UNIVERSITY OF KWAZULU NATAL

AN INVESTIGATION INTO THE CLINICAL OUTCOMES OF WOMEN WITH PERIPARTUM CARDIOMYOPATHY AT KLERKSDORP/TSHEPONG HOSPITAL COMPLEX

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MMedSc (Med)

2015

An Investigation into the Clinical Outcomes of Women with Peripartum Cardiomyopathy at Klerksdorp/Tshepong Hospital Complex.

By

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Dissertation submitted in fulfilment of

the requirements for the degree of

Masters of Medical Science in the

School of Clinical Medicine,

College of Health Sciences

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2015

DECLARATION

I, **Dr Farai Russell Sigauke** declare that:

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Dedications

To my wife Tafadzwa and our two daughters, Vanessa and Melissa.

To my late parents Russel and Marian Olive Sigauke.

Acknowledgements

I would like to thank the following:

My research participants for their patience and understanding.

The department of Medicine especially Professor Luke, Dr Kurian, and Dr Mosam for their support and confidence.

Kennedy Otwombe and Dr Neil Martinson for assistance with statistical calculations.

Professor Ebrahim Variava for his unconditional support and extraordinary clinical knowledge.

My supervisor Dr Kennedy Nyamande for the guidance and encouragement.

My wife Tafadzwa and two daughters Vanessa and Melissa for their unwavering support.

To the Lord Almighty for his love and favour.

Abstract

Introduction: Peripartum Cardiomyopathy (PPCM) is defined on the basis of 4 criteria:

- The development of cardiac failure in the last month of pregnancy and up to 5 months after delivery;
- Absence of an identifiable cause of cardiac failure,
- Absence of a recognizable structural heart disease prior to the last month of pregnancy;
- And left ventricular dysfunction demonstrated by classic echocardiographic criteria, such as depressed fractional shortening <30% or ejection fraction <45% and left ventricular end diastolic dimension >2.7 cm/m^2.

The incidence of PPCM is not always known because population-based estimates are not available as data is primarily based on case series from single centres. In the USA it ranges from 1 per 3000 to 1 per 4000. Some studies conducted in South Africa showed an incidence of 100-300 per 100 000 live births.

Aim of the study:

The aim of the study was to investigate the factors which contribute to the clinical outcomes of peripartum cardiomyopathy (PPCM) at Klerksdorp/Tshepong Hospital Complex in Klerksdorp South Africa, by means of quantitative research.

Methods:

A single centre, non randomised, retrospective cohort, chart review together with prospective assessment of patient outcomes was done on 34 patients attending Specialist Medical Outpatient Department Clinic at Klerksdorp/Tshepong Hospital Complex from January 2011 to September 2014. The patients would have delivered between January 2011 and March 2014. Recruitment followed the inclusion and exclusion criteria based on the definition of peripartum cardiomyopathy. The patient files were reviewed at the time of diagnosis and at six months looking at the background history, therapy, clinical progression and outcome. The last assessment was done with the patient. Demographic data, obstetric and medical history, clinical

progression measured by serial signs and symptoms were collected. Chest radiograph, electrocardiograph and echocardiograms were also registered and correlated to the clinical outcome.

Findings:

A total of 38 patients were recruited with a diagnosis of peripartum cardiomyopathy. Four patients were excluded from the study. Of the 34 patients who completed the study 47% recovered, whilst 26.5% remained stable and 26.5% progressively declined. Three patients, 8.8% died. Thromboembolic phenomena were noted in 20.6% of patients whilst 33.3% were on anticoagulants. The period prevalence was 0.33% (3 per thousand live births). The mean proportion in different clinical outcome groups was compared using Tukey's Studentised Range (HSD) test for result. There was a significant difference in the mean proportions between the three groups ($p=0.0001$). In the pairwise comparisons, the mean proportion of the recovered group was significantly higher than that of the stable ($p<0.05$). There was no difference in the mean proportion of the recovered and deteriorated groups ($p>0.05$). All the patients received standard cardiac failure treatment.

Discussion:

The prevalence of PPCM at Klerksdorp/Tshepong Hospital Complex was higher than other parts of South Africa. The clinical outcome distribution from the study faired with the reported 50% recovery, 25% stable and 25% progressive deterioration. The patients received standard medical therapy. Low usage of anticoagulants could have attributed to the high rate of thromboembolic events. Device therapy is indicated in refractory heart failure if resources permit. It was recommended that a high-quality, large, multicenter prospective study be conducted to better understand the clinical outcomes of PPCM and its influencing factors.

Conclusion:

PPCM is a rare condition, multifactorial in origin with a good clinical outcome in the majority of cases if treated appropriately. It should be considered in any patient who presents with acute dyspnea in the perinatal period. Patients with PPCM are being optimally treated at Klerksdorp/Tshepong Hospital Complex. Anticoagulation is recommended in patients with low ejection fractions. Further, large progressive studies are required to fully understand the aetiology and the effect of novel therapies.

Preface

The Biomedical Research Ethics Committee (BREC), University of KwaZulu Natal, approved this study.

Ethics Clearance Certificate No: B376/14

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Acronyms

3TC: Lamuvidine

6MWT: Six minute walk test

ABC: Abacavir

ACE-I: Angiotension converting enzyme inhibitor

ARV: Antiretroviral

AZT: Zidovudine

BB: Beta-blockers

CD4: Cluster differentiation 4

CS: Caesarean section

CTR: Cardiothoracic ratio

CXR: chest x-ray

D4T: Stavudine

ECHO: Echocardiography

EF: Ejection Fraction

EFV: Efavirenz

ESHF: End Stage Heart Failure

EtOH: Alcohol

FS: Fractional shortening

FTC: Emtricitabine

Hx: history

HF: Heart Failure

HF-PEF: Heart Failure with ‘preserved’ ejection fraction

HF-REF: Heart Failure with reduced ejection fraction

HICRA: Hatter Institute for Cardiovascular Research in Africa, University of Cape Town

JVP: Jugular venous pressure

K/T: Klerksdorp/Tshepong Hospital Complex

LV: Left ventricle

LVEDD: Left ventricular end diastolic dimension

LVESD: Left ventricular end systolic dimension

LVESV: Left ventricular end systolic volume

MLHFQ: Minnesota living With Heart Failure Questionnaire

MRA: Mineralocorticoid receptor antagonist

NICE: National Institute of Clinical Excellence

NVD: Normal vaginal delivery

NYHA: New York Heart Association dyspnea classification

PET: Pre-eclamptic toxemia

PND: Paroxysmal nocturnal dyspnea

PPCM: Peripartum Cardiomyopathy

RWMA: Right wall motion abnormality

SOCRU: Soweto Cardiovascular Research Unit, University of Witwatersrand

TDF: Tenofovir

UKZN: University of KwaZulu Natal

VL: Viral load

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Chapter One: Literature Review

1.1 Introduction

As early as the late 18th century, physicians had noted a relationship between pregnancy and heart failure.[1,2] Fraser (1935) showed that heart failure was one of the leading causes of maternal mortality, not due to obstetric complications.[3,4] Hull and Hidden were the first to document peripartum cardiomyopathy (PPCM) in New Orleans in 1936, and then called "toxic" postpartal heart disease.[5] Peripartum cardiomyopathy is also called postpartum cardiomyopathy (PCMO) and pregnancy-related heart failure. It is a form of cardiomyopathy which is basically enlargement and weakening of the heart associated with ineffective pumping of blood around the body.[6]

Much research has been done worldwide, with South Africa leading in efforts to understand the aetiology, pathophysiology, management and progression of PPCM. The leading institutions in this field have been, the Hatter Institute for Cardiovascular Research in Africa (HICRA), University of Cape Town and the Soweto Cardiovascular Research Unit, University of Witwatersrand (SOCRU).[7,8]

One of the clinical trials done in South Africa noted that the use of Bromocriptine in the postpartum period was associated with recovery. The study showed that the addition of bromocriptine to standard therapy resulted in significant rates of left ventricular recovery at 6 months. The study was limited by a small sample size. Coupled to this was the aversion of nursing mothers to deprive their babies of milk as the drug is used for cessation of lactation.[9]

Studies of this nature have motivated and inspired medical scientists to do more research in a bid to fully understand the condition so that research knowledge can translate to evidence based practices and programs.

1.2 Statement of the problem

1.2.1 Background

Peripartum cardiomyopathy is a form of dilated cardiomyopathy of unknown aetiology associated with a high rate of morbidity and mortality, both to the mother and the fetus.[10] In 2000, the National Heart Lung and Blood Institute (NHLBI), and The Office of Rare Diseases workshop recommended that PPCM be defined as: "the development of cardiac failure in the last month of pregnancy or 5 months of delivery; absence of an identifiable cause of cardiac failure, absence of a recognizable structural heart disease prior to the last month of pregnancy; and left ventricular dysfunction demonstrated by classic echocardiographic criteria, such as depressed fractional shortening <30% or ejection fraction <45% and left ventricular end diastolic dimension >2.7 cm/m^2".[11]

1.2.2 Nature of the problem

Peripartum cardiomyopathy is a life threatening condition whose epidemiology, aetiology and pathophysiology are poorly understood because of low incidence, geographic variation and diversity in manifestation. The prognosis of PPCM remains guarded even in the best of care with up to 50% of afflicted women gradually deteriorating.[12,13] Maternal and neonatal morbidity and mortality reduction are one of the most important goals of the Department of Health of South Africa and World Health Organisation. In 2000, South Africa joined the rest of the world by signing the Millennium Development Goals (MDGs) with targets to reduce child deaths by two thirds and maternal deaths by three quarters.[14,15]

The relative high incidence of PPCM at Klerksdorp/Tshepong Hospital Complex provided a unique opportunity in understanding the pathophysiology and prognostication of the condition. This was the rationale of performing the study. Knowledge of PPCM epidemiology and clinical outcomes potentially leads to high index of suspicion in healthcare professionals, and hopefully, early diagnosis and better clinical care.

1.2.3 Contributing factors to the problem

Peripartum cardiomyopathy is a rare condition of unknown aetiology. Making a diagnosis of PPCM is daunting to physicians as other identifiable causes of heart failure have to be excluded.[12] The definition of PPCM requires echocardiograph which can be interchangeable with cardiac magnetic resonance (CMR).[16,17] In primary health care facilities in South Africa and most developing countries, there are no ultrasound sound scan machines, let alone echocardiograms. Cardiac magnetic resonance is still under development even in the first world. The expertise to measure the fraction shortening and ejection fraction is lacking in most physicians. There is need for workshops and training programs in this regard. Postpartum cardiomyopathy requires a multi-disciplinary effort between obstetricians, pediatricians, cardiologists and generalists.[18]

1.2.4 Prior research

The Study Group on Peripartum Cardiomyopathy was founded in 2009 as one of the groups in the Heart Failure Association (HFA) committee of the European Society of Cardiology (ESC).[19,20] It aims to be an international platform for sharing knowledge and clinical experience on PPCM. There is growing concern that the previous definition is underdiagnosing PPCM as some patients present before the last month of pregnancy and after 5 months postpartum threshold.[20]

Many such organizations have been formed in an attempt to fully categorise the condition. The Hatter Institute of Cardiovascular Research in Africa (HICRA) has a Cardiac Disease and Maternity research group that is looking into the pathogenesis of PPCM with special attention into the biomarkers.[7] One of the landmark studies at HICRA was the discovery of the link between bromocriptine and recovery.[9,21,22]

1.2.5 What still needs to be done?

There is so much more that needs to be known about PPCM.[10] The aetiology and pathogenesis need to be well researched so as to know which patients need to be screened antenatal.[13] The undertaking of clinical trials in expecting mothers has ethical dilemma, as the safety of the mother and unborn child is a priority. It is not known how long patients should be on treatment and when to stop. Most case series follow up patients for 6 to 12 months. There is need for longer patient follow up.[13]

Patients who develop PPCM are young women who have not completed their families and still need to have more children but are advised to use contraception.[13] Research still needs to be done into which parameters to focus on in those who have had cardiac recovery and good reserve function with a view to determine which patients may safely have another pregnancy.[23]

1.3.1 Definition of PPCM

In 2010 the Study group of Postpartum Cardiomyopathy of the European Society of Cardiologist (ESC) defined PPCM as an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. It is a diagnosis of exclusion.[24] The left ventricle may not be dilated but the ejection fraction is nearly always reduced below 45%.[20]

1.3.2 Aetiology

The cause of peripartum cardiomyopathy is unknown.[10] There are a number of risk factors that have been found to be associated with the disease which include multi-parity, twin gestation, and breast feeding for an extended period, history of preeclampsia, smoking, alcohol, and use of illicit drug, African ancestry and family history of the disease.[4,11,25] Long term use of tocolytics, age and gestational hypertension has also been associated with PPCM. The risk factors are grouped into probable and proposed as shown in figure 1.1. Patients with a history of the condition are likely to have a relapse or deteriorate in subsequent pregnancies.[24]

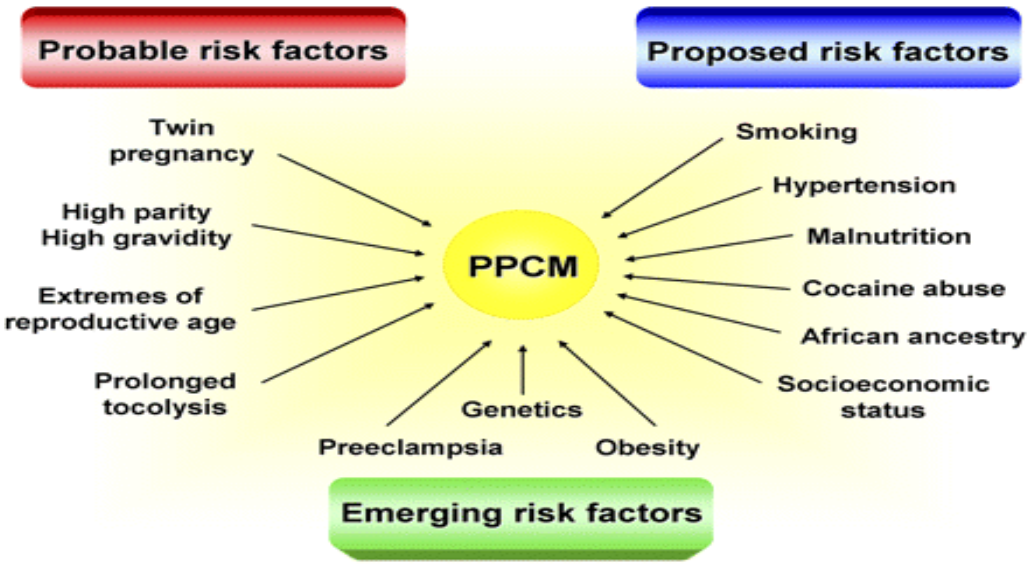


Figure 1.1: Factors contributing to Peripartum cardiomyopathy. PPCM (peripartum cardiomyopathy) [10]

1.3.2.1 Proposed risk factors

The proposed risk factors for PPCM include being of African ancestry, malnutrition, low socioeconomic status, hypertension, smoking and cocaine use.[20] A collaborative study in Georgia and Tennessee in United States of America showed that African-American women had a higher risk of developing PPCM.[26, 27]

1.3.2.2 Probable risk factors

Incidence of PPCM has been found to be higher in multiple pregnancy, high parity, high gravidity and extremes of reproductive age.[1,28,29] The prolonged use of tocolytics in preterm labour to suppress uterine contractions has been associated with a predilection for developing PPCM.[30]

1.3.2.3 Emerging risk factors

Recent studies have noted an increased risk of PPCM in pre-eclamptics and obese patients. Familial genes and previous viral infections including CMV, EBV and HIV have been reported to predispose patients to cardiomyopathy.[9,13,31]

1.3.2.4 New Developments

Bromocriptine is a dopamine antagonist which blocks the effects of prolactin, a 23kDa molecule released from the anterior pituitary. Prolactin degradation product in high oxidative states produces a 16kDa subform which is pro-apoptotic and anti-angiogenetic.[21,22] This is associated with reduced cardiomyocyte and endothelium metabolism, eventually leading to poor cardiac function.[21]

Tumour necrosis factor-alpha (TNF-α) is an inflammatory mediator which is elevated in PPCM.[32,33,34] Pentoxifylline, a xanthine-derived inhibitor of TNF-α, have been found to be associated with favourable outcomes in clinical trials done at Chris Hani Baragwanath Hospital, Johannesburg South Africa in 2002. Batchelder et al's systemic review in 2005 suggested the need for large trials to confirm the efficacy and safety of pentoxifylline in PPCM.[35]

Immunoglobulins (Ig) are anti-inflammatory chemicals produced by the body to combat infection. Transfused immunoglobulins in the acute decompensated phase of

PPCM failed to show superiority compared to standard therapy in 6 months and 12months.[36]

1.3.3 Epidemiology

Peripartum cardiomyopathy is a universal condition with incidence rate of 1:3000-15000.[25] The highest rate in the world and Africa are found in Haiti and Nigeria, respectively. Peak incidence of PPCM in Nigeria is found in the Hausa tribes of Zaira district.[10] This has been associated with the postpartum traditional practices of high salt intake 'kanwa', and lying on heated mud beds for up to two times a day, for 40 days, in humid conditions in a bid to boost milk production. [10,37]

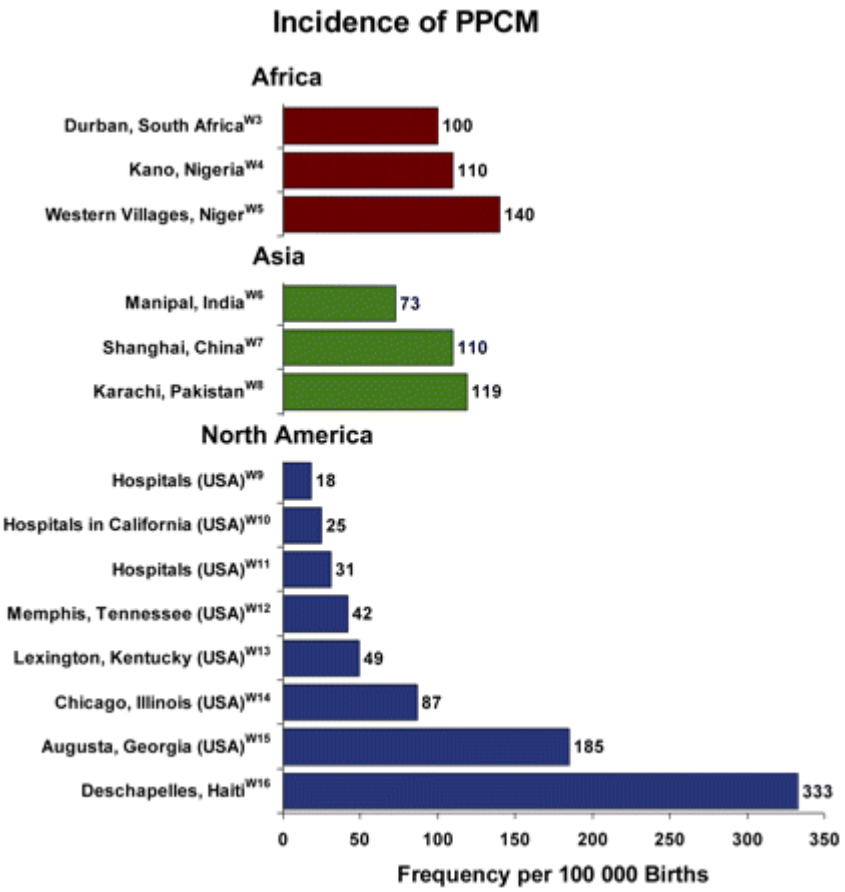


Figure 1.2: The distribution of PPCM in different countries[10]

In Asia it is more common in the Chinese, Korean and Japanese women. In the USA African-American women from the southern parts of the country are more afflicted.[10]

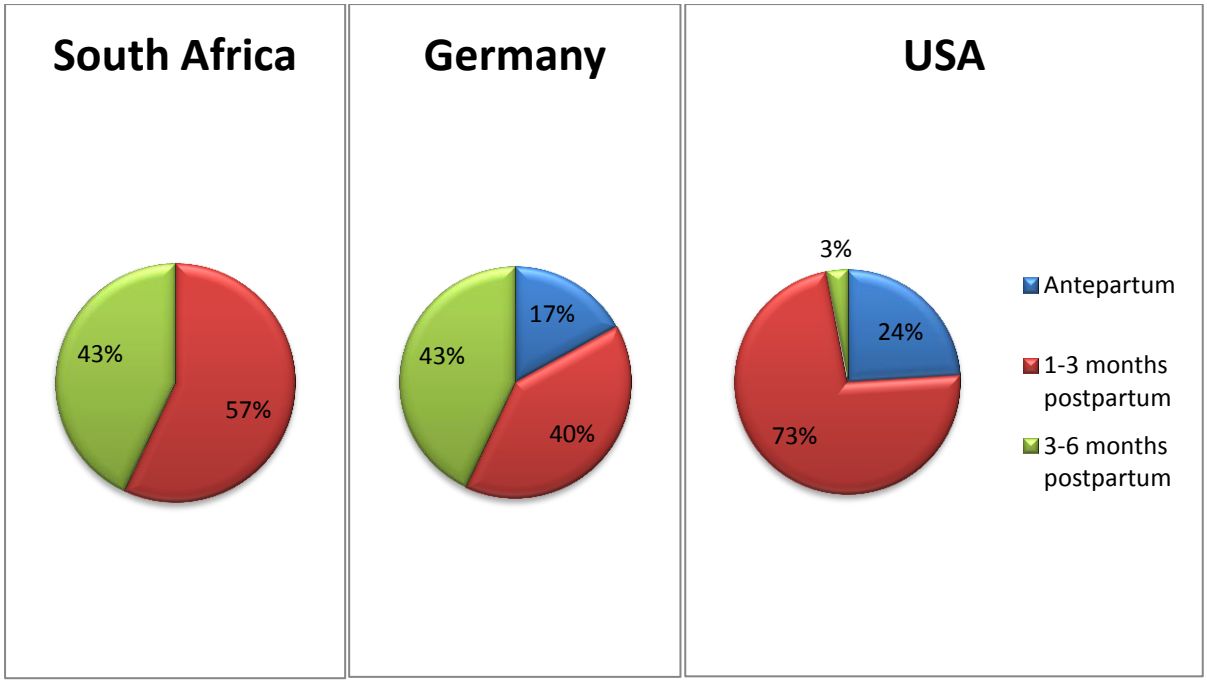


Figure 1.3: Time of onset of symptoms of peripartum cardiomyopathy in South Africa, Germany and USA[38]

The incidence of PPCM in Durban and Johannesburg are 1:1000 and 1:3000, respectively.[18,39] Normally, PPCM presents in the last weeks of pregnancy and first months postpartum in previously healthy women. Figure 1.3 presents the time of onset of symptoms in relation to delivery in South Africa, Germany and United States of America.[38]

Peripartum cardiomyopathy affects all age groups of fertile women, though it has preponderance for women greater than 35 years.[12] In these women there may be several confounders as there are likely to be previously undiagnosed diseases. Furthermore, diseases like hyperthyroidism, mitral stenosis and hypertension in pregnancy can lead to pulmonary edema which can be erroneously diagnosed as PPCM.[24] Seventy five percent (75%) of PPCM patients are diagnosed within the first month after delivery, 45% in the first week postpartum, and 19% diagnosed in the last month of gestation.[13,24,40]

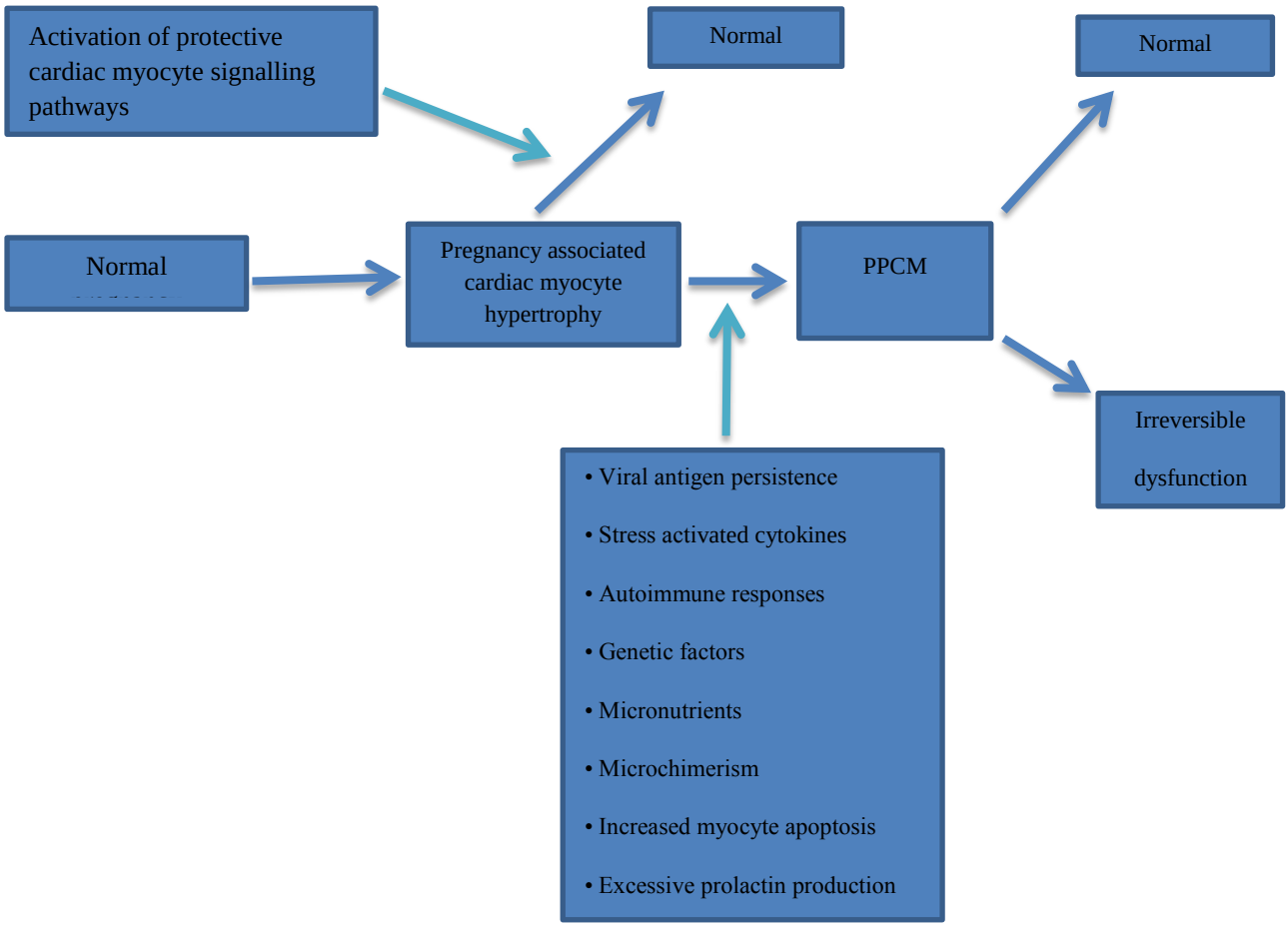


Figure 1.4: Proposed factors contributing to the pathogenesis of PPCM. (PPCM=peripartum cardiomyopathy)[43]

1.3.4.1 Pathophysiology

It has been postulated that a number of insults to the myocardium prior or during pregnancy herald the inflammatory process that is propagated during gestation as highlighted in figure 1.3.[41] This in concert with the physiological changes that occur in pregnancy, further stretches the weakened heart making it fail to adapt thus leading to heart failure.[11,24] Figure 1.4 illustrates the vicious cycle that leads to the propagation of cardiac failure.[42] The probable and possible risk factors act as insults to the heart.[10] This leads to a diseased heart with decreased cardiac output. Reduced cardiac function activates the neuroendocrine system with release of catecholamines, vasopressin, renin, angiotensin, and aldosterone. These hormones result in peripheral vasoconstriction and fluid retention, with inotropic and

chronotopic effects on the heart.[16,43] There is increase of venous return, cardiac afterload and end diastolic volume. Consequently, the energy required to contract by the diseased myocardium is escalated.[11,20]

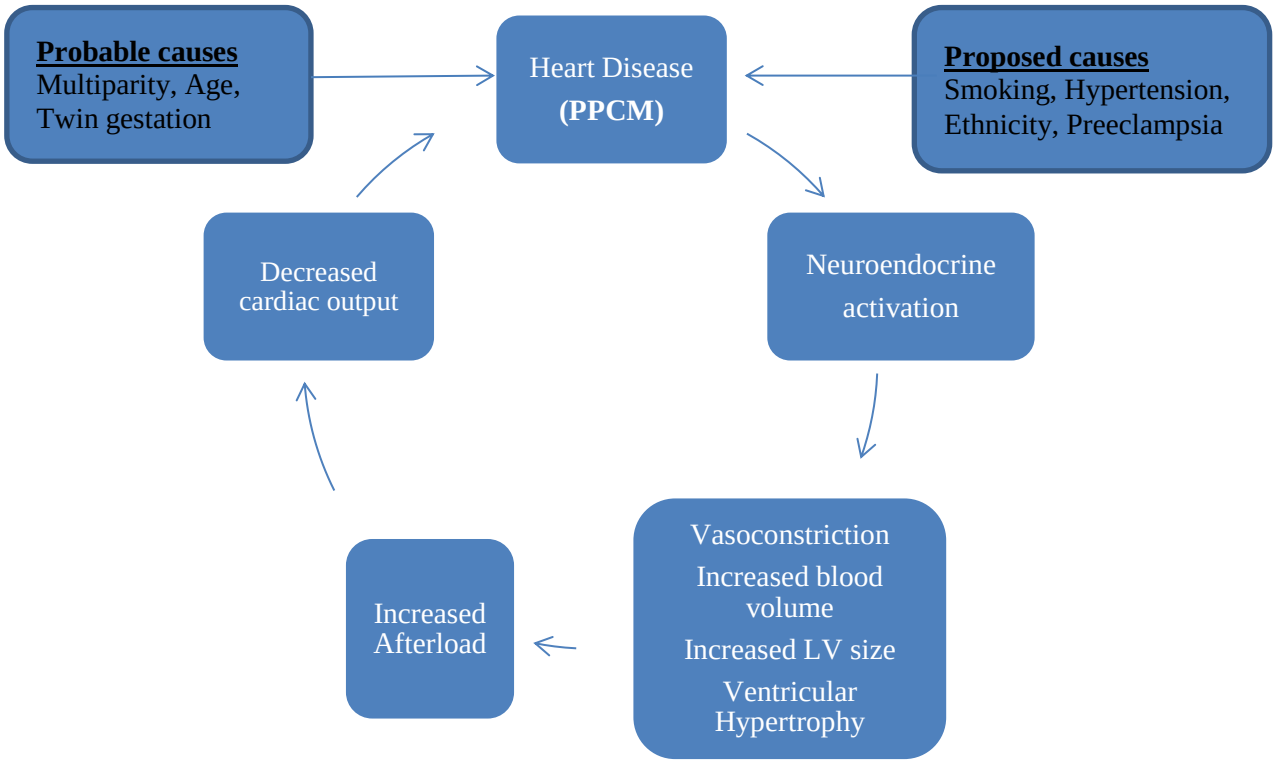


Figure 1.4: Pathophysiology of Peripartum Cardiomyopathy. LV (left ventricle). PPCM (peripartum cardiomyopathy).[42]

1.3.4.2 Ventricular remodeling

Ventricular remodeling is a term used to describe the architectural changes that occur to the heart after an insult. Grossly, there is pathological increase in left ventricular volume and disruption of the normal elliptical chamber configuration to a more spherical shape.[44] The Valsartan in acute myocardial infarction trial (VALIANT) noted three echocardiographic patterns of left ventricular remodeling when the ejection fraction was below 35% namely; concentric, concentric hypertrophy and eccentric hypertrophy. All these patterns are associated with poor cardiac function.[45]

Many case series of PPCM patients who had endomyocardial biopsies showed myocarditis. Sanderson et al studied 11 African women and endomyocardial biopsy showed healing myocarditis.[46] At autopsy the following features were noted;

(1) Macroscopically: dilated heart, pale myocardium, endocardial thickening, and pericardial fluid.

(2) At microscopic level: myofibre hypertrophy and degeneration, fibrosis, interstitial edema and lymphocytic infiltration were noted on haematoxylin and eosin-stained specimen. In addition, an increase in interstitial collagen was found. [24,46]

1.3.5 Presentation

Table 1.1: Signs and symptoms of PPCM[43]

Symptoms	**Signs**
Shortness of breath at rest or during exercise, orthopnoea, paroxysmal nocturnal dyspnoea	Tachycardia, tachypnoea
Cough	Displaced apical impulse
Fatigue	Elevated jugular venous pressure
Weight gain or weight loss	Gallop rhythm
Somnolence or diminished mental acuity	Rales, rhonchi, or wheezes
Tachypnoea	Pedal oedema, hepatomegaly, ascites, anasarca

The signs and symptoms of PPCM are summarized in table 1.1. The common symptoms include cough, dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea and pedal oedema whilst specific signs are elevated jugular venous pressure and gallop rhythm. Pedal oedema and anasarca can be present in other organ dysfunction, namely hepatic and renal failure.[47] Table 1.2 summarizes the approach to assessing a patient with PPCM.

Table 1.2: Assessments to be made at clinical review[47]

Assessment of functional capacity	Chiefly from history, but more objectively by use of New York Heart Association class, specific quality-of-life Questionnaires, 6-minute walk test, or maximal exercise test. Note: not all of these tests are likely to be necessary, or appropriate, at each assessment.
Assessment of fluid Status	Chiefly by physical examination – changes in body weight, extent of jugular venous distension, lung crackles and hepatomegaly, extent of peripheral oedema, and lying and standing blood pressure (postural drop in blood pressure may indicate hypovolaemia)
Assessment of cardiac rhythm	Chiefly by clinical examination, but may require 12-lead electrocardiogram (ECG) or 24-hour electrocardiographic ('Holter') monitoring if there is suspicion of arrhythmia
Laboratory assessment	Checking of serum biochemistry (urea, electrolytes, creatinine) is essential, but other tests (such as thyroid function, haematology, liver function, level of anticoagulation) may also be required depending on the medication prescribed and co-morbidity

1.3.6 Differential Diagnosis

Acute shortness of breath, pedal oedema and heart failure can emanate from a host of different diseases in the peripartum period. Common ailments are cardiovascular and pulmonary in origin. Conditions affecting the heart blood supply, valves or musculature can result in poor cardiac output.[17] Ischaemic Heart Disease (IHD) results in inadequate oxygen supply to the myocardium and reduced ejection fraction. Aortic and mitral valve stenosis or regurgitation, eventually leads to heart failure.[48] The heart can be dilated and loses its effective contractility in cardiomyopathy (CMO). Cardiomyopathy can be from alcohol abuse, thyroid disease or hypertrophic obstructive cardiomyopathy (HCM), but in most instances the cause remains idiopathic. Gestational hypertension or pregnancy induced hypertension and

preeclampsia are associated with propagation or precipitation of cardiac failure. Pulmonary disease can reduce blood oxygenation, and presents with dyspnoea. These conditions include pneumonia, asthma and pulmonary hypertension. Infectious causes like tuberculosis are common. Coxsackie, Epstein-Barr virus (EBV) are common viral causes of myocarditis. Human immunodeficiency virus (HIV) is now the commonest cause of viral cardiomyopathy.[16] Metabolic diseases like glycogen storage disorders and Duchenne Muscular Dystrophy (DMD) are rare causes of heart failure.[17,48]

Conditions that can masquerade as heart failure need to be excluded. These are obesity, hepatic and renal failure, hypoalbuminaemia, hypothyroidism and severe anaemia.[16]

1.3.7. Investigations

Heart failure is the final common pathway from a number of aetiological insults to the myocardium.[17] A summary to the approach to making a diagnosis of heart failure is illustrated in figure 1.5. Many criteria have been used to assist in making a diagnosis of heart failure. They include Framingham, Duke and Boston Criterion. These criteria combine patient history, examination and investigations in determining the likelihood of having cardiac failure.[16] Peripartum cardiomyopathy is a diagnosis of exclusion. Investigations are done to confirm or refute its presence and determine severity. Basic tests like urine analysis and blood work can be the starting point.[48] Urine analysis (UA) and urine protein: creatinine ratio (UPCR) can be done. Blood tests include full blood count (FBC), urea and electrolytes (U&E), liver function tests (LFT), thyroid function tests (TFT), erythrocyte sedimentary rate (ESR), C-reactive protein (CRP) and cardiac enzymes. Viral, rickettsia, syphilis and Chagas disease myocarditis must be excluded by specific antibody tests.[24] These tests are used to find the aetiology and precipitant of cardiac failure. More so, they are used to stratify the severity of disease. Chest X-ray (CXR), electrocardiogram (ECG) and echocardiogram are some of the mandatory tests done to visualize the structure of the heart and its electrical activity.[16]

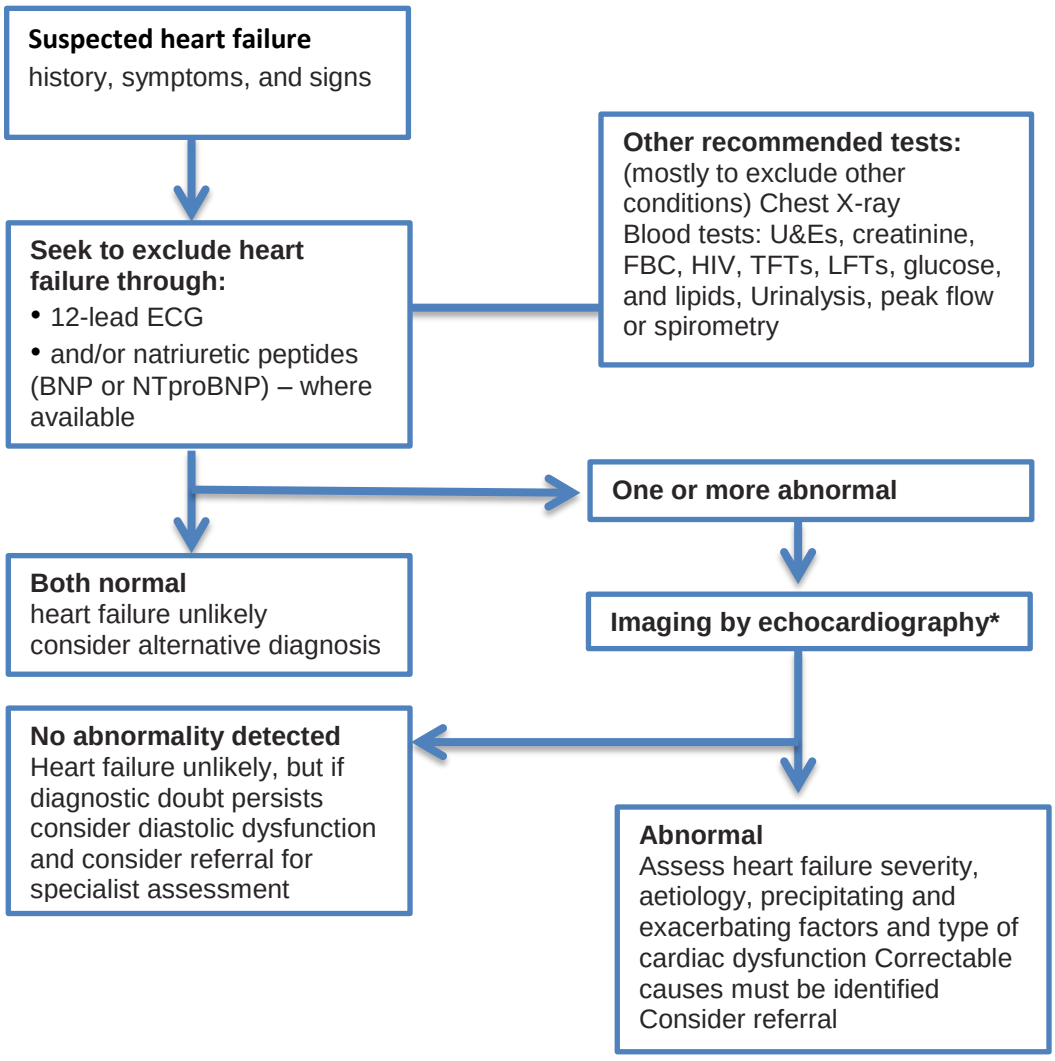


Figure 1.5: Algorithm summarising recommendations for the diagnosis of heart failure. (BNP = B-type natriuretic peptide; FBC = full blood count; LFT = liver function test; NTproBNP = N-terminal pro B-type natriuretic peptide; TFT = thyroid function test; U&E = urea and electrolytes).[47]

1.3.7.1 B-type natriuretic peptide

B-type natriuretic peptide (BNP) is a protein produced by the myocytes in response to left ventricular strain. BNP has vasodilator, diuretic and natriuretic effects. It suppresses the sympathetic drive and the renin-angiotensin-aldosterone system (RAAS).[16] It is specific to heart failure and is used to confirm the diagnosis in patients who present with acute dyspnoea and anasarca.[17] Figure 1.5 shows the clinical application of BNP in the diagnosis of heart failure. Table 1.3 shows the

interpretation of BNP levels. B-type natriuretic peptide is also used to prognosticate and monitor treatment in cardiac failure.[16]

Table 1.3: BNP interpretation[43]

BNP level	< 100pg/ml (normal)	100-399pg/ml (raised)	>400pg/ml (high)
Clinical significance	Heart failure unlikely	Probable	Heart failure

1.3.7.2 Chest radiograph

The chest radiograph is one of the most accessible and reproducible investigations in heart failure. Radiological changes include cardiomegaly and pulmonary infiltrates.[16] Cardiomegaly is defined as an increase in the cardio-thoracic ratio beyond 50%.[49] It is a measure of the most lateral borders of the cardiac shadow compared to the diameter of the chest at the same level.[49,50] Pulmonary infiltrates increase with the degree of pulmonary venous hypertension which depicts the mean capillary wedge pressure. Below is table 1.4 which illustrates the four stages of radiographic findings in congestive cardiac failure (CCF). In chronic stable PPCM the chest radiograph may be normal or there will be increased cardiothoracic ratio.[49]

1.3.7.3 Electrocardiograph

The electrocardiogram (ECG) is the recording of electrical activity of the heart.[48] In heart failure there are no pathognomic changes, but it is performed to exclude other causes of heart failure like arrhythmia, myocardial ischaemia, aberrant conduction and structural anomalies.[24,31] In left ventricular systolic dysfunction non-specific changes like dysrhythmia, axis deviation, ST changes and ventricular hypertrophy are noted.[43]

Table 1.4: Radiological changes in Heart Failure[49]

STAGE	Mean Capillary Wedge Pressure	X-ray Findings
I-(Cephalization)	10-20mmHg	In upright CXR there is apical blood flow
II-(Interstitial Oedema)	20-25mmHg	Kerley B-lines; thin white lines due to interstitial oedema
III-(Alveolar Oedema)	25-30mmHg	Opacity around the hilar in a "bat wing appearance"
IV-(Chronic Pulmonary Venous Hypertension)	>30mmHg	Bilateral interstitial infiltrates and bilateral pleural effusions

1.3.7.4 Echocardiograph

Echocardiograph is essentially ultrasound of the heart and is the preferred screening and monitoring method to assess cardiac function.[51] It assesses the cardiac chambers size and presence of intra-cardiac masses, valve morphology, and the pericardium for effusion. Below is the Simpson method for calculation of ejection fraction which is used to measure cardiac performance.[52]

The Simpson Method for Ejection fraction *= {(End Diastolic Volume – End Systolic Volume)/ End Diastolic Volume} x 100*

Echocardiography is extremely valuable in the diagnosis, monitoring and assessing of prognosis in PPCM.[53] Ejection fraction and left ventricular end diastolic dimensions at the time of diagnosis are predictive of long-term cardiac dysfunction.[52,54]

1.3.8 Management

The management of PPCM is similar to other forms of dilated cardiomyopathies.[48] It aim to improve hemodynamic status, minimize signs and symptoms, and optimize the long term outcomes.[55,56] The treatment depends on the severity of the disease,

and whether it is acute or chronic. Critically ill patients are nursed in the intensive care unit with invasive hemodynamic monitoring, ventilator and inotropic support. In the acute setting oxygen and intravenous furosemide are administered.[16] Figures 1.5 and 1.6 illustrates the recommended approach to diagnosing and managing PPCM by the National Institute of Clinical Excellence (NICE).

In decompensated cardiac dysfunction or acute heart failure syndrome (AHFS), diuretics and oxygen are used to alleviate the fluid overload.[16] Angiotensin converting enzyme (ACEI) inhibitors and beta blockers (BB) are first line therapy in heart failure when the patients have stabilized.[47] These drugs have been proved to have mortality (death) and morbidity (disease) benefit in the Survival and Ventricular Enlargement (SAVE) and Cardiac Insufficiency Bisoprolol Study (CIBIS) clinical trials, respectively.[20,57] If the patient remains symptomatic mineralo-corticosteroid receptor antagonist (MRA) are subsequently added as second line therapy. Digoxin is of benefit in sedentary patients with reduced ejection fraction especially if there is atrial fibrillation.[16] In high-resource centres end stage heart failure (ESHF) patients can be considered for cardiac resynchronization therapy (CRT)/ biventricular pacing, ventricular assist device (VAD) or heart transplant.[11,47]

1.3.8.1 Decompensated Peripartum cardiomyopathy

Patients with acute decompensated peripartum cardiomyopathy need to be managed in intensive care or high dependency units with continuous cardiopulmonary monitoring, and maintenance of the airway, breathing and circulation systems.[17] This is achieved by oxygen supplementation and at times intubation with mechanical ventilation. Diuretics are used to alleviate the fluid overload whilst monitoring the central venous pressure invasively. If there is profound hypotension, inotropic support with dobutamine or dopamine will be necessary.[40,41] In refractory cardiac failure interventions like intra-aortic balloon pump, ventricular-assist device, extracorporeal membrane oxygenation and cardiac transplantation are considered if resources permit.[16,42]

1.3.8.2 Compensated Peripartum cardiomyopathy

Management of chronic PPCM patients involves lifestyle changes and pharmacotherapy.[58] Antepartum, hydralazine and isosorbide dinitrate combination

(H-ISDN) is used instead of ACEI as they are teratogenic.[40] The table below illustrate the different categories of drugs and safety in pregnancy.

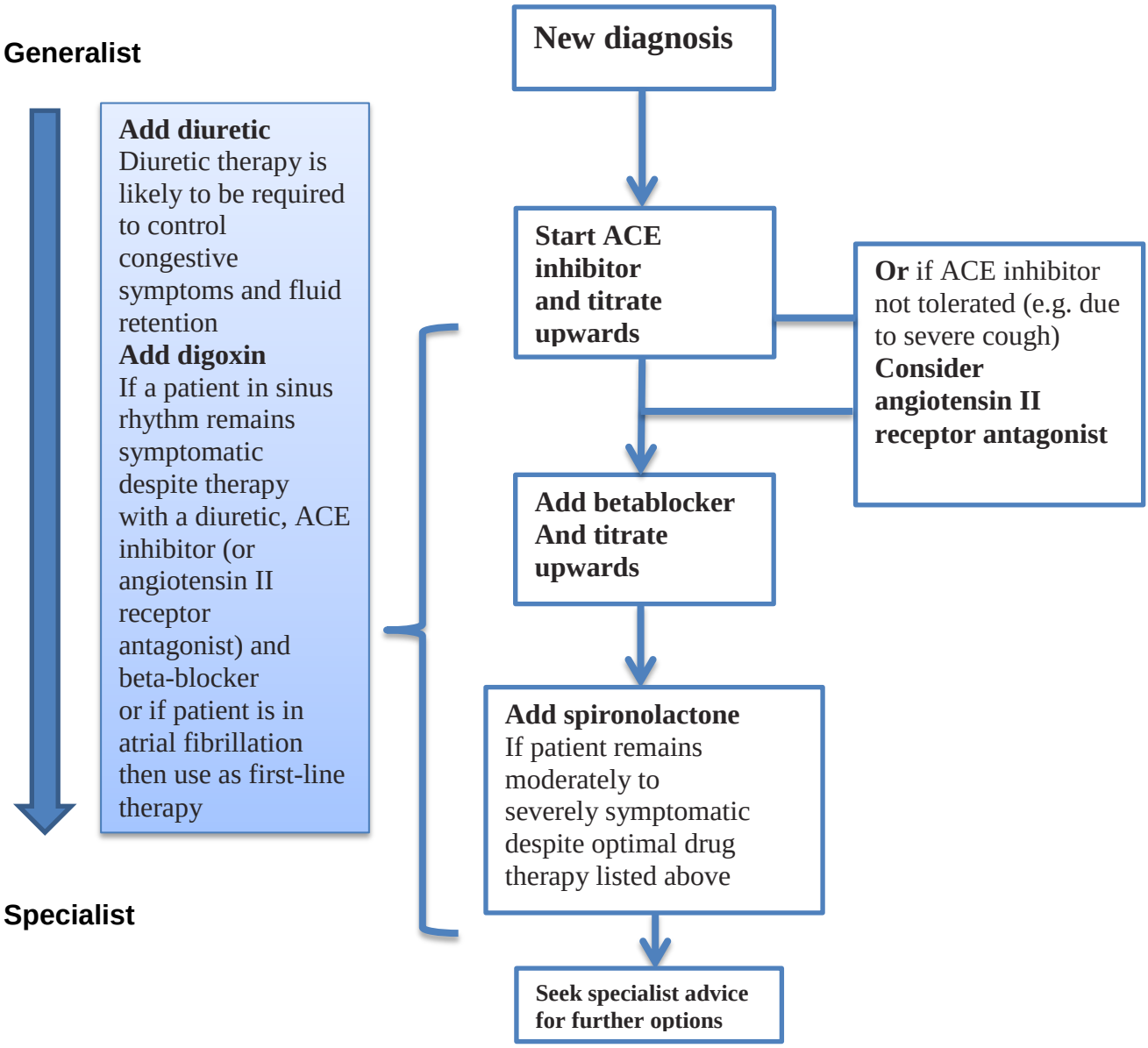


Figure 1.6: Algorithm for the pharmacological treatment of symptomatic heart failure due to left ventricular systolic dysfunction. (ACE=Angiotensin converting enzyme inhibitors)[47]

1.3.8.3 Non-pharmacological management

Lifestyle changes that aid in the recovery of the ailing heart with an overloaded peripheral system include weight reduction, fluid restriction and low salt diet. In acute

heart failure, daily weights and, monitoring of input and output is instituted with the aim to achieve a negative fluid balance.[16] Salt causes water retention. Low salt foods containing less than 150mg per 100g are recommended. Patients are advised to drink less than 2 litres of fluids per day.[12] Other lifestyles changes that have an impact on recovery involve smoke cessation, stress reduction and low fat diet. Physiotherapy can assist with graded exercises, and psychologist with psychological support.[59,60]

Table 1.5: Categories of Drugs in pregnancy[61]

Category	
A	Adequate and well-controlled studies have failed to demonstrate a risk to the foetus in the first trimester of pregnancy, no evidence of risk in later trimesters.
B	Animal reproduction studies have failed to demonstrate a risk to the foetus and there are no adequate and well-controlled studies in pregnant women. (*heparin, methyldopa*)
C	Animal reproduction studies have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. (*digoxin, Beta blocker, Furosemide, hydralazine and isosorbide dinitrate combination*)
D	There is positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. (*angiotensin converting enzyme inhibitors*, *mineralocorticoid receptor antagonists, hydrochlorothiazide, warfarin*)
X	Studies in animals or humans have demonstrated foetal abnormalities and/or there is positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits (*statins*).

1.3.8.4 Pharmacotherapy

Many drugs are used in the treatment of PPCM with angiotensin converting enzyme inhibitors and beta blockers as first line.[61] Table 1.5 illustrates the classes of drugs in pregnancy categorized according to safety profiles with examples, whilst Table 1.6 highlights landmark clinical trials in cardiac failure.

1.3.8.4.1 Angiotensin converting enzyme inhibitor

Angiotensin converting enzyme (ACE-I) is located mainly in the lung endothelium cell membrane and it converts angiotensin I (decapeptide) to angiotensin II (octapeptide).[43] Angiotensin II activates the release of aldosterone resulting in water and sodium retention, renal efferent arteriolar and systemic vasoconstriction. ACE-I attenuates the effects of Angiotensin II, and blocks the degradation of bradykinin, a powerful vasodilator. Patients intolerant to ACE-I can be given angiotensin receptor blockers (ARB).[43]

ACE-I significantly reduce hospitalization and improve morbidity and mortality in all functional classes (NHYA I-IV). These drugs are first line therapy in PPCM. Many clinical trials have demonstrated ACE-I survival benefit. These drugs slow the rate of ventricular remodeling.[11,42]

1.3.8.4.1 Beta-blockers

Beta adrenergic receptor antagonist or beta-blockers (BB) are first line therapy in PPCM. These drugs block the cardiac effects of chronic sympathetic stimulation which include myocyte toxicity.[43] This is not a class effect as only metoprolol, bisoprolol and carvedilol are recommended.[42] Beta blockers are started at low dose and up-titrated to optimal dose over weeks to months. Synergism is demonstrated in mortality benefit when BB are used in conjunction with ACE-I. There is a reduction in frequency of hospitalization in cardiac failure patients.[57]

Table 1.6: Major Clinical trials in heart failure.

Class of drugs	Clinical Trial	Results
ACE-I (e.g. Captopril, Enalapril, Fosinopril, Lisinopril Perindopril, Ramipril, Trandopril)	CONSENSUS (Cooperative North Scandinavian Enalapril Survival) SAVE (Survival and Ventricular Enlargement) SOLVD (Studies of Left Ventricular Dysfunction)	27% risk reduction in all cause-mortality, reduction in hospitalization[64] 19% risk reduction in mortality with captopril[65] 29% risk reduction in morbidity and mortality with enalapril.[66]
BB (e.g. bisoprolol, carvedilol, metoprolol, nebivolol)	CIBIS/ CIBIS II (Cardiac Insufficiency Bisoprolol Study) MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Heart Failure) COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival Trial)	Reduction in all cause-mortality, hospitalization and death[67,68] reduction in all cause-mortality with metoprolol compared to placebo (7.2% vs 11.0%, p=0.00009)[64] 5% decrease in deaths in the carvedilol group vs placebo.[70]
MRI (e.g. spironolactone, eplerenone)	RALES (Randomized Aldactone Evaluation Study Mortality Trial) EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study)	30% risk reduction in deaths and progression in heart failure. 35% less hospitalization. 15% reduction in risk of death.[66]
Digoxin	DIG (Digitalis Investigation Group)	Reduction of hospitalization without survival benefit.[71]
Diuretics (thiazides, furosemide)		No survival benefits have been demonstrated with loop diuretics.[47]

1.3.8.4.3 Mineralocorticoid receptor antagonist

Mineralocorticoid/Aldosterone receptor antagonists (MRA) are potassium sparing diuretics. Mineralocorticoid receptor antagonist is an add-on drug to ACE-I and BB in heart failure with an ejection fraction (EF) < 35 % and persistent symptoms, NYHA II-IV.[12] Randomised control trials have shown reduction in cardiac failure hospitalization and risk of premature death.[20]

1.3.8.4.4 Hydralazine and isosorbide dinitrate combination

Hydralazine and isosorbide dinitrate combination (H-ISDN) is first line therapy in pregnancy where teratogenic ACE-I and ARBs are contraindicated. After pregnancy it is second line after ACE-I and BB.[20]

1.3.8.4.5 Digoxin

Digoxin is a cardiac glycoside with inotropic effect. It is third line therapy which is associated with symptom relief but no survival benefit.[16] It is more useful in patients with concomitant atrial fibrillation with a fast ventricular response or atrial flatter as it delays impulse conduction through the atrioventricular node.[43]

1.3.8.4.6 Diuretics

Low dose loop diuretics can be used in chronic heart failure. Loop diuretics like furosemide do not have survival benefit.[42]

1.3.8.4.7 Anticoagulation

Pregnancy is a hypercoagulable state with an increase in prothrombotic factors which may persist up to 8 weeks postpartum.[20] This is compounded by immobility.[10] In PPCM; the poor cardiac function can result in development of intra-cardiac, arterial or venous clots. These can manifest as cerebrovascular accidents, pulmonary embolus or deep venous thrombus from thromboembolism.[17,48] Prophylactic anticoagulation is indicated for low ejection fraction (< 35%) and therapeutic for thromboembolic phenomena like LV thrombus. Aspirin, heparin and warfarin are used for anticoagulation.[12] Foetotoxicity of warfarin makes it the preferred agent of choice postpartum whilst low-molecular heparin is used in the last weeks of pregnancy.[20]

1.3.8.5 Devices

Patients with intractable PPCM should be considered for cardiac devices. These include cardiac resynchronization therapy (CRT) with or without intra-cardiac defibrillator (ICD) and ventricular assist device (VAD).[16, 20]

1.3.9 Prognosis

Peripartum cardiomyopathy is a life threatening condition if not diagnosed early and managed appropriately.[13] The heart failure can be progressive leading to poor effort tolerance and poor quality of life, and ultimately death. Maternal complications include; hypoxia, thromboembolism in up to 50%, progressive cardiac failure, arrhythmias, and sudden cardiac death.[16] Intrapartum misinterpretation of invasive haemodynamic monitoring is associated with inadequate treatment because of exaggerated concern for the fetus.[13] Peripartum cardiomyopathy can be misdiagnosed as preeclampsia, which requires a different treatment regime thus increasing morbidity and mortality.[24]

1.3.10 Complications

1.3.10.1 Fetal Complications

Fetal complications may be due to fetal distress either from maternal hypoxia or placental hypo-perfusion caused by reduced cardiac output induced by excessive diuresis or reduction in blood pressure from aggressive afterload reduction. Prematurity, still birth and neonatal death are also among some of the fetal complications. [13, 62]

1.3.10.2 Maternal Outcomes

About 50% of patients with PPCM recover clinically with NYHA I/II and favourable echocardiographic finding of good left ventricular function. 23-41% of patients' left ventricular dimensions return to normal. It is associated with a good prognosis.[11,51] Old age and smaller LVESD at diagnosis are predictors of good prognosis.[13] Approximately, 25% progressively decline clinically and eventually succumb whilst 25% remain stable with poor functional status.[12,20] "*The usual causes of death in patients with PPCM are progressive heart failure, arrhythmia or thromboembolism.*

The mortality rate related to embolic events has been reported to be as much as 30%".[56] The majority of the fatalities occur in the first 3 months.[23]

1.3.10.3 Predictors of clinical outcome

In the first 6 months post diagnosis of PPCM there is ventricular remodeling and exponential left ventricular recovery.[44] The initial LV dimensions and ejection fraction did not predict long-term functional outcome in some studies.[54] Higher NYHA functional class and Fas/Apo-1 at diagnosis are associated with mortality.[31] Novel findings reported young age and low body mass index at diagnosis as independent predictors of mortality.[63]

1.3.11 Future Pregnancy

Long term contraception is advised as future pregnancies are likely to weaken the heart especially in those with persistent cardiac failure.[24,62,75] *"Currently, there is no consensus regarding recommendations for future pregnancy after PPCM. Nevertheless the risk of developing PPCM, with future pregnancies, remains high. Particularly in the presence of If there is persistent left ventricular dysfunction, a subsequent pregnancy should be discouraged and avoided*."[55,76]

1.3.12 Patient follow-up

Initially, patients are followed up ideally every fortnight, with the treatment titrated against symptoms, blood pressure and heart rate.[56] The frequency of visits can be reduced in stable patients and vice versa if the condition deteriorates. Exercise and work are tailored to the patients' tolerability.[13] Patients are encouraged to exercise and to cease when they are not able to complete a sentence because of shortness of breath. Sexual activity can be resumed when a patient is able to go up two staircases or walk for 275 metres.[13,59] The Minnesota Living with Heart Failure Questionnaire (MLHFQ) is used to assess the effect of disease and therapy on activities of daily living.[73] The sum from the 21 questions is the Minnesota score. It decreases as the patient improves and conversely with PPCM deterioration. The questionnaire is annexed in Appendix F. A 6 minute walk test (6MWT) is used to assess physical endurance and monitor recovery objectively.[74] The participant walks for six minutes on flat ground and effort tolerance is quantified by the degree of

shortness of breath, oxygen desaturation, number of stops and blood pressure changes.[73,74]

1.3.13 Patient compliance and adherence

Patient education and counselling have been found to be associated with increased patient awareness of PPCM and, better self-confidence and self-management which translates to better outcomes.[59,75] This can be achieved by explaining clearly what PPCM is by the doctor and nurse.[56,76] In addition, a PPCM condition pamphlet can be given to the patient. The health facility should have a supportive system for patients with PPCM. Chronic heart failure medication should always be available for the afflicted patients.[12,59]

Chapter Two: Methods

2.1 Aim of study

To investigate the outcomes and the factors which contribute to the clinical outcomes of peripartum cardiomyopathy (PPCM) at Klerksdorp/Tshepong Hospital Complex in Klerksdorp, South Africa.

2.2 Research questions

1. What is the incidence and prevalence of PPCM at Klerksdorp/Tshepong Hospital Complex?

2. What are the clinical outcomes of PPCM?

3. What are the factors that contribute to the clinical outcomes of PPCM?

4. How is PPCM managed at Klerksdorp/Tshepong Hospital Complex?

2.3 Objectives

- To determine the incidence and prevalence of PPCM.
- To describe the outcomes of PPCM.
- To analyze factors that determines the clinical outcomes of peripartum cardiomyopathy.
- To audit the current management of PPCM

2.4.1 Ethical Consideration

Research protocol approval was sought from the UKZN Biomedical Research Ethics Committee (BREC) before study initiation and this complies with the Declaration of Helsinki.[77,78,79] The research protocol underwent a formal review process and a favourable opinion was given. Concomitantly, permission was granted by the Klerksdorp/Tshepong Hospital Complex Patient Support Group (PSG) local review board in conjunction with the Northwest province department of Health (NWDH). Appendix D and E are the respective ethics approval from BREC and NWDH.

2.4.2 Informed consent

The study was explained to the patients with benefits, risks, and alternatives emphasized.[77,78,79] Patients had the right to join or decline participation. No coercion was done. The patients retained the right to withdraw from the study at any time. Appendix C was condition pamphlet used to help participants to understand PPCM and the study. Appendix A is the informed consent form which the participant signed.

2.5 Research design

The study included a retrospective review of patient records together with a prospective assessment of patient outcomes. The cohort was patients diagnosed with PPCM at Klerksdorp/Tshepong Hospital Complex in the Obstetrics department and following up in the Medicine department from January 2011 to March 2014. Patients who were actively attending the clinic were recruited. A chart review was done with the aid of an investigator administered data collection tool (Appendix B). Patient information at diagnosis and six months were collated from their medical record. The duration between time of diagnosis and last assessment varied from a few months to 3 years in participants diagnosed in 2014 and 2011, respectively. The last assessment was done on the actual patient on the study visit which coincided with the routine review date.

2.6 Study Area

The study was performed at Tshepong Hospital, at the Specialist Medical Outpatient Department Clinic in Klerksdorp, South Africa. Klerksdorp/Tshepong Hospital Complex is made up of two hospitals, Klerksdorp Hospital and Tshepong Hospital. These hospitals function as a unit with different specialties in different hospitals. The Obstetrics and Gynaecology department is at Klerksdorp Hospital, whilst the Medicine department is at Tshepong Hospital. Pregnant women are followed up at Klerksdorp Hospital. If a diagnosis of heart failure is made during the antenatal period the gravid woman is referred to the Medical department at Tshepong Hospital for further management. After delivery, management is continued at Tshepong Hospital.

The hospital complex is a satellite teaching center for the University of Witwatersrand. It is a tertiary level hospital serving districts in the southern west parts of Northwest province. These districts include Bloemhof, Christina, Ganyesa, Hartbeesfontein, Leeudoringstad, Orkney, Ottosdal, Schweizer-Reneke, Stilfontein,

Taung, Wolmaranstad, Vryurg and Taung. In special circumstances it accepts patients from the northern parts of Northwest province and the proximal parts of Free State province.

2.7 Study Methods

2.7.1 Inclusion criteria

- Women of child bearing age of any ethnicity.
- Heart failure in the last month of pregnancy or 5 months postpartum.
- Depressed fractional shortening <30% or ejection fraction <45% and left ventricular end diastolic dimension >2.7 on echocardiography.

2.7.2 Exclusion criteria

- Presence of another identifiable cause of cardiac failure.
- Presence of a recognizable structural heart disease prior to the last month of pregnancy.

2.7.3 Patient recruitment

Patients who fulfilled the above mentioned PPCM criteria, and had presented with new onset symptoms to the departments of Obstetrics and Gynaecology (OBGYN) and Internal Medicine in January 2011 to March 2014 were enrolled into the study. Recruitment commenced when the UKZN Biomedical Research Ethics Committee and Northwest department of health had approved the research protocol. The nature of the study was explained to the patient in the language they understood with the assistance of the clinic nurse. The informed consent form and condition pamphlet were given to the patient for perusal at their own time so that they could fully comprehend the study. These documents are attached as appendix A1, A2 and C.

2.7.4 Study Visit

Enrolled patients were interviewed using a researcher administered questionnaire on the scheduled study visit which coincided with patients' routine review date. Vital signs including blood pressure, pulse, and respiratory rate were collected. This was followed by a physical examination. The resident cardiologist who was following up

the patients did the echocardiogram. Two-dimensional targeted M-mode echocardiograph with Doppler colour flow was used to measure the cardiac structural function. The study visit constituted the patient's last assessment or 'current status'.

2.8 Data Collection

The data was captured using an investigator administered questionnaire reviewing the patient hospital file. The questionnaire is annexed as appendix B.

2.9 Study limitation

The study was partly retrospective. The data was sometimes not adequately recorded in the charts. During the study visit the outstanding information was obtained as much as possible from the patient. There was selection bias as only patients who were actively attending the clinic at the time of the study were enrolled. The questionnaires were administered by the investigator.

2. 10 Data analysis

The data collated was analysed with the aid of a statistician. The demographic data, presenting symptoms, examination findings, investigations and clinical outcomes were expressed as mode, mean ±SD or median (range). Diagrams, graphs and tables were used for data analysis to compare the variables. We tested the hypothesis that the mean proportion of participants recovering, stable or deteriorating was similar against the alternative that at least one differs using the one way Analysis of Variance. Data for each of the categories was presented as proportions and the three groups were independent. The Tukey Studentised Range (HSD) test was used for pairwise comparisons between the three groups of patients. Analysis was performed using SAS 9.3 (SAS Institute, Cary NC) and assumed a two-sided analysis.

2.11 Dissemination of Results

The results of the research were presented at Klerksdorp/Tshepong Hospital Complex in the department of internal medicine weekly meeting. Research participants were educated and counselled on clinical outcomes and the findings and

recommendations of the project. The information was disseminated with the hope to improving clinical practice.

2.12 Incidence

The incidence of a disease is defined as the *number of new cases of PPCM* in a given at-risk population over a specified period of time. This is the number of patients with newly acquired disease. It is calculated by dividing the number of new cases in a given population by total population at risk during that time.[80,81]

2.13 Prevalence

Prevalence is the *total number of cases of PPCM* at a moment in time. It includes new and old cases.

$$\text{Prevalence} = \frac{number\ of\ cases\ of\ PPCM\ in\ the\ measured\ period}{number\ of\ live\ births\ in\ the\ same\ period} \times 100$$

In chronic cases the prevalence is greater than the incidence. In epidemics prevalence is equal to incidence.[80,81] The period prevalence is the summation of patients who already had PPCM and the new cases in the period January 2011 to March 2014.

2.14 The clinical outcomes

The natural progression of PPCM is that 50% of the patients recover, 25% remain with heart failure and 25% progressively deteriorate.[13] Poor cardiac function is associated dizziness, dyspnoea, palpitations, tiredness, and development of clots in the heart and vascular system. Patient follow up involved monitoring the above signs and symptoms. It also entailed recognition of complications like arrhythmias, cerebrovascular accidents, acute pulmonary oedema and venous thromboembolism (VTE) in the form of pulmonary embolus and deep vein thrombosis.[12]

Recovery was noted by resolution of shortness of breath and fatigue, coupled with good effort tolerance.[74] Effort tolerance was measured by the New York Heart Association (NYHA) functional classification. Class I have no symptoms and limitation to ordinary physical activity, whilst Class IV have severe limitation and experience symptoms at rest.[73] Patient recovery is accompanied with an ejection fraction (EF) and fractional shortening (FS) on echocardiography of more than 45%

and 30%, respectively. The left ventricular end diastolic volume (LVEDD) will be less than 2.7cm^2.[51]

The study involved the follow up of patients diagnosed with Peripartum Cardiomyopathy from January 2011 to March 2014 focusing on clinical outcomes and their contributing factors. Clinical progression was assessed at the time of diagnosis, at six months and current status. The three clinical outcomes were:

a) **total recovery** clinically and on echocardiograph: in this group anti-heart failure medication was eventually stopped,
b) **stable**, these are patient that remained with heart failure but had mild physical limitation: New York Heart Association (NYHA) functional class I/II
c) **progressive deterioration**, this group of patients had moderate to severe heart failure with profound limitation of activities of daily living: NHYA III/IV.[20]

The patient outcome was recorded on the questionnaire in the assessment section.

2.15 Risk factors

Data on probable, proposed and emerging risk factors for the aetiology of PPCM like multiple gestation, multiparity, preeclampsia, socio-economic status, age and ethnicity were collated in the demography section of the questionnaire. The clinical response was assessed by noting the progression of signs and symptoms. Furthermore, special investigations like chest radiograph, electrocardiograph and serial echocardiograph were utilised to objectively assess the outcome.

2.16 Standard of care of PPCM

Data on how the patients were managed was collated from charts review. At follow-up review the scripts were reviewed to note whether the drugs were at optimum doses. In recovering patients with good heart function a note was made on whether dose alteration was made.

2.17 Patient follow-up after the study

According to literature, 50% of patients with peripartum cardiomyopathy recover by 6 months and this coincides with completion of ventricular remodeling.[54] This was the rationale for ending the inclusion period in March 2014, so that there was more than

6 months of follow-up after diagnosis. Patients who had a diagnosis of peripartum cardiomyopathy after March 2014 were not included in the study.

2.18 Research funding

A scholarship of R30, 000 was obtained from the University of KwaZulu Natal for the Master of Medical Science in Internal Medicine (**MMedSc (Med)**) Degree. The scholarship covered tuition remission. The study did not have any external funding and there was no conflict of interest. No money was given to patients for participation.

Chapter Three: Results

3.1 Introduction

A total of 38 patients with a diagnosis of peripartum cardiomyopathy who attended the Specialist Medical Outpatient Clinic between January 2011 and March 2014 were recruited. Four patients were excluded from the study. Three of them had identifiable causes of heart failure. One patient's file could not be retrieved from the records department. The identifiable causes of heart failure were congenital atrial septal defect, severe mitral valve stenosis and primary pulmonary hypertension.

3.2 Demographics

3.2.1 Age

The age of the patients ranged from 19 years to 46 years. The mean age was 33.9 years with standard deviation of 6.1.

3.2.2 Race

Ninety-four percent of the research participants were African in origin. No whites, Indians or Asians were involved in the study.

3.2.3 Ethnicity

The majority of the participants 26 (76.5%) were of the Tswana tribe. The coloured (mixed) and Xhosa ethnicities had two recruits each, whilst the Zulu and Sotho had one representative each. The regional countries were represented with a patient each from Zimbabwe and Mozambique. The indigenous people of Klerksdorp area are Tswana speaking. Klerksdorp is a mining and farming community with the working class coming from various parts of South Africa.

3.2.4 Level of education

Most of the participants were educated and literate. The majority of them attended high school as shown in Figure 3.1. Thirty-two percent of the recruits matriculated, with 4 (12%) having earned tertiary education. Only 3 (9%) had primary education. Of the 34 participants, 5 (15%) were employed and the rest were unemployed. This is shown in Figure 3.2.

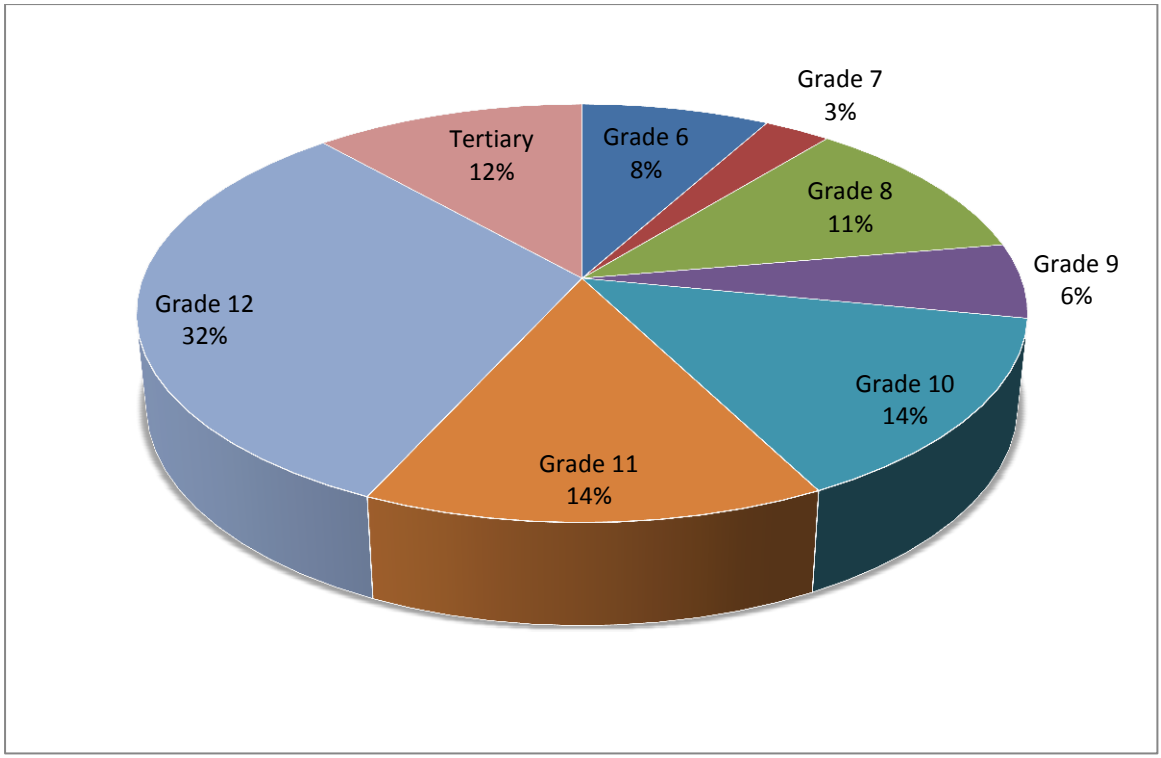


Figure 3.1: Level of Education

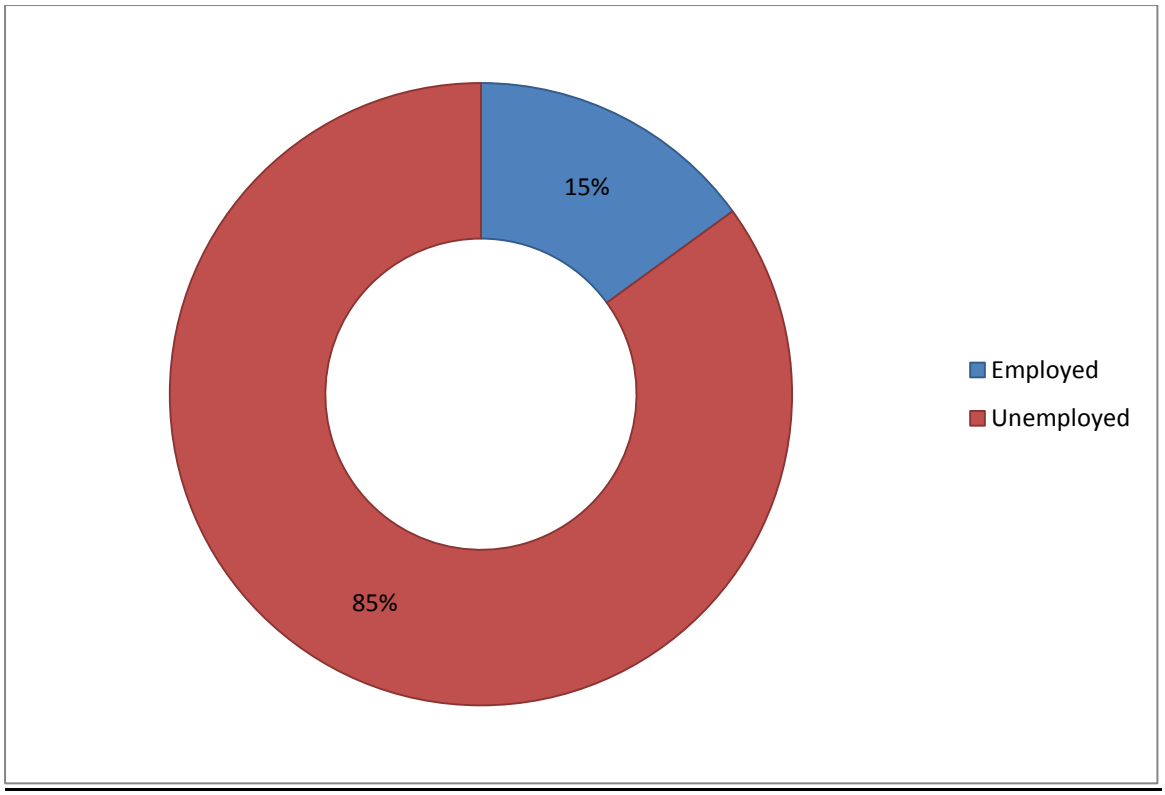


Figure 3.2: Occupation

3.3 Obstetric History

3.3.1 Date of Delivery

The study recorded deliveries from 2011 to 2014. The majority of patients delivered in 2012 and 2013 with 11 and 15 deliveries, respectively. In 2011 there were 6 deliveries and 2 in 2014.

3.3.2 Time of Diagnosis

The time of diagnosis ranged from -1 to +5 months in relation to the time of delivery as shown in figure 3.3. It was obtained by subtracting the date of diagnosis from the date of delivery. The highest number of PPCM cases was in the first month postpartum. Twelve percent of study patients were diagnosed in the antepartum period, with 68% in the first three months postpartum and 20% greater three months.

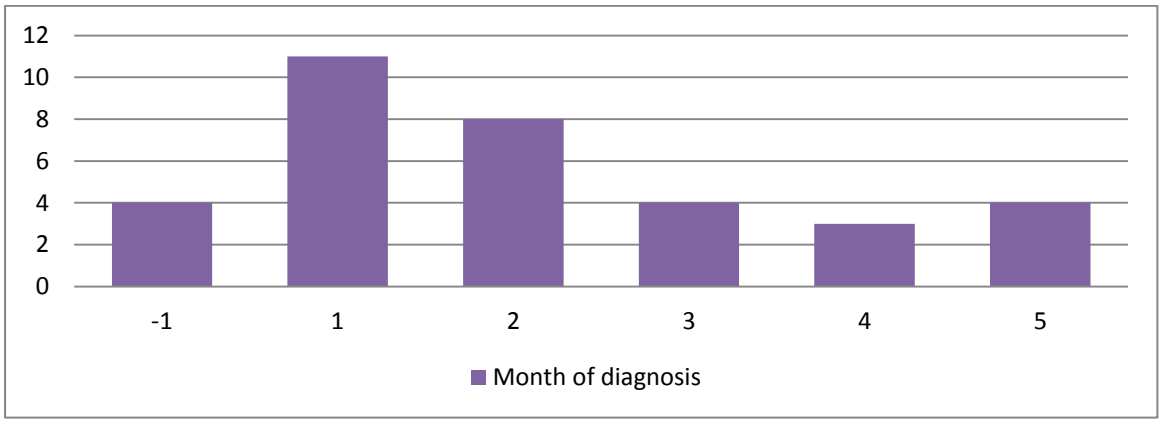


Figure 3.3: Time of diagnosis

3.3.3 Mode of delivery

Most of the patients had normal spontaneous vaginal delivery, 23 (68%) whilst 11 (32%) had caesarean section.

3.3.4 Number of pregnancy

The gravidity (number of pregnancies) and parity (number of deliveries after 24 weeks) ranged from 1 to 6 pregnancies as shown in the figure 3.4.

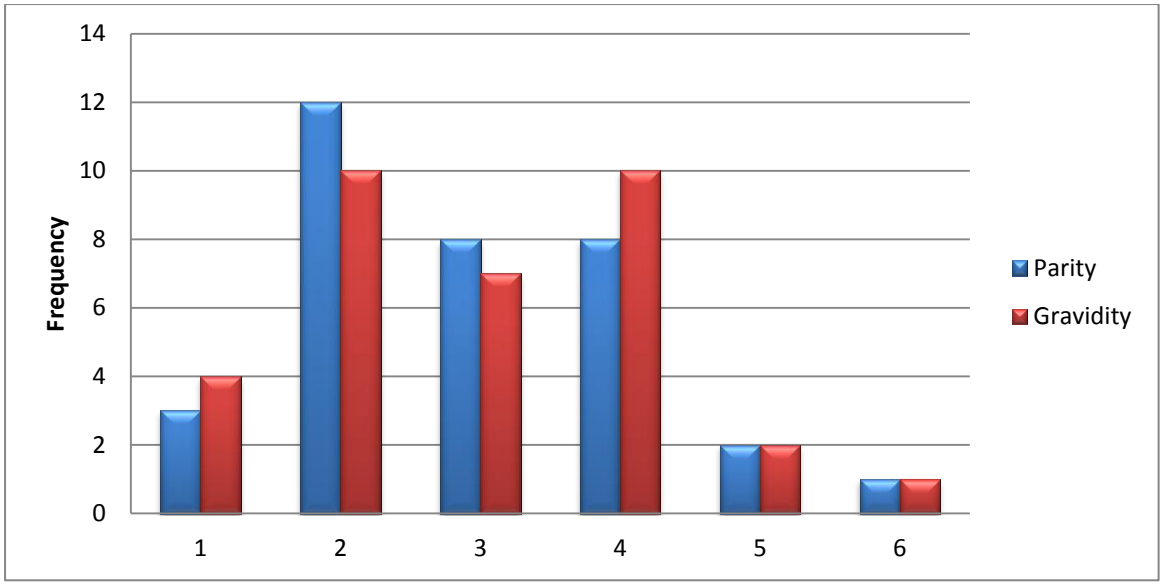


Figure 3.4: Parity and gravidity

3.3.5 Hypertensive disorders in Pregnancy

Gestational hypertension (HTN) was noted in 20 (58.8%) whilst 17 (50%) went on to develop pregnancy induced toxaemia (PET).

3.3.6 General obstetric history

There were 5 (15%) neonatal deaths in the study participant. In the postpartum period, 18 (53%) breastfed their children and 28 (82%) used contraception as a method of prevention for further pregnancies. Only 3 (9%) of the patients who did not breastfeed received bromocriptine. History of PPCM in prior pregnancy, and multiple gestation were noted in 2 (6%) of patients.

3.4 Medical History

3.4.1 Hospital admission

The average number of hospital admissions in acute decompensated heart failure was 1.7. Eighteen percent of the participants were admitted in Intensive Care Unit as exhibited in figure 3.5, whilst figure 3.6 shows the number of days in ICU.

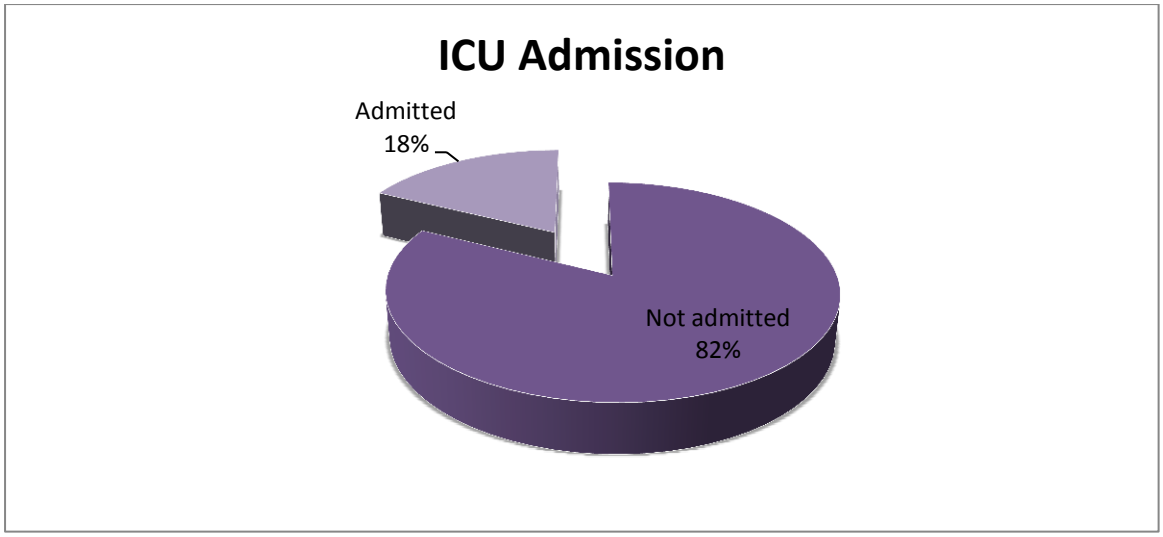


Figure 3.5: Intensive Care Unit admission

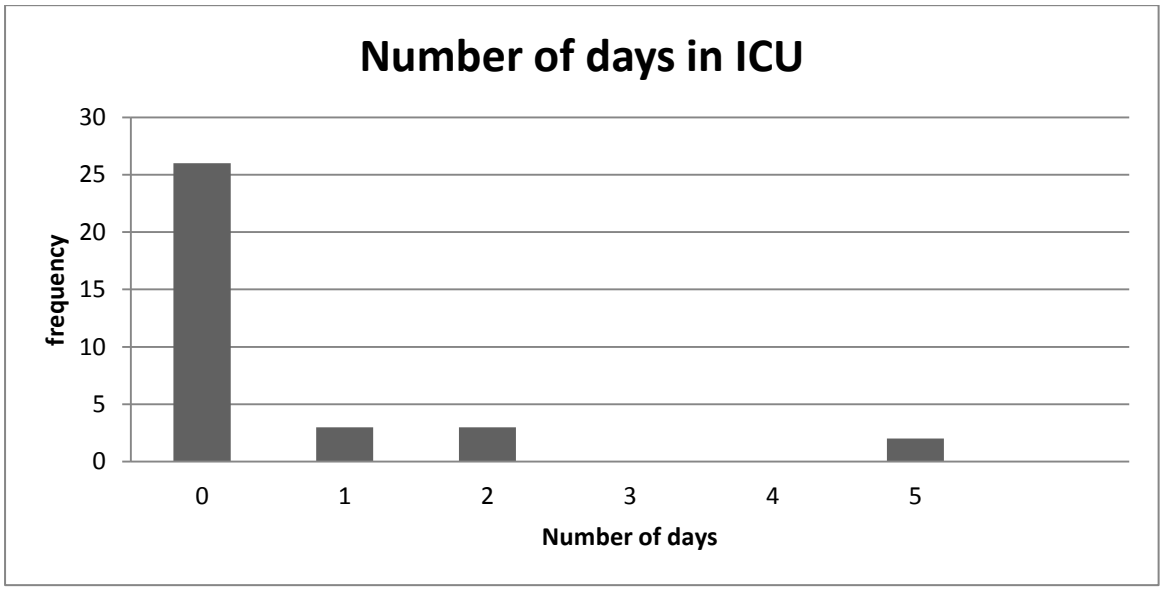


Figure 3.6: Number of days in ICU

3.4.2 HIV status

Fifty-three percent of the participants were HIV negative, whilst 47% were HIV positive. Previous history of tuberculosis (TB) was found in 14.7 % (5).

3.5 Incidence and Prevalence

3.5.1 Incidence

The incidence rate of PPCM in the period January 2011 to March 2014 was 34. All the patients involved in the study were new cases.

3.5.2 Prevalence

The prevalence of PPCM at Klerksdorp/Tshepong in the period January 2011 to March 2014 was 51. This included new cases (incidence) and old patients who had PPCM and were being followed up at Specialist Medical Outpatient Department. The number of live births in Obstetrics department of Klerksdorp/Tshepong Hospital in the 39 months was 15561.

$$\text{Prevalence} = \frac{number\ of\ cases\ of\ PPCM\ in\ the\ measured\ period(\ 51)}{number\ of\ live\ births\ in\ the\ same\ period\ (\ 15561\ )} \times 100$$

$$=0.3277\%$$

This translates to 3 per 1000 live births.[76]

3.6 Patient Presentation

The symptoms and signs at diagnosis, six months and current state of the participants were used to assess clinical progression.

3.6.1 Symptoms

Patient symptoms were followed up sequentially from time of diagnosis, 6 months and last assessment. Overall, there was a reduction in the intensity of symptoms. The trend for dyspnoea, cough and leg swelling are shown in figure 3.7.

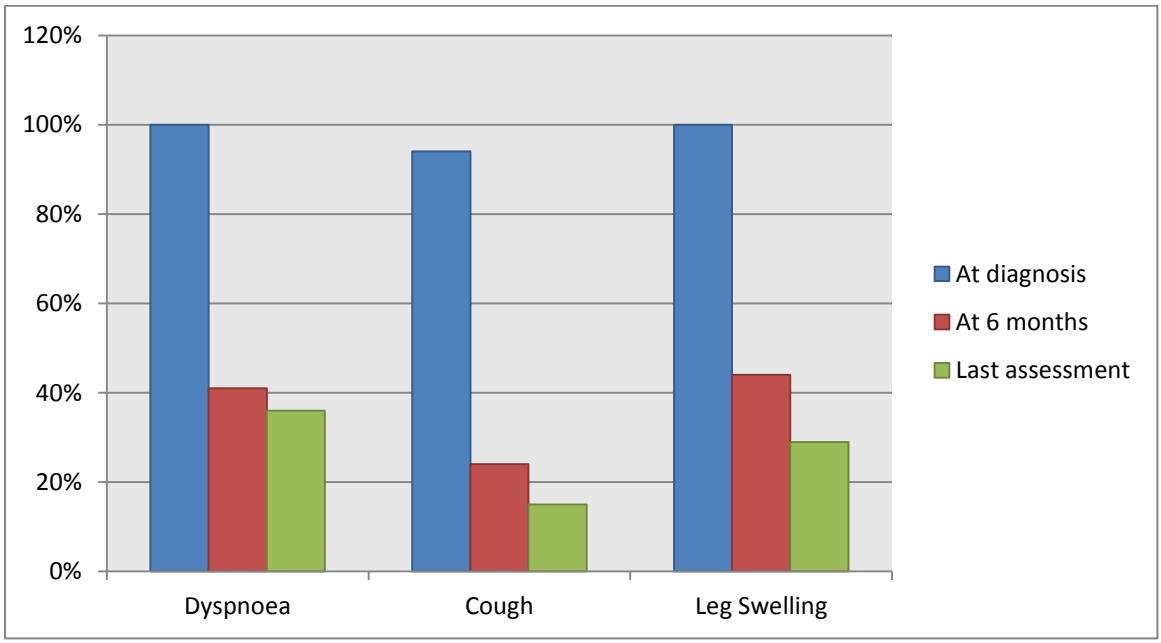


Figure 3.7: Symptoms

3.6.2 Physical Findings

Physical signs were assessed at the same interval times as the symptoms. Mostly, there was an improvement in all physical signs as shown in figure 3.8.

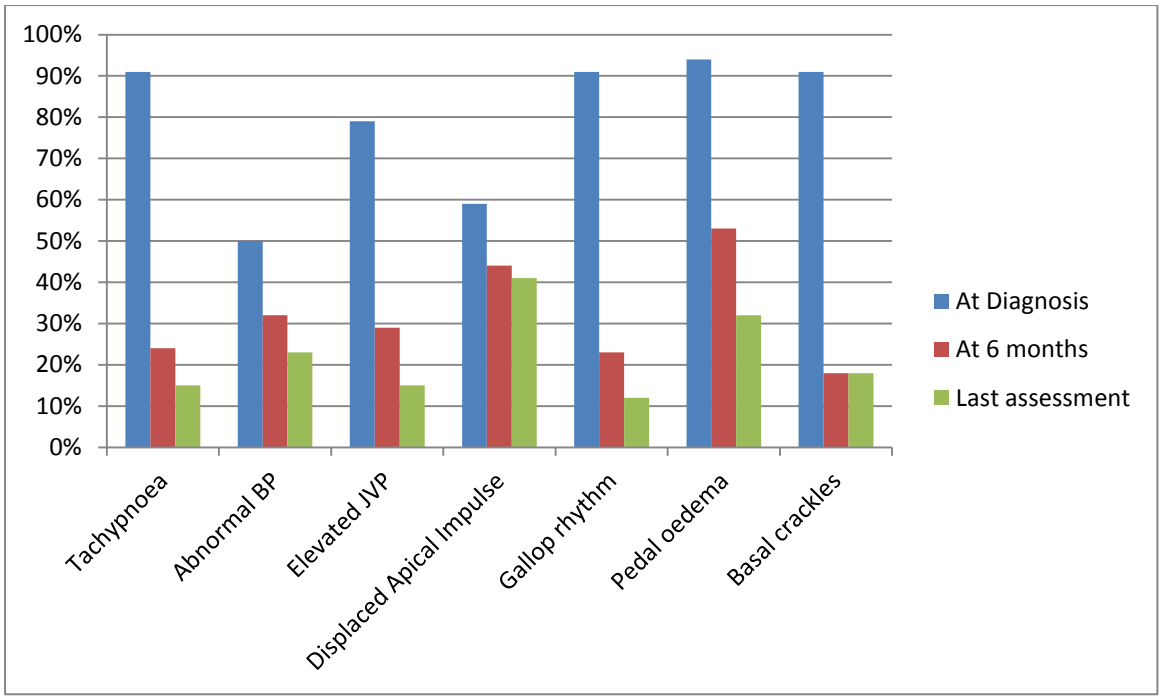


Figure 3.9: Physical findings

3.6.3 New York Heart Association (NYHA) functional status

Most patients showed improvement in physical activity to full recovery. At diagnosis there were 41.20% of participants in class IV and 14.70% in class I. Beyond six months 2.90% were in class IV and 58.80% were in class I. Detailed variations in the NYHA are disclosed in figure 3.9.

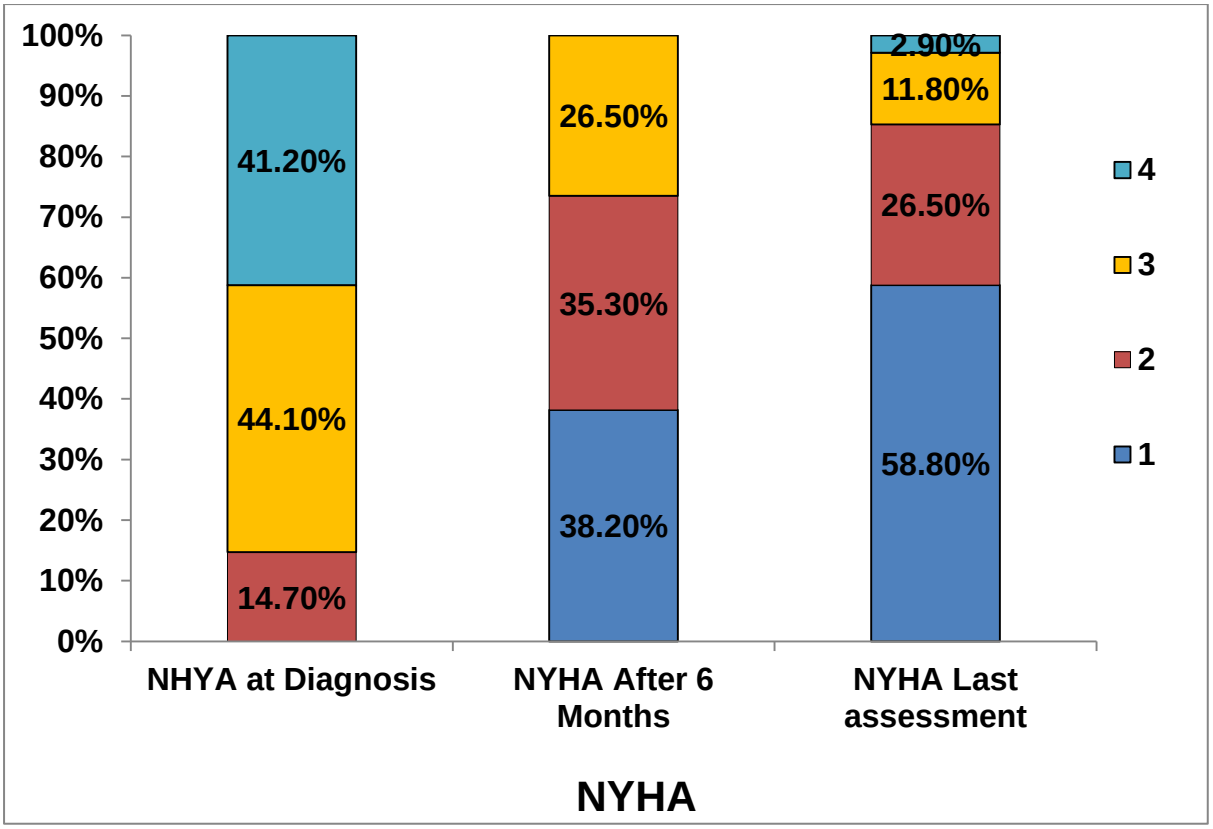


Figure 3.9: New York Heart Association functional status

3.7 Investigations

3.7.1 Chest radiograph

The chest radiograph findings at diagnosis are shown in Table 3.1.

Table 3.1: Chest radiograph findings at diagnosis

	Cardio-thoracic ratio (CTR)	Upper lobe diversion	Kerley-B lines	Alveolar infiltrates	Fluid in the fissure	Pleural effusion
patients	76.47%	91.18%	61.76%	85.29%	44.12%	41.18%

3.7.2 Electrocardiography

Electrocardiograms (ECG) of study patients at diagnosis were reviewed and tachycardia was noted in 76.5% (26) of participants, and 67.6% (23) had ventricular hypertrophy. Aberrant ventricular conduction (bundle branch block) was found in 17.6% (6) of patients.

3.7.3 Echocardiography

The mean LVEDD at diagnosis is 57.0 with a standard deviation of 7.9 which greater than the up limit of normal of 55 millimeters (mm). At last assessment it had normalized to 53.6mm. The mean ejection fraction at diagnosis was 33.5, and increased to 43.7 at last assessment. The fractional shortening mean was 16.02% at diagnosis and increased to 23.38%, at last assessment. Tables 3.2, 3.3 and 3.4 show the mean LVEDD, EF and FS over the three periods.

Table 3.2: Left Ventricular End Diastolic Dimension (LVEDD)

Normal range (35-55) mm	LVEDDD at Diagnosis (mm)	LVEDD After 6 months (mm)	LVEDD Current (mm)
Mean	57.0	55.8	53.6
Std. Deviation	7.9	7.7	8.4

Table 3.3: Ejection Fraction (EF)

Normal range (55-70)%	EF at Diagnosis (%)	EF After 6 months (%)	EF Current (%)
Mean	33.5	38.6	43.7
Std. Deviation	8.2	9.6	15.9

Table 3.4: Fractional Shortening (FS)

Normal range (25-45)%	FS at Diagnosis (%)	FS After 6 months (%)	FS Current (%)
Mean	16.0	19.1	23.4
Std. Deviation	4.7	5.1	9.0

3.8 Management

All participants were treated with first line therapy which consist of an angiotensin converting enzyme- inhibitor (ACE-I) and beta-blocker (BB). The ACE-I received was either perindopril or enalapril, whilst the BB was carvedilol. Spironolactone a mineralocorticoid receptor inhibitor (MRI) was prescribed to 94.12% of participants. All patients were treated with furosemide in the acute decompensated stage of heart failure. Digoxin was used in 33.33% of patients. Anticoagulants were also prescribed in 33.33% of patients. Aspirin, clexane and warfarin were used for anticoagulation. Table 3.5 shows the different types of medications taken by the recruits and their frequency.

Table 3.5: Pharmacotherapy

Drug type	ACE-I	BB	MRI	Digoxin	Anticoagulation	Loop Diuretics
% use of participant	100%	100%	94.12%	33.33%	33.33%	100%

3.9 Thromboembolism

The table below shows the complication rates from thromboembolic events

Table 3.6: Thromboembolism

	Stroke	Pulmonary Embolus	Deep Venous Thrombus
% of participants affected	5.89%	2.94%	11.76%

3.10 Patient Outcome

Patient outcome was stratified into three categories: recovered, stable and deteriorated. Figure 3.10 shows the distribution of patient outcome. 47% of patients recovered, whilst 26.5% remained stable and 26.5% deteriorated. The mortality rate was 9%. The year of diagnosis was correlated with clinical outcomes in figure 3.11.

In year 2012 and 2013 there were the highest proportion of patients who recovered whilst 2011 and 2014 was otherwise.

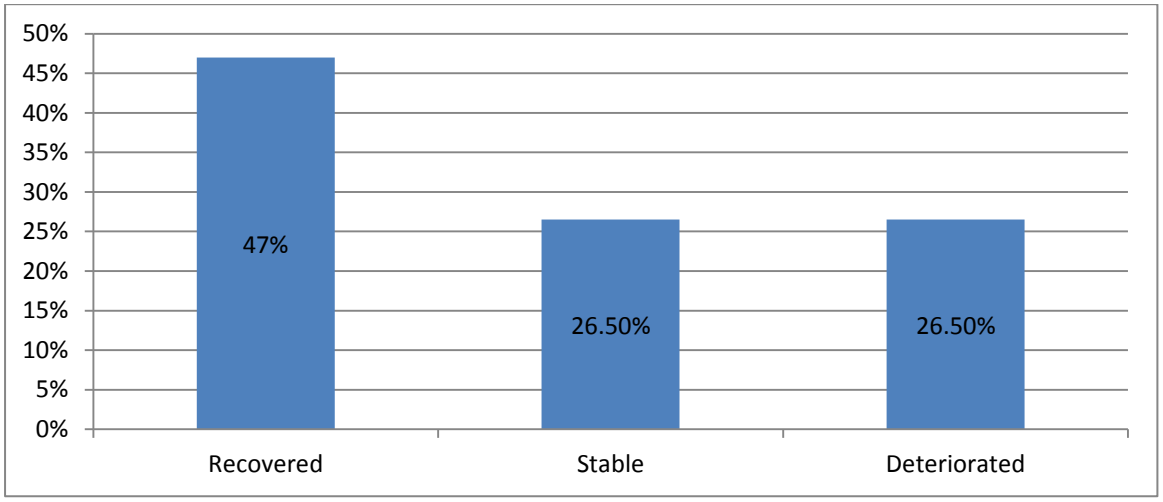


Figure 3.10: Patient outcome

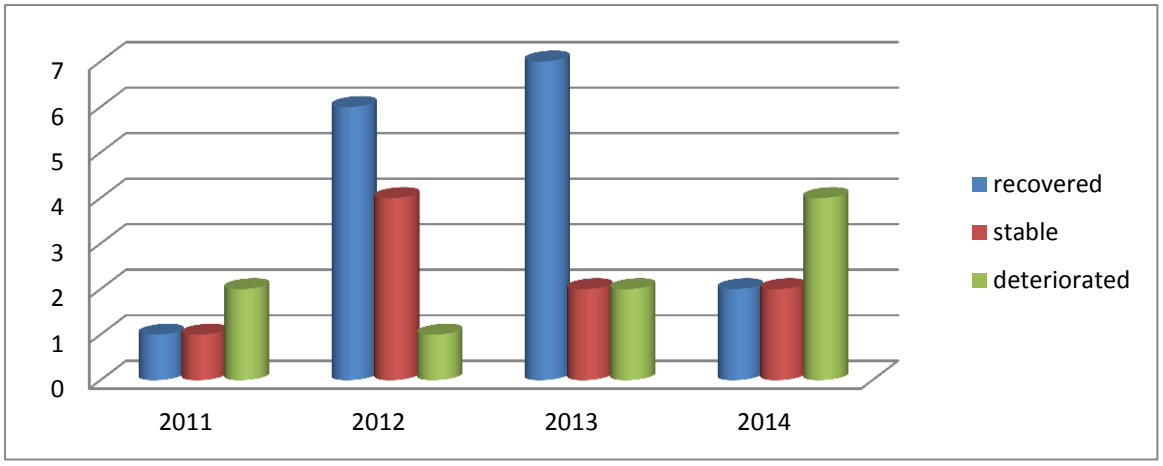
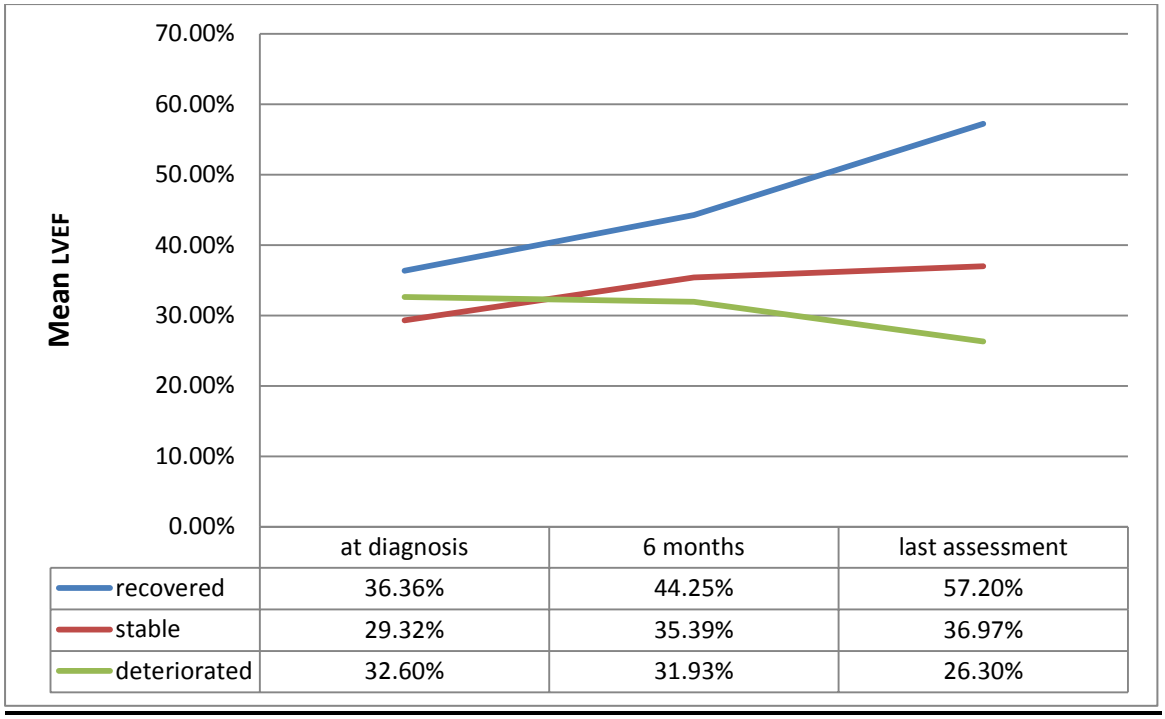


Figure 3.11: Year of diagnosis with patient outcome

The mean left ventricular ejection fraction (LVEF) of study patients generally increased in the groups that recovered and remained stable whilst there was a gradual decline in the group that deteriorated as shown in fig 3.12.



	at diagnosis	6 months	last assessment
recovered	36.36%	44.25%	57.20%
stable	29.32%	35.39%	36.97%
deteriorated	32.60%	31.93%	26.30%

Figure 3.12: Mean LVEF at diagnosis, 6 months and last assessment

Figure 3.13 compares the clinical outcomes of the patients who breastfed and those that did not. Most of the study patients recovered. The patients who did not breastfed had more participants who deteriorated.

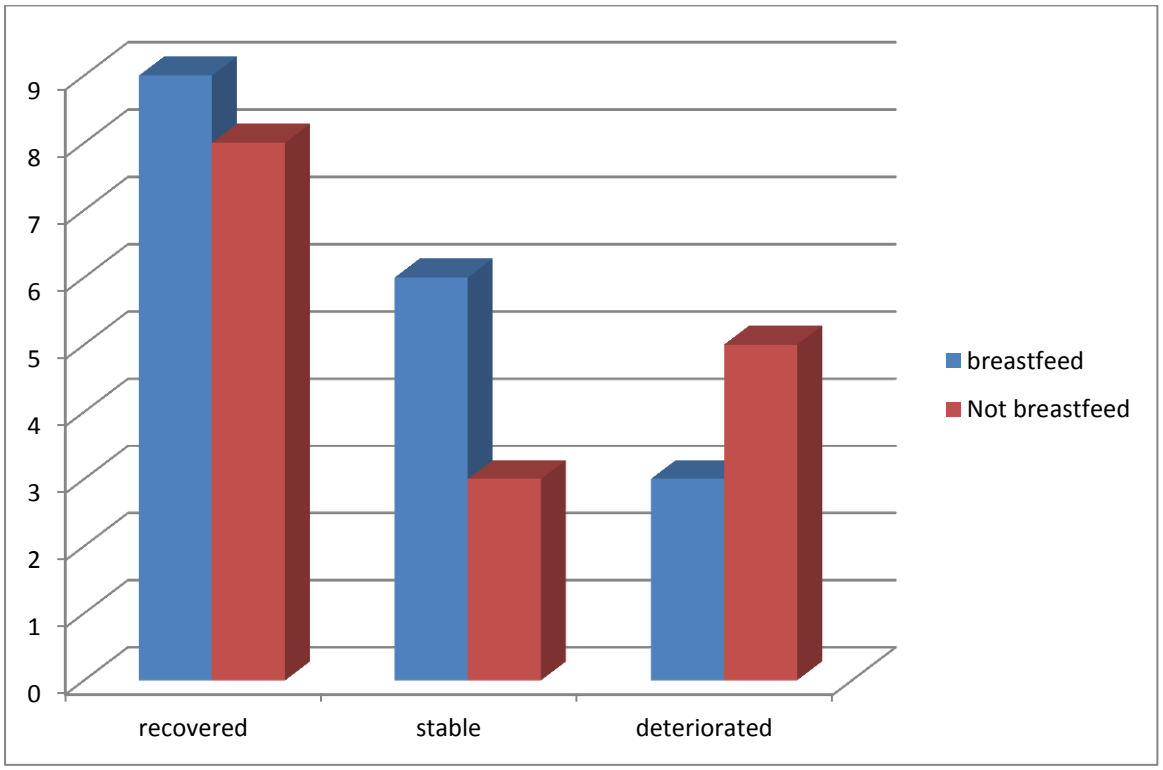


Figure 3.13: Breastfeeding and clinical outcome

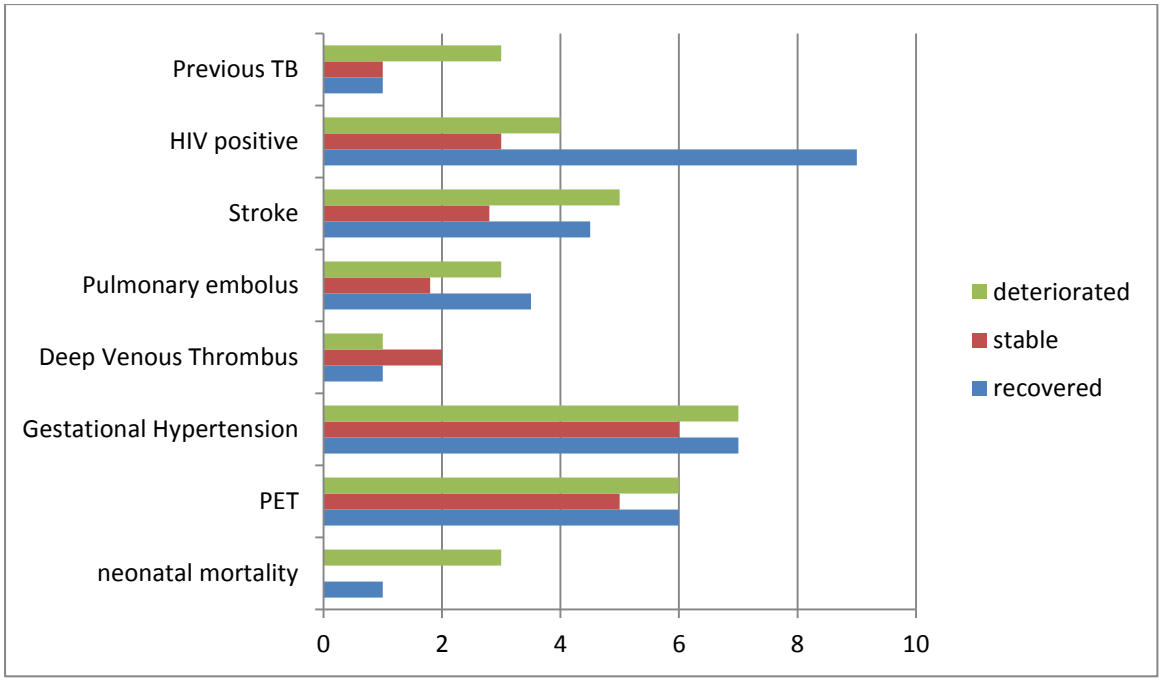


Figure 3.14: Relationship between clinical outcomes and risk factors

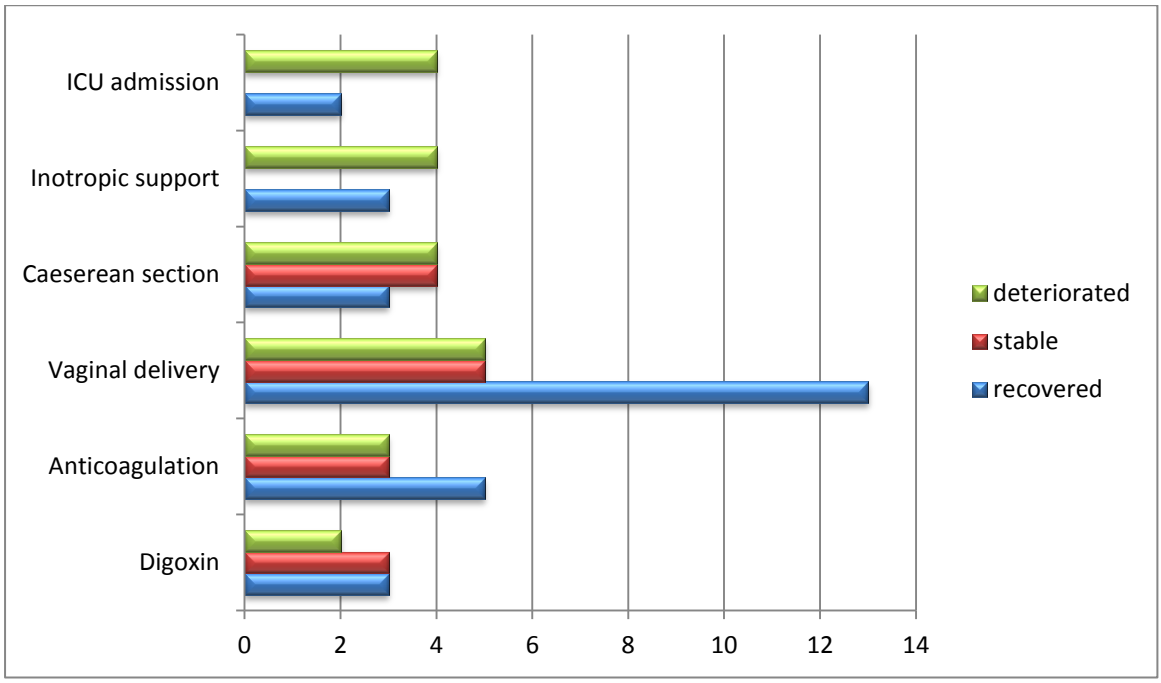


Figure 3.15: Relationship between clinical outcomes and interventions

The relationship between clinical outcomes with risk factors and interventions are shown in fig 3.14 and 3.15, subsequently. Retroviral positive patients had the highest fraction of patients who recovered, whilst those with prior history of tuberculosis and neonatal death deteriorated. The outcomes of HIV positive and negative patients were equivalent with 56% and 50% recovering, accordingly. Of the patients who deteriorated, 22% were seronegative whilst 25% were seropositive. The average

CD4 count of study participants was greater than 400 and 82% were not on antiretroviral. Two patients had CD4 counts of less than 200 and both of them recovered.

Risk factors like gestational hypertension and preeclampsia had comparable clinical outcomes, so was patients with thromboembolic phenomena. Vaginal delivery was the intervention noted to have the highest proportion of patients recovering. Patients were noted to deteriorate than recover if there had been a history of ICU admission and inotropic support.

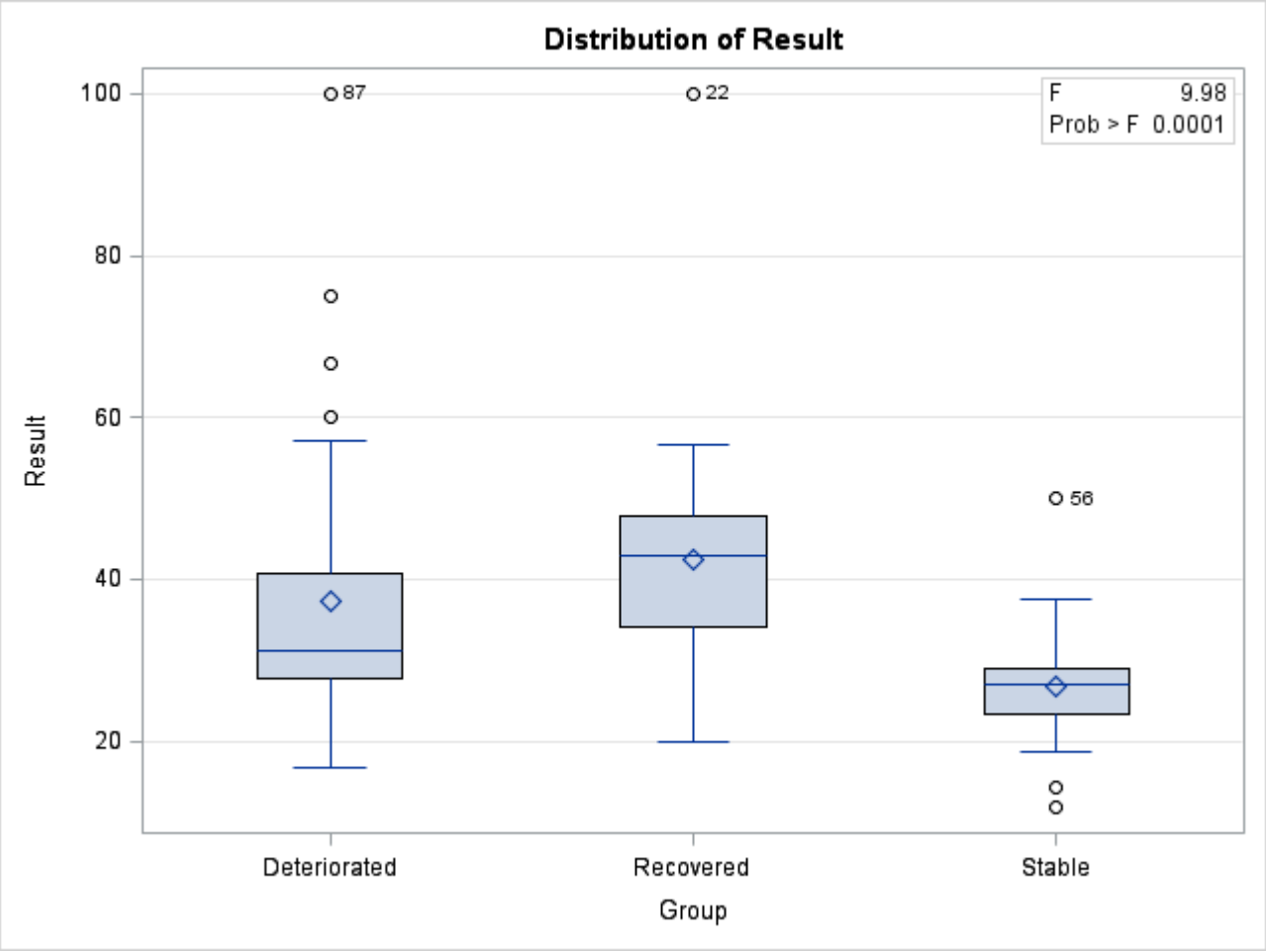


Figure 3.16: Distribution of the mean proportion in different groups

Appendix H shows the relationship between the risk factors and clinical outcomes. The distribution of the mean proportion in different clinical outcome groups is shown in figure 3.16. There was a significant difference in the mean proportions between the three groups ($p=0.0001$). In the pairwise comparisons, the mean proportion of the recovered group was significantly higher than that of the stable ($p<0.05$). There was no difference in the mean proportion of the recovered and deteriorated groups ($p>0.05$). Appendix I show the comparison of means of proportions in the different groups calculated using Tukey's studentised range (HSD) test for result.

Chapter Four: Discussion and conclusions

The aim of the study was to investigate the outcomes and factors which contribute to the clinical outcomes of peripartum cardiomyopathy (PPCM) at Klerksdorp/Tshepong Hospital Complex in Klerksdorp, South Africa. There were four overall objectives, including determining the incidence and prevalence of PPCM, describing the outcomes and analyzing the factors that determine the clinical outcomes and auditing the management of PPCM.

4.1: Demographics

Most of the study participants were black Africans who constitute 74% of the population in Klerksdorp. Most Africans seek medical attention in public hospitals compared to other races, hence the absence of Whites, Indians and Asians. Study participants were of low socio-economic status, with 85% unemployed and only 12% having obtained tertiary level education. The poor utilize health services in the public sector whilst the middle and upper classes are likely to be on medical aid and use private hospitals. This concurred with earlier studies in Haiti, Nigeria and USA where under privileged women were likely to develop PPCM.[7,8,10,31]

Peripartum cardiomyopathy has been found to be higher in extremes of reproductive age.[12] It has a predilection to older woman, of age greater than 30.[17] The study average age of 33.9 was central. Risk factors like hypertensive disorders during pregnancy and multiparity were noted in more than 50% and 91% of participants, correspondingly.[12,16] In contrast, Elkayam et al, found approximately a third (27-30%) of presentations to be primiparous women.[82] Few patients in the primary data had prior history of PPCM and multiple gestation.[61] Due to the design of the study some obstetric data like antepartum and intrapartum management could not be obtained, henceforth some risk factors like prolonged use of tocolysis could not assessed.

4.2: Incidence and Prevalence of PPCM

The prevalence of 0.33% is higher than rates in previous studies done in Durban and Johannesburg of 0.15% and 0.3%, respectively.[18,39] The study prevalence was equivalent to the world's highest rates of 0.35%, recorded in Haiti, Niger and Nigeria.[10] The variation in incidence rates could be a result of geographic and reporting difference.[20] According to Sliwa et al, the unavailability of echocardiography

in some areas may lead to over reporting of PPCM.[57] Internationally, there has been an increase in the incidence of PPCM attributable to enhanced awareness through research and publication.[38,57,83] In addition, national and international PPCM registries like EURObservational Research Programme (EORP) of the European Society of Cardiology is aiding in disease profiling across the world with 90 participating centres in 42 countries [20,84]

In a study done by Desai and Moodley in South Africa, no patients were diagnosed with PPCM before delivery.[39] On the contrary, 12% of our study participants were diagnosed prior to delivery with German and USA having 17% and 24%, respectively.[38] In general, most patients are diagnosed in the first three months post-delivery.[10] PPCM is a diagnosis of exclusion hence requires the healthcare professional to have a high index of suspicion.[10] The astute medical practitioner has to be equipped with good clinical acumen to distinguish the signs and symptoms of cardiac failure, and echocardiography skill to comprehensively make a diagnosis of PPCM.[18] The availability of both these factors in industrialised countries and at Klerksdorp/Tshepong Hospital Complex could have attributed to the diagnosis being made early.

4.3: Clinical outcomes

The clinical outcomes were stratified into three groups, namely, recovered, stable and deteriorated. The research outcomes were similar to that of recent studies performed in other countries. Generally, 50% of patients recover, 25% remain stable and 25% progressively deteriorate.[16] Study outcomes concurred, as 47% recovered, 26.5% remained in a stable state whilst 26.5% gradually deteriorated. Overall, the signs and symptoms of cardiac failure improved from the time of diagnosis to the last assessment. Notably, the proportion of patients with NYHA functional status class I improved from 14.7% at diagnosis to 58.8% in their last assessment. The study maternal mortality rate of 9% was low. Reported mortality rates range from 2-50% with half of them occurring within 3 months of delivery.[10,30] Neonatal mortality rate was 4%. The high percent of patient recovery and low maternal and neonatal mortality rates at Klerksdorp/Tshepong Hospital Complex may be accredited to the high quality of care with a multi-disciplinary approach involving the obstetricians, paediatricians and physicians.

The CXR findings at diagnosis were consistent with acute decompensated cardiac failure. Chest radiograph is recommended in the antepartum period as there is negligible radiation exposure to the foetus. Other centres are withholding the infant shielding practice.[13] Electrocardiogram results at diagnosis were non-specific with sinus tachycardia and ventricular hypertrophy.

The echocardiographic definition of PPCM is fractional shortening <30% or ejection fraction <45% and left ventricular end diastolic dimension >2.7 cm/m^2. The mean fractional shortening (FS) and left ventricular end diastolic dimension (LVEDD) were initially deranged at diagnosis and eventually normalised at last assessment. The mean ejection fraction remained lower than normal throughout the study. Ordinarily, the echocardiographic parameters of patients with PPCM improve.[17] Despite, patient recuperation with restoration of normal ejection fraction and functional status, residual cardiac myocyte damage remains at microscopic level.[17] This underscores the need for dobutamine stress test which is the gold standard for detecting vestigial cardiac dysfunction. Objective recommendations for future pregnancy can be made if there is full recovery of LV function on both echocardiography and dobutamine stress echocardiography as adverse outcomes are relatively low.[13,62] Patients with persistent cardiac failure should be advised against pregnancy because the heart cannot adapt to the increased workload.[57] Johnson-Coyle et al, reported a 19% higher risk of maternal death in women with previous PPCM.[55] Six percent of our study patients had prior PPCM in their first pregnancy succeeded by normalisation of ejection fraction before their subsequent pregnancy. All of them had a relapse of PPCM followed fully recovery in the second pregnancy.

4.4: Analysis of factors that determine clinical outcomes

The past medical history, clinical presentation, investigations and management of study participants were correlated with the clinical outcomes. Appendix H shows the relationship between risk factors and clinical outcomes. The mean proportion in different clinical outcome groups was compared using Tukey's Studentised Range (HSD) test for result. There was a significant difference in the mean proportions between the three groups. In the pairwise comparisons, the mean proportion of the recovered group was significantly higher than that of the stable but there was no difference in the mean proportion of the recovered and deteriorated groups.

The mean left ventricular ejection fraction (LVEF) of study patients progressively increased in the recovered and stable groups whilst there was a gradual decline in

the group that deteriorated. Fett et al, followed up patients with PPCM for over five years at Albert Schweitzer District hospital in Haiti and noted a gradual increase cardiac function on echocardiography well beyond the initial 6-12 months after diagnosis.[41,85] The study time of diagnosis ranged from 2011 to 2014. It was noted that patients who recovered and remained stable followed a normal distribution. Patients who deteriorated had peaks in 2011 and 2014. This could be explained by the study design being retrospective and quasi-prospective. Most of the patients who were diagnosed in 2011 and 2012, and had recovered, no longer actively attending Klerksdorp/Tshepong Hospital Complex were not recruited into the study.

Bromocriptine, a dopamine analogue that inhibit the secretion of prolactin has been associated with prevention of cardiac dysfunction and progressive dilation that occurs in PPCM when added to standard therapy.[38,83] The use of bromocriptine and not breastfeeding has been topical lately, with many physicians divided on whether to use it or not. Currently, there is not enough evidence to support the use of bromocriptine as standard PPCM therapy as large, multicenter, randomized, controlled studies are in progress.[55,60,83] Hilfiker-Kleiner et al, discovered that patients with PPCM had low levels STAT3 protein, and raised levels of activated cathepsin D and 16-kD prolactin.[9,21,22,,20,38,83] Lactation is associated with elevated prolactin serum levels. The study clinical outcomes of breastfeeding mothers and those who did not were almost equivalent.

Sub-Saharan Africa has been greatly affected by the HIV/AIDS pandemic.[86,87] In the study almost half of the participants were seropositive. There was no significant difference between the clinical outcomes of those who were HIV positive and negative. A diagnosis of HIV cardiomyopathy was unlikely because the patients met the criteria for PPCM. However, the role of HIV as an insult leading to myocarditis in the pathogenesis of PPCM cannot be refuted.[86,87,88,89] This principle could apply also to the patients with prior history of tuberculosis. There was no literature on TB myocarditis and PPCM. In a study by Forster et al, HIV infection did not influence clinical outcome.[86,87] Non-dilated ventricles often found at presentation on echocardiograph in HIV cardiomyopathy can be used as the distinguishing feature from PPCM.[20] Due to the fact that the study sample size was small, the association between PPCM and HIV/AIDS was not adequately addressed.

4.5 Audit of the management of PPCM

All patients received standard therapy. The acute and chronic management of heart failure was in line with the ESC, NICE and Heart Failure Society of South Africa (HeFSSS) guidelines.[20,47,57] Medications were adjusted in accordance with patients' NYHA functional class, vitals and echocardiographic findings.

Notably, only 33.33% of the patients received anticoagulation and 20.59% had thromboembolic events, namely, cardiovascular accidents, pulmonary embolus and deep venous thrombus. Anticoagulation is indicated in patients with PPCM with ejection fraction of less the 35% or if there is a left ventricular thrombus.[13,18,55,90] The low usage of anticoagulation could have attributed to the high thromboembolic events in the study.

Refractory heart failure is not being managed adequately because of the lack of expertise and resources. These patients require device therapy or cardiac transplantation.[16,55]

4.6 Limitations of the study.

The study was a single-centre, non-randomised and partly retrospective at Klerksdorp/Tshepong Hospital Complex. The complex is a public hospital hence affluent patients were not involved in the study. The patient antenatal care (ANC) files with perinatal history were not reviewed due to technical issues. At the hospital there was no formal medical conditions database, henceforth it is highly probable that a sampling error could have been introduced by not capturing all patients with PPCM. More so, patients who had been down referred or recovered, and no longer actively attending the clinic were not enrolled. Despite the fact that, the study recruited patients who had delivered in 2011 to 2014 it had a small sample size.

4.7 Conclusion

Peripartum cardiomyopathy is a rare condition which needs consideration in any patient who presents in the perinatal period with dyspnoea.[90] Physicians and patients alike need education on current issues regarding aetiology, pathophysiology, management and prognosis of PPCM. It is an unfamiliar condition with a high prevalence in developing countries. It is one of the reversible causes of heart failure, and is associated with a high morbidity and mortality if not diagnosed early. The study endeavored to investigate the clinical outcomes of postpartum cardiomyopathy at Klerksdorp/Tshepong Hospital Complex in terms of prevalence, management, clinical outcomes, and factors affecting the outcomes. By and large, the study objectives were achieved.

The study prevalence of 3 per 1000 live births was higher than previous studies in South Africa. It was equivalent to countries with the highest rates in the world. The level of patient care at Klerksdorp/Tshepong Hospital Complex was comparable to industrialised countries, with 12% of patients being diagnosed in the antenatal period and 47% recuperating. Patients who remained stable and those who deteriorated were 26.5% apiece. In general, patients' symptoms and echocardiograph parameters improved from the time of diagnosis to the last assessment. The mean proportions between the patients, who recovered, remained stable and those who deteriorated were significantly different.

Basing on results from the study, the following recommendations were made. Peripartum cardiomyopathy is an intricate condition which requires a multidisciplinary approach involving anaesthesiologists, cardiologist, obstetricians, physicians and paediatricians in order to deliver optimal care for the mother and fetus. In view of the limited data available, there is need to perform larger, multicentre, prospective studies with longer follow up periods to adequately describe the disease and, test the safety and efficacy of novel therapies like bromocriptine. Patients with intramural thrombus or low ejection fraction less than 35% should be anticoagulated. The relationship between PPCM and the dual epidemic of HIV/AIDS and TB need to be elucidated. The creation of a patient condition database at Klerksdorp/Tshepong Hospital Complex is also proposed. Finally, it is advised that hospitals be encouraged to participate in local and international PPCM registries.

The study was the first of such a kind at Klerksdorp/Tshepong Hospital Complex and it set the stage for future studies. The results were presented to the local health care practitioners and policy makers with the hope of translating research knowledge into favorable clinical outcomes.

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APPENDICES

Appendix A1: Information sheet and Consent Form in English

Dear patient,

You are kindly invited to participate in this study, which is explained in the information you have received. I am a master's student at the University of KwaZulu Natal, School of Medicine in the College of Health Sciences. I will be conducting the study; it is part of the requirements for my Masters of Medical Science degree in Medicine (MMedSc (Med)).

The study will take place at Tshepong Hospital in Klerksdorp at the medical outpatient department. You will be asked questions on how you are feeling. Your hospital file will be reviewed with special attention to your previous investigations. Your progression since diagnosis will be noted. An electrocardiogram (heart tracing), and ultrasound scan of the heart (echocardiogram) will be done. Your medication will be reviewed and adjusted. Your name and personal information will remain confidential. If you agree to participate you will retain the right to withdraw at any time without change or compromise to the care you receive in the clinic.

This study has been ethically reviewed and approved by the UKZN Biomedical research Ethics Committee (BREC). The approval number is **BE376/14**. You can contact BREC at: **BIOMEDICAL RESEARCH ETHICS ADMINISTRATION** Research Office, Westville Campus, Govan Mbeki Building Private Bag X 54001, Durban 4000, KwaZulu-Natal, SOUTH AFRICA Tel: 27 31 2604769 - Fax: 27 31 2604609 Email: BREC@ukzn.ac.za

I (Name of Patient)__have been informed about the study entitled *Investigations into the clinical outcomes of postpartum cardiomyopathy at Klerksdorp/Tshepong hospital complex* by Dr Farai Russell Sigauke. I understand the purpose of the study. I have been given an opportunity to answer questions about the study and have been given satisfactory answers to my questions. I declare that my participation in this study is entirely voluntary and that I may withdraw at any time without affecting any treatment or care that I would usually be entitled to.

Signature of patient…… date …….

Signature of witness ……. date……..

For further information contact Dr F.R. Sigauke on 0788326685 Email: frsigauke@gmail.com

Appendix A2: Information sheet and Consent Form in Tswana

Molwetsi yo o rategang,

O kopiwa go nna le seabe mo patlisisong eno, e e tlhalosiwang mo tshedimosetsong e o e amogetseng. Patlisiso eno e tlile go tsamaisiwa ke nna mme e okametswe ke University of KwaZulu Natal, School of Medicine in the College of Health Sciences. Ke bontlhanngwe jwa dilo tse di batlegang mo dikiriing ya me ya Masters of Medical Science in Medicine (MMedSc (Med)).

Patlisiso eno e tlile go diragalela kwa Tshepong Hospital kwa Klerksdorp kwa lefapheng la tsa kalafi la balwetse ba ba okelwang kwa ntle ga bookelo. O tlile go bodiwa dipotso tse di malebang le kafa o ikutlwang ka teng. Faele ya gago ya mo bookelong e tlile go sekasekiwa go etswe tlhoko ditlhatlhobo tse di dirilweng mo go wena mo nakong e e fetileng, go bona kafa o tswelelang ka teng. Leina la gago le tshedimosetso ya gago ya poraefete e tlile go nna e le khupamarama. Fa o dumela go nna le seabe, o tlile go tswelela o na le tshwanelo ya go ikgogela morago ka nako epe fela kwantle ga gore tlhokomelo e o e bonang mo tliliniking e fetoge kgotsa gore o ineele mo go seno.

Patlisiso eno e sekasekilwe le go rebolwa go ya ka tsa maitsholo a mantle ke UKZN Biomedical Research Ethics Committee (BREC). Nommoro ya thebolo ke **BE376/14**. O ka nna wa ikgolaganya le BREC mo nommorong eno: **BIOMEDICAL RESEARCH ETHICS ADMINISTRATION,** Research Office,Westville Campus, Govan Mbeki Building, Private Bag X 54001, Durban 4000, KwaZulu-Natal, SOUTH AFRICA Tel:27312604769
Fax:27312604609, Email:BREC@ukzn.ac.za

Nna (Leina la Molwetse)__ke sedimoseditswe ka patlisiso e e bidiwang *Investigations into the clinical outcomes of postpartum cardiomyopathy at Klerksdorp/Tshepong hospital complex* e e dirwang ke Dr Farai Russell Sigauke. Ke tlhaloganya gore boikaelelo jwa patlisiso eno ke eng. Ke filwe sebaka sa go botsa dipotso tse di leng kaga patlisiso eno mme ke filwe dikarabo tse di nkgotsofatsang. Ke itsise semmuso fano gore ke nna le seabe mo patlisisong eno ka go ithaopela seno le gore nka nna ka ikgogela morago ka nako epe fela kwantle ga gore seo se

ame kalafi ya me kgotsa tlhokomelo ya me e ka gale ke neng nka tshwanela go e amogela.

Tshaeno ya Molwetse…… Letlhatshi …….

Tshaeno ya Basupi ……. Letlhatshi…….

O ka nna wa ikgolaganya nomoro ya mogala: Dr F.R. Sigauke 0788326685 Email: frsigauke@yahoo.co.uk

Appendix B: Data Collection Sheet

Study code: ……. Age:……

Race:……. Ethnicity:……

Suburb:……. Level of education:…….

Occupation: …….

Date of Delivery: / / Child Alive: N/Y

Date of Dx: / /

Background hx

OBGYN hx:

Gestational HTN	PET	Mode Of Delivery	Para	Gravida	Still-birth	Miscarriage	Contraception	B/F	Planned pregnancy
N/Y	N/Y	NVD/CS			N/Y	N/Y	N/Y	N/Y	N/Y

ICU Admission: N/Y Number of Days in ICU:

Inotropic Support: N/Y Ventilator support: N/Y

Number of admissions for cardiac failure since diagnosis:

HIV status (/ /)	CD4(/ /)	VL (/ /)

Drug Hx:

ARV

TDF	FTC	3TC	EFV	AZT	D4T	ABC	Aluvia
N/Y	N/Y	N/Y	N/Y	N/Y	N/Y	N/Y	N/Y

Previous/ Current Tuberculosis: N/Y Anti-Tuberculosis Treatment: N/Y

Current Anti- heart failure treatment:

	ACE	BB	MRI	Digoxin	Anticoagulation	Diuretic
	N/Y	N/Y	N/Y	N/Y	N/Y	N/Y
Date started						
Type						
Dosage						

Other drugs:

FH:

_____

SH:

_____

Venous Thromboembolism (VTE)

Stroke: N/Y Pulmonary Embolus (PE): N/Y

Deep Venous Thrombus	N/Y
Location	

Previous Ix:

_____

Presentation

	At diagnosis	After 6 months	Current
Dyspnoea	N/Y	N/Y	N/Y
NYHA class	1/2/3/4	1/2/3/4	1/2/3/4
Orthopnoea	N/Y	N/Y	N/Y
pillows used	1/2/3	1/2/3	1/2/3
PND	N/Y	N/Y	N/Y
Leg swelling	N/Y	N/Y	N/Y
Cough	N/Y	N/Y	N/Y
Weight gain	N/Y	N/Y	N/Y
Chest pain	N/Y	N/Y	N/Y
Tachypnoea	N/Y	N/Y	N/Y
Fatigue	N/Y	N/Y	N/Y
Dizziness	N/Y	N/Y	N/Y
Palpitations	N/Y	N/Y	N/Y
Syncope	N/Y	N/Y	N/Y
Headache	N/Y	N/Y	N/Y
Somnolence	N/Y	N/Y	N/Y

Examination

	At diagnosis	At 6 months	Current
General	JACCOL	JACCOL	JACCOL
BP normal	N/Y	N/Y	N/Y
RR normal	N/Y	N/Y	N/Y
Pulse normal	N/Y	N/Y	N/Y
Temp. normal	N/Y	N/Y	N/Y
Weight gain	N/Y	N/Y	N/Y
Cardiovascular Increased JVP	N/Y	N/Y	N/Y
Murmur	N/Y	N/Y	N/Y
Displaced Apical Impulse	N/Y	N/Y	N/Y
Gallop	N/Y	N/Y	N/Y
Pulse character	N/Y	N/Y	N/Y
Pulse volume	N/Y	N/Y	N/Y
Cold & clammy	N/Y	N/Y	N/Y
Pedal oedema	N/Y	N/Y	N/Y
Respiratory Tachypnoea	N/Y	N/Y	N/Y
Basal crackles	N/Y	N/Y	N/Y
Cyanosis	N/Y	N/Y	N/Y
Wheezes	N/Y	N/Y	N/Y
↓ Breath sounds	N/Y	N/Y	N/Y

Abdomen	**At diagnosis**	**At 6 months**	**Current**
Hepatomegaly	N/Y	N/Y	N/Y
Ascites	N/Y	N/Y	N/Y
Neurological Confusion	N/Y	N/Y	N/Y
focal deficits	N/Y	N/Y	N/Y

ECG at diagnosis:

Rate: B/N/T	Sinus Rhythm : N/Y	Axis: N/Y	BBB: N/Y	LVH:N/Y	RVH:N/Y

ECHO:

Dimensions	**At Diagnosis**	**At 6 months**	**Current**	**Normal values**
LVEDD				(36-55mm)
LVESD				(20-40mm)
EF				(55-70%)
IVSsd				(6-11mm)
IVSdd				(7-11mm)
FS				(25-45%)
AR				Mild/Mod/Severe
TR				Mild/Mod/Severe
MR				Mild/Mod/Severe
RWMA				
Clots	N/Y	N/Y	N/Y	Location: LV/RV/LA/RA

CXR at diagnosis:

CTR	Upper lobe Diversion	Kerley-B lines	Alveolar infiltrates	'Bat wing' hilar shadow	Pleural effusion	Fluid in fissure
N/Y	N/Y	N/Y	N/Y	N/Y	N/Y	N/Y

Assessment:

_____

Recommendations:_____

_____

_____

_____

_____

_____

_____

_____

Investigator: …….. Signature:…… Date: __/__/__

Appendix C: PPCM Patient Pamphlet

What is Peripartum Cardiomyopathy (PPCM)?

English: It is heart failure which occurs in the last month of pregnancy or 5 months after in someone without any other reason, serve for the pregnancy itself.

Tswana: Ke bolwetsi jwa pelo bo bo tlhagelelang mo kgweding ya bofelo ya boimana kgotsa kgwedi tse tlhano morago ga go belega. Bo diriwa ke mabaka a a sa itsegeng.

Who gets it?

English: Any pregnant woman can develop PPCM

Tswana: Mosadi mongwe le mongwe yo o mo mmeleng/ o ithweleng.

What will you be feeling?

English: It presents with shortness of breath, chest pain, fatigue and leg swelling

Tswana: Bo bonagala ka go hupelwa, setlhabi mo pelong, letsapa le go ruruga maoto.

How do doctors make the diagnosis?

English: A couple of tests are done to ascertain the diagnosis and stratify the severity of the disease. These include chest x-ray, ECG, blood tests, and echocardiography/ECHO (ultrasound scan of the heart)

Tswana: go dirwa diteko tse di latelang go batlisisa ka ga bolwetsi bo: go tsewa madi, diteko tsa pelo ECG, ECHO le CXR.

How are you treated?

English: Patient treatment depends on the severity of the condition or degree of the difficulty breathing. It ranges from admission in intensive care unit in critically ill patients with administration of intravenous drugs, oxygen and invasive cardiac monitoring to oral drugs in stable patients.

Tswana: Tlhokomelo ya molwetsi e tla laolwa ke maemo a molwetsi jaaka go hupelwa, o ka okiwa mo bookelong kgotsa wa fiwa melimo go ikoka ko gae.

What to expect?

English: Most women recover normal heart function with treatment, 1 in 4 have persistent heart failure and 1 in 4 progressive deteriorate.

Tswana: Bontsi jwa basadi bothata jwa pele bo a fola ka melemo, ke palo e ko tlase fela e sa foleng bolwetsi ba pelo

Appendix D: Full Ethics Approval from Biomedical Research Ethic Committee (BREC)

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

14 November 2014

Dr Farai Sigauke
Castle Corner
2 Mispel Avenue
Doringkruin
Klerksdorp, 2574
frsigauke@yahoo.co.uk

PROTOCOL: An investigation into the Clinical Outcomes of Women with Peripartum Cardiomyopathy at Klerksdorp/Tshepong Hospital Complex: Degree Purposes (MMedSc). BREC REF: BE376/14.

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 05 August 2014.

The study was provisionally approved pending appropriate responses to queries raised. Your responses received on 04 November 2014 to queries raised on 04 November 2014 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval.

This approval is valid for one year from **14 November 2014.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its meeting taking place on **09 December 2014.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor D.R Wassenaar
Chair: Biomedical Research Ethics Committee

Appendix E: Full Ethics Approval from Northwest Department of Health

health
Department of
Health
North West Province
REPUBLIC OF SOUTH AFRICA

3801 First Street
New Office Park
MAHIKENG, 2735

Enq: Keitumetse Shogwe
Tel: 018 391 4505
kshogwe@nwpg.gov.za
www.nwhealth.gov.za

POLICY, PLANNING, RESEARCH, MONITORING AND EVALUATION

To : **Dr F.R Sigauke**

From : **Policy, Planning, Research, Monitoring & Evaluation**

Subject : **Research Approval Letter- An investigation into the Clinical outcomes of women with Peripartum Cardiomyopathy at Klerksdorp/ Tshepong Hospital Complex.**

To inform the researcher that permission to undertake the above mentioned study has been granted by the North West Department of Health. The researcher is expected to arrange in advance with the chosen districts or facilities, and issue this letter as prove that permission has been granted by the provincial office.

Upon completion, the department expects to receive a final research report from the researcher.

Kindest regards

Director: PPRM&E
Dr F Reichel

04/11/2014
Date

Healthy Living for All

DEPARTMENT OF HEALTH
PRIVATE BAG X2068
2014 -11- 04
SUPERINTENDENT GENERAL

Appendix F: Translation Certificate

Translation Certificate

Informed Consent

This is to certify that translation into Setswana of the document referred to above has been rendered to the best of our ability and is true to the meaning and wording of the original English text. The translation was carried out by the following translator:

English to Setswana: Mr Simon Kemisho – *Sworn Translator in the High Court, Accredited Translator by South African Translators' Institute, Post Graduate Diploma in Translation and Interpreting*

Signed on this 13th day of October 2014

Simon R. Kemisho
(Managing Member)

S. Kemisho (MD) - T. Kemisho (Administrator) - website:
www.translationworld.co.za - email: skemisho@global.co.za Tel: 086 111
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Appendix G: MINNESOTA LIVING WITH HEART FAILURE QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during past 4 months?

	No					Very little Too Much
1. Causing swelling in your ankles or legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. Making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4. Making your working around the house or yard difficult?	0	1	2	3	4	5
5. making your going places away from home difficult?	0	1	2	3	4	5
6. Making your sleeping well at night difficult?	0	1	2	3	4	5
7. Making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8. Making your working to earn a living difficult?	0	1	2	3	4	5
9. Making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. Making your sexual activities difficult?	0	1	2	3	4	5
11. Making you eat less of the foods you like?	0	1	2	3	4	5
12. Making you short of breath?	0	1	2	3	4	5
13. Making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14. Making you stay in a hospital?	0	1	2	3	4	5
15. Costing you money for medical care?	0	1	2	3	4	5

16. Giving you side effects from treatments? 0 1 2 3 4 5

17. Making you feel you are a burden to your family or friends? 0 1 2 3 4 5

18. Making you feel a loss of self-control in your life? 0 1 2 3 4 5

19. Making you worry? 0 1 2 3 4 5

20. Making it difficult for you to concentrate or remember things? 0 1 2 3 4 5

21. Making you feel depressed? 0 1 2 3 4 5

Appendix H: Relationship of patient clinical outcome to risk factors

Risk factor	Number of patients affected (%)	% Patients of variable who recovered	% Patients of variable who remained stable	% Patients of variable who deteriorated
Neonatal mortality	4 (11.8)	25.0		75.0
Not breastfeed	16 (47.1)	50.0	18.8	31.2
Gestational HTN	20 (58.8)	35.0	30	35
Pregnancy induced toxaemia (PET)	17 (50)	35.3	29.4	35.3
Vaginal delivery	23 (67.7)	56.6	21.7	21.7
Caesarean section	11 (32.4)	27.2	36.4	36.4
ICU Admission	6 (17.7)	33.3		66.7
Inotropic support at diagnosis	7 (21.0)	42.9		57.1
HIV sero-positive	16 (47.1)	56.2	18.8	25
Previous TB	5 (14.7)	20	20	60
Mineralo-corticosteroid receptor inhibitor	32 (94.1)	43.8	28.1	28.1
Digoxin	11 (32.4)	27.3	27.3	45.46
Anticoagulation	11 (32.4)	45.4	27.3	27.3
Cough	32 (94.1)	43.8	25.00	31.2
Tachypnoea	31 (91.1)	42.0	29.0	29.0
Abnormal blood pressure	17 (50)	47.1	11.8	41.1
Elevated jugular venous pressure	27 (79.4)	40.8	25.9	33.3
Displaced apical impulse	20 (58.8)	35.0	30.0	35.0
Gallop rhythm	31 (91.1)	42.0	29.0	29.0
Pedal oedema	32 (94.1)	43.8	28.1	28.1
Basal crackles	31 (91.1)	48.4	25.8	25.8
Stroke	2 (5.9)			100
Pulmonary embolus	1 (2.9)	100		
Deep venous thrombus	4 (11.8)	25	50	25
Abnormal cardiac rate	33 (97.1)	45.4	27.3	27.3
Sinus rhythm	32 (94.1)	46.9	25	28.1
Bundle branch block	6 (17.7)	50	33.33	16.67
Left ventricular hypertrophy	15 (44.1)	33.3	26.7	40.00
Right ventricular hypertrophy	8 (23.5)	25	37.5	37.5
Increased cardiothoracic ratio	26 (76.5)	38.5	26.9	34.6
Upper lobe diversion	31 (91.1)	51.6	25.8	22.6
Kerley-B lines	21 (61.8)	52.4	19.0	28.6
Alveolar infiltrates	29 (85.3)	41.4	27.6	31.0
Pleural effusion	14 (41.2)	42.9	14.2	42.9

Column 2 represents the number of patients who had the concerned risk factor, represented as a percentage of study participates in brackets. Columns 3, 4 and 5 shows the distribution of each risk factor in the three outcome groups, namely, recovered, stable and deteriorated

Appendix I: Comparison means of proportions in different groups

Tukey's Studentised Range (HSD) Test for Result

Comparisons significant at the 0.05 level are indicated by *.**

Group Comparison	Difference Between Means	Simultaneous 95% Confidence Limits		
Recovered - Deteriorated	5.051	-3.212	13.314	
Recovered - Stable	15.799	7.246	24.352	***
Deteriorated - Recovered	-5.051	-13.314	3.212	
Deteriorated - Stable	10.748	2.195	19.301	***
Stable - Recovered	-15.799	-24.352	-7.246	***
Stable - Deteriorated	-10.748	-19.301	-2.195	***