higher among cases (6.12) than non cases (0.23; P<.001). Neonates whose mothers developed peripartum cardiomyopathy, experienced poorer clinical outcomes.

Jeong et al. (54) published a review on clinical management and prognosis of PPCM in which they wrote despite maximal medical treatment, 20% to 25% of patients progress to end-stage HF over time. Cardiac transplantation or LV assist device treatment is performed in 4% to 11% of PPCM patients but reported maternal mortality was 3.3% to 30% over a period of greater than 6 months. The majority of deaths occur within the first 3 to 6 months after diagnosis. Major causes of death include progression to refractive HF, ventricular arrhythmia, and thromboembolism, approximately one-third of survivors suffer from neurologic sequelae following cardiac arrest or stroke.

MATERIALS AND METHODS

A hospital based prospective cohort study was done to determine the relation between predictors of Peripartum cardiomyopathy in hypertensive disorders of pregnancy.

Place of study: Department of Obstertics And Gynaecology In B.L.D.E. (Deemed To Be University) Shri B.M. Patil's Medical College, Hospital and Research Centre, Vijayapura

Field of study: Teritary health care center.

Study duration: Novemeber 2018- 30th April 2020.

Study population: Patients with hypertensive disorders of pregnancy.

Study design: A hospital based prospective cohort study.

SOURCE OF DATA:

Patients with hypertensive disorders of pregnancy

INCLUSION CRITERIA

1. All patients diagnosed as hypertensive disorders of pregnancy(gestational hypertension, preeclampsia , eclampsia i.e. antepartum and postpartum eclampsia) who is in labor or the delivery is planned with in 24hours.
2. Gestational age > 24 weeks
3. Patients giving informed and written consent for investigations and follow up

EXCLUSION CRITERIA

1.Gestational Diabetes Mellitus

2.Pre Existing Cardiac Disorders

3.Chronic Hypertensive Patients

4.Patient's with Hemoglobin level less than 7gm/dl.

SAMPLE SIZE: 265 patients

METHODOLOGY:

1. All Hypertensive patients were included in the study

- Gestational hypertension is defined as blood pressure > 140/90 mmHg for the first time in pregnancy after 20 weeks without proteinuria

- Preeclampsia is defined as hypertension to the extent of 140/90 mmHg or more with proteinuria after 20th week in previously normotensive and non –proteinuric woman

a) Mild Preeclampsia: Defined as blood pressure of >140/100 mmHg , with minimal proteinuria , normal haematological and biochemical parameters with no fetal compromise.
b) Severe preeclampsia: Defined as blood pressure of >160/100mmHG , with proteinuria>5gm/24 hours , oliguria <400ml/24 hours, platelet count <100000/mm3 , HELLP syndrome , cerebral or visual disturbances , IUGR.

- Eclampsia is defined as preeclampsia complicated with convulsions or coma

2. Consent was taken for sending investigations and follow up

3. These patients were observed for clinical features of cardiomyopathy for one week in hospital. If they develop the clinical features of PPCM like breathlessness, pedal oedema, tachycardia, decreasing in saturation (Spo2) .2D ECHO was done to confirm the diagnosis.

4. If they do not develop any features during hospital stay, they were discharged, but patients were followed in OPD at 1 month , 3 month and 6 months to know whether any of them developed any cardiac problems. If they could not come for follow up , they were contacted on phone for to ask for features of PPCM. If they had any features they were called for ECHO.

INVESTIGATIONS

- Complete blood count (TOTAL LEUCOCYTE COUNT)
- Serum Prolactin
- Troponin I
- ECHO CARDIOGRAPHY, when patients develop symptoms and signs of PPCM.

RESULTS

Table 1. Distribution of study participants as per their age.

Age (in years)	No PPCM		PPCM		Value	df	P Value
	No. of study participants	Percent	No. of study participants	Percent			
18-20	54	22.3	8	34.8	3.076	6	.799*
21-23	80	33.1	6	26.1			
24-26	66	27.3	5	21.7			
27-29	23	9.5	3	13.0			
30-32	10	4.1	1	4.3			
33-35	6	2.5	0	0.0			
>36	3	1.2	0	0.0			
Total	**242**	**100.0**	**23**	**100.0**			

***p =0.799<0.05 – Not Significant**

It is observed from the above table that maximum number of participants ie 80 (33.1%) among the patients without evidence of PPCM and 6 (26.1%) with PPCM were from the age group of 21-23 years. While only 3(1.2%) participants among patients without evidence of PPCM and none of the patients among PPCM group had evidence were more than 36 years of age. The mean age of PPCM group was 24+/- 5.2 years while that of other group was 23+/-3.5 years. The difference between the groups is not significant as proved by Chi-square test (P=0.79>0.05)

Figure 1. Distribution of study participants as per their age.

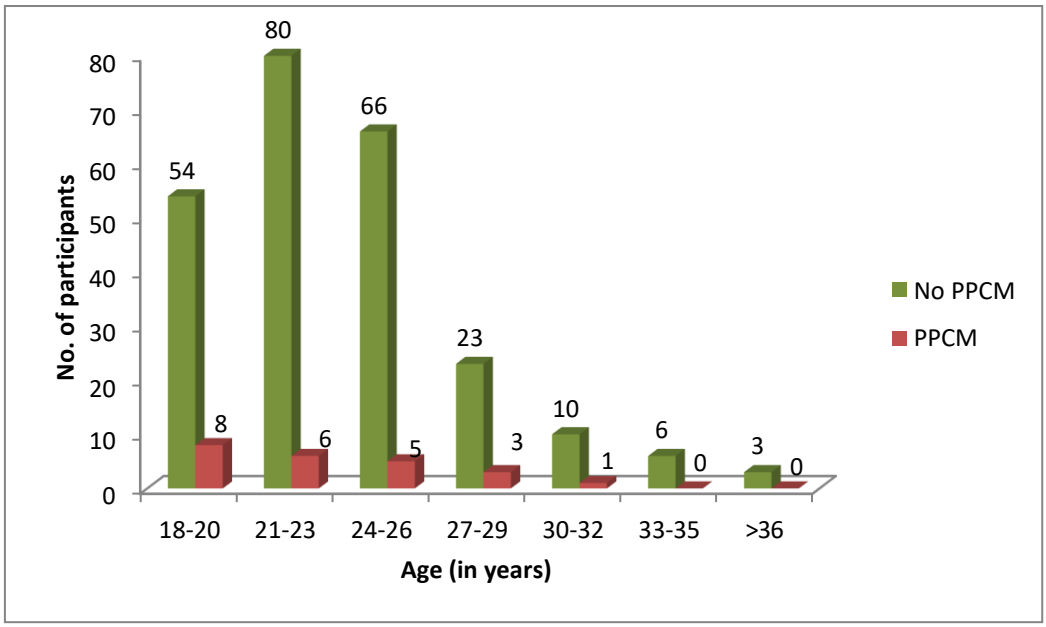


Table 2. Distribution of study participants as per their occupation.

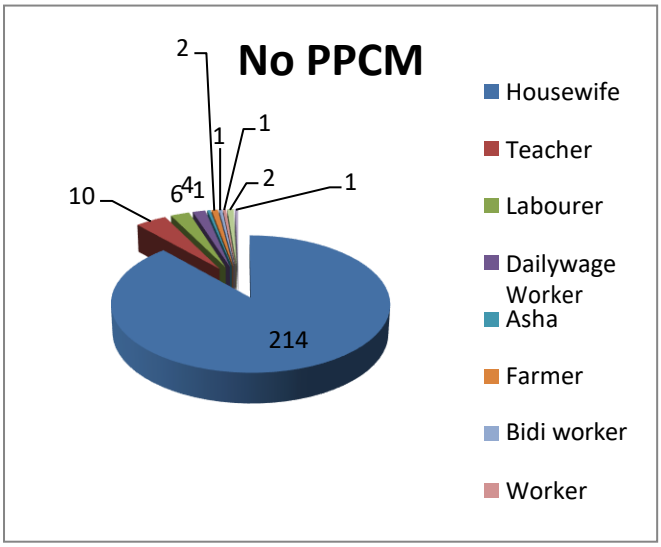
Occupation	No PPCM		PPCM		Value	Df	P Value
	No. of study participants	Percent	No. of study participants	Percent			
Housewife	214	89.0	20	86.96	2.169	10	0.99*
Teacher	10	4.1	1	4.35			
Labourer	6	2.5	1	4.35			
Daily wage Worker	4	1.7	0	0.00			
Asha	1	.4	0	0.00			
Farmer	2	.8	0	0.00			
Bidi worker	1	.4	0	0.00			
Worker	1	.4	0	0.00			
Engineer	2	.8	1	4.35			
Nurse	1	.4	0	0.00			
Total	**242**	**100.0**	**23**	**100.0**			

***p =0.99>0.05 – Not Significant**

It is observed from the above table that majority of the study participants 89% in patients who had no PPCM and 86% in PPCM patients were housewives. 4.1% among patients who didn't have PPCM and 4.35% in PPCM group were

teachers. While other occupations among the study participants were farming, bidi making etc. The difference between the groups is not significant as proved by Chi-square test (P=2.169>0.05)

Figure 2. . Distribution of study participants as per their occupation.



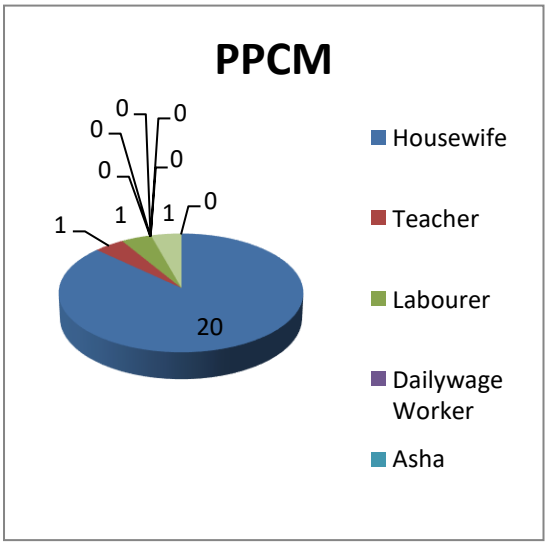


Table 3. Distribution of study participants as per parity.

Parity	No PPCM		PPCM		Value	df	P Value
	No. of study participants	Percent	No. of study participants	Percent			
0	105	43.4	1	4.3	14.88	4	0.00
1.0	87	36.0	16	69.6			
2.0	36	14.9	3	13.0			
3.0	10	4.1	3	13.0			
4.0	4	1.7	0	0			
Total	242	100.0	23	100.0			

***p =0.00<0.05 –Significant**

It is observed from the above table that majority of the women ie 43.4% in patients who had no PPCM and only 4.3% in patients who had PPCM were Primipara. 87(36%), women in patients who had no PPCM while 69.6% who were having PPCM were second para. There were also 13% patients among PPCM group who were parity 2 and 4 respectively. The difference between the groups is significant as proved by Chi-square test (P=3.893>0.05)

Figure 3. Distribution of study participants as per parity.

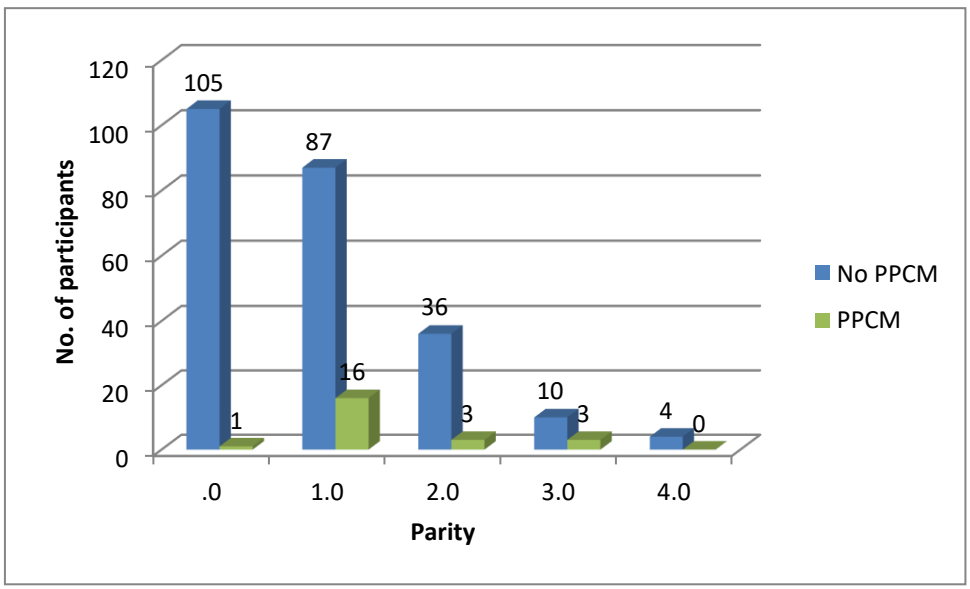


Table 4. Distribution of study participants as per the occurrence of abortion.

Abortion	No PPCM		PPCM		Value	df	P Value
	No. of study participants	Percent	No. of study participants	Percent			
Yes	32	13.2	5	21.7	3.620[a]	3	0.31*
No	210	86.8	18	78.3			
Total	242	100.0	23	100			

***p =0.799>0.05 – Not Significant**

It is observed from the above table that 5(21.7%) of the study participants in the group with PPCM had history of abortion while 32(13.2%) patients in the non PPCM group had history of abortion. Although the difference in occurrence of abortion is not significant as proved by Chi-square test (P=3.620>0.05).

Figure 4. Distribution of study participants as per the occurrence of abortion.

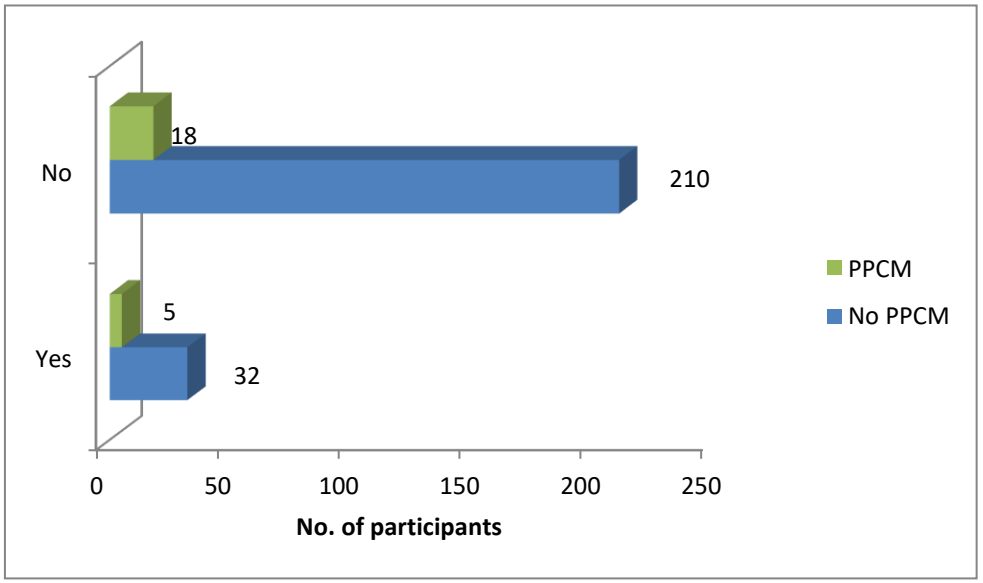


Table 5. Distribution of study participants as per their gestational age.

Gestational age (Weeks. Days)	No PPCM		PPCM		Value	df	P Value
	No. of study participants	Percent	No. of study participants	Percent			
25-28.1	3	1.2	1	4.3			
28.2-31.3	17	7.0	0	0			
31.4-34.5	26	10.7	5	21.7			
34.6-37.7	59	24.4	5	21.7	5.266[a]	5	0.38*
37.7-40.8	126	52.1	11	47.8			
40.9-44	11	4.5	1	4.3			
Total	**242**	**100.0**	**23**	**100.0**			

***p =0.799>0.05 – Not Significant**

It is observed from the above table that majority 126 (52.1%) study participants in patients with no PPCM and 11(47.8%) among patients with PPCM had gestational age of 37.7-40.8 weeks. Followed by 59 (24.4%) patients with no PPCM and 5(21.7%) in Patients with PPCM had a gestational age of 34.6-37.7 weeks. While only 3 (1.2%) study participants in no PPCM group and 1(4.3%) in PPCM group had gestation age of 25-28.1 years. The mean gestation age among PPCM group was 36.95+/-3.5 years while that in the no PPCM group was 37.1+/-3.1 years. The difference between various gestational age groups is not significant as proved by Chi-square test (P=0.38>0.05)

Figure 5. Distribution of study participants as per their gestational age.

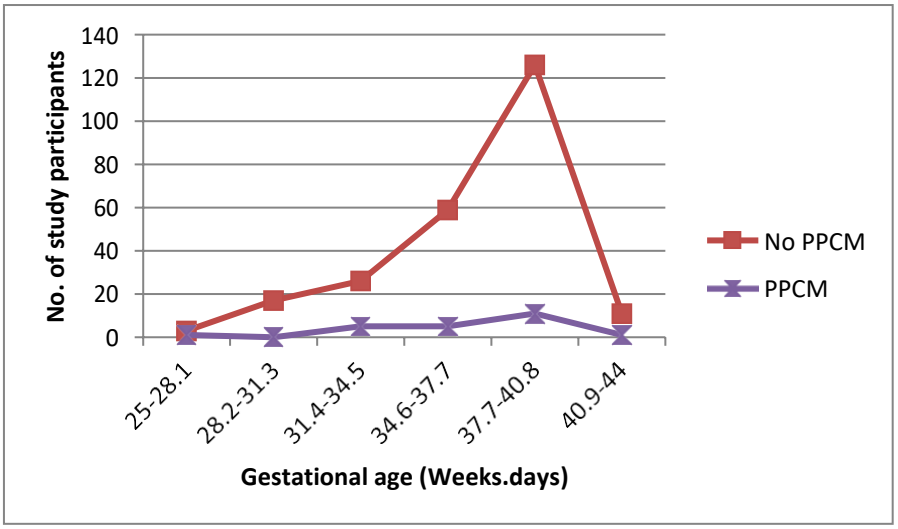


Table 6. Distribution of study participants as per past history of HTN.

P/H/O Hypertension	No PPCM		PPCM		Value	Df	P Value
	No. of study participants	Percent	No. of study participants	Percent			
Yes	9	3.7	4	17.4	5.74	1	0.02*
No	233	96.3	19	82.6			
Total	**242**	**100**	**23.0**	**100**			

P=0.02<0.05 (Significant)

It is observed from the above table that 3.7% of the study participant who didn't have PPCM were having past history of hypertension while 17.4% study participants who had PPCM had past history of hypertension. The difference between the group is significant as proved by Chi-square test (p=0.02<0.05)

Figure 6. Distribution of study participants as per past history of HTN.

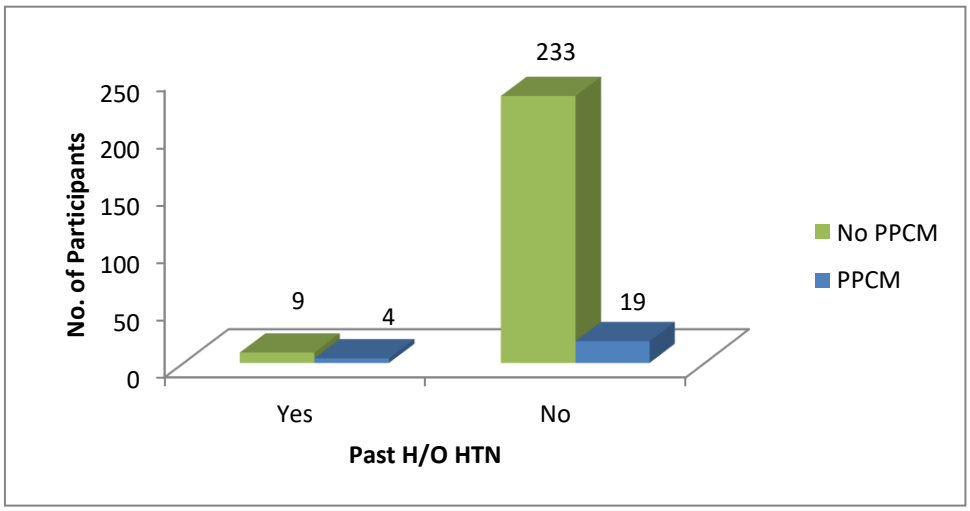


Table 7. Distribution of study participants as per hypertension in mother.

Hypertension in mother	No PPCM		PPCM		Value	Df	P Value
	No. of study participants	Percent	No. of study participants	Percent			
Yes	7	2.9	3	13.04	3.49	1	0.05
No	235	97.1	20	86.95			
Total	**242**	**100**	**23.0**	**100**			

P=0.02<0.05 (Significant)

It is observed from the above table that 2.9% of the study participant who didn't have PPCM had past history of hypertension in mother while 13.04% study participants who had PPCM had the same. The difference between the group is significant as proved by Chi-square test (p=0.02<0.05)

Figure 7. Distribution of study participants as per hypertension in mother.

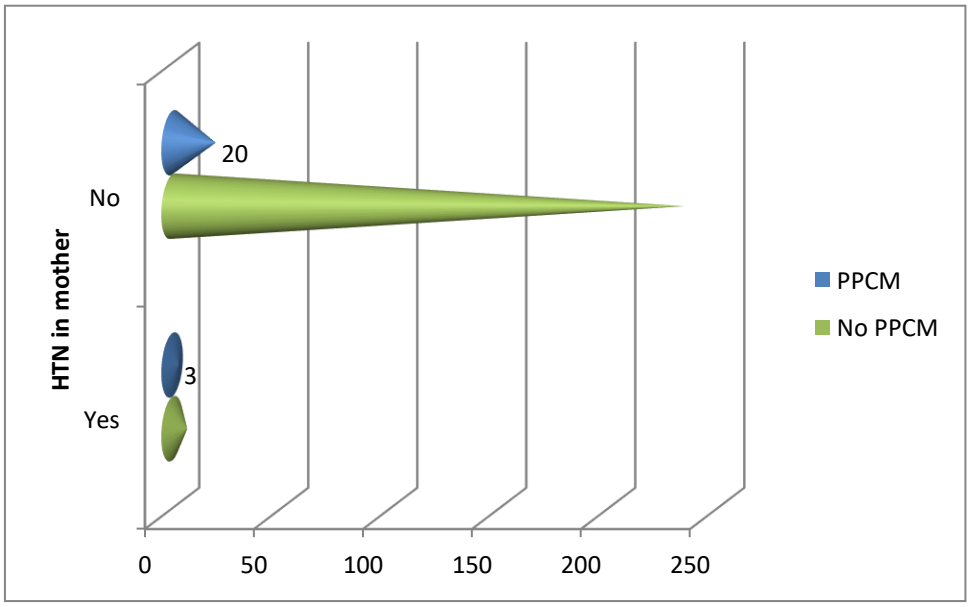


Table 8. Distribution of study participants as per hypertension in father.

Hypertension in Father	No PPCM		PPCM		Value	Df	P Value
	No. of study participants	Percent	No. of study participants	Percent			
Yes	8	3.3	0	0	.095	1	0.76*
No	234	96.7	23	100			
Total	242	100	23.0	100			

***p =0.095>0.05 – Not Significant**

It is observed from the above table that 3.3% patient who had no PPCM had no history of hypertension in father while none of the patient who had PPCM had history of hypertension in father. The difference between the groups is not significant as proved by Chi-square test (P=0.095>0.05)

Figure 8. Distribution of study participants as per hypertension in father.

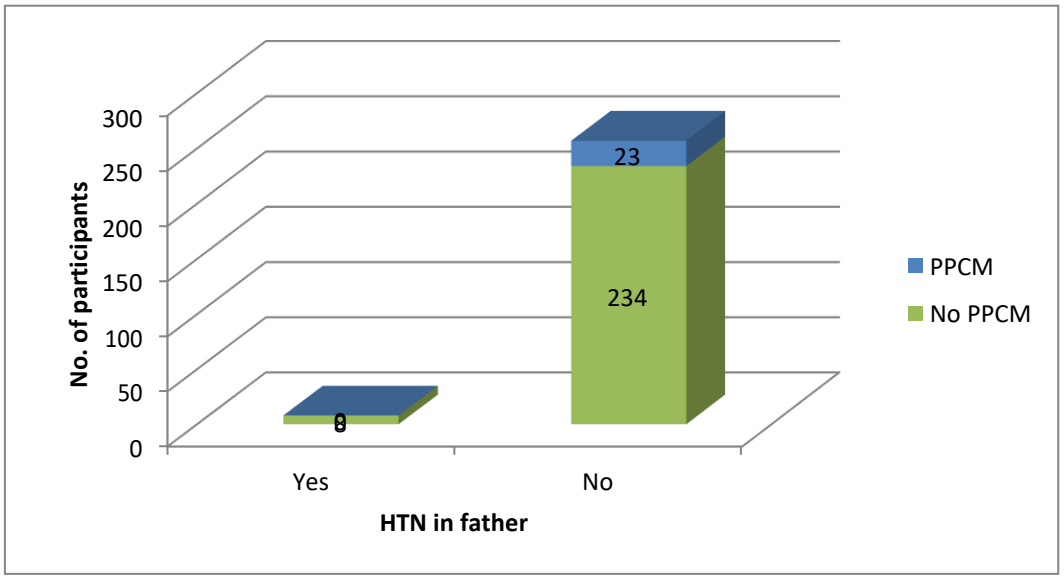


Table 9. Distribution of study participants as per previous history of PPCM.

H/O PPCM	No PPCM		PPCM		Value	df	P Value
Yes	1	.4	3	13.04	14.84	1	0.001*
No	241	99.6	20	86.9			
Total	242	100	23.0	100			

***p=0.001<0.05= Significant**

It is observed from the above table that among patients with PPCM, 13.04% had previous history of PPCM while only 0.4% in the patients who didn't have PPCM were having previous history of PPCM. The difference between the groups is significant as proved by Chi-square test (0.001<0.05)

Figure 9. Distribution of study participants as per previous history of PPCM.

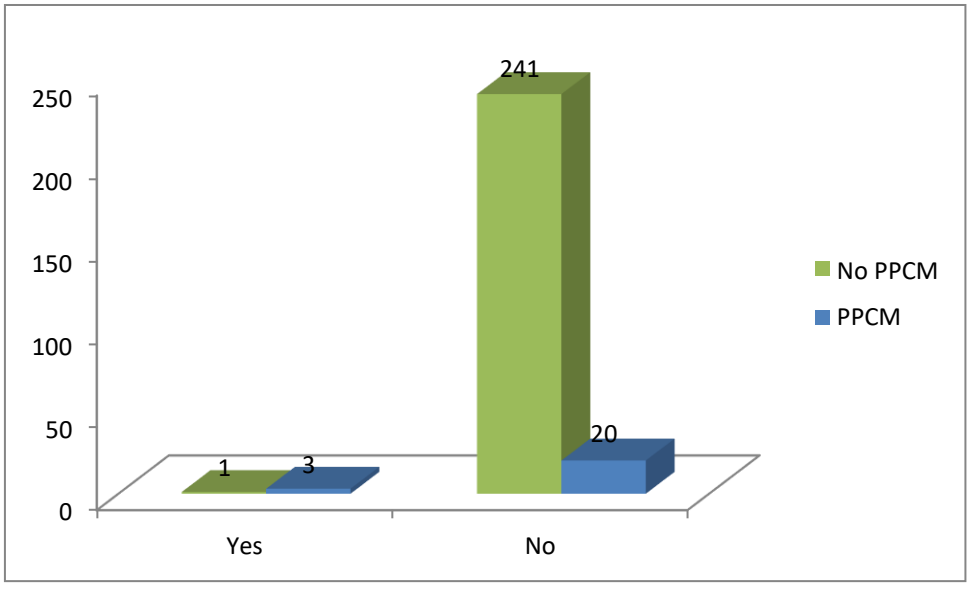


Table 10. Distribution of study participants as per grade of hypertension

Blood Pressure	Morbidity	N	Mean	Median	Std. Deviation	Mean difference	Std. Error Difference	t	df	P Value*
Systolic	PPCM	23	143.565	150.000	11.7544	2.04	2.31	0.88	263.00	0.38
	No PPCM	242	141.529	140.000	10.4929					
Diastolic	PPCM	23	91.304	90.000	3.4435	-1.67	1.09	-1.54	263.00	0.13
	No PPCM	242	92.975	90.000	5.0957					

***p=0.3<0.05= Non Significant**

It is observed from the above table that among PPCM group mean systolic BP was 143.56 and diastolic BP was 91.30 while among non PPCM the mean systolic BP was 141.52 and diastolic BP was 02.97. The difference between systolic and diastolic BP among the groups was not significant as prove by Unpaired T test

Table 11a. Distribution of study participants as per severity of gestational hypertension

Gestational Hypertension	No PPCM		PPCM		Value	df	P Value
Yes	24	9.9	2	8.7	0.035	1	0.85
No	218	90.1	21	91.3			
Total	242	100.0	23	100.0			

It is observed from the above table that in patients with PPCM 8.7% had gestational hypertension while 9.9% had gestational hypertension among patients who did not develop PPCM. The difference between the groups is not significant as proved by Chi-square test (0.85>0.05).

Figure 10. Distribution of study participants as per severity of gestational hypertension

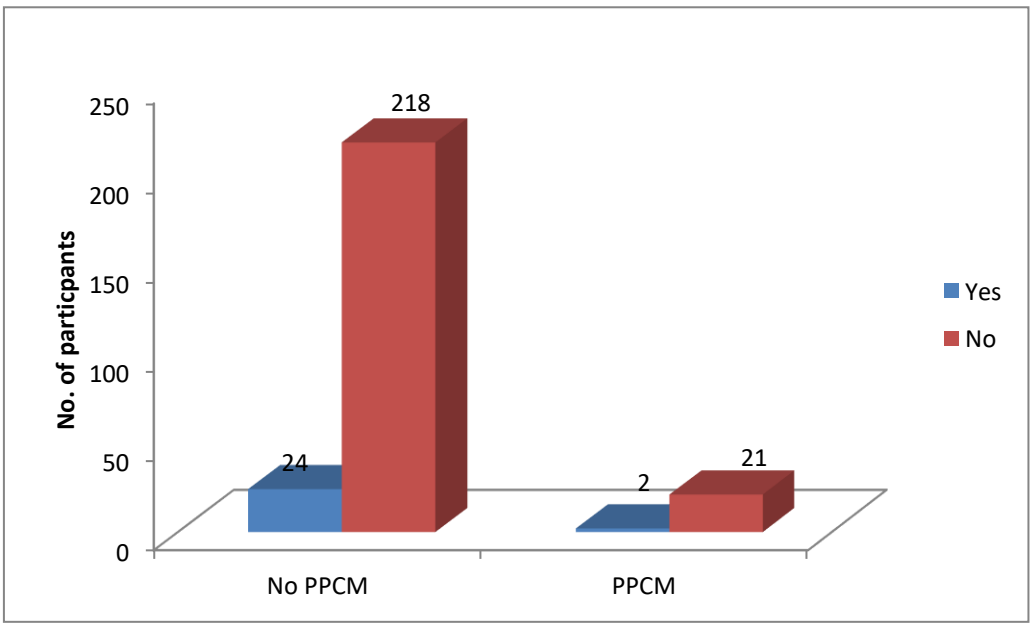


Table 11b. Distribution of study participants as per severity of preeclampsia

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Preeclampsia	No PPCM	Percent	PPCM	Percent	Value	df	P Value
Mild	58	42.0	2	11.8	4.64	1	0.03*
Severe	80	57.6	15	88.2			
Total	138	99.3	17	100.0			

***p=0.002<0.05= Significant**

It is observed from the above table that in patients with PPCM only 11.8% had mild preeclampsia while 88.2% had severe pre-eclampsia. In the patients with no PPCM 42% patients had mild PPCM while 57.6% had severe pre-eclampsia. The difference between the groups is significant as proved by Chi-square test (0.002<0.05).

Figure 11. Distribution of study participants as per severity of preclampsia.

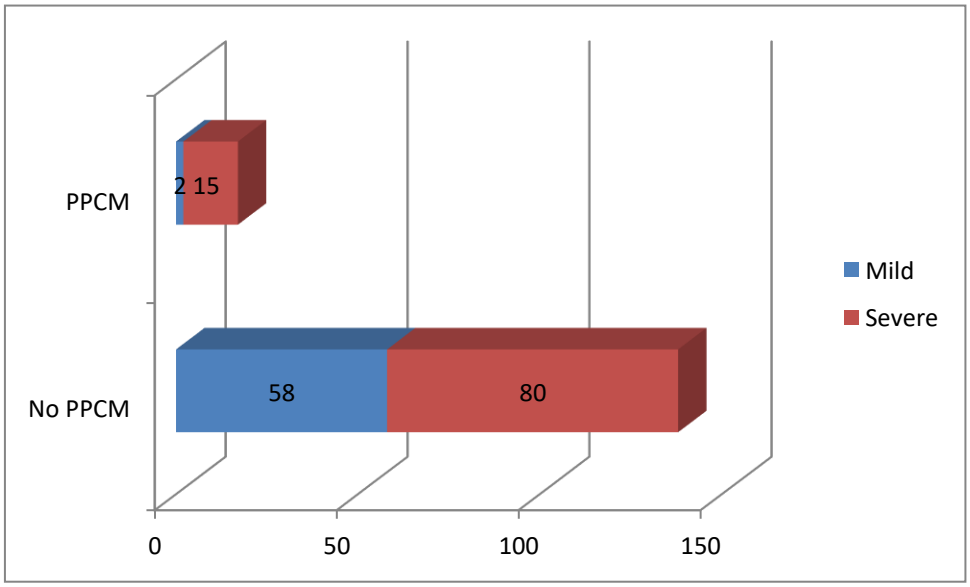


Table 12. Distribution of study participants as per severity of eclampsia.

Eclampsia	No PPCM		PPCM		Value	Df	P Value
	No. of study participants	Percent	No. of study participants	Percent			
Yes	74	30.6	4	17.4	2.566[a]	3	0.46
No	162	66.9	19	82.6			
Eminent	4	1.7	0	0.0			
Antepartum	2	.8	0	0.0			
Total	242	100.0	23	100.0			

***p=0.46>0.05 – Not Significant**

We observe in the above table that 30.6% patients in the patients who didn't have PPCM developed and 17.4% patient in the PPCM group had eclampsia. The difference between the groups is significant as proved by Chi-square test (0.46>0.05).

Figure 12. Distribution of study participants as per severity of eclampsia.

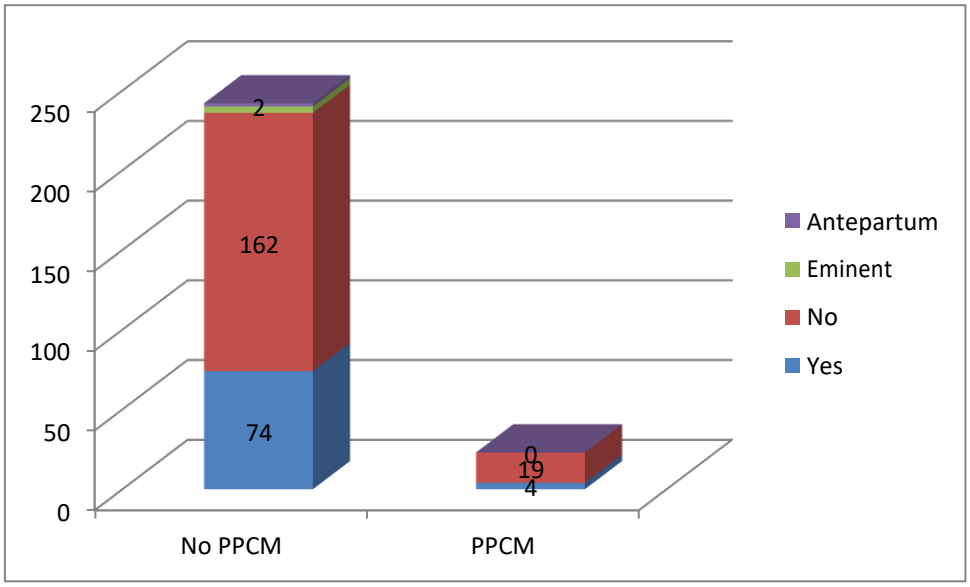


Table 13. Comparison of leucocyte count among the study participant.

TLC	N	Minimum	Percentile 25	Median	Percentile 75	Maximum	Mean	Std. Deviation
PPCM	**23**	8940	10790	17000	22280	41490.0	17166.1	9105.3
No PPCM	**242**	1120	10030	13365	18350	22260	15056.3	8711.2

Figure 13. Comparison of leucocyte count among the study participant.

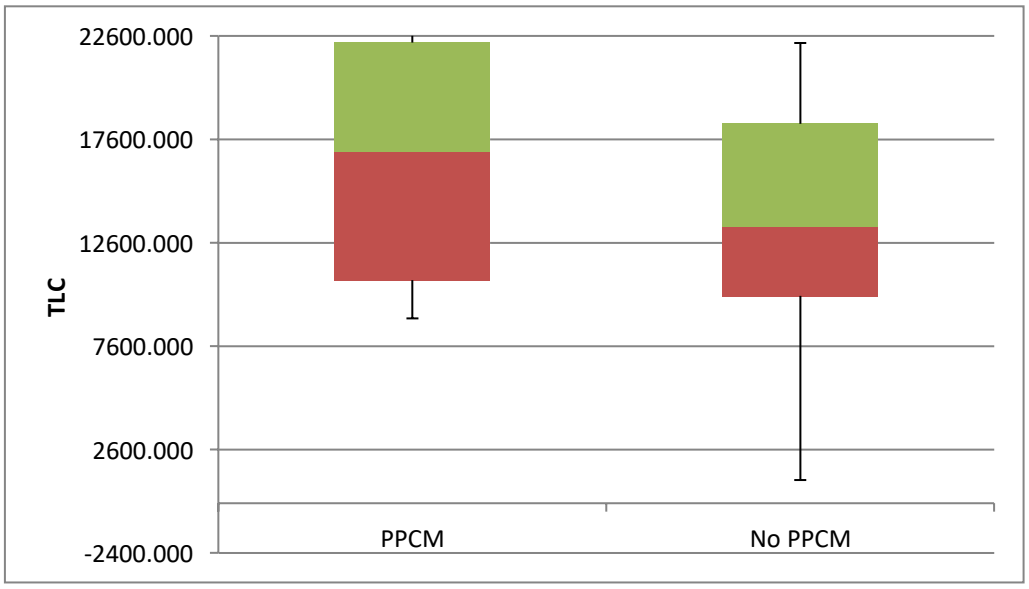


Table 14. Comparison of leucocyte count among the study participant.

TOTAL LEUCOCYTE COUNT								
Morbidity	**N**	**Mean**	**Std. Deviation**	**Mean difference**	**Std. Error Difference**	**t**	**Df**	**P Value***
PPCM	23	17166.1	9105.3	2109.7646	1908.1171	1.1057	263	0.05
No PPCM	242	15056.3	8711.2					

***p=0.05=0.05 –Significant**

We observe from the above table that mean leucocyte count among PPCM patients was 17166+/_ 9105.3 while that in patients who didn't have PPCM was 15056+/_8711.2. The difference in mean leucocyte count among PPCM and Non PPCM group was statistically significant as proved by Unpaired T test.

Table 15. Comparison of serum prolactin among the study participant.

Serum Prolactin	N	Minimum	Percentile 25	Median	Percentile 75	Maximum	Mean	Std. Deviation
PPCM	**23**	2	123.41	200.00	204.25	912	171.30	72.074
No PPCM	**242**	3	112.00	118.00	200.00	202	129.35	61.658

Figure 14. Comparison of serum prolactin among the study participant.

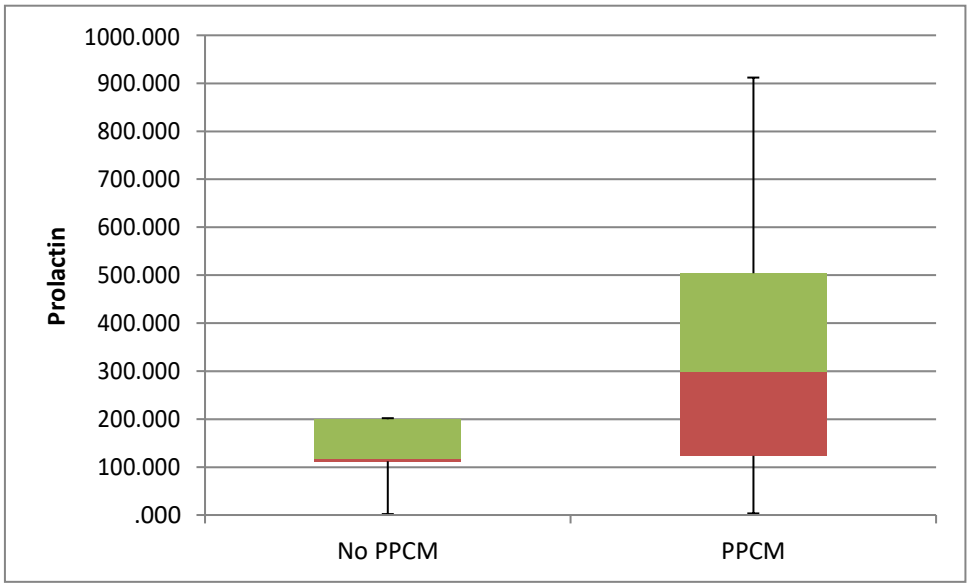


Table 16. Comparison of serum prolactin among the study participant.

Serum Prolactin								
Morbidity	**N**	**Mean**	**Std. Deviation**	**Mean difference**	**Std. Error Difference**	**t**	**df**	**P Value***
PPCM	23	171.3	72.1	41.9500	15.5490	-2.698	263	0.007
No PPCM	242	129.4	61.7					

***p=0.007<0.05 –Significant**

We observe from the above table that mean serum prolactin among PPCM patients was 171.30+/_ 72.07 while that in patients who didn't have PPCM was 129.35+/_61.65. The difference in serum prolactin among PPCM and Non PPCM group was statistically significant as proved by Unpaired T test.

Table 17. Comparison of Troponin I among the study participant.

Troponin I	N	Minimum	Percentile 25	Median	Percentile 75	Maximum	Mean	Std. Deviation
PPCM	**23**	.011	.011	.012	.014	.030	.064	.233
No PPCM	**242**	.001	.007	.009	.011	0.023	.04	3.91

Figure 15. Comparison of Troponin I among the study participant.

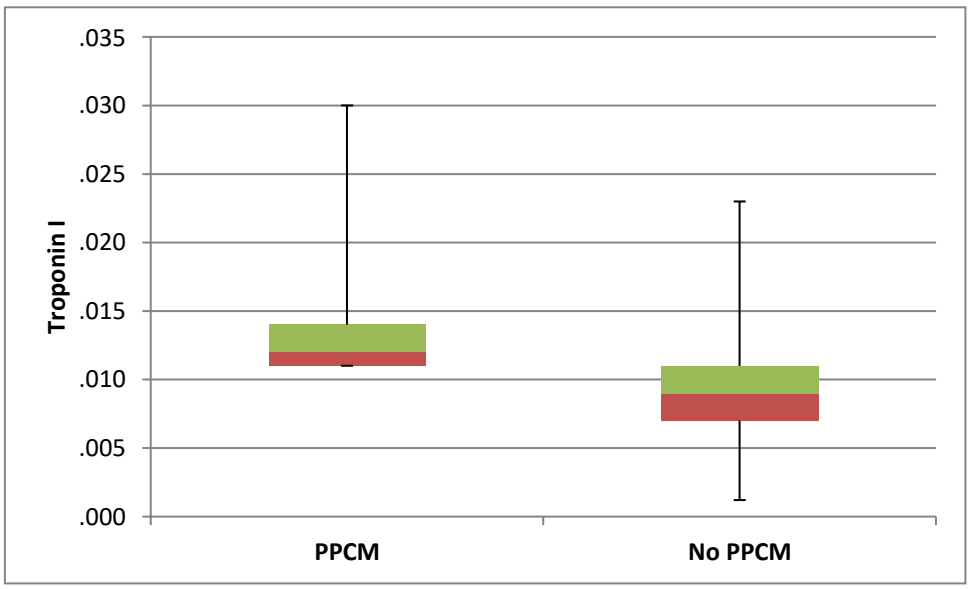


Table 18. Comparison of Troponin I among the study participant.

Troponin I								
Morbidity	**N**	**Mean**	**Std. Deviation**	**Mean difference**	**Std. Error Difference**	**t**	**Df**	**P Value***
PPCM	23	0.064	0.233	-0.3181	0.8184	-.389	263	.049
No PPCM	242	0.04	3.91					

***p=0.04<0.05 – Significant**

We observe from the above table that mean Troponin I level among PPCM patients was 0.64+/_ 0.2 while that in patients who didn't have PPCM was 0.4+/_3.9. The difference in mean Troponin I among PPCM and Non PPCM group was statistically significant as proved by Unpaired T test.

Table 19. Distribution of study subjects as per mode of delivery

Mode of delivery	No PPCM		PPCM		Value	df	P Value
	No. of study participants	Percent	No. of study participants	Percent			
Vaginal	82	33.9	2	8.7	4.1	1	0.04
LSCS	154	63.6	19	82.6			
Instrumental	4	1.7	2	8.7			
Total	240	99.2	23	100.0			

P= 0.04<0.05= Significant

It is observed from the above table that 33% of the patients who didn't have PPCM deliverer vaginally.63.6% underwent caesarean section and 1.7% had delivered with instrument assistance. While in patients with PPCM only 8.7% delivered vaginally, 82.6% underwent caesarean section and 1.7% had delivered with instrument assistance. The difference in the mode of delivery among the groups was statistically significant as proved by Chi-Square test.

Figure 16. Distribution of study subjects as per mode of delivery.

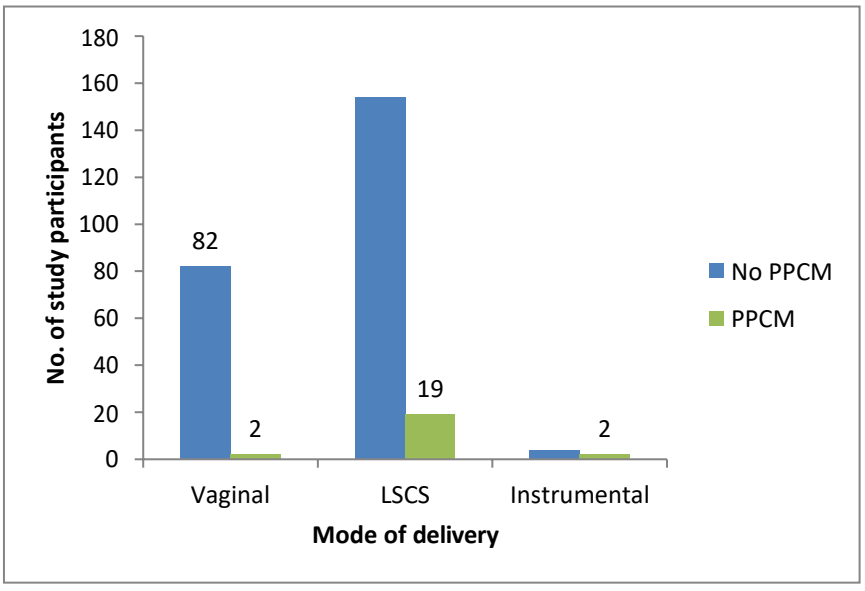


Table 20. Distribution of babies of study subjects as per their clinical status

Place of baby	No PPCM		PPCM		Value	Df	P Value
	No. of study participants	Percent	No. of study participants	Percent			
Mother side	109	45.0	3	26.1	4.25	2	0.04
NICU	90	37.2	13	43.5			
Mortality	43	17.8	7	30.4			
Total	242	100.0	23	100.0			

P= 0.04<0.05= Significant

It is observed from the above table that 45.4% babies of patients who didn't have PPCM were free of any complications, 37.2% were in NICU and 17.8% expired. While in patients with PPCM only 26.1% PPCM were free of any complications, 43.5% were in NICU and 30.4% expired. The difference in the place of baby among the groups was statistically significant as proved by Chi-Square test.

Figure 17. Distribution of babies of study subjects as per their clinical status.

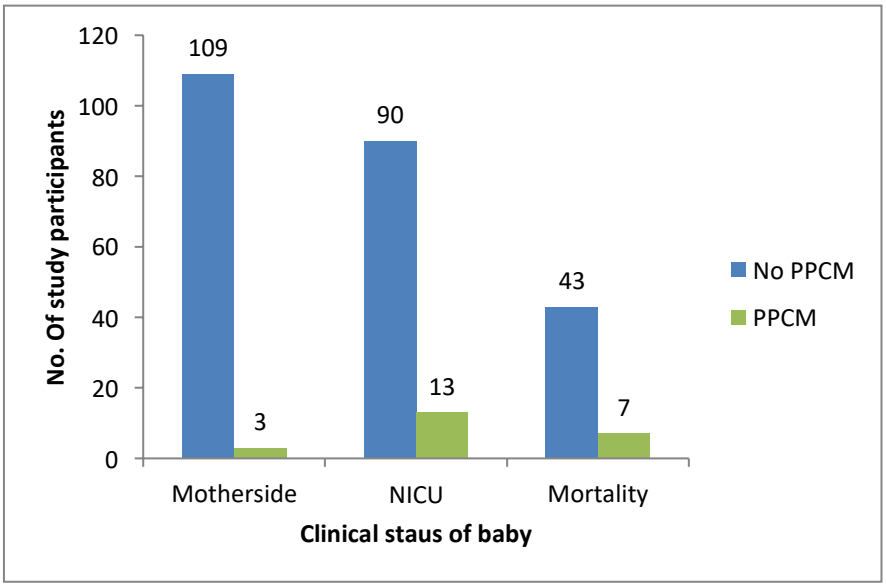


Table 21: Distribution of Obstetric Complications experienced by the participants

Any Other Complication	PPCM	No PPCM	Total
Abnormal Doppler	1	2	3
Abruption Placenta	1	2	3
Aflp	1	0	1
Aph	0	1	1
HELLP	1	7	8
HELLP,AKI	0	1	1
Hellp, Abruption	0	1	1
Hellp, Iud	1	0	1
Hellp,Iugr	0	1	1
Iud	0	4	4
Iud , Abruption	1	0	1
Iugr	2	10	12
Iugr , Oigohydraminos	0	1	1
Iugr , Pulmonary Edema	1	0	1
Iugr ,Anhydraminos	0	1	1
Oligohydraminos	1	8	9
Oligohydromnios	0	3	3
Oligohydromnios, Iugr	0	3	3
Pulmoanry Edema	1	0	1
Twins	1	1	2
Grand Total	**12**	**46**	**58**

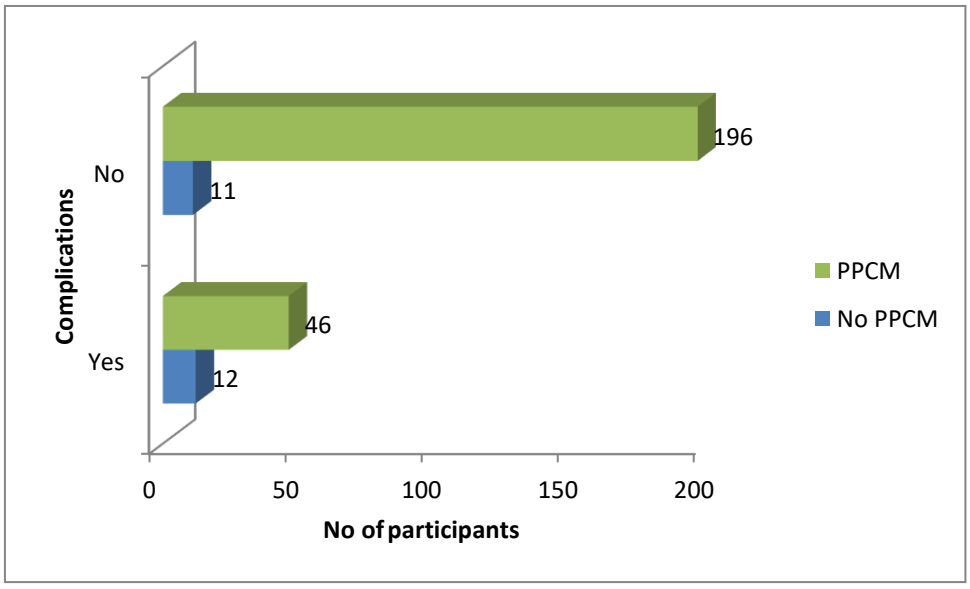
Table 22: Association of Obstetric Complications with PPCM

Obstetric Complications	No PPCM		PPCM		Value	Df	P Value*
	No. of study participants	Percent	No. of study participants	Percent			
Yes	12	52.2	46	19.0	13.51	1	0.0002
No	11	47.8	196	81.0			
Total	23	100.0	242	100.0			

***P= 0.0002<0.05= Significant**

It is observed from the above table that complication among PPCM group was found in 12 (52.5%) participants while in patients who didn't have PPCM 46 (19%) developed complication. The difference between the occurrence of obstetric complication is significant among the groups as proved by Chi-square test.

Figure 18: Association of Obstetric Complications with PPCM



Discussion

Cardiomyopathy is a group of disorders in which the heart muscle is structurally and functionally abnormal in the absence of other diseases that could cause observed myocardial abnormality. Cardiomyopathy either causes a decrease in preload or pumping capacity of the heart, which results in decreased ejection fraction of the heart. The main types of cardiomyopathy include dilated hypertrophic and restrictive cardiomyopathy. It causes weakness of the cardiac muscles results in an inability of the heart to pump blood with full force which results in the reduced ejection of blood from the left ventricle, i.e. the ejection fraction of the heart decreases. Risk factors for PPCM include advanced maternal age, multiparty, African race, twinning, gestational hypertension, and long-term tocolysis. Pre-existing cardiovascular disease (such as hypertension, diabetes, and smoking) also has been found to increase the risk. Although no causative relationship has been established. Till date, there is no definitive test for diagnoses of PPCM though various markers have been proposed which guide diagnosis of the condition. As inflammation may play a role in the pathophysiology of PPCM several inflammatory markers are proposed to be associated with PPCM but there is no diagnostic evidence. The present study was conducted to find out markers associated with PPCM which would help in the early diagnosis and thus improve the survival. The results obtained are discussed in the

following sessions in the context of available evidence. The results obtained the present study are compared and contrasted with the studies conducted on the related topics.

Age distribution of the patients

In our study 33.1% among the patients without evidence of PPCM and 26.1% with PPCM were from the age group of 21-23 years. While only 1.2% participants among patients without evidence of PPCM and none of the patients among PPCM group had evidence were more than 36 years of age. The mean age group of the patients was 23.5+/- 3.7 years. Similarly G. Huang et al.(38) conducted a study in which the age group of patients was from 19-38 years. Goland et al.(29) conducted a study to find out the clinical predictors of PPCM, the mean age group of study participants in his study was 29+/-7 years.34.8% of PPCM were from 18-20 years , 26% from 21-23 years , this shows that PPCM is more common in young people than elderly.

Thus our study finding was similar to the published literature that cases of PPCM most commonly occurs in the second or third decade of life.

Occupation

We observed in our study that majority of the study participants were housewives followed by teachers and labourers. **Huang et al.**(38) reported 88.5% patients of PPCM in their study to be farmers. The difference in the type of occupations among the study participants in the current study and published literature may be a chance finding occurring due to the studies being conducted in different socioeconomic and cultural background.

Parity

In our study majority of the women ie 43.4% in patients who had no PPCM and only 4.3% in patients who had PPCM were Primipara. 87(36%), women in patients who had no PPCM while 69.6% who were having PPCM were second para. We found a significant difference in parity among PPCM and no PPCM patients. Yameogo et al. (52) in their study on maternal and foetal prognosis with PPCM reported a gravidity rate of 2.3 ± 0.5. Irrizari et al. conducted a study on patients with PPCM reported 49.5% study participants were multiparous. Simillarly, Veile(53) published a review on PPCM in which he concluded that PPCM occurs more frequently in multiparous women although it is not restricted to this group. Thus our study finding is in line with that of published literature that PPCM occurs more commonly in multiparous female. Though pre

eclampsia is more common in primigravida when any multiparous women develops hypertension, she is more prone for PPCM.

Abortion

We found in our study that 21.7% study participants among the PPCM group had history of abortions while only 13.2% patients had no abortion in the non PPCM group. Elkayam et al. (54) conducted a study to find out the outcome of subsequent pregnancy in diagnosed case of PPCM, they reported 16.7% abortion in patients with history of PPCM compared to 4.1% in patients with no history of PPCM. Yameogo et al.(52) similarly conducted a study to assess the fetal outcomes in mothers with history of PPCM and found that 20.9% study participants had abortions. We have studied past history of abortion in PPCM diagnosed cases.

Gestational Age

We found in our study that majority of the study participants in both patients with PPCM and no PPCM were in the third trimester with gestation of 37.7-40.8 weeks. The mean gestational age among PPCM group was marginally less that that of the no PPCM group. Alkhayuru et al.(55) conducted a study to compare the clinical characteristics of patients with PPCM and eclampsia and found a statistically significant difference in gestational age of presentation of patients. The mean

gestational age of presentation among PPCM group was 38.4 weeks while that among no PPCM group was 36.1 weeks. Similarly Katz et al.(56) found in their study that onset of PPCM occurs in the later trimester or postpartum. Thus our study findings match the published literature findings, haemodynamic stress in the later part of the pregnancy puts stress on the heart and aggravates the disease.

Past History of hypertension in pregnancy

We observed that 17.4% patients of PPCM while only 3.7% of the patients without PPCM had past history of hypertension. Pre-existing hypertension and occurrence was significantly related. Owens et al.(4) conducted a study to find out the neonatal and maternal outcomes in pregnant women with cardiac disease and reported that mothers with pre-existing hypertension had greater chance of having heart disease than mothers without it. In their study, Ersboll et al.(19) reported 54.1% of women with PPCM had HDP. Thus we see our study findings are similar to punished literature that preexsisting hypertension is a risk factor to the development of PPCM.

Family history of hypertension

We found that among study participants who had PPCM, 13.1% of their mothers had hypertension while in participants without PPCM only 2.9%

had history of hypertension in mothers. Also 3.3 % study participants in patients who didn't have PPCM and none had history of hypertension in father. Also history of hypertension in mother was significantly associated with occurrence of PPCM in study subjects than father. Auger et al.(57) mentioned in their review that women with PPCM had 2.7 times the chance of having a relative with heart failure compared with women without PPCM. Christiansen et al. also reported in their study, relatives of patients with PPCM tended to have a higher prevalence of hypertension and ischaemic heart disease, outcomes unrelated to primary DCM. The current finding is congruent with the published literature and supports the notion of shared aetiology between PPCM and other forms of cardiac morbidities.

Previous history of PPCM

In our study 13% patients with PPCM had previous history of PPCM while only 0.4% in the patients who didn't have PPCM had previous history of PPCM. A significant association was established between history of PPCM during previous pregnancy and PPCM. **Auger et al.**(57) reported in their review that women with PPCM even those who appear to recover fully may themselves be at increased risk of cardiovascular disease later in life, including heart failure due to dilated cardiomyopathy. **Fett et al.**(58) similarly studied 61 post-PPCM pregnancies, in the United

States, and described relapses of PPCM in 29% of the entire group, with a significantly higher rate (46%) in women with LVEFs <55%. **Hagika et al.**(26) also reported a positive family history of cardiomyopathy in 16.5 % patients. Thus our study findings are congruent with the published literature.

Gestational Hyprtension

We found that in our study there was no significant difference in systolic BP and diastolic blood pressure among the study participants. **Behrnes et al.**(46) in their study on association of hypertensive disorder of pregnancy and PPCM reported gestational hypertension was strongly and significantly associated with PPCM, with the strength of the association appearing to increase with hypertension severity. **Elkayam et al.**(31) similarly reported history of hypertension during pregnancy in 43% of the patients with PPCM. **Uri et al**.(54) has also reported 15% to 68% (mean 23%) of patients with PPCM in the United States. The difference in our study finding and that of the published literature may be due to the fact that only patients with hypertension in pregnancy were included in our study so both systolic and diastolic BP was raised in both the groups. No studies have tired to see the level of SBP and DBP in relation to PPCM.

Preeclampsia

Our study found majority of the study participants in PPCM group had severe preeclampsia while in the patient who didn't had PPCM mild and severe preeclampsia patients were equally distributed. We also found a significant association between preeclampsia and PPCM. **Bello et al.**(47) reported in their systemic review, patients with PPCM have a prevalence of preeclampsia more than 4 times the average global rate expected in the general population. Similarly **Lindley et al.**(20) reported Seventeen of 39 women (44%) with PPCM had preeclampsia. **Behrens et al.**(46) reported in their study relationship of severe preeclampsia, RR 21.2, 95% confidence interval [CI] 12.0–37.4; moderate preeclampsia, RR 10.2, 95% CI 6.18–16.9; gestational hypertension, RR 5.16, 95% CI 2.11–12.6 with PPCM. They also concluded HDPs were associated with substantial increases in PPCM risk that depended on HDP severity. Thus our study finding matches with that of the published literature.

Eclampsia

We found in our study 30.6% patients in the patients who didn't have PPCM and 17.4% patient in the PPCM group had eclampsia. **Kao et al**.(59) conducted a systemic review in which he found only 2.1% cases of eclampsia in cases of PPCM. **Gunderson et al.**(60) conducted a study in which they reported 11.9% patients had eclampsia among patients who

developed PPCM. Thus our study findings were similar to the published findings.

Total leucocyte count

In our study we found that total leucocyte count was significantly elevated in patients who had PPCM as compared to patients who didn't have PPCM. **Huang et al.** (38) in their study to find out the risk factors of PPCM found that mean total leucocyte count in PPCM patient was 11.0 ± 4.5 while that in control group was 8.8 ± 3.6 which was significantly less than the cases. **Wang et al.**(61) Similarly reported in their study conducted on PPCM patients in emergency department that total leucocyte count among PPCM patient was 11.5+/-1.17 much higher than comparison group. Pentoxifylline, a TNF-a inhibitor, has been shown to significantly improve outcomes in South African PPCM patients by **Silwa et al.** (62). It is clear that there is cardiac tissue injury in PPCM and that recovery from this injury involves remodelling and fibrosis. Thus, this injury is implicated in the pathogenesis of human PPCM, the normal cascade of events would require a pro-inflammatory response to eliminate the pathogenic agent and get rid of the dying cardiomyocytes followed by TGF-b-mediated fibrosis, healing and turning off the pro-inflammatory response. Thus our study finding are similar to the published literature, the reason for increase in leucocyte count may be related to the cardiomyopathy being an inflammatory

pathogenesis of PPCM and may also be related to increased risk of respiratory infection in PPCM patients.

Prolactin

We found in our study that prolactin levels were significantly raised in women who had PPCM as compared to other group. **Koenig et al.**(63) in their review on PPCM reported an oxidative stress-mediated cleaved 16-kDa fragment of the nursing hormone prolactin is thought to damage endothelial cells and cardiomyocytes causing cardiomyopathy. An antiangiogenic prolactin fragment with a molecular mass of 16 kDa is a key pathological mediator of peripartum cardiomyopathy (PPCM) this fragment is enzymatically generated by the cleavage of full-length prolactin with the lysosomal aspartyl protease cathepsin D. Upon excessive generation, possibly due to high pituitary prolactin secretion near term or *postpartum* and an enhanced oxidative microenvironment, this prolactin fragment would impair myocardial microvascularization and thereby contribute to myocardial dysfunction.(64) PPCM, being a disease of late pregnancy and early postpartum, might be triggered by factors specifically present in the late-gestational period. The nursing hormone prolactin is among the prominent hormones in the peripartum phase, and large quantities of prolactin are released from the pituitary gland into the circulation during lactation.44 Prolactin can exert opposing effects on angiogenesis depending on proteolytic processing of the

potentially proangiogenic, full-length, 23 kDa form of the hormone into an antiangiogenic, 16 kDa derivative.44 The 16 kDa form of prolactin, also called vasoinhibin, was initially identified as a potent antiangiogenic factor.45 This prolactin variant is generated from full-length prolactin by cathepsin D. The 16 kDa form of prolactin inhibits angiogenesis at various levels by inducing endothelial cell cycle arrest at the G0–G1 and G2–M stages,48 in parallel with inhibition of mitogen-activated protein kinase activation induced by basic fibroblast growth factor and VEGF.49 Additionally, 16 kDa prolactin induces endothelial-cell apoptosis by activating caspase-3 and nuclear factor (NF)-κB,50 inhibits endothelial-cell migration. **Kleiner et al.**(15) Conducted a study on mice and reported that in them, cardiac cathepsin D expression and activity is enhanced and associated with the generation of a cleaved antiangiogenic and pro-apoptotic 16 kDa form of the nursing hormone prolactin. Treatment with bromocriptine, an inhibitor of prolactin secretion, prevents the development of PPCM, whereas forced myocardial generation of 16 kDa prolactin impairs the cardiac capillary network and function, thereby recapitulating the cardiac phenotype of PPCM. **Forster et al.**(15) in their study on effect of reversal of inflammatory markers on PPCM outcome found that IFN-γ and prolactin was significantly raised in PPCM patients 22.7 as compared to 7.4 among controls. IFN-γ and prolactin are associated with poor outcome in PPCM, suggesting a

potential role of these factors in the pathophysiology of PPCM and for risk stratification of PPCM patients. **Tabruyun et al**.(65) conducted a study to see for molecular basis of increase in prolactin in patients of PPCM and found that prolactin is increased in cases of PPCM which further act as a primer for increase in leucocyte activation. Thus our study finding are in congruence with published literature that increased prolactin predisposes to PPCM.

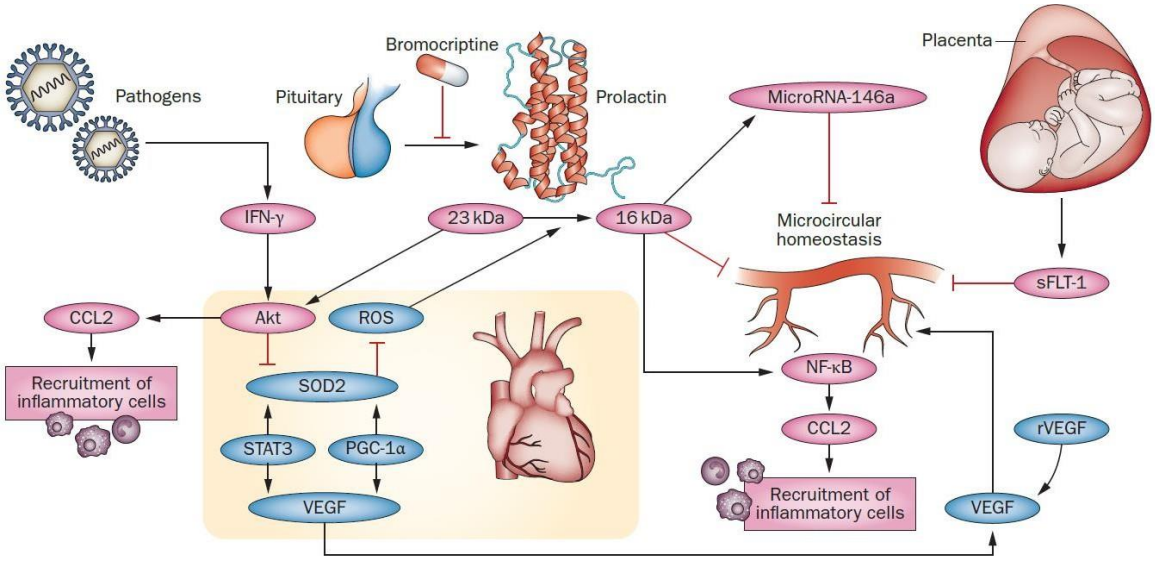


Figure 2 | Pathophysiological mechanisms in PPCM. Prolactin is released from the pituitary gland and, under conditions of oxidative stress in the myocardium, is proteolytically cleaved to a 16 kDa fragment by proteases, such as cathepsin D

Troponin I

Cardiac troponin T (cTnT) and troponin I (cTnI) are cardiac regulatory proteins that control the calcium mediated interaction between actin and myosin. The cardiac forms of these regulatory proteins are coded by specific genes and theoretically have the potential of being unique to the myocardium. Indeed, cTnI has not been identified outside the myocardium.1 Cardiac troponin T is expressed to a small extent in

skeletal muscle; however, the current cTnT assay does not identify skeletal troponins. An injury to the cardiac myocyte cause increase in these proteins in the blood. We observed in our study that mean troponin levels were significantly high among PPCM group in comparison to non PPCM group. **Fleming et al**.(66) reported in their study on association of Troponin I with hypertensive diseases of pregnancy that serum cardiac troponin I levels are elevated in association with hypertension in pregnancy, and that proteinuric hypertension is associated with the highest levels. They concluded due to the established specificity of this isoform of troponin I for cardiac tissue1 the most likely explanation for these findings is that some degree of myofibrillary damage occurs in association with hypertension in pregnancy. **Haghika et al**.(42) in their case control study reported anti- Troponin I were detected in the serum of 46 % of PPCM patients and in 8 % of healthy controls. In PPCM the presence of either one of these AABs was associated with significantly lower baseline LVEF and lower rate of full cardiac recovery at follow-up. They also found that patients with higher troponin I was associated with poorer prognosis. **Bhattacharya et al.**(32) reported in systemic review high cardiac troponin T levels (>0.4 ng/mL) within 2 weeks of peripartum cardiomyopathy onset significantly predicted smaller LVEF and persistent LV dysfunction at 6-month follow-up. Huang et al. also found similar significant increased Troponin I levels in patients(0.17) of

PPCM as compared to controls(0.06). Hu et al.(67) in their study on association of troponin I values with PPCM found that a troponin I concentration cut off of >0.04 ng/ml, predicting persistent left ventricular dysfunction with a sensitivity of 54.9% and a specificity of 90.9%. Among 106 recruited patients, there were 33 patients with Troponin I concentrations >0.04 ng/ml and 73 patients with Troponin I concentrations of 0.04 ng/ml. After a 6 month follow-up there were significantly less left ventricular ejection fraction in patients with Troponin I >0.04 ng/ml than in patients with Troponin I <0.04 ng/ml. But none of the studies have seen whether increased troponin I in hypertensive patient leads to PPCM. Ours is the first of its kind study to know the efficacy of Troponin I as predictor of PPCM. A value of > 0.06 was associated with increased risk PPCM .So if any patients has increased levels can be referred to higher center where cardiac monitoring is possible.

Brain natriuretic peptide

The release of BNP increases in patients with heart failure since ventricular stretching due to increased filling pressure stimulates BNP secretion. During a normal pregnancy, BNP levels are approximately 2-fold higher than those in non-pregnant status and do not significantly

fluctuate during pregnancy and after delivery (4–6 weeks postpartum) . The increase in BNP levels was associated with chamber enlargement and progress of decreased haemoglobin. These findings indicate that LV stretching caused by plasma volume increase and heart strain due to bleeding during delivery increase BNP levels. However, this change in BNP levels is significantly lower than that observed in patients with heart failure, such as those with PPCM. Therefore, BNP levels during pregnancy and after delivery should be useful as an indicator of PPCM.(45) Due to unavailability of kits to test for BNP and high cost involved in testing this marker could not be evaluated in the current study.

Mode of delivery

We found in our study that vaginal and assisted deliveries were more among the patients who had no PPCM as compared to the patients who had PPCM. **Haghika et. al**(26) reported in their study that the incidence of caesarean section was significantly higher in PPCM patients compared to controls (p\0.01), though their control collective had a higher rate compared to the overall rate. Emergency C-section was performed in 12.5 % (8 of 64 C-sections) of PPCM patients. In a study by **Kimura et al**.(45) caesarean section accounted for 16% of deliveries and approximately one third of women underwent induction of labour using

oxytocin in our study 82% of them had LSCS. Thus our study finings are congruent with that of published literature.

Foetal Outcome

In our study adverse outcomes among the foetus like NICU admissions and mortality was significantly more among the mothers who developed PPCM as compared to mothers who didn't develop the disease. Gunderson et al.(60) in their study on PPCM patients concluded neonates whose mothers developed peripartum cardiomyopathy experienced poorer clinical outcomes. Elkayam U.(68) reported in his review on PPCM that 21 of 35 women who did not have an abortion had normal vaginal delivery, and 14 women delivered by cesarean section. Premature delivery occurred in 13% of women with normal LV function and in 50% of patients with persistent LV dysfunction. Thus our study finings match that of the published literature that PPCM is associated with adverse foetal outcomes.

Obstetric Complications

We found in our study that the occurrence of obstetric complication was significantly more in PPCM group as compared to the group which didn't have PPCM.

Owens et al.(4) reported in their study obstetric complications were higher among women with heart disease than without it. He also found placental insufficiency, postpartum haemorrhage, postpartum infection,

and venous complications were more common in mothers with HD. Kao et al.(59) in their study to compare the outcome of PPCM in different races of population found that caesarean section rates among PPCM patients was 70.5% as compared to control group and still birth rate was 2% in patients with PPCM as compared to 1% in control group **Phan et al.**(69) reported in their study that mothers with PPCM had higher chance of having PPCM as compared to those who had no heart disease. Thus our study findings are in congruence with the published literature.

SUMMARY AND CONCLUSION

Hypertensive disorders complicating pregnancy are the most common and serious medical disorder and constitute up to 2–10% of all pregnancies. (70) Gestational hypertension (GH), pre-eclampsia (PE), and eclampsia are a part of a spectrum of hypertensive disorders that complicate pregnancy as specified by the National High Blood Pressure Education Program (NHBPEP) working group. (71). It has been proved in studies that hypertensive disorder of pregnancy cause elevation of cardiac Troponin I, which points towards cardiac myocyte damage. (16) It is also elevated in PPCM.Since PPCM is most commonly seen in HDP We wanted to see any markers can be used to predict PPCM in HDP. So , we studied Total Leucocyte count , serum prolactin , Troponin I which were increased in PPCM as predictors. The study was conducted in the department of OBSTERTICS AND GYNAECOLOGY at B.L.D.E. (DEEMED TO BE UNIVERSITY) Shri B.M. Patil's Medical College, Hospital and Research Centre, Vijayapura after obtaining ethical committee clearance, It was a prospective cohort study conducted over 265 patients over a period of 2 year.. All Hypertensive patients were included in the study and markers were sent and observed for clinical features of cardiomyopathy for one week. If they develop the clinical features of PPCM like breathlessness, pedal oedema, tachycardia,

decreasing in saturation (Spo2) 2D ECHO was done to confirm the diagnosis. If they did not develop any features during hospital stay, they were discharged, and followed up in OPD at 1 month, 3 month and 6 months to know whether any of them developed any cardiac problems. If OPD follow up is missed in the due date , then the patients were contacted on phone for knowing the details of cardiac symptoms . If cardiac symptoms occurred patient was called for 2D ECHO.

The salient findings of our study are as follows

1) The study participants were housewives belonging to young age group.
2) We observed that PPCM was diagnosed more commonly among multiparous women as compared to nulliparous.
3) Past history of hypertension and family history of hypertension in mother was significantly associated with occurrence of PPCM in study participants.
4) PPCM occurs more commonly in association with pre-eclampsia.
5) Total leucocyte count (p value =0.05), serum prolactin (p value=0.007)nd Troponin I(p value=0.049) was significantly elevated in patients who later developed PPCM.
6) Patients diagnosed with PPCM underwent bad obstetric outcome as compared to patients who didn’t have PPCM.

7) Babies born to mothers diagnosed as PPCM need intervention as compared to those who did not have PPCM.

Thus we conclude that markers like Total leucocyte count, serum prolactin and Troponin I can be used for early prediction of the disease so as to prevent further complications. Such patients can be followed up meticulously for 5 months to look for development of PPCM

LIMITATION

1. The sample size in the present study is small. A larger sample would have given more representative inferences.
2. Brain natriuretic peptide which has been found to be a marker of PPCM could not be evaluated due to financial issues and not easily available.

Further studies which can be conducted from this study are-

1. Dopamine antagonists like Bromocriptine and cabergoline can be tried for treatment as prolactin is a causative factor.
2. Role of anti-inflammatory markers in the diagnosis of PPCM can be evaluated.

Bibliography

1. Schaufelberger M. Cardiomyopathy and pregnancy. Vol. 105, Heart. BMJ Publishing Group; 2019. p. 1543–51.
2. Berg CJ, Callaghan WM, Syverson C, Henderson Z. Pregnancy-related mortality in the United States, 1998 to 2005. Obstet Gynecol. 2010 Dec;116(6):1302–9.
3. Kassebaum NJ, Barber RM, Dandona L, Hay SI, Larson HJ, Lim SS, et al. Global, regional, and national levels of maternal mortality, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016 Oct;388(10053):1775–812.
4. Owens A, Yang J, Nie L, Lima F, Avila C, Stergiopoulos K. Neonatal and maternal outcomes in pregnant women with cardiac disease. J Am Heart Assoc. 2018;7(21).
5. Raddino R, Bonadei I, Teli M, Chieppa F, Caretta G, Robba D, et al. [Peripartum cardiomyopathy]. Monaldi Arch chest Dis = Arch Monaldi per le Mal del torace. 2008 Mar;70(1):15–23.
6. Honigberg MC, Givertz MM. Peripartum cardiomyopathy. Vol. 364, BMJ (Online). BMJ Publishing Group; 2019.
7. Sliwa K HDPMMAPBBERVSMTL van VDWHSASPEUPSPZMFMJ. 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 - Sliwa - 20. Eur J Heart Fail. 2014;
8. Kezerle L, Sagy I, Shalev L, Erez O, Barski L. A Population-based Study of Peripartum Cardiomyopathy in Southern Israel: Are Bedouin Women a New High-risk Group? Rambam Maimonides Med J. 2018 Apr;9(2):e0011.
9. Abboud J, Murad Y, Chen-Scarabelli C, Saravolatz L, Scarabelli TM. Peripartum cardiomyopathy: A comprehensive review. Vol. 118, International Journal of Cardiology. Int J Cardiol; 2007. p. 295–303.
10. Sliwa K, Fett J, Elkayam U. Peripartum cardiomyopathy. Vol. 368, Lancet. Lancet; 2006. p. 687–93.
11. Kodogo V, Azibani F, Sliwa K. Role of pregnancy hormones and hormonal interaction on the maternal cardiovascular system: a

literature review. Vol. 108, Clinical Research in Cardiology. Dr. Dietrich Steinkopff Verlag GmbH and Co. KG; 2019. p. 831–46.

12. Hibbard JU, Lindheimer M, Lang RM. A modified definition for peripartum cardiomyopathy and prognosis based on echocardiography. Obstet Gynecol. 1999;94(2):311–6.

13. Forster O, Hilfiker-Kleiner D, Ansari AA, Sundstrom JB, Libhaber E, Tshani W, et al. Reversal of IFN-γ, oxLDL and prolactin serum levels correlate with clinical improvement in patients with peripartum cardiomyopathy. Eur J Heart Fail. 2008 Sep;10(9):861–8.

14. 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;128(3):589–600.

15. Sliwa Karen, Forster Olaf, Libhaber Elena, Fett D James, Sundstrom Bruce jay, Hilfiker Kleiner Denise, et al. Peripartum Cardiomyopathy: Inflammatory Markers as Predictors of Outcome in 100 Prospectively Studied Patients - PubMed. Eur Heart J. 2006;27(4):441–6.

16. Fleming SM, O'Gorman T, Finn J, Grimes H, Daly K, Morrison JJ. Cardiac troponin I in pre-eclampsia and gestational hypertension. Br J Obstet Gynaecol. 2000;107(11):1417–20.

17. Davis MB, Arany Z, McNamara DM, Goland S, Elkayam U. Peripartum Cardiomyopathy: JACC State-of-the-Art Review. Vol. 75, Journal of the American College of Cardiology. NLM (Medline); 2020. p. 207–21.

18. Barton A, Docherty K, Campbell R, Simpson J, Jackson A, Dalzell J, et al. PREVALENCE AND PREDICTORS OF MYOCARDIAL RECOVERY IN PERIPARTUM CARDIOMYOPATHY: A SYSTEMATIC REVIEW. J Am Coll Cardiol. 2019 Mar;73(9):842.

19. Ersbøll AS, Bojer AS, Hauge MG, Johansen M, Damm P, Gustafsson F, et al. Long-term cardiac function after peripartum cardiomyopathy and preeclampsia: A Danish nationwide, clinical follow-up study using maximal exercise testing and cardiac magnetic resonance imaging. J Am Heart Assoc. 2018 Oct;7(20).

20. Lindley KJ, Conner SN, Cahill AG, Novak E, Mann DL. Impact of Preeclampsia on Clinical and Functional Outcomes in Women with

Peripartum Cardiomyopathy. Circ Hear Fail. 2017 Jun;10(6).

21. Kuklina E V., Callaghan WM. Cardiomyopathy and other myocardial disorders among hospitalizations for pregnancy in the united states: 2004-2006. Obstet Gynecol. 2010 Jan;115(1):93–100.

22. Fett JD, Christie LG, Carraway RD, Ansari AA, Sundstrom JB, Murphy JG. Unrecognized peripartum cardiomyopathy in Haitian women. Int J Gynecol Obstet. 2005;90(2):161–6.

23. Brar SS, Khan SS, Sandhu GK, Jorgensen MB, Parikh N, Hsu JWY, et al. Incidence, Mortality, and Racial Differences in Peripartum Cardiomyopathy. Am J Cardiol. 2007 Jul 15;100(2):302–4.

24. Kolte D, Khera S, Aronow WS, Palaniswamy C, Mujib M, Ahn C, et al. Temporal trends in incidence and outcomes of peripartum cardiomyopathy in the United States: A nationwide population-based study. J Am Heart Assoc. 2014;3(3).

25. Gunderson EP, Croen LA, Chiang V, Yoshida CK, Walton D, Go AS. Epidemiology of peripartum cardiomyopathy: Incidence, predictors, and outcomes. Obstet Gynecol. 2011 Sep;118(3):583–91.

26. Haghikia A, Podewski E, Libhaber E, Labidi S, Fischer D, Roentgen P, et al. Phenotyping and outcome on contemporary management in a German cohort of patients with peripartum cardiomyopathy. Basic Res Cardiol [Internet]. 2013 Jul 28 [cited 2020 May 11];108(4):366. Available from: http://link.springer.com/10.1007/s00395-013-0366-9

27. Patten IS, Rana S, Shahul S, Rowe GC, Jang C, Liu L, et al. Cardiac angiogenic imbalance leads to peripartum cardiomyopathy. Nature. 2012 May 17;485(7398):333–8.

28. Arany Z, Elkayam U. Peripartum cardiomyopathy. Circulation. 2016 Apr;133(14):1397–409.

29. Goland S, Modi K, Bitar F, Janmohamed M, Mirocha JM, Czer LSC, et al. Clinical Profile and Predictors of Complications in Peripartum Cardiomyopathy. J Card Fail [Internet]. 2009 Oct [cited 2020 May 12];15(8):645–50. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1071916409000992

30. DEMAKIS JG, RAHIMTOOLA SH, SUTTON GC, MEADOWS WR, SZANTO PB, TOBIN JR, et al. Natural Course of Peripartum

Cardiomyopathy. Circulation [Internet]. 1971 Dec [cited 2020 May 17];44(6):1053–61. Available from: https://www.ahajournals.org/doi/10.1161/01.CIR.44.6.1053

31. 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 [Internet]. Vol. 111, Circulation. Lippincott Williams & Wilkins; 2005 [cited 2020 May 17]. p. 2050–5. Available from: https://www.ahajournals.org/doi/10.1161/01.CIR.0000162478.36652.7E

32. Bhattacharyya A, Basra SS, Sen P, Kar B. Peripartum cardiomyopathy: A review. Vol. 39, Texas Heart Institute Journal. Texas Heart Institute; 2012. p. 8–16.

33. Lampert MB, Lang RM. Peripartum cardiomyopathy. Am Heart J. 1995;130(4):860–70.

34. Hilfiker-Kleiner D, Struman I, Hoch M, Podewski E, Sliwa K. 16-kDa Prolactin and Bromocriptine in Postpartum Cardiomyopathy. Curr Heart Fail Rep [Internet]. 2012 Sep 23 [cited 2020 May 23];9(3):174–82. Available from: http://link.springer.com/10.1007/s11897-012-0095-7

35. Forster O, Hilfiker-Kleiner D, Ansari AA, Sundstrom JB, Libhaber E, Tshani W, et al. Reversal of IFN-γ, oxLDL and prolactin serum levels correlate with clinical improvement in patients with peripartum cardiomyopathy. Eur J Heart Fail. 2008 Sep;10(9):861–8.

36. Jahns BG, Stein W, Hilfiker-Kleiner D, Pieske B, Emons G. Peripartum cardiomyopathy-a new treatment option by inhibition of prolactin secretion. Am J Obstet Gynecol. 2008 Oct 1;199(4):e5–6.

37. Sliwa K, Förster O, Libhaber E, Fett JD, Sundstrom JB, Hilfiker-Kleiner D, et al. Peripartum cardiomyopathy: inflammatory markers as predictors of outcome in 100 prospectively studied patients.

38. Huang GY, Zhang LY, Long-Le MA, Wang LX. Clinical characteristics and risk factors for peripartum cardiomyopathy. Afr Health Sci. 2012;12(1):26–31.

39. Sarojini A, Sai Ravi Shanker A, Anitha M. Inflammatory markers-serum level of c-reactive protein, tumor necrotic factor-α, and interleukin-6 as predictors of outcome for peripartum

cardiomyopathy. J Obstet Gynecol India. 2013 Aug;63(4):234–9.

40. Biteker M, Özlek B, Özlek E, Çil C, Çelik O, Doğan V, et al. Predictors of early and delayed recovery in peripartum cardiomyopathy: a prospective study of 52 Patients. J Matern Neonatal Med. 2020 Feb 1;33(3):390–7.

41. Marino A, Koczo A, Hanley-Yanez K, McNamara D. PROINFLAMMATORY CYTOKINE IMBALANCE AND MYOCARDIAL RECOVERY IN PERIPARTUM CARDIOMYOPATHY. J Am Coll Cardiol. 2020 Mar;75(11):1031.

42. Haghikia A, Kaya Z, Schwab J, Westenfeld R, Ehlermann P, Bachelier K, et al. Evidence of autoantibodies against cardiac troponin I and sarcomeric myosin in peripartum cardiomyopathy. Basic Res Cardiol. 2015 Nov 1;110(6).

43. GREER IA, HADDAD NG, DAWES J, JOHNSTONE FD, CALDER AA. Neutrophil activation in pregnancy-induced hypertension. BJOG An Int J Obstet Gynaecol. 1989;96(8):978–82.

44. Canzoneri BJ, Lewis DF, Groome L, Wang Y. Increased neutrophil numbers account for leukocytosis in women with preeclampsia. Am J Perinatol. 2009;26(10):729–32.

45. Kimura Y, Kato T, Miyata H, Sasaki I, Minamino-Muta E, Nagasawa Y, et al. Factors associated with increased levels of brain natriuretic peptide and cardiac troponin I during the peripartum period. Ai T, editor. PLoS One [Internet]. 2019 Feb 7 [cited 2020 May 24];14(2):e0211982. Available from: https://dx.plos.org/10.1371/journal.pone.0211982

46. Behrens I, Basit S, Lykke JA, Ranthe MF, Wohlfahrt J, Bundgaard H, et al. Hypertensive disorders of pregnancy and peripartum cardiomyopathy: A nationwide cohort study. PLoS One. 2019 Feb 1;14(2).

47. Bello N, Rendon ISH, Arany Z. The relationship between pre-eclampsia and peripartum cardiomyopathy: A systematic review and meta-analysis. J Am Coll Cardiol. 2013 Oct;62(18):1715–23.

48. Pergialiotis V, Prodromidou A, Frountzas M, Perrea DN, Papantoniou N. Maternal cardiac troponin levels in pre-eclampsia: a systematic review. Vol. 29, Journal of Maternal-Fetal and Neonatal Medicine. Taylor and Francis Ltd; 2016. p. 3386–90.

49. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE,

Howard DL, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med. 2000 Apr 13;342(15):1077–84.

50. Raddino R, Bonadei I, Teli M, Chieppa F, Caretta G, Robba D, et al. Peripartum Cardiomyopathy. Monaldi Arch Chest Dis. 2016 Jan;70(1).

51. Kim MJ, Shin MS. Practical management of peripartum cardiomyopathy. Vol. 32, Korean Journal of Internal Medicine. Korean Association of Internal Medicine; 2017. p. 393–403.

52. Yaméogo NV, Samadoulougou AK, Kagambèga LJ, Kologo KJ, Millogo GRC, Thiam A, et al. Maternal and fetal prognosis of subsequent pregnancy in black African women with peripartum cardiomyopathy. BMC Cardiovasc Disord [Internet]. 2018 Jun 18 [cited 2020 Sep 9];18(1). Available from: https://pubmed.ncbi.nlm.nih.gov/29914408/

53. Veille JC. Peripartum cardiomyopathies: A review [Internet]. Vol. 148, American Journal of Obstetrics and Gynecology. Am J Obstet Gynecol; 1984 [cited 2020 Sep 12]. p. 805–18. Available from: https://pubmed.ncbi.nlm.nih.gov/6367478/

54. Elkayam U. Clinical characteristics of peripartum cardiomyopathy in the United States: Diagnosis, prognosis, and management. Vol. 58, Journal of the American College of Cardiology. Elsevier USA; 2011. p. 659–70.

55. Alkhayru A, Tappuni B, Kaseer B, Ghazi F, Wilson J, Smith K, et al. CLINICAL CHARACTERISTICS OF PERIPARTUM CARDIOMYOPATHY COMPARED TO PREECLAMPSIA. J Am Coll Cardiol. 2019 Mar;73(9):795.

56. Katz R, Karliner JS, Resnik R. Effects of a natural volume overload state (pregnancy) on left ventricular performance in normal human subjects. Circulation [Internet]. 1978 [cited 2020 Sep 12];58(3):434–41. Available from: https://pubmed.ncbi.nlm.nih.gov/679433/

57. Auger N, Ukah U V., Potter BJ. Peripartum cardiomyopathy: A family affair? [Internet]. Vol. 105, Heart. BMJ Publishing Group; 2019 [cited 2020 Sep 12]. p. 1051–2. Available from: https://pubmed.ncbi.nlm.nih.gov/30910820/

58. Fett JD, Fristoe KL, Welsh SN. Risk of heart failure relapse in

subsequent pregnancy among peripartum cardiomyopathy mothers. Int J Gynecol Obstet [Internet]. 2010 [cited 2020 Sep 13];109(1):34–6. Available from: https://pubmed.ncbi.nlm.nih.gov/19945699/

59. Kao DP, Hsich E, Lindenfeld JA. Characteristics, adverse events, and racial differences among delivering mothers with peripartum cardiomyopathy. JACC Hear Fail [Internet]. 2013 Oct [cited 2020 Sep 13];1(5):409–16. Available from: /pmc/articles/PMC3806506/?report=abstract

60. Gunderson EP, Croen LA, Chiang V, Yoshida CK, Walton D, Go AS. Epidemiology of peripartum cardiomyopathy: Incidence, predictors, and outcomes. Obstet Gynecol [Internet]. 2011 Sep [cited 2020 Sep 13];118(3):583–91. Available from: https://pubmed.ncbi.nlm.nih.gov/21860287/

61. Wang WW, Wang Y. Peripartum women with dyspnea in the emergency department Is it peripartum cardiomyopathy? Med (United States) [Internet]. 2018 Aug 1 [cited 2020 Sep 14];97(31). Available from: /pmc/articles/PMC6081098/?report=abstract

62. Karen Sliwa OFELJDFJBSDH-KAAA. Peripartum cardiomyopathy: inflammatory markers as predictors of outcome in 100 prospectively studied patients | European Heart Journal | Oxford Academic. 2006 Feb 4 [cited 2020 May 23];27(4):4412–46. Available from: https://academic.oup.com/eurheartj/article/27/4/441/485450

63. Koenig T, Hilfiker-Kleiner D, Bauersachs J. Peripartum cardiomyopathy. Herz [Internet]. 2018 Aug 16;43(5):431–7. Available from: http://link.springer.com/10.1007/s00059-018-4709-z

64. Triebel J, Clapp C, de la Escalera GM, Bertsch T. Remarks on the prolactin hypothesis of peripartum cardiomyopathy [Internet]. Vol. 8, Frontiers in Endocrinology. Frontiers Research Foundation; 2017 [cited 2020 Sep 20]. p. 77. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5387077/

65. Välimäki M AC. Cochrane Database of Systematic Reviews Virtual reality for treatment compliance for people with serious mental illness (Review) Virtual reality for treatment compliance for people with serious mental illness. www.cochranelibrary.com Virtual reality for t. Cochrane Collab. 2014;

66. Fleming SM, O'Gorman T, Finn J, Grimes H, Daly K, Morrison JJ. Cardiac troponin I in pre-eclampsia and gestational hypertension. Br J Obstet Gynaecol. 2000;107(11):1417–20.

67. 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 [Internet]. 2007 Apr [cited 2020 Sep 14];93(4):488–90. Available from: /pmc/articles/PMC1861492/?report=abstract

68. Elkayam U. Risk of subsequent pregnancy in women with a history of peripartum cardiomyopathy [Internet]. Vol. 64, Journal of the American College of Cardiology. Elsevier USA; 2014 [cited 2020 Sep 11]. p. 1629–36. Available from: https://pubmed.ncbi.nlm.nih.gov/25301468/

69. Phan D, Duan L, Ng A, Shen AYJ, Lee MS. Characteristics and outcomes of pregnant women with cardiomyopathy stratified by etiologies: A population-based study. Int J Cardiol [Internet]. 2020 Apr 15 [cited 2020 Sep 15];305:87–91. Available from: https://pubmed.ncbi.nlm.nih.gov/31889561/

70. WHO | The World Health Report 2005 - make every mother and child count. WHO. 2013;

71. Roccella EJ. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol. 2000;183(1).

72. Kolte D. Understanding the association between hypertensive disorders of pregnancy and peripartum cardiomyopathy. Eur J Heart Fail [Internet]. 2017 Dec 1 [cited 2020 May 25];19(12):1721–2. Available from: http://doi.wiley.com/10.1002/ejhf.941

ANNEXURES

ETHICAL CLEARANCE CERTIFICATE

B.L.D.E (Deemed to be University)
SHRI.B.M.PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE
VIJAYAPUR – 586103

IEC/NO:286/2018
17-11-2018

INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 13-11-2018 at 03-15 PM scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has accorded Ethical Clearance.

Title : A prospective cohort study to determine the predictors of peripartum cardiomyopathy in hypertensive disorders of pregnancy.

Name of P.G. Student : Dr Sridevi.H.S.
Department of Obstetrics & Gynaecology,

Name of Guide/Co-investigator: Dr Neelamma Patil, Associate Professor of Obstetrics & Gynaecology,

DR RAGHAVENDRA KULKARNI
CHAIRMAN
Institutional Ethical Committee
B.L.D.E. (Deemed to be University)
Shri B.M. Patil
Medical College Hospital & Research Centre
Vijayapur-586103.

Following documents were placed before E.C. for Scrutinization:

1) Copy of Synopsis/Research Project
2) Copy of informed consent form.
3) Any other relevant documents.

INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/RESEARCH

I, the undersigned,_____, S/O D/O W/O _____, aged_____years, ordinarily resident of _____do hereby state/declare that Dr. SRIDEVI H S of Shri. B. M. Patil Medical College Hospital and Research Centre has examined me thoroughly on_____at_____(place) and it has been explained to me in my own language that I am suffering from _____disease (condition) and this disease/condition mimic following diseases. Further Dr. SRIDEVI H S informed me that he/she is conducting dissertation/research titled "A Prospective Cohort Study Of Predictors of Peripartum cardiomyopathy in hypertensive disorders of pregnancy" under the guidance of Dr. Neelamma Patil requesting my participation in the study. According to this my blood sample will be taken to assess certain predictors of PPCM which I may develop as a complication of my condition. I also need to be in touch with the doctor and inform them as and when I develop any cardiac complications upto 6 month. I will also report to OBG OPD at 1 week, 3 month and 6 month for follow up regarding my condition . Further Doctor has informed me that my participation in this study help in evaluation of the results of the study which is useful reference to treatment of other similar cases in near future.

The Doctor has also informed me that information given by me, observations made/ photographs/ video graphs taken upon me by the investigator will be kept secret and not assessed by the person other than me or my legal hirer except for academic purposes.

The Doctor did inform me that though my participation is purely voluntary, based on information given by me, I can ask any clarification during the course of treatment / study related to diagnosis. At the same time I have been informed that I can withdraw from my participation in this study at any time if I want or the investigator can terminate me from the study at any time from the study but not the procedure of treatment and follow-up unless I request to be discharged.

After understanding the nature of dissertation or research, diagnosis made, mode of treatment. I am giving consent for the blood investigations and also for the follow up.

I the undersigned Shri/Smt_____under my full conscious state of mind agree to participate in the said research/dissertation.

Signature of patient:

Signature of doctor:

Witness: 1.

2.

Date:

PROFORMA

Name: IPNo:

Age: Case.no:

Address: Occupation:

DOA: Contact no: 1.

DO Study: Mobile no : 2.

1.Obstetric History :

1. Obstetric score : G P L A
2. Gestational age:

2.Past History:

History of hypertension : YES NO

3.Family History:

1. HYPERTENSION YES NO
2. HISTORY OF HYPERTENSION IN MOTHER YES NO
3. HISTORY OF PPCM IN MOTHER YES NO
4. HISTORY OF HYPERTENSION IN FATHER YES NO

4. BLOOD PRESSURE ON ADMISSION:

5. CATEGORY OF HYPERTENSION:

- Gestational hypertension :
- Pre eclampsia : Mild

Severe

- Eclampsia:

5. Any other complication:

(eg: HELLP , Asphyxia , oligohydraminos , IUGR)

7.STUDY PARAMETERS :

1. TOTAL LEUCOCYTE COUNT:

2. HIGHLY SENSITIVE C-REACTIVE PROTEIN:

3. SERUM PROLACTIN :

4. TROPONIN I:

5. ECHO CARDIOGRAPHY:

8. MODE OF DELIVERY:

- Vaginal delivery:
- Instrumental delivery:
- LSCS: Indication:

9.PERINATAL OUTCOME:

- Mother side:
- NICU:

- Mortality:

10. FOLLOW UP:

INTERVAL	PPCM	
1 WEEK	YES	NO
1 MONTH	YES	NO
3 MONTH	YES	NO
6 MONTH	YES	NO

REMARKS:

KEY TO MASTER CHART

IP NO: INPATIENT NUMBER

NICU: NEONATAL INTENSIVE CARE UNIT

LSCS: LOWER SEGMENT CEASEREAN SECTION

IUGR: INTRAUTERINE GROWTH RESTRICTION

HELLP : HEMOLYSIS ELEVATED LIVER ENZYMNES LOW PLATELET