MATERNAL AND FETAL OUTCOME OF SUBSEQUENT PREGNANCY IN PATIENTS WITH DOCUMENTED PERIPARTUM CADIOMYOPATHY

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DECLARATION

I …..David Sifiso Masuku…. hereby declare that the work on which this dissertation/thesis is based on my original work(except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, or is to be submitted for another degree in this or any other university. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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To my parents, thank you for your unwavering support and love and, most importantly, for giving me an opportunity to educate myself.

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LIST OF ABBREVIATIONS

PPCM	Peripartum Cardiomyopathy
HF	Heart Failure
SSP	Subsequent Pregnancy
CAD	Coronary Artery Disease
CRT	Cardiac Resynchronization therapy
MI	Myocardial Infarction
BNP	B type Natriuretic Peptide
NT proBNP	N Terminal pro B Natriuretic Peptide
LVEF	Left Ventricular Ejection Fraction
SHFT	Standard Heart Failure Treatment
BR	Bromocriptine
CXR	Chest X-rays
ECG	Electrocardiography
NYHA	New York Heart Association
LBBB	Left Bundle Branch Block
LVEDD	Left Ventricular End Diastolic Diameter
LVESD	Left Ventricular End Systolic Diameter
ICD	Implantable Cardioverter Defibrillator
DCMO	Dilated Cardiomyopathy
oxLDL	Oxidative low density lipoprotein

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ABSTRACT

AIM

Subsequent pregnancies (SSPs) in patients with peripartum cardiomyopathy (PPCM) have a high risk of heart failure relapse. We report on outcome of SSPs in PPCM patients in South Africa.

METHODS AND RESULTS

Of the 18 PPCM patients with a SSP, 3 patients died within 6-months follow-up. Overall relapse rate, left ventricular ejection fraction (LVEF) <50% or death after at least 6 months follow-up, was 30%, with 16% (3/18) mortality. Persistently reduced LVEF (<50%) before entering SSP was present in 44% of patients, while full recovery (LVEF≥ 50%) was present in 85%. Persistently reduced LVEF before SSP was associated with a higher mortality (27% vs 0%) and a lower rate of full recovery at follow-up. Patients obtaining standard therapy for heart failure and bromocriptine immediately after delivery displayed significantly better LVEF at follow-up and a higher rate of full recovery, with no patient dying, compared with patients obtaining standard therapy for heart failure alone.

CONCLUSION

Full recovery of LVEF before SSP was associated with lower mortality and better cardiac function at follow-up. Addition of bromocriptine to standard therapy for heart failure immediately after delivery was safe and appeared to be associated with better outcome of SSP in our patients.

PROTOCOL

INTRODUCTION

Peripartum cardiomyopathy (PPCM) is a disorder of unknown origin in which symptoms of heart failure occur between the last month of pregnancy and 5 months postpartum. By definition, PPCM occurs in the absence of an identifiable cause of heart failure, and in the absence of recognisable heart disease, prior to the last month of pregnancy. Some authors go beyond this defined time frame to include patients diagnosed with heart failure as early as 3 months pregnancy {Elkayam, 2005 #30}.

Diagnosis requires echocardiographic evidence of left ventricular systolic dysfunctional (ejection fraction (EF) <45%) {Chapa, 2005 #111}. Heart failure that occurs in earlier pregnancy may be caused by previously unsuspected familial or other forms of cardiomyopathy that (unmarked by the hemodynamic and hormonal stress of pregnancy) forms a different entity. Diagnosis of PPCM should be established by ruling out other causes of perinatal heart failure, such as infectious diseases, metabolic disorders and ischaemic or vulvar heart disease. Complications of late pregnancy that may have similar symptoms and signs of PPCM include pre-eclampsia, amniotic or pulmonary embolism, haemolysis, elated liver enzymes and low platelets {Kist, 2008 #25}.

The American College of Cardiology (ACC) guidelines classify PPCM as an entity on its own {Maron, 2006 #26}. However, in the recently published European Society of Cardiology classification, PPCM is not listed as a specific disease and is placed under the category of “unclassified cardiomyopathies”. Although approximately 20% of women with the disorder either die or survive only because they receive cardiac transplants, the majority recover partially or completely. Although the women who recover may desire to become pregnant again, there is a concern that these SSPs may be associated with an increased risk of recurrence of cardiomyopathy.

PPCM is most common in women of African descent, but it has been reported in all major ethnic populations. The incidence varies from 1:100 to 1:1000 between geographic regions due to diagnostic limitations, including limited access to echocardiography and the incidence

may, in some areas, be over-estimated. There is considerable controversy regarding the aetiology of human PPCM, but a number of recent publications have contributed to a better understanding of its pathogenesis. A number of mechanisms have been proposed in the development of PPCM, including nutrition deficiencies, genetic disorders, viral or autoimmune aetiologies, hormonal imbalances, volume overload, alcohol, physiologic stress of pregnancy and unmasking of latent idiopathic dilated cardiomyopathy (DCMO){Sliwa, 2006 #27}. However, none of these mechanisms have been confirmed in detailed investigations or prospective studies {Fett, 2002 #128}. The rare incidence of PPCM and the paucity of relevant animal models have limited guided research and the understanding of pathogenic mechanisms involved. Some authors have suggested that multiparty may be a risk factor for PPCM. However, a study by Elkayam et al 2005 does not support this theory within a cohort in the United States as almost 40% of the cases occurred in association with a first pregnancy, and more than 50% within the first two pregnancies. Features of a normal pregnancy include expansion of blood volume, an increase in metabolic demands, relative anaemia and changes in vascular resistance that are associated with mild ventricular dilatation and an in increase in cardiac output. These physiologic changes are due to an increase in preload and heart rate, accompanied by a decrease in afterload. Decompensation of patients with subclinical vulvular ischaemic or myophathic heart disease usually occur during the second or third trimester of pregnancy {Elkayam, 2005 #30}.

The onset of PPCM can be easily missed because many symptoms and signs of pregnancy and post pregnancy stages are similar to those of early congestive heart failure (CHF), e.g. dyspnoea, abdominal discomfort and fatigue {MB., 1995 #168}. In a study by Elkayam et al(2005) reported that 7% of their patients in the United States were diagnosed within 1 month before delivery, whereas 75% were diagnosed during the first month postpartum, the remainder having fulfilled criteria for PPCM before the last 1 month of pregnancy{Elkayam, 2005 #30}. In contrast, a study by Sliwa K et al (2000) patients in South Africa and Haiti developed symptoms almost exclusively within the postpartum period. The symptoms and signs are similar to those in patients with idiopathic DCMO.

PPCM often presents with acute onset of heart failure (AHF). The presentation, with reduced cardiac output, tissue perfusion, increase in the pulmonary capillary wedge pressure and tissue congestion, is often life-threatening and requires urgent treatment. Chest radiography

and other imaging modalities should be conducted early for all patients with AHF to evaluate pre-existing chest or cardiac conditions and to assess pulmonary congestion {Sliwa, 2000 #56}.

A number of laboratory tests should be used in all patients with PPCM presenting with AHF - full blood count, urea and electrolytes, C-reactive protein (CRP) blood glucose, D-dimer, creatine Kinase-MB (CK-MB) and cardiac troponin–T (cTnT). In severe heart failure, international normalised ratio and arterial blood gas should be performed. Transaminases, urinalysis, plasma B–type natriuretic peptide (BNP) or N-terminal pro B-type natriuretic peptide (NT proBNP) can be considered).

Over the past decade, accumulating evidence has suggested distinct pathogenetic mechanisms for PPCM, which may differ from those of other forms of dilated cardiomyopathy (DCMO). Apoptotic events, systematically and in the myocardium, appear to causally associate with PPCM. The apoptotic signalling surface receptor Fas/Apo1 is known to trigger cell death in a variety of cell types. Patients with PPCM had significantly higher plasma levels of Fas/Apo1, compared with healthy volunteers {Sliwa, 2000 #91}.

In a study by Forster et al (2008) the serum markers related to cardiac function, apoptosis, oxidative stress, remodelling, inflammation and the nursing hormone prolactin were analysed in PPCM patients and healthy controls. The kinetics of these biomarkers were compared between patients with Improved cardiac function(IMP) and those patients who did not improve(NIMP), over 6 months follow up. After 6 months, NT- proBNP, oxLDL, Interferon gamma were significantly lower in IMP group and the decrease in oxLDL, interferon gamma and prolactin was significant in IMP group but not in NIMP. Significant correlations were observed between the kinetics of NT-proBNP, oxLDL,, prolactin and interferon gamma in PPCM patients{Forster, 2008 #169}. One of the most common issues for women surviving an episode of PPCM is whether it is safe to become pregnant again. If a subsequent pregnancy occurs, it should be managed in close collaboration between the obstetrician and the attending physician or a cardiologist. Most authors agree that PPCM patients with persistent left ventricular dilatation and dysfunction are at high risk for complications and death should they become pregnant again {Sliwa, 2006 #27}. In contrast, the issue of whether patients with PPCM and recovered left ventricular function can safely undergo a SSP remains controversial. A review study conducted by Elkayam et al (2001) among members of the American College

of Cardiology (ACC) in the United States and one hospital in South Africa and described the outcome of 60 SSPs in 44 women with a history of PPCM. Among the first SSPs in the 44 women, 28 occurred among women in whom left ventricular function had returned to normal (group 1) and 16 occurred in women with persistent left ventricular dysfunction (group2). These pregnancies were associated with a reduction in mean LVEF in each group. 19% of PPCM patients with a sustained impaired systolic function, who then conceived their first SSP eventually died {Elkayam, 2001 #164}. Although the likelihood of maternal death seems to be very low in women who recorded their left ventricular function before a SSP, a reduction in LVEF and symptomatic heart failure will occur in the majority of PPCM patients in SSPs.

Echocardiography is an essential tool for evaluating the functional and structural changes underlying or associated with acute heart failure. The most important measurement of ventricular function is LVEF for distinguishing patients with cardiac systolic dysfunction from those with preserved systolic function. Echocardiography with Doppler imaging should be used to evaluate and monitor regional and global left and right ventricular function, vulvular structure and function, possible pericardial pathology and mechanical complications..

Information about the outcome of additional pregnancies is, however, limited. There is therefore no consensus regarding recommendations for future pregnancies in women who have had PPCM.

HYPOTHESIS

Patients with PPCM are at increased risk of recurrence of cardiomyopathy with SSPs.

AIMS

To investigate both foetal and maternal outcome (clinically and radiologically) of subsequent pregnancy in patient with Peripartum Cardiomyopathy.

OBJECTIVES

Maternal Outcome

- To determine the survival of mothers with peripartum cardiomyopathy with a SSP in terms of LV systolic function using transthoracic echocardiogram e.g. ejection fractions (maternal outcome).

- Cytokine measurement especially TNF & at 6 months and 12 months post-partum.

Foetal Outcome

- To assess the outcome of pregnancies (foetal) of mothers with PPCM that were not terminated. The viability of the product of pregnancy using the birth weight and general health of the baby (foetal outcome).
- Mode of delivery e.g. vaginal or Caesarean section
- Premature delivery – defined as delivery at less than 37 weeks gestation
- Abortions – whether therapeutic or spontaneous.

What the study hopes to add to the current knowledge

To determine the impact of PPCM in SSPs, with the aim of improving awareness and management of per partum cardiomyopathy patients by health care professionals. Following this, proactive strategies can be developed to help patients manage family planning and other risk factors associated with PPCM.

METHODS

This is a retrospective, longitudinal follow-up cohort sub-study of 20 South African patients with PPCM who attended Chris Hani Hospital and Groote Schuur Hospital. Twenty patients subsequently fell pregnant despite being advised not to fall pregnant.

STUDY DESIGN AND PATIENT RECRUITMENT

The study was conducted at Chris Hani Baragwanath Hospital (CHB), Soweto and Groote Schuur Hospital (GSH), South Africa. Patients were referred from local clinics, secondary hospitals and the Department of Obstetrics at Chris Hani Baragwanath and Groote Schuur Hospital.

History of pre-existing cardiac signs or symptoms, pre-eclampsia or eclampsia and mode of delivery were obtained from the patient and confirmed by examining the obstetric card carried by each patient. Signs and symptoms (baseline) were recorded during first presentation at the cardiac unit at Chris Hani Baragwaneth and Groote Schuur Hospital and after a follow-up period of 6 months and 12 months of therapy.

Inclusion Criteria

1. Age ≥16 - ≤40.
2. New York Heart Association classification (NYHA) stage 1 to 4.
3. Symptoms of heart failure in the last month of pregnancy or postpartum (5 months).
4. LVEF ≤ 45% echocardiography
5. Sinus rhythm.

Exclusion Criteria

1. Organic valvular disease.
2. Systolic blood pressure ≥170 and blood pressure >05 mmHg
3. Clinical conditions other than PPCM that would increase cytokines level (HIV, Rheumatic Arthritis).

Clinical assessment, echocardiography and cytokine measurements (namely BNP etc.) were performed at baseline and after 6 months and 12 months of therapy. Among the 176 patients included in the study, 164 (93%) received treatment with furosemide and 141 (80%) were treated with an ACE inhibitor. Digoxin was being taken by 113 (64%) of the 176 patients. Patients with LVEF <25% or LV thrombus were treated with warfarin. Carvedilol was initiated in 100 (57%) of the 176 patients after resolution of overt heart failure. ACE inhibitor and carvedilol doses were titrated upward as tolerated throughout the 6 months study period. Patients attended the cardiac clinic monthly. These patients were strongly advised to avoid new pregnancies and also advised on different modes of contraception and were followed up prospectively.

In the group of patients with SSPs, echocardiogram was performed at 6 months of pregnancy and 6 and 12 months postpartum. At the same time intervals blood was taken for cytokine measurements.

Echocardiography, assessment of New York Heart Association (NYHA) functional class and non-invasive blood pressure measurements were undertaken.

Two-dimensional and targeted M-mode echocardiography with Doppler colour flow mapping were performed using a Hewllett Packard Sonos 5500 echocardiograph (Philips, Bothell, Washington) attached to a 2,5 or 3,5 – MHZ transducer.

Systolic and LV dimensions were measured according to American Society of Echocardiography (ASE) guidelines. LV dimensions and functions were determined using the mean of three or more cycles. Echocardiography was taped on video or CD and stored within the Soweto cardiovascular research unit division for further reference and audit purposes.

The NYHA functional class of each patient at baseline and follow-up visits was evaluated by a physician, who was provided with the clinical information but blinded to the protocol and unaware of the results of the laboratory tests.

Blood pressure and heart rate were measured non-invasively with a Critilcon Dinamap vital signs monitor 1846 and calculated as mean values from five readings. Measurements were made after a 30-minute resting period in the sitting position, with 2 minute intervals between successive measurements.

Research Specific blood tests

Fifteen millilitres of blood was drawn from an antecubital vein and collected in pre-chilled evacuated tubes containing ethylenediaminetetra acetic acid or clot activator and mixed rapidly. Plasma or serum was separated by centrifugation at 2,500 rpm for 12 minutes within 15 minutes of collection; the aliquots were frozen at -70^{o}C. TNF-α measurements were performed using a commercially available enzyme – linked immunoassay (Amersham, Maidstone, United Kingdom).

STATISTICAL ANALYSIS

Database management and statistical analysis will be performed with advice of a biostatistician and using an appropriate statistical software.

Continuous data will be expressed as mean ± SD or median (range). Comparison of means and proportions between groups at baseline will be performed by using independent t–tests (for continuous data) and X Statistics or Fisher exact test for categorical data, respectively. Wilcoxon rank sums test will be used for comparison of non-parametric baseline data and the results at 6 months and 12 months after SSP. Significance will be assumed at a two sided p-value of <0, 05. Regression analysis will be used to show association of outcome variables for survival (Echo values) with predictors (cytokine levels, blood pressure). The sample size is based on the available data for 176 patients

Storage of data and information

All physical data collected during the study will be kept confidentially in a locked area and will only be available to authorized staff. Electronic data will also be stored in password–restricted computers only accessible to authorized staff.

Publication of Data

There are no restrictions on the publication of the outcomes of the study.

Conflict of Interest

There is no conflict of interest in the outcome of the study.

REFERENCES

1. Sahn DJ, DeMaria A ,Kisslo J, weyman A. Recommendation regarding quantitation I M mode echocardiography: results are a survey of echocardiographic measurements. Circulation 1978; 58(6): 1072 – 1083
2. Pearson GD, Veille JC, Rahimtoola S, et al. Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Hearth) workshop recommendations and review. J Am Med Assoc 2000, 283 (9): 1183-1188 [PMID: 10703781].
3. Slaw K, Skudicky D, Candy G, Bergmann A, Hopley M, Sareli P. The addition of pentoxifyline to conventional therapy improves outcome in patients with Peripartum Cardiomyopathy. Eur J Heart fail 2002, 4:305 – 309
4. Tibazarwa K, Sliwa K. Peripartum Cardiomyopathy in in Africa: Challenges in diagnosis, prognosis, and therapy. Prog Cardiovasc Dis 2010, 52(4):317-325 (PMID: 20109601).
5. Sliwa K, Tibazarwa K, Hiilfiker-kleiner D. Management of Peripartum Cardiomyopathy. Curr Heart Fail Rep 2008, 5: 238-244 (PMID:19032920).
6. Boomsma LJ. Peripartum cardiomyopathy in rural Nigerian hospital. Trop Geogr Med 1989: 41, 197-200 [PMID; 2595797].
7. Sliwa K, Forster O, Tibazarwa K, et al. Long-term outcome of Peripartum Cardiomyopathy in a population with high seropositivity for Human Immunodeficiency Virus. Int J Cardiol 2011, 147(2): 202-208. Epub 2009 Sep 13 (PMID: 19751951).
8. Elkayam U, Tummala PP, Rao K, et al. Maternal and fetal outcomes of subsequent pregnancies in women with Peripartum Cardiomyopathy. N Engl J Med 2001, 344(21): 1567-1571. Erratum in: N Engl J Med 2001, 345(7): 552 (PMMID: 11372007).
9. Sliwa K, Foster O, Zhanje F, et al. Outcome of subsequent pregnancy in patients with documented Peripartum Cardiomyopathy. Am J Cardiol 2004,93: 1441-1443 (PMID: 15165937).
10. 2010 Sliwa K, Blauwet L, Tibazarwa K, et al. Evaluation of bromocriptine in the treatment of acute severe Peripartum Cardiomyopathy: a proof-of-concept pilot study. Circulation, 121(13): 1465-1473 (PMID 20308616).

HISTORICAL CONTEXT

The concept of heart muscle disease has a notable and evolving history. In the mid-1850s, chronic myocarditis was the only recognised cause of heart muscle disease. In 1900, the designation of primary myocardial disease was introduced, and it was not until 1957 that the term "cardiomyopathy " was used for the first time by Maron, Towbin (1).

In 1968, the WHO defined cardiomyopathies as "disease of different and often unknown aetiology in which the dominant feature is cardiomegaly and heart failure (2, 3).

In the original 1980 WHO classification, cardiomyopathies were defined only as a "heart muscle disease of unknown cause" reflecting a general lack of information available about causation and basic disease mechanisms.

In 2006, the American Heart Association (AHA) proposed the following definition: "Cardiomyopathies are heterogeneous a group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to variety of causes that are frequently genetic. Cardiomyopathies are either confined to the heart, or are part of generalised systemic disorders, often leading to cardiovascular death or progressive heart failure- related disability".

Within this broad definition, cardiomyopathies are usually associated with failure of myocardial performance, which may be mechanical (e.g. diastolic or systolic dysfunction) or a primary electrical disease prone to life-threatening arrhythmias.

The AHA divides cardiomyopathies into two major groups based on predominant organ involvement. Primary cardiomyopathies (genetic, mixed/non-genetic and acquired) are solely or predominantly confined to heart muscle and are relatively less common. Secondary cardiomyopathies show pathological myocardial involvement as part of a several number of systemic pathologies (4).

PPCM has been recognised as a serious complication of pregnancy since the 18th century. In 2000 Pearson et al. defined PPCM as a cardiomyopathy of unknown cause that is characterised by symptoms and signs of heart failure associated with decreased left ventricular systolic function, occurring between the commencement of the last of pregnancy and the end of the fifth month, or in the postpartum period, in women without pre-existing symptoms, signs or history of heart disease (5). The disease is associated with a high morbidity and mortality, but its aetiology remains unknown.

In 2010, the Working group on PPCM from the Heart Failure Association of the European Society of Cardiology (ESC) proposed the following definition of PPCM: "Peripartum Cardiomyopathy is an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular systolic dysfunction towards the end of pregnancy, or in the five months following delivery, where no other cause of heart failure is found"(6). It is a diagnosis of exclusion. The left ventricle may not be dilated but the EF is nearly always below 45%. No additional specific criteria have been identified to allow distinction between a peripartum patient with new onset heart failure and the left ventricular systolic dysfunction as PPCM and another form of dilated cardiomyopathy. This was based on the fact that about 10% of cases present with symptoms or are diagnosed 6 months postpartum or even later. Therefore, all other causes of dilated cardiomyopathy with heart failure must be systematically excluded before accepting the designation of PPCM (7).

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

The current epidemiological profile of PPCM is largely unknown, with most available data coming from Africa, Haiti, and the USA.

Epidemiological studies are complicated by the potential difficulty in initially distinguishing PPCM from other forms of cardiomyopathy, such as familial or pre-existing idiopathic dilated cardiomyopathy (DCM). Data suggest a wide variation in the estimated incidence of PPCM according to geographical region.

In South Africa, a King Edward VIII hospital study in Durban by Desai, Moodley et al showed a high incidence of PPCM in the local population (1:1000) and high complication rate (35%)(8).

A Haitian study in 2005 demonstrated an incidence of 1 per 299 live births (9). In USA a study by Brar, Khan et al (2007) showed an overall incidence of PPCM 1 per 4025 live births, with African-Americans having the greatest incidence - 7-fold that of Hispanics and 2.9 fold higher compared with Whites (10). The incidence of PPCM in Australia, Europe and Asia is uncertain and requires more epidemiological studies. The real reason for this geographical variation in the incidence of PPCM is unknown, but it may be linked to genetic predisposition and ethnic factors (10).

Disease presentation in different ethnic groups might influence left ventricular recovery and survival. Outcomes in African-American patients diagnosed with PPCM were similar to those in Haiti and South Africa, but lower than those in white US women. Socioeconomic factors could limit access to timely and advanced medical care (11). Interestingly, an increase in the incidence of PPCM has been reported in the USA, from 1 per 4350 live births in 1990 - 1993, to 1 per 2289 live births in 2000 - 2002. The actual increase may be related to the increasing maternal age and the rates of multiple births (12). However, it most likely due to increased awareness. Enhanced awareness has been promoted by the ESC, the activities of a specialised Working Group on PPCM and an international registry of patients with PPCM, as well as the international registry of patients with PPCM which is part of the EURObservational Research Programme (www.esc.org)

A study by Ntusi, N; Mayosi, B (2009) proposed various mechanisms for aetiology and risk factors of PPCM (Fig 1). They conclude that there is conflicting evidence on the pathogenetic role of viral myocarditis, abnormal immune response to pregnancy, abnormal response to the haemodynamic stress of pregnancy, accelerated myocyte apoptosis, cytokine-induced inflammation, malnutrition, genetic factors, excessive prolactin production, abnormal hormonal function, increased adrenergic tone, and myocardial ischaemia. The authors postulate a number of factors which increase the development of PPCM. These include non-Caucasian ethnicity, advanced maternal age, multiparty, poor socioeconomic status, multiple pregnancy and prolonged tocolytic use (13).

FAMILIAL AND GENETIC PREDISPOSITION

Pregnancy places physiological stress on the human heart and, unsurprisingly, can unmask genetic forms of cardiomyopathy. The increased incidence in particular geographic regions suggests that genetic predisposition might have an important role (7). Morales, Painter et al (2010), were able to identify a subset of PPCM patients from their DCM database, designed for family-based genetic studies, to be carriers of mutations associated with familial forms of DCM involving mutations in PC3, MYH6, MYH7, PSEN2, SCN5A, TNNC1 and TNNT2. Therefore, a subset of patients with PPCM may, in fact, be presenting with an initial manifestation of familial DCM (14). However, additional genetic factors, independent of the known cardiomyopathy, inducing mutations, could potentially also contribute to susceptibility to peripartum heart failure (15).

OXIDATIVE STRESS AND ANGIOGENIC IMBALANCE

Oxidative stress is caused by an imbalance between the production of reactive oxygen species (ROS: reactive molecule that contain oxygen ions and peroxides are highly reactive owing to the presence of unpaired valance- shell electrons) and a biological systems' capacity to detoxify ROS or repair the resulting damage. A study by Toescu, Nuttall et al (2002) demonstrated that the level of oxidative stress rises during pregnancy and that late pregnancy is associated with the formation of particles that are susceptible to oxidation (high LDL cholesterol levels) and an increase in oxidative damage. An efficient antioxidant defence may even be relevant to the long-term cardiovascular health of women, particularly those of high parity or those at high risk of cardiovascular disease (women with diabetes or hypertension) (16).

PROLACTIN AND ITS CLEAVED PRODUCTS

The role of prolactin in the pathogenesis of PPCM has been raised in the past. Prolactin is associated with an increase in blood volume, decreased blood pressure, decreased angiotensin responsiveness, reduced renal excretion of water, sodium and potassium. Prolactin also increases the levels of circulating erythropoietin, and, hence, the haematocrit

(17). An important advance in this field has been the intriguing discovery of the possible role of the production of a 16kDa versus the 23 kDa prolactin in the pathogenesis of PPCM in mice and women (18, 19). Prolactin can exert opposing effects on angiogenesis depending on proteolytic processing of the potentially proangiogenic, full-length, 23kDa derivative (20). The 16kDa N terminal fragment of prolactin is generated from full- length prolactin by cathepsin D, or other proteolytic enzymes such as matrix metalloproteinase's (MMP): MMP-1, MMP-2, MMP-3, MM-8, MMP-9, and MMP-13 produced and secreted by chondrocytes generate biologically functional 16kDa prolactin. This 16kDa prolactin is a potent antiangiogenic factor (21). A high incidence of PPCM has been discovered in mice with a knockout of the cardiac tissue specific signal transduction and activator of transcription-3 (STAT-3), a DNA binding protein that is activated by interleukin-6. STAT-3, in addition to mediating cardiomyocyte hypertrophy and myocardial angiogenesis also protects the heart from oxidative stress by up-regulating antioxidative enzymes such as superoxide dismutase. A reduction in STAT-3 leads to increased oxidative stress, activation of cathepsin D which leads to the cleavage of prolactin into an antiangiogenic and proapoptic 16kDa isoform. The treatment of STAT-3 deficient mice with the inhibitor of prolactin secretion, bromocriptine, prevents the development of PPCM in these knockout mice (18). Evidence suggests that the angiostatic and proapoptic 16kDa prolactin might have a causal role in the initiation and progression of PPCM. Suppression of the prolactin release using the D2 dopamine receptor agonist, bromocriptine, prevented the onset of disease in several animal models of PPCM (22). This notion is supported by initial clinical data from case reports and proof-of-concept pilot studies, which show that the addition of bromocriptine to standard therapy for heart failure is associated with improvement in both left ventricular function and a composite clinical outcome (remaining in NYHA functional class III- IV, failure to improve EF by >10 absolute units, and death) in women with acute severe PPCM (23, 24). A few case reports linked the use of bromocriptine, used to suppress lactation, with increased incidence of maternal hypertension, strokes, seizures, myocardial infarction, an increased pro- coagulant profile, resulting in both arterial thrombosis, including intracardiac thrombus formation (25).

In a study by Sliwa, Blauwet et al (2012) it was demonstrated that bromocriptine was well tolerated with no thrombotic complications (24). Moreover, although bromocriptine stopped lactation and breastfeeding in PPCM patients, the growth and survival of those infants were

normal. However, the study was very small and the findings were not definitive. On the other hand, these findings are encouraging and suggests that a larger study should be considered.
A first larger prospective German PPCM cohort study looked at the aetiology, risk factors, underlying pathophysiology, co-morbidity, prognosis, biomarker profile and therapeutic concepts of PPCM in Western European societies. A high percentage of patients in this cohort study were treated with prolactin blocker, bromocriptine, in addition to standard treatment for heart failure. This study suggested that patients obtaining the combination of the three (ACE inhibitors/ARB, beta blocker and bromocriptine) may have a higher chance for partial and full recovery (26). A larger, multicentre, randomised study evaluating bromocriptine on top of standard care, versus standard care alone, is currently underway (27).

The EuroObservational Registry on PPCM (www.esc.org), which will have outcome on 1000 patients with PPCM, many on bromocriptine, will provide additional information. As PPCM presents heterogeneously, has a spontaneous recovery rate even without therapy and the fact that therapy with bromocriptine cannot be blinded makes a well-powered multicentre study difficult (27).

In a multicentre trial conducted by Hilfiker- Kleiner et al (2017), 63 PPCM patients with LVEF) <35% were randomly assigned to short-term (1W: bromocriptine, 2.5mg, 7 days) or long-term bromocriptine treatment (8W, 5mg for 2 weeks followed 2.5mg for 6 weeks), in addition to SHFT (28).

Bromocriptine treatment was associated with a high rate of full LV recovery and low morbidity and mortality in PPCM patients, compared with other PPCM cohorts not treated with bromocriptine. No significant differences were observed between 1W and 8W treatment, suggesting that 1 week addition of bromocriptine to SHFT is already beneficial, with a trend for better full recovery in the 8W group (28).

VGF SIGNALLING AND PRE ECLAMPSIA

A study by Bello, Rendon et al (2013) showed that the prevalence of pre-eclampsia, hypertensive disorders and multiple gestations in women with PPCM is markedly higher than

in the general population. Their findings supported the concept of shared pathogenesis between pre-eclampsia and PPCM and highlighted the need for awareness of the overlap between these two diseases. Another antiangiogenic factor that is released in high quantities from the placenta during mid to late gestation is sFTL-1. A markedly elevated serum level of sFTL-1 has been associated with pre-eclampsia, a common maternal complication of mid- to late gestation that affects 3-5% of pregnancies worldwide (29).

Another study by Rana, Powe et al (2012) showed that in women with suspected pre-eclampsia presenting ≤34 weeks, circulating sFLT-1/PIGF ratio predicts adverse outcomes occurring within 2 weeks. Despite these finding the authors of the study concedes that additional studies are warranted to validate these findings (30).

Some reports indicate that pre-eclampsia frequently occurs in patients who subsequently develop PPCM. A study by Patten, Rana et al (2012) showed a potential connection between the two diseases. In that study, a mice developed PPCM that is associated with an increased level of sFLT-1 and insufficient upregulation of cardiac expression of VEGF, a potent proangiogenic factor that is antagonised by sFLT-1. This model of PPCM also shows compromised protection from oxidative stress and enhanced cleavage of prolactin. PPCM was ameliorated by the addition of recombinant VEGF (rVEGF) or bromocriptine, but full rescue from PPCM was obtained only with combination of rVEGF and bromocriptine. These results suggest that PPCM might be a "two-hit" phenomenon. Firstly, systemic antiangiogenic signals occur during late pregnancy. Secondly, antiangiogenic factors are further upregulated during the peripartum phase, together with host susceptibility in the form of insufficient local proangiogenic defences in the heart (22).

RISK FACTORS

MULTIPLE PREGNANCIES, PARITY AND MATERNAL AGE

Earlier series of patients with PPCM suggested that the syndrome was more prevalent in older women. However, more recently, the clinical entity has been demonstrated to occur in women with a wide range of ages. In the original description by Demakis and Rahimtoola et al (1971), where he proposed clinical criteria for diagnosing the condition, he included 27

patients with the diagnosis of PPCM. Fourteen of these patients were older than 30 years, while 13 patients were younger than 30 years of age(31).

A study by Gunderson, Croen et, al (2011) demonstrated in a large, multi-racial and ethnic pregnancy cohort in Northern California, that approximately one of every 2066 pregnant women who delivered a live born neonate developed confirmed PPCM. The strongest independent risk factor for PPCM was a maternal age of 40 years or older. The lowest risk of PPCM was associated with a maternal age younger than 24 years (32). In the United States of America, a National Hospital Discharge Survey was conducted of 3.6 million patient's discharges from 1990 to 2002. There were an estimated 16296 cases of PPCM from 1990 to 2002. Patients with PPCM were older, with ae mean age of 29.7 years (12).

A South African single-centre study of 176 newly diagnosed patients with PPCM at Baragwanath Hospital looked at predictors of outcome in patients with PPCM. Clinical assessment, echocardiography and laboratory results were obtained at baseline and at 6 months. Older age appears to be a novel predictor of LV recovery, while younger age, low BMI, increased left ventricular end diastolic diameter (LVEDD), increased left ventricular end systolic diameter(LVESD) and a higher New York Heart Association (NYHA) functional class all seem to be predictors of mortality (33).

Recently, Shani, Kuperstein et al (2014) conducted a retrospective cohort study of 36 women diagnosed with PPCM in a tertiary medical centre and compared the findings with 10370 women who gave birth during a single calendar year at the same institution. Women diagnosed with PPCM were older (mean 33.5 years) than the controls. In most of these studies, the prevalence was highest in women in the higher and lower extremes of child-bearing age.

PPCM has been documented in primiparous and multiparous women. The researchers demonstrated that a significantly higher proportion of women with PPCM (63,9%) were primiparous, carrying multifoetal pregnancies (33,3%) (34).

A recent study by Hilfiker- Kleiner et al (2017) showed that age, gravida and twin pregnancies, hypertension in pregnancy, and/or smoking did not differ between patients with fully recovered cardiac function after SSP and those who remained in heart failure or died, suggesting that these factors do not have a substantial impact on SSP outcome (35).

GENETIC PREDISPOSITION ESPECIALLY THOSE WITH AFRICAN DESCENT

The PPCM high incidence areas of South Africa and Haiti reinforce the potentially strong genetic influence for those with African heritage. In one large study, Brar, Khan et al (2007) identified a significant difference in the incidence of PPCM in ethnic groups in the USA: 1 per 1421 in African-American women and 1 per 2675 in Asian women, but that the greatest incidents of PPCM occurred in African-American women, which was 2.9-fold higher compared with Whites and 7-fold higher than in Hispanics in the USA (10). In another study Kao, Hsich et al (2013) identified clinical features associated with PPCM and possible racial differences. Hospital records from six USA states were screened for PPCM. In total, 535 of 4003914 records of delivering mothers specified a diagnosis of PPCM. The prevalence of PPCM was highest among African-Americans and similar in Caucasians and Hispanics. Established risk factors including maternal age above 30 years, African-American race, hypertension, preeclampsia/eclampsia and multi gestational status were associated with PPCM (36).

In a more recent study Hilfiker-Kleiner, Haghikia et al (2017) found that the prevalence of patients entering SSPs with persistently reduced LVEF was higher among patients of African ethnicity. In addition, three out of four patients who died during or after SSP were African women, suggesting that they may indeed have a higher risk of a fatal outcome of SSP (28).

PROLONGED TOCOLYSIS

Prolonged tocolysis refers to the use of tocolytic agents for a period greater than four weeks (37). Pulmonary oedema occurring in the peripartum period has long been associated with the administration of tocolytic drugs, which include terbutaline, salbutamol, isoxsurprine and magnesium sulphate (38). Beta adrenergic agonists are commonly used as tocolytic agents, and act by increasing intracellular levels of cyclic adenosine monophosphate, which decreases the activity of myosin light chain kinase, the rate limiting enzyme in the signal pathway to uterine contraction. The physiological effects of these beta mimetic drugs, which include

tachycardia, hyperglycaemias, hypokalaemia, and water retention, are modulated by their interaction with beta1 and beta2 receptors (39).

SELENIUM AND MALNUTRITION

Nutritional disorders, such as deficiencies in selenium and other micro nutrients, were thought to play a role in the pathogenesis of PPCM. Deficiencies of selenium increase cardiovascular susceptibility to viral infections, hypertension and hypocalcaemia. However, Fett (2013) concluded that neither low serum levels of selenium nor deficiencies of other micronutrients (vitamin A, B12, C, E and ß-carotene) played a significant role in the development of PPCM in Haitian women (40). In contrast, Cenac, Simonoff et al (1992) found that women from the Sahelian region of Niger in Africa had low levels of selenium (41). A Nigerian case control study, conducted in three hospitals in 2015, aimed to determine if selenium deficiency, serum ceruloplasmin and traditional birth practices are risk factors for PPCM and PPCM patients were followed up for six months. A total of 39 PPCM patients and 50 controls were consecutively recruited. This study showed that selenium deficiency is a risk factor for PPCM in Kano, Nigeria, and is related to rural residency. However, serum ceruloplasmin, customary birth practices and some other characteristics were not associated with PPCM in the study area (42).

DIAGNOSIS AND CLINICAL MANIFESTATION OF PPCM

PPCM is a diagnosis of exclusion - all patients should have a thorough investigation to identify any alternative aetiology of heart failure. Both cardiac and non-cardiac causes of symptoms should be considered. Fig 2 demonstrates an example of a diagnostic approach to patients presenting in heart failure(43).

The diagnosis of PPCM is based on symptoms and clinical findings in combination with appropriate investigations such as electrocardiogram (ECG), chest X-ray, biomarkers (e.g. BNP) and echocardiography (Fig 1). Recently, Blauwet, Libhaber et al. (2013) showed in a prospective cohort study of 176 African women, in a single tertiary institution, in a large series of patients from South Africa, that increased left-ventricular end systolic diameter (LVESD), lower body mass index (BMI) and lower serum cholesterol at baseline, possibly as a marker

of increased immune activation, may be independent predictors of poor outcome in patients with PPCM, while older age and smaller LVESD at baseline appear to be independently associated with a greater chance of LV recovery,(33).

According to Sliwa, Tibazarwa et al (2008), clinical features of normal pregnancy include increased blood volume, increased metabolic demands, mild anaemia, changes in vascular resistance associated with mild ventricular dilatation and increased cardiac output. Thus, the onset of PPCM can easily be masked and missed because the manifestations can mimic those of mild heart failure. Women with PPCM most commonly have dyspnoea, dizziness, chest pain, cough, neck veins distention, fatigue and peripheral oedema (44). A study by Pearson Veille (2000) illustrates that women with PPCM can also have arrhythmias, embolic events due to the dilated, dysfunctional left ventricle, and acute myocardial infarction due to decreased perfusion to the coronary arteries (6). They can also have other indications typical of heart failure: hypoxia, jugular venous distention, S3 and S4 gallop rhythm, rales and hepatomegaly. Blood pressure is often normal or decreased, and tachycardia is common (5). The definitive diagnosis of PPCM depends on echocardiographic identification of new- onset heart failure during a limited period around parturition. A diagnosis of PPCM requires the exclusion of other causes of heart failure such as myocardial infarction, sepsis, severe eclampsia, pulmonary embolism, valvular disease and other forms of cardiomyopathy (45).

Chest radiographs should be obtained in suspected cases of PPCM. These radiographs may be helpful in acute pulmonary oedema, but much less so if no clinical evidence of pulmonary congestion and pleural effusions are evident (46). However, diagnosing cardiomegaly on the basis of a chest radiography in a pregnant patient is difficult because the heart is pushed upwards and laterally, giving the false impression of cardiomegaly. Electrocardiograms should also be obtained. In PPCM, the tracings may be normal or may show left ventricular hypertrophy, ST-T wave abnormalities, dysrhythmia, Q-waves in the anteroseptal precordial leads and prolonged PR and QRS intervals (5). Several laboratory tests should be performed: complete blood counts and serum levels of troponin, urea, creatinine, and electrolytes (44). Liver function tests should be done and levels of thyroid stimulating hormone should be measured. In the initial evaluation, the serum level of troponin may be helpful in ruling out

myocardial infarction. However, an increase in troponin in the acute phase of PPCM, without myocardial infarction can occur (46).

According to Ntusi and Mayosi (2009) measuring levels of B-type natriuretic peptide and N terminal pro B-type natriuretic peptide can help in confirming the diagnosis (13).

Echocardiography is a non-invasive investigation and allows serial evaluations in pregnant women (47). In a study by Sliwa, Tibazarwa et al (2008), they demonstrated that serial echocardiography with Doppler imaging is used to evaluate and monitor regional and global left and right ventricular function, valvular structure and function, possible pericardial pathological changes, and mechanical complications. Findings in women with PPCM are consistent with that of those in heart failure: decreased EF, global dilatation, and thinned out cardiac walls (44).

STANDARD TREATMENT STRATEGY

The management of heart failure around pregnancy is challenging and according to ESC guidelines there is significant peculiarities and challenges (Box1) (48). In the absence of evidence–based data, the initial management of patients with PPCM is similar to management of AHF of other aetiologies. Interdisciplinary approaches of cardiologists, intensivists, obstetricians, neonatologists, anaesthetists and cardiac surgeons are necessary in cases of severe AHF. Fig 3 demonstrates an example of interdisciplinary work-up of a patient with heart failure in pregnancy (48). The initial treatment of patients with confirmed PPCM without cardiopulmonary distress depends on the time-point of onset. Patients who present after delivery should be treated according to the ESC guidelines for heart failure (48). For patients presenting during pregnancy, joint cardiac and obstetric care in observance of the ESC guidelines for management of cardiovascular disease in pregnancy is recommended (49). Fig 4 is an example of a treatment algorithm of patients with PPCM (48).

Patients with signs of cardiopulmonary distress and /or circulatory shock need rapid and more aggressive therapy and should be admitted to the intensive care unit. Initial therapy includes five main elements: optimization of the preload , optimization of oxygenation, restoration of haemodynamics with inotropes and/or vasopressors; urgent delivery if heart failure occurs during pre-partum; and consideration of adjunctive therapies with bromocriptine (2.5mg twice daily for 2 weeks, followed by 2.5mg per day for 6weeks) (48). Patients with haemodynamic instability despite treatment should undergo urgent delivery irrespective of gestation duration. Caesarean section with combined spinal and epidural analgesia and involvement of an experienced interdisciplinary team are recommended (49).

Management of patients with acute peripartum cardiomyopathy without cardiopulmonary distress depends on the time point of onset. Patients who presents after delivery should be treated according to the ESC guidelines for heart failure (49). For patients presenting during pregnancy, joint cardiac and obstetric care in observance of cardiovascular diseases in pregnancy is recommended. During pregnancy, ACE inhibitors, ARBs and renin inhibitors are contraindicated because of foetal toxicity. Hydralazine and nitrates can be used instead. After delivery ACE inhibitors can be started, but during breastfeeding captopril or enalapril should be preferred. Despite an increased risk of foetal growth restriction, beta blockers are indicated in all patients in a stable condition. Mineralocorticoid receptor antagonists (MRA) should be avoided during pregnancy and lactation, but should be started afterwards in stable patients. Diuretics should be administered with caution during pregnancy as they may impair perfusion of the placenta (48). Bromocriptine, in addition to the heart failure therapy, should be considered because it has shown promising results, with improved LV systolic function and clinical outcomes in several case studies (24). In the multicentre randomised study by Hilfiker-Kleiner et al (2017) on the benefit of bromocriptine for the treatment of PPCM it was demonstrated that bromocriptine treatment was associated with a high rate of full LV recovery and low morbidity and mortality in PPCM patients, compared with other PPCM cohorts not treated with bromocriptine. In this multicentre trial, 63 PPCM patients with LVEF <35% were randomly assigned to short-term (1W: bromocriptine 2.5mg, 7 days) or long-term bromocriptine treatment (8W: 5mg for 2 weeks, followed by 2.5mg for 6 weeks), in addition to SHFT. No significant differences were observed between 1W and 8W treatment, suggesting

that 1 week addition of bromocriptine to SHFT is already beneficial with a trend for better full recovery in the 8W group (28).

While diuretics should be tapered when possible after stabilization and when LVEF improves, ACE inhibitors, beta blockers, and MRAs should probably be given in guideline- based dosages and not discontinued during the first 12 months after complete recovery of LV dimensions and systolic functions. Earlier, stepwise discontinuation of heart failure therapy might be considered if both complete recovery of ventricular function and normal exercise response are achieved. Ivabradine should be given according to established indications. Furthermore, early treatment with Ivabradine even before or parallel with beta blockers may be considered, as it appears to be safe and effective[i](50).

Prevention of sudden cardiac death

Severely impaired ventricular function is associated with increased risk of life-threatening arrhythmias. Current ESC guidelines for treatment of heart failure recommend implantation of ICD (implantable cardioverter defibrillator) for primary prevention in patients with symptomatic heart failure and LVEF ≤ 35%, despite optimal pharmacological treatment or for secondary prevention in patients with documented ventricular arrhythmia causing haemodynamic instability (51). In the context of PPCM, where a young women with the potential for complete recovery of ventricular function are involved, decision about implantation of ICD should be taken with caution. After diagnosis of PPCM, clinicians are faced with the uncertainty about the subsequent evolution of ventricular function. Therefore, the related decision of whether to implant an ICD or not may be very challenging (48).

Several publications reported recovery of LV function in at least 50% of patients within 6 months after diagnosis (52). However, a Turkish study reported a delayed recovery (after 6 months) in a significant proportion of patients (53). In the year 2014 in United States of America, a retrospective study showed a complete recovery of LV function in 23% of patients and partial recovery in another 19%, over a mean duration of 33±21 months, confirming frequent delayed recovery over 6 months (83%) In that study, Afro-Americans women

showed a lower rate of recovery compared to Caucasians and post-partum diagnosis was a predictor of good recovery (54). In a South African study, age and low end diastolic diameter were predictors of recovery, whereas LVEF was not (33). In light of these findings, early implantation of an ICD in patients with newly diagnosed PPCM is not appropriate. However, postponement of ICD implantation beyond the time point when further recovery of ventricular function is unlikely (6 – 12 months) exposes young mothers to an unacceptable risk of sudden death. Novel therapies such as a wearable cardioverter-defibrillator (WCD) are an interesting alternative for the prevention of sudden cardiac death in the first months after diagnosis, until a definitive decision about ICD implantation can be made (35).

In patients without recovery despite 3-6 months on optimised heart therapy, a conventional recommendation for the primary prophylactic implantation of an ICD applies (51). In patients without Left bundle branch block (LBBB) or symptomatic sick sinus syndrome, single chamber ICDs are recommended. Subcutaneous ICDs (S-ICD) represent an alternative to Trans-venous systems in these young patients. Subcutaneous systems avoid intravascular leads and, thus, the potential complication of infections leading to endocarditis and lead extractions. On the other hand, subcutaneous systems can provide neither anti-tachycardia pacing (ATP) nor post-shock pacing and, therefore, might not be an optimal choice for patients with recurrent ventricular tachycardia successfully terminated by ATP (43). In patients with heart failure, LVEF ≤ 35% despite optimal medical therapy for at least 3-6 months and LBBB, cardiac resynchronization therapy (CRT) is indicated, although no large studies have assessed the value of CRT in patients with PPCM. Significant improvement of LV function in two PPCM patients undergoing CRT device implantation for persistent symptomatic LV dysfunction was reported (55). According to the current ESC guidelines on CRT, in patients with symptomatic heart failure, persistent LVEF ≤35% and complete LBBB (QRS duration >130ms), CRT should be offered. In patients with wide QRS complex with non-LBBB morphology (QRS duration >150ms) CRT may be considered (51). Although no data on device therapy in patients with PPCM exist, recommendations for device therapy may be applied as in patients with dilated cardiomyopathy (48).

LITERATURE REVIEW

REVIEW ON MATERNAL OUTCOME ON SUBSEQUENT PREGNANCY IN PATIENTS WITH PPCM

In a study by Elkayam, Tummala et al (2001) an early survey was conducted that relied solely on a questionnaire filled out by physicians. They obtained information about SSPs s in women who had PPCM by sending out a questionnaire, in 1997 and 1998, to all members of the American College of Cardiology in the United States (approximately 15,000 persons) and to two members of one cardiology group in South Africa, seeking information about women with PPCM who had SSPs. Of the approximately 15,000 physicians contacted, 409 returned the questionnaire. On the basis of responses, they identified 92 women with a history of PPCM who had a SSP. The survey was aimed at assessing the maternal and foetal outcomes of SSPs in women with PPCM (56).

Maternal outcome during the first SSP indicated that 6 of the 28 women in group 1 (21%) and 7 of the 16 women in group 2 (44%) had symptoms of heart failure. Twenty one of the women in group 1 and 25% of those in group 2 had a decrease of more than 20% in the left ventricular EF during the first SSP, and 14% of the women in group 1 and 31% of those in group 2 had a decreased ejection fraction at the last follow-up. None of the women in group 1 died during or after the first SSP. Two of the women died suddenly (one died two months following SSP, and the other two years after the SSP). One woman died of progressive heart failure two months after the SSP. This study demonstrated that in women who had PPCM, SSPs may be associated with deleterious foetal and maternal outcomes such as premature delivery and maternal cardiac dysfunction, including symptomatic heart failure and even death (56).

Another study by Avila, de Carvalo et al (2002) reported no maternal complications in 6 patients with SSPs with normal LV function and the development of heart failure in 30% of 11 patients, with LV dysfunction that was associated with pulmonary embolism in 1 patient and death in another. Two of the surviving patients had a >20% reduction in their EF postpartum (57).

A South African study by Sliwa, Forster et al (2004) reported on 6 indigenous black South African women known to have PPCM (ages 26 to 39) who had a SSP. This was the first prospective study of left ventricular function and cytokine measurement in women with documented PPCM with SSP. Four patients were Para 2 and gravida 2 and two were Para 3 and gravida 3. The SSP occurred 1 to 2 years after the initial pregnancy in all patients. None were twin or multiple pregnancies and none of the patients had pregnancy related hypertension or eclampsia. All had normal vaginal delivery at term. All 6 patients were in NYHA class I at the onset of SSP and remained asymptomatic until delivery. All patients developed heart failure in the postpartum period and were placed on optimal anti failure treatment. Unfortunately, two patients died within 8 weeks after delivery from severe refractory heart failure despite admission to intensive care unit and optimal medical treatment. The remaining 4 patients continued to remain asymptomatic. Deterioration of left ventricular function occurred uniformly postpartum. Both deaths occurred in patients who had persistent cardiomegaly and impaired EF at onset of SSP (58).

A Chart review study by Chapa, Heiberger et al (2005) of patients with PPCM between 1988 and 2001. Data from echocardiography, including fractional shortening and left ventricular end diastolic dimension, were recorded both at the time of diagnosis and at follow-up. Left ventricular dysfunction was defined by echocardiography as a fractional shortening less than 30 degrees and left ventricular end diastolic dimension of 4.8 cm or more. The results of the study showed 13 (41%) patients had recovery of ventricular function, while 19 (59%) continued to have persistent left ventricular dysfunction. Those who did not recover cardiac function had a higher left ventricular end diastolic dimension and a lower fractional shortening at diagnosis than those who recovered. A fractional shortening of less than 20% and a left ventricular end diastolic dimension 6 cm or greater at the time of diagnosis was associated with a more than 3-fold higher risk for persistent left ventricular dysfunction (59).

A Haitian observational study by Fett, Christie et al. (2006) focused on Haitian women with SSPs among 99 prospectively identified patients with PPCM who were enrolled in the Hospital Albert Schweitzer Peripartum Cardiomyopathy Registry from 1 February 2000 to 31 January 2005. Patients had a clinical and echocardiographic examination at least every 6 months and

were counselled to avoid pregnancy until ventricular function returned to normal. They identified 16 SSPs in 15 patients with PPCM who had an index pregnancy with a diagnosis of PPCM. Mean interval between the index pregnancy and delivery of SSP was 26 months (range, 16 to 37 months). All but 1 patient with SSP became pregnant before full recovery of left ventricular function and against medical advice. Eight of 15 patients (53%) had worsening heart failure during SSP, and only one of these patients regained normal left ventricular systolic function after the SSP. One patient died of severe heart failure 10 months after SSP. Seven patients (47%) showed no worsening heart failure with SSP and they recovered normal left ventricular systolic function during or after the SSP. One patient had 2 SSPs after the index pregnancy, with worsening heart failure occurring after the second SSP, but not after the first SSP (60).

A study in United States of America by Habli, O Brien et al (2008) assessed the prognostic value of EF at index and SSP on long-term outcome in patients with PPCM. It was a retrospective analysis of data on patients with a diagnosis of PPCM, from January 2000 to January 2006, at the University of Cincinnati in Cincinnati, Ohio. The overall follow-up period from index pregnancy to last available follow-up was 3.4 ± 1.9 years (range, 1 - 6 years). The mean interval between a pregnancy complicated with PPCM and a first SSP in those who had early termination or successful SSPs was 2.19± 0.7 and 2.7 ± 0.5 years, respectively. There were no statistical significant differences among the groups with regard to LVEF at the index pregnancy, at interval follow-up or at the first SSP, and at the last follow-up available. Persistent left ventricular dysfunction was noted in women with PPCM and no SSPs and in those who had early termination during the follow-up period, as compared with those with successful SSPs. Among the 70 patients with PPCM, 28 (40%) had an EF of 25% or less and 42 (60%) had an EF greater than 25%. Among those with EF of 25% or less, 57% (n=16) had an end-stage cardiac disease requiring cardiac transplant, as compared with none who had end-stage cardiac disease if EF was greater than 25%. Their findings revealed that women with PPCM with a baseline LVEF 25% or less at the time of diagnosis is associated with a poor long-term outcome and a higher rate of subsequent need for cardiac transplant. They also revealed that SSPs in women with PPCM have a deleterious maternal effect on maternal cardiac

function, as manifested by either worsening cardiac symptoms or persistent cardiac left ventricular dysfunction(61).

In a study by Williams, Mozurkewich et al (2008) it was suggested that dividing women into 2 categories (recovered vs non-recovered left ventricular function) is most appropriate for counselling on future pregnancies. Even though the cardiac function has normalised in the group of women with recovered cardiac function, the left ventricular contractile reserve may remain impaired and recurrence of PPCM is still possible (46).

A study in United States of America by Modi, Illum et al (2009), conducted in the United Stated, looked at the clinical and echocardiographic data of 44 (39 African-American women) patients with PPCM over an 11 year period (1992-2003). During a mean follow-up of 24 months, 7 (15.9) patients died and LV function returned to normal in 14 (35%). The study concluded that LV function recovery and survival rates of PPCM patients observed in this study are similar to those reported from Haiti and South Africa and different to what is generally accepted in the United States (62).

In 2010 Fett, Fristoe et al (2010) conducted a study to assess the risk of heart failure relapse in SSPs in PPCM women. Prospectively identified PPCM patients, volunteering between 2003 and 2009, were identified from the PPCM Registry of Hospital Albert Schweitzer, in Haiti. Of the 61 post PPCM pregnancies identified, there were 18 relapses (29.5%) of heart failure. Of the 26 pregnancies with a LVEF of less than 55% prior to the pregnancy, relapse occurred in 12 (46.2%) pregnancies. Of the 35 pregnant women with an LVEF of 55% or greater prior to the pregnancy, relapse occurred in 6 (17, 1%) ($P<0.01$). No relapses occurred in 9 women who also demonstrated adequate contractile reserve (63).

Mandal, Mandal et al (2011) conducted a study in India to analyse the pregnancy outcomes of pregnant women with PPCM, as well as its effect on SSPs. All patients hospitalised with PPCM between July 2006 and June 2009 in the Departments of Cardiology and Obstetrics and Gynaecology at the Institute of Post Graduate Medical Education were included in the study. A total of 36 women aged between 15 and 45 years, with 42 pregnancies (36 first pregnancies

and 6 second pregnancies) were analysed. Patients were evaluated by physical examination, investigations (routine blood examinations, electrocardiography [CXR, posterior-anterior views] and echocardiography). Maternal outcome was assessed by documenting associated complications and maternal death. Primiparus constituted 39% (14/36) of the total study population. Twenty six women (72%) were clinically improved and in 17 (48%) the left ventricular functional status returned to normal. Five cases (14%) developed persistent cardiomyopathy (persistent left ventricular dysfunction beyond six months of presentation), and 5 women (14%) presented with thromboembolic events and anticoagulation was used as secondary prophylaxis. Maternal mortality was 14% (5/36). Of the 6 women with SSPs, one patient with persistent cardiomyopathy died after delivering a stillborn baby. The remaining 5 cases with normal left ventricular functional status had favourable foetal outcomes; however, the mothers experienced morbidities such as symptoms of heart failure (two cases) and one of them progressed to persistent cardiomyopathy (64).

A recent study by Hilfiker- Kleiner et al (2017) on the outcome of subsequent pregnancies in patients with a history of peripartum cardiomyopathy. Subsequent pregnancies (SSP) in 34 patients with clearly diagnosed index PPCM were treated and /or managed either at university hospitals, in tertiary hospitals, or by cardiologists in private practice in South Africa, Scotland and Germany. 12% of the pregnancies ended prematurely and the rest were full term. Overall relapse rate (LVEF≤ 50% or death after at least 6 months) was 56%, with 12% mortality. Persistently reduced LVEF (≤ 50%) before entering SSP was present in 47% of patients, while full recovery (LVEF ≥ 50%) was present in 53%. The majority of patients entering SSP with persistently reduced LVEF were of African ethnicity (75%). Persistently reduced LVEF before SSP was associated with a higher mortality (25% vs 0%) and a lower rate of full recovery at follow-up (35).

FETAL OUTCOME ON SUBSEQUENT PREGNANCY IN PATIENTS WITH PPCM

There is limited information available on the foetal outcome in SSPs of patients with PPCM. A survey by Elkayam, Tummala et al (2001) of members of the American College of Cardiology identified 44 women who had PPCM and had a total of 60 subsequent pregnancies (SSP). They

reviewed the medical records of these women and interviewed their physicians. Among the 35 women who had a SSPs and did not have an abortion, 21 had a normal vaginal delivery and 14 delivered by Caesarean section. Premature delivery (defined as delivery at less than 37 weeks gestation) occurred in 3 women (13% of the subgroup - women with normal LV function before SSP) in group 1, and in 6 women (50% of the subgroup - women with persistent LV dysfunction before SSP) in group 2. There was no perinatal mortality. Of the 9 abortions, 5 were therapeutic (56).

An Indian observational study by Mandal, Mandal et al (2011) assessed both maternal and foetal outcome in patients with PPCM. All 36 mothers had given birth to neonates. The birth weight of the babies ranged from 800 to 900 grams. Two premature babies with Apgar scores of <8 suffered from asphyxia and subsequently died in the neonatal period. Another 2 had intrauterine growth restriction (64).

METHODS

DATA COLLECTION

Our local ethics committees approved this study. SSPs in 18 patients with clearly diagnosed index PPCM were managed or treated at university hospitals, tertiary hospitals, or by cardiologists in private practice in South Africa. All 18 PPCM patients with SSPs matched the diagnostic criteria for PPCM at their index PPCM (LVEF ≤45%) and had absence of previously known cardiomyopathy. All patients provided written informed consent. Minimal requirement for enrolment was fulfilling the criteria for the diagnosis of PPCM, including availability of baseline LVEF at the index pregnancy and LVEF after SSP. Clinical and laboratory assessments were performed in all 18 patients with confirmed index PPCM at the time of diagnosis, before SSP, during SSP, after delivery, and after at least 6 months (Fig 5).

ANALYSIS OF OUTCOME

Patients were classified with regard to recovery according to the 2016 ESC guidelines defining preserved LV function as LVEF ≥49%. Accordingly, patients were defined as entering SSP with fully recovered function if LVEF was ≥50% and persistently reduced LV function if LVEF was ≤50%, either measured before SSP or assessed within the first trimester of the SSP.

Table 1: **Clinical presentation and outcome of subsequent pregnancies (SSPs) in patients entering SSP with persistently reduced (LVEF≤50%) or fully recovered left ventricular function (LVEF≥50%)**

	LVEF ≤50%(n=11)	**LVEF ≥50%(n=7)**
LVEF(%)at diagnosis of index PPCM(mean)	34%	30.4%
LVEF(%)before SSP(mean)	44%	56%
LVEF(%)after delivery of SSP(mean)	38%	54%
LVEF(%)SSP follow-up(mean)	30%	43%
Full recovery from PPCM after SSP	18%(2/11)	85%(6/7)
Death	27%(3/11)	0%(0/7)

LVEF, left ventricular ejection fraction; PPCM, peripartum cardiomyopathy; SSP, subsequent pregnancy

Table 2: **Comparison of cardiac and clinical parameters in patients receiving standard therapy for heart failure alone or with addition of bromocriptine**

	SHFT + BR (N=10)	**SHFT(N=8)**
LVEF % At index PPCM(mean)	34%	32%
LVE F% before SSP(mean)	47%	48%
LVEF ≥50% prior SSP(mean)	57%	56%
LVEF % after SSP(mean)	51%	35%
LVEF % at follow-up SSP(mean)	49%	30%
Full recovery from PPCM after SSP	60%(6/10)	12.5%(1/6)

Note: SHFT= standard heart failure treatment; LVEF= left ventricular ejection fraction; PPCM = peripartum cardiomyopathy; SSP= subsequent pregnancy; BR=bromocriptine. Early after delivery of SSP was measured in the first few days after delivery before discharged, when medical treatment had already started. Follow-up LVEF after SSP was analysed at least 6 months after delivery of SSP. Three patients died on follow-up.

RESULTS

Patients in Table 1 were divided into a group entering SSP with persistently reduced LVEF (≤50%) and a group with fully recovered LVEF (≥50%).

Gravity, cardiac function at index peripartum cardiomyopathy and at delivery of subsequent pregnancy

The 18 PPCM patients presented with a mean LVEF of 33% at the index pregnancy and a mean of 48% before SSP. The median gravity at SSP in all 18 patients was 2. The follow-up data, 6 months post SSP, 3 patients had died and mean LVEF 42%. Recovered PPCM (LVEF ≥ 50%) at follow-up was observed in 40% (6/15). Persistent reduced LVEF (≤ 50%) was present in 60% (9/15). The overall mortality rate in this collective of PPCM patients with SSP was 16% (3/18).

Clinical presentation and outcome of subsequent pregnancies in patients who entered subsequent pregnancies with recovered versus not recovered left ventricular function

To analyse the effect of LV function before SSP in our group, we divided patients into those who displayed full recovery (LVEF≥50%) and those who had reduced LVEF (≤50%) when entering SSP. Full recovery from PPCM before SSP was observed in 7/18 patients, while persistent reduced LV function was present in 11/18patients. Among the 11 patients entering SSP with unrecovered LV function, 3 patients had died at 6 months follow-up. Their mean LVEF early after delivery was significantly lower compared with the 7 patients entering SSP with fully recovered LV function. At follow-up (6months after delivery), the proportion of patients with stable full recovery(LVEF≥50%) tended to be higher in patients entering SSP with fully recovered LV function, compared with those entering SSP with persistently reduced LVEF.

Outcome of patients receiving standard therapy for heart failure alone or with addition of bromocriptine immediately after delivery of subsequent pregnancy

All 18 patients received beta-blocker therapy and ACE inhibitors, defined as SHFT. Of these, 10 patients received SHFT and bromocriptine (which was started immediately after delivery) and 8 received SHFT alone. No significant differences were observed between the two groups with regards to LVEF at the index PPCM, or LVEF before SSP (Table3). A comparable proportion of patients in both groups entered SSP with recovered cardiac function (LVEF≥50) and received beta-blockers and ACE inhibitors. The SHFT + bromocriptine group displayed a trend to better LVEF in the first week after delivery, with significantly better LVEF at follow-up of SSP, compared with the group treated with SHFT alone (Table 2). More patients in the SHFT + bromocriptine group displayed full recovery from PPCM with LVEF ≥50% at follow-up, compared with patients in the SHFT group (Table 3). In addition, no patient in the SHFT + bromocriptine group died during follow-up of SSP, while 3 patients died in the SHFT group.

DISCUSSION

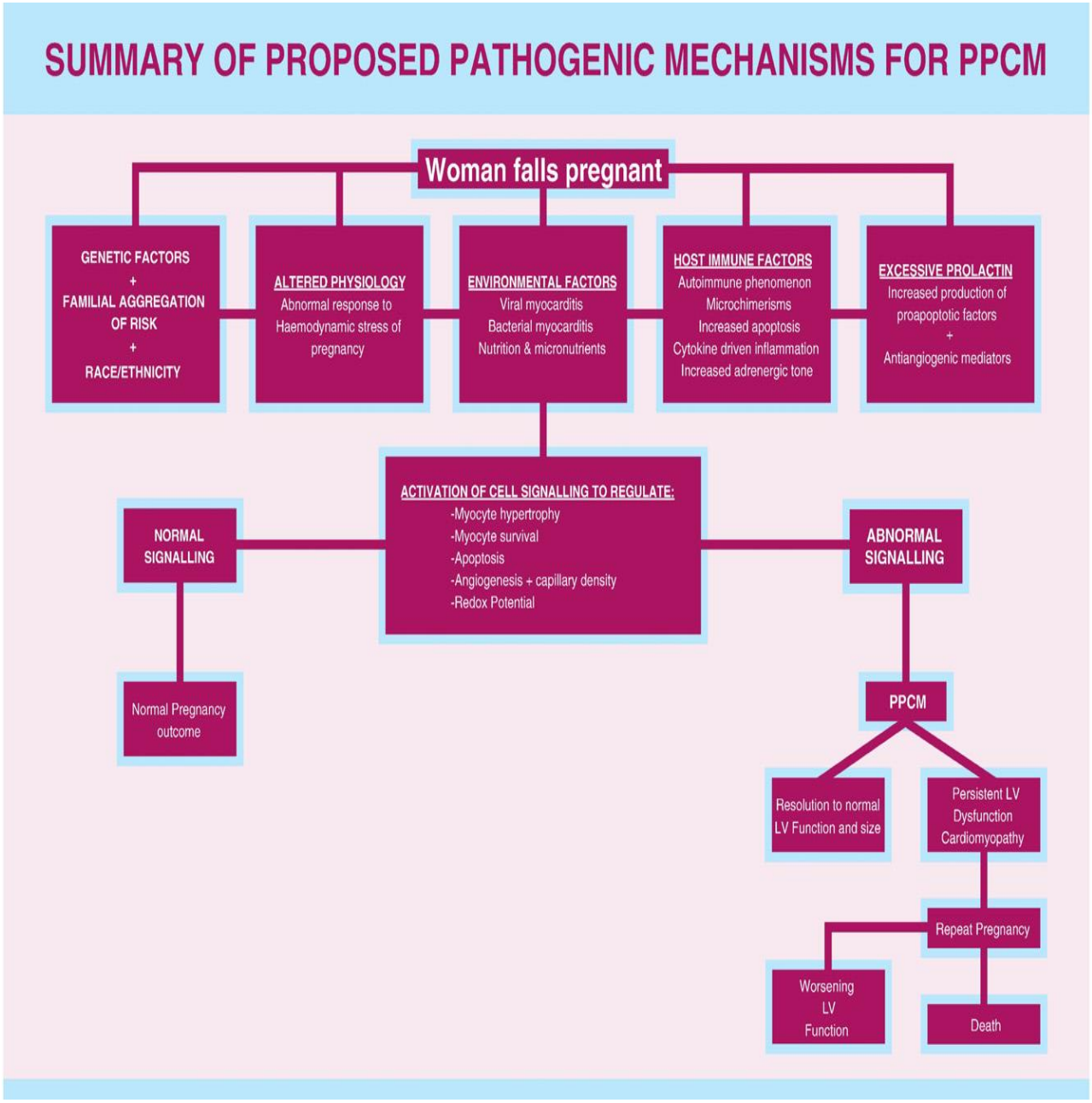
Previous studies suggest that some degree of cardiac dysfunction recurs in most PPCM patients in the postpartum phase of an SSP, with a higher risk for adverse outcome when LV structure and functions had not completely recovered before SSP(58). In this study we report data from two university hospitals in South Africa (Baragwanath and Groote Schuur Hospital). In our observation there was a significantly high risk of relapse of heart failure - more than half of our patients presenting with SSP in this study entered with LV function not fully recovered. These patients with persistently unrecovered LV function had a significantly high risk of fatal outcome of SSPs, as supported by all 3 patients who died after SSP had entered the SSP with LVEF ≤ 50%. Moreover, persistently reduced LV function before entering SSP was associated with lower cardiac function in the early phase after SSP delivery and had a lower chance for full recovery during the follow-up. Interestingly, in patients entering SSP with fully recovered cardiac function (LVEF≥ 50%), stable full recovery at follow-up of SSP was observed in 85%, showing that PPCM patients with fully recovered LV function have a reduced risk of relapse in SSP. However, the number of patients in this study was too small to draw any major conclusions. The majority of the patients were treated with standard heart failure treatment (SHFT), as suggested by ESC guidelines. Only 10 patients received bromocriptine in addition

to SHFT, with 8 patients not receiving bromocriptine. The 3 patients who died were from the group that was treated with SHFT without bromocriptine. Whether addition of bromocriptine in addition to SHFT in this study was beneficial or not could not be evaluated as the number of patients was too small to draw conclusion. In a study by Hilfiker-Kleiner et al (2017) of 34 patients with clearly diagnosed index PPCM from tertiary hospitals , cardiologists in private practice in South Africa, Germany or Scotland between 2005 and 2015. They looked at the risk of relapse during or after a SSP. They observed that despite high risk of a relapse of heart failure, half of the patients presenting with an SSP in the study were entering it with LV function not fully recovered. These patients had a substantially higher risk of fatal outcome of SSP as all patients who died during or after SSP in the present study had entered the SSP with a LVEF that was not fully recovered. Moreover, persistently reduced LV function before entering SSP was associated with lower cardiac function in the early phase after SSP delivery and lower chance for full recovery during follow up. However, even in patients entering SSP with fully recovered cardiac function, stable full recovered at follow up of SSP was only observed in 56%, showing that PPCM patients with fully recovered LV function also have substantial risk for relapse in SSP.

CONCLUSION

Counselling of all PPCM patients regarding the risk of worsening heart failure, and even death in SSP is of paramount importance as the risk is substantial, even in patients with recovered LV function before SSP. There is significant high risk of fatal outcome of SSP, particularly with persisting heart failure or death and is particularly high if patients enter SSP with a LVEF that is not fully recovered. In SSP in a PPCM patients, management by an interdisciplinary team of cardiologists, obstetricians, anaesthetists and neonatologists is recommended. All patients need to be monitored carefully for at least 6 months postpartum and, perhaps, lifelong. Despite major limitations such as small cohort size and non-randomised design, our data

suggest that progression of heart failure and fatal outcome of SSP may be prevented if a SHFT +BR therapy is initiated immediately after delivery in SSPs. However, larger and long-term outcome data are urgently needed. Unfortunately there was not enough data to comment on the foetal outcome of SSPs in our study. We recommend a large randomised controlled study to focus on both foetal and maternal outcome in SSPs in patients with documented PPCM.



Adapted from:(13)

Fig 1: Summary of proposed pathogenetic mechanism of PPCM

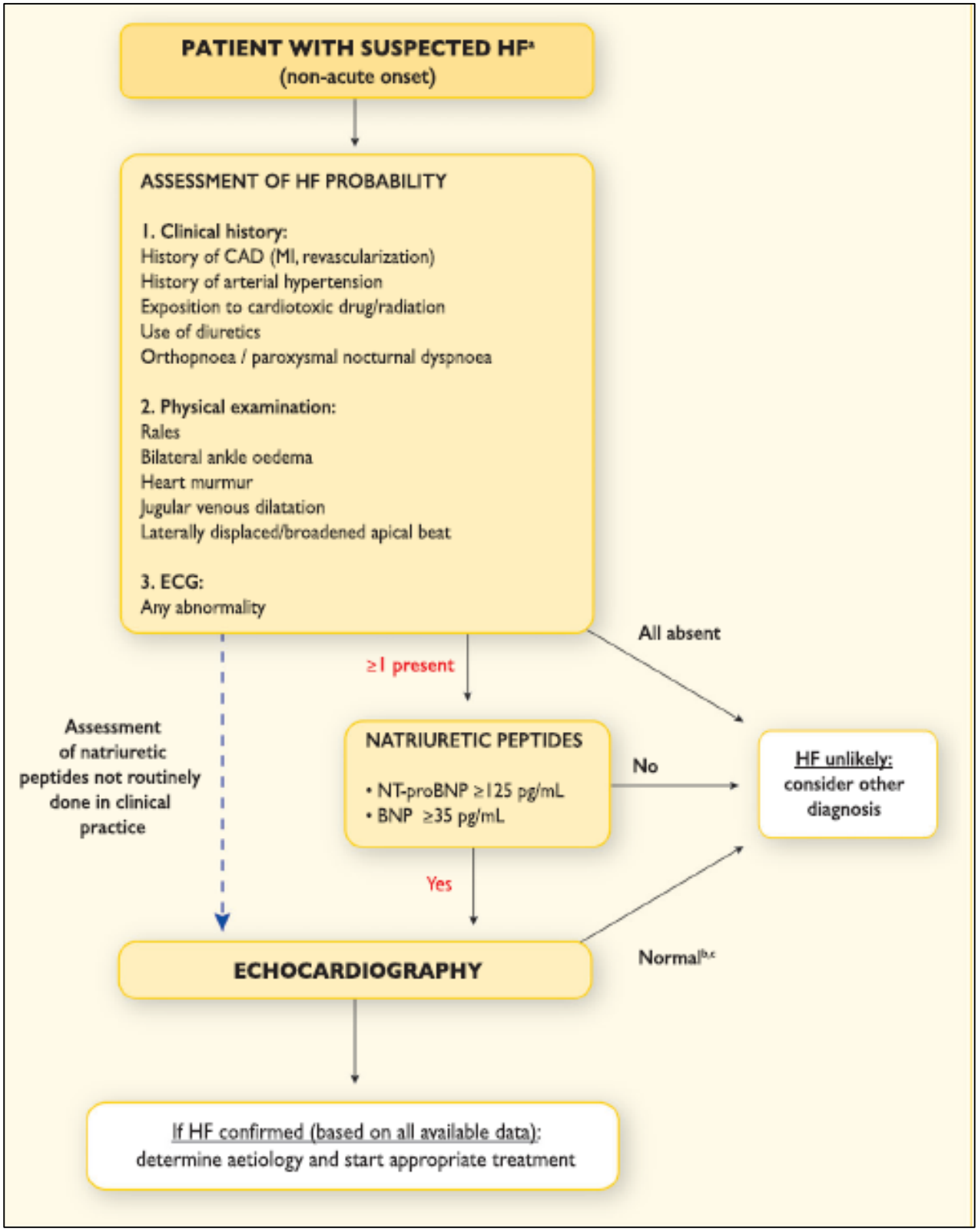

PATIENT WITH SUSPECTED HF[a]
(non-acute onset)
ASSESSMENT OF HF PROBABILITY
1. Clinical history:
History of CAD (MI, revascularization)
History of arterial hypertension
Exposition to cardiotoxic drug/radiation
Use of diuretics
Orthopnoea / paroxysmal nocturnal dyspnoea
2. Physical examination:
Rales
Bilateral ankle oedema
Heart murmur
Jugular venous dilatation
Laterally displaced/broadened apical beat
3. ECG:
Any abnormality
All absent
≥1 present
Assessment of natriuretic peptides not routinely done in clinical practice
NATRIURETIC PEPTIDES
• NT-proBNP ≥125 pg/mL
• BNP ≥35 pg/mL
No
HF unlikely: consider other diagnosis
Yes
ECHOCARDIOGRAPHY
Normal[b,c]
If HF confirmed (based on all available data):
determine aetiology and start appropriate treatment

Fig 2: Diagnostic algorithm for a diagnosis of heart failure on non- acute onset : BNP= B type natriuretic peptide; CAD= coronary artery disease; MI= myocardial infarction; NT pro BNP= N terminal pro-B type natriuretic peptide(43)

Box 1: Peculiarities in the management of acute heart failure caused by peripartum cardiomyopathy

- Multidisciplinary approach with focus on health of mother and foetus.
- Avoidance of heart failure (HF) drugs with foetal toxicity during pregnancy (i.e. ACE inhibitors/ARBs, mineralocorticoid receptor antagonists) and breastfeeding; thereafter
- standard HF therapy
- Consideration of bromocriptine (2.5 mg twice daily for 2 weeks, followed by 2.5 mg per day for 6 weeks) in addition to standard HF therapy.
- Anticoagulation with heparin to avoid cardio-embolic complications in patients with LVEF ≤35% or treated with Bromocriptine (if no contraindication exists).
- In the case of cardiogenic shock, consideration of levosimendan (0.1 µg/kg/min for 24 h) instead of catecholamines as first-line inotropic drug. Early transfer to experienced centre. Early evaluation of mechanical circulatory support according to the centre's experience.
- Prevention of sudden cardiac death, early consideration of wearable cardioverter-defibrillator devices in patients with LVEF ≤35%.

BOX 1 (35, 48)

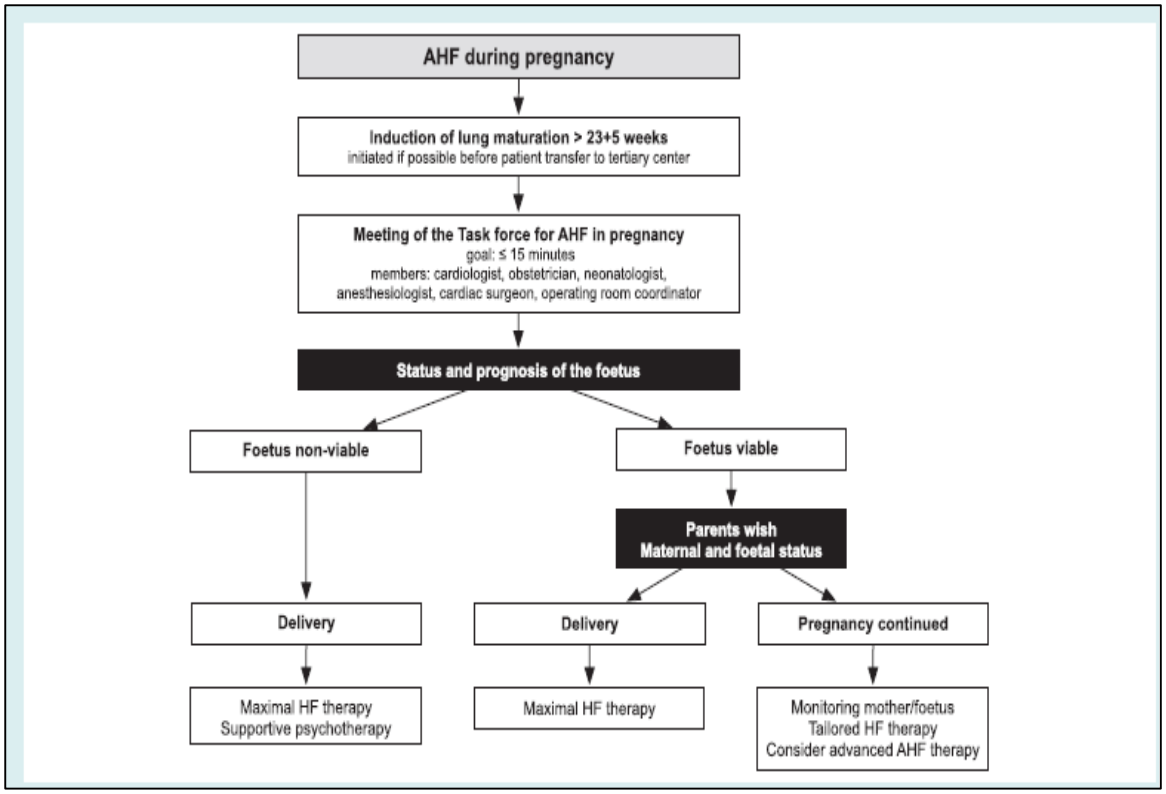


Fig 3: Example of interdisciplinary work-up for acute heart failure (AHF) during pregnancy (modified from the protocol of the medical school Hannover) (48)

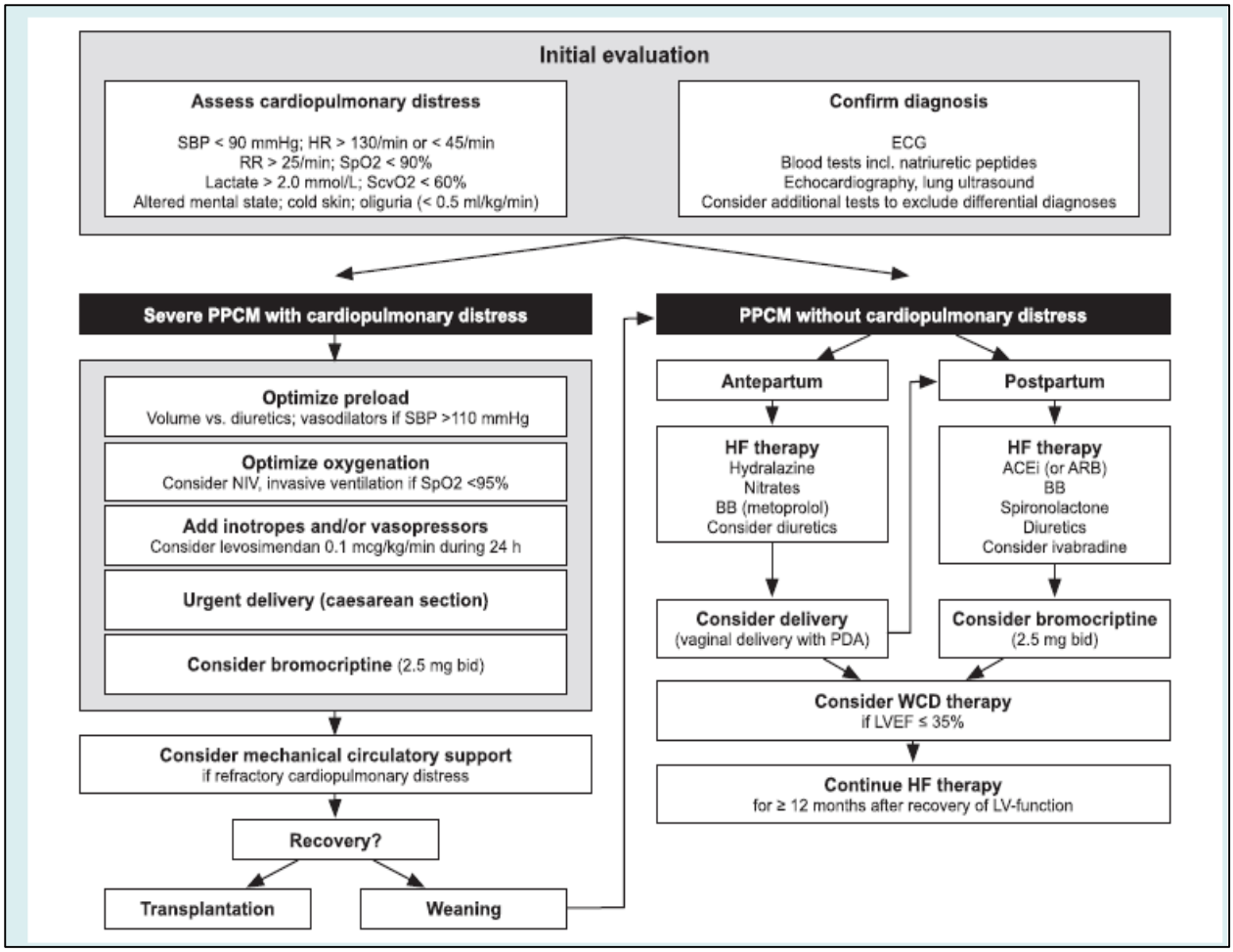


Fig 4: Algorithm for initial management of PPCM: BB=beta blocker, HF=heart failure, RR=respiratory rate, SBP=systolic blood pressure, SpO2 peripheral oxygen saturation WCD=wearable cardioverter defibrillator; PDA = peridural anaesthesia (48)

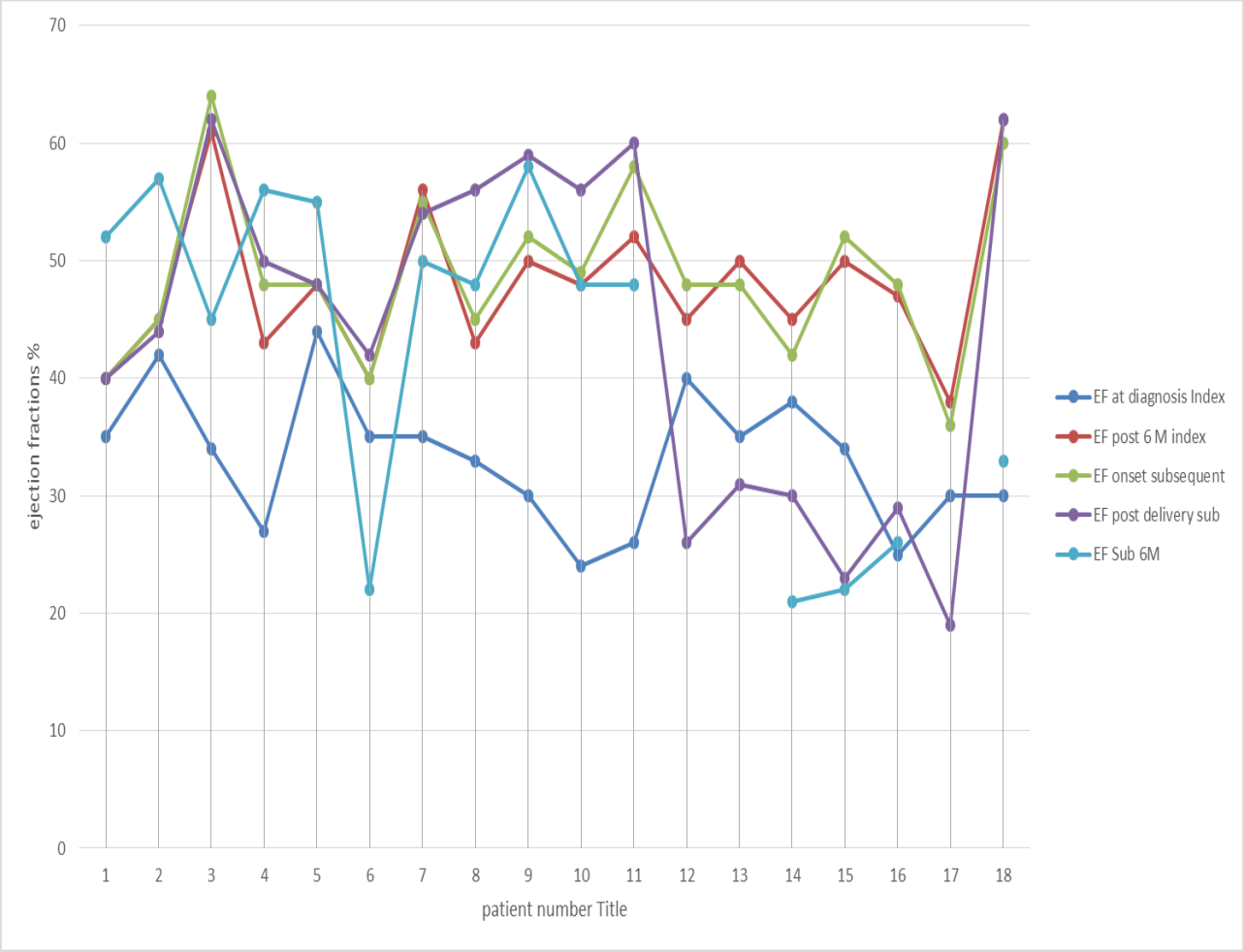


Fig 5: Time course of left ventricular ejection fraction at diagnosis index PPCM, 6 months post- index pregnancy, onset of SSP, post-delivery of SSP and 6 month follow-up after SSP.

REFERENCES

[i]1. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation. 2006;113(14):1807-16.

2. Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies. Circulation. 1996;93(5):841-2.

3. Abelmann WH. Classification and natural history of primary myocardial disease. Prog Cardiovasc Dis. 1984;27(2):73-94.

4. Sisakian H. Cardiomyopathies: Evolution of pathogenesis concepts and potential for new therapies. World J Cardiol. 2014;6(6):478-94.

5. Pearson GD, Veille JC, Rahimtoola S, Hsia J, Oakley CM, Hosenpud JD, et al. Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. Jama. 2000;283(9):1183-8.

6. Sliwa K, Hilfiker-Kleiner D, Petrie MC, Mebazaa A, Pieske B, Buchmann E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. European journal of heart failure. 2010;12(8):767-78.

7. Sliwa K, Fett J, Elkayam U. Peripartum cardiomyopathy. Lancet. 2006;368(9536):687-93.

8. Desai D, Moodley J, Naidoo D. Peripartum cardiomyopathy: experiences at King Edward VIII Hospital, Durban, South Africa and a review of the literature. Trop Doct. 1995;25(3):118-23.

9. Fett JD, Christie LG, Carraway RD, Ansari AA, Sundstrom JB, Murphy JG. Unrecognized peripartum cardiomyopathy in Haitian women. Int J Gynaecol Obstet. 2005;90(2):161-6.
10. Brar SS, Khan SS, Sandhu GK, Jorgensen MB, Parikh N, Hsu JW, et al. Incidence, mortality, and racial differences in peripartum cardiomyopathy. Am J Cardiol. 2007;100(2):302-4.
11. Goland S, Modi K, Hatamizadeh P, Elkayam U. Differences in clinical profile of African-American women with peripartum cardiomyopathy in the United States. J Card Fail. 2013;19(4):214-8.
12. Mielniczuk LM, Williams K, Davis DR, Tang AS, Lemery R, Green MS, et al. Frequency of peripartum cardiomyopathy. Am J Cardiol. 2006;97(12):1765-8.
13. Ntusi NB, Mayosi BM. Aetiology and risk factors of peripartum cardiomyopathy: a systematic review. Int J Cardiol. 2009;131(2):168-79.
14. Morales A, Painter T, Li R, Siegfried JD, Li D, Norton N, et al. Rare variant mutations in pregnancy-associated or peripartum cardiomyopathy. Circulation. 2010;121(20):2176-82.
15. van Spaendonck-Zwarts KY, Posafalvi A, van den Berg MP, Hilfiker-Kleiner D, Bollen IA, Sliwa K, et al. Titin gene mutations are common in families with both peripartum cardiomyopathy and dilated cardiomyopathy. European heart journal. 2014;35(32):2165-73.
16. Toescu V, Nuttall SL, Martin U, Kendall MJ, Dunne F. Oxidative stress and normal pregnancy. Clin Endocrinol (Oxf). 2002;57(5):609-13.
17. Corbacho AM, Martinez De La Escalera G, Clapp C. Roles of prolactin and related members of the prolactin/growth hormone/placental lactogen family in angiogenesis. J Endocrinol. 2002;173(2):219-38.
18. Hilfiker-Kleiner D, Kaminski K, Podewski E, Bonda T, Schaefer A, Sliwa K, et al. A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. Cell. 2007;128(3):589-600.
19. Hilfiker-Kleiner D, Sliwa K. Pathophysiology and epidemiology of peripartum cardiomyopathy. Nature reviews Cardiology. 2014;11(6):364-70.

20. Lkhider M, Castino R, Bouguyon E, Isidoro C, Ollivier-Bousquet M. Cathepsin D released by lactating rat mammary epithelial cells is involved in prolactin cleavage under physiological conditions. J Cell Sci. 2004;117(Pt 21):5155-64.
21. Macotela Y, Aguilar MB, Guzman-Morales J, Rivera JC, Zermeno C, Lopez-Barrera F, et al. Matrix metalloproteases from chondrocytes generate an antiangiogenic 16 kDa prolactin. J Cell Sci. 2006;119(Pt 9):1790-800.
22. Patten IS, Rana S, Shahul S, Rowe GC, Jang C, Liu L, et al. Cardiac angiogenic imbalance leads to peripartum cardiomyopathy. Nature. 2012;485(7398):333-8.
23. Habedank D, Kuhnle Y, Elgeti T, Dudenhausen JW, Haverkamp W, Dietz R. Recovery from peripartum cardiomyopathy after treatment with bromocriptine. European journal of heart failure. 2008;10(11):1149-51.
24. Sliwa K, Blauwet L, Tibazarwa K, Libhaber E, Smedema JP, Becker A, et al. Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: a proof-of-concept pilot study. Circulation. 2010;121(13):1465-73.
25. Ruch A, Duhring JL. Postpartum myocardial infarction in a patient receiving bromocriptine. Obstet Gynecol. 1989;74(3 Pt 2):448-51.
26. Haghikia A, Podewski E, Libhaber E, Labidi S, Fischer D, Roentgen P, et al. Phenotyping and outcome on contemporary management in a German cohort of patients with peripartum cardiomyopathy. Basic Res Cardiol. 2013;108(4):366.
27. Sliwa K, Hilfiker-Kleiner D, Mebazaa A, Petrie MC, Maggioni AP, Regitz-Zagrosek V, et al. EURObservational Research Programme: a worldwide registry on peripartum cardiomyopathy (PPCM) in conjunction with the Heart Failure Association of the European Society of Cardiology Working Group on PPCM. European journal of heart failure. 2014;16(5):583-91.
28. Hilfiker-Kleiner D, Haghikia A, Berliner D, Vogel-Caussen J, Schwab J. Bromocriptine for the treatment of periparttum cardiomyopathy: a multicentre randomized study. European heart journal. 2017;00:1-9.
29. Bello N, Rendon IS, Arany Z. The relationship between pre-eclampsia and peripartum cardiomyopathy: a systematic review and meta-analysis. J Am Coll Cardiol. 2013;62(18):1715-23.

30. Rana S, Powe CE, Salahuddin S, Verlohren S, Perschel FH, Levine RJ, et al. Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia. Circulation. 2012;125(7):911-9.
31. Demakis JG, Rahimtoola SH, Sutton GC, Meadows WR, Szanto PB, Tobin JR, et al. Natural course of peripartum cardiomyopathy. Circulation. 1971;44(6):1053-61.
32. Gunderson EP, Croen LA, Chiang V, Yoshida CK, Walton D, Go AS. Epidemiology of peripartum cardiomyopathy: incidence, predictors, and outcomes. Obstet Gynecol. 2011;118(3):583-91.
33. Blauwet LA, Libhaber E, Forster O, Tibazarwa K, Mebazaa A, Hilfiker-Kleiner D, et al. Predictors of outcome in 176 South African patients with peripartum cardiomyopathy. Heart. 2013;99(5):308-13.
34. Shani H, Kuperstein R, Berlin A, Arad M, Goldenberg I, Simchen MJ. Peripartum cardiomyopathy - risk factors, characteristics and long-term follow-up. J Perinat Med. 2014.
35. Hilfiker-Kleiner D, Haghikia A, Masuko D, Nonhoff J, Held D, Libhaber E, et al. Outcome of subsequent pregnancies in patients with a history of peripartum cardiomyopathy. European journal of heart failure. 2017.
36. Kao DP, Hsich E, Lindenfeld J. Characteristics, adverse events, and racial differences among delivering mothers with peripartum cardiomyopathy. JACC Heart Fail. 2013;1(5):409-16.
37. Bassett JM, Burks AH, Levine DH, Pinches RA, Visser GH. Maternal and fetal metabolic effects of prolonged ritodrine infusion. Obstet Gynecol. 1985;66(6):755-61.
38. Lampert MB, Hibbard J, Weinert L, Briller J, Lindheimer M, Lang RM. Peripartum heart failure associated with prolonged tocolytic therapy. Am J Obstet Gynecol. 1993;168(2):493-5.
39. Ingemarsson I, Arulkumaran S, Kottegoda SR. Complications of beta-mimetic therapy in preterm labour. Aust N Z J Obstet Gynaecol. 1985;25(3):182-9.
40. Fett JD. Earlier detection can help avoid many serious complications of peripartum cardiomyopathy. Future Cardiol. 2013;9(6):809-16.
41. Cenac A, Simonoff M, Moretto P, Djibo A. A low plasma selenium is a risk factor for peripartum cardiomyopathy. A comparative study in Sahelian Africa. Int J Cardiol. 1992;36(1):57-9.

42. Karaye KM, Yahaya IA, Lindmark K, Henein MY. Serum selenium and ceruloplasmin in nigerians with peripartum cardiomyopathy. International journal of molecular sciences. 2015;16(4):7644-54.

43. ponikowski P, voors AA, Anker SD. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: Task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology(ESC). British heart journal. 2016.

44. Sliwa K, Tibazarwa K, Hilfiker-Kleiner D. Management of peripartum cardiomyopathy. Curr Heart Fail Rep. 2008;5(4):238-44.

45. Pyatt JR, Dubey G. Peripartum cardiomyopathy: current understanding, comprehensive management review and new developments. Postgrad Med J. 2011;87(1023):34-9.

46. Williams J, Mozurkewich E, Chilimigras J, Van De Ven C. Critical care in obstetrics: pregnancy-specific conditions. Best Pract Res Clin Obstet Gynaecol. 2008;22(5):825-46.

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

48. Bauersachs J, Arrigo M, Hilfiker-Kleiner D, Veltmann C, Coats AJ, Crespo-Leiro MG, et al. Current management of patients with severe acute peripartum cardiomyopathy: practical guidance from the Heart Failure Association of the European Society of Cardiology Study Group on peripartum cardiomyopathy. European journal of heart failure. 2016;18(9):1096-105.

49. Hilfiker-Kleiner D, Westhoff-Bleck M, Gunter HH, von Kaisenberg CS, Bohnhorst B, Hoeltje M, et al. A management algorithm for acute heart failure in pregnancy. The Hannover experience. European heart journal. 2015;36(13):769-70.

50. Haghikia A, Tongers J, Berliner D, Konig T, Hilfiker-Kleiner D. Early Ivabradine treatment in patients with acute peripartum cardiomyopathy: subanalysis of the German PPCM registry. International journal of Cardiology. 2016;2016(216):165- 7.

51. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Revista espanola de cardiologia. 2016;69(12):1167.

52. Elkayam U. Risk of subsequent pregnancy in women with a history of peripartum cardiomyopathy. J Am Coll Cardiol. 2014;64(15):1629-36.
53. Biteker M, Libhaber E, Biteker G, Duman D. Delayed recovery in peripartum cardiomyopathy: an indication for long-term follow-up and sustained therapy. European Journal in heart failure. 2012;14:895-901.
54. pilarisetti J, kondur A, Alani A, Reddy M, Reddy M. peripartum cardiomyopathy predictors of recovery and current state of implantable cardioverter- defibrillator use. J Am Call Cardiology. 2014(63):2831-9.
55. Mouquet F, Mostefa KM, Lamblin N, Coulon C. unexpected and rapid recovery of the left ventricular function in patients with peripartum cardiomyopathy: impact of cardiac resynchronisation therapy. European journal of heart failure. 2012;14(2012):526-9.
56. Elkayam U, Tummala PP, Rao K, Akhter MW, Karaalp IS, Wani OR, et al. Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. N Engl J Med. 2001;344(21):1567-71.
57. Avila WS, de Carvalho ME, Tschaen CK, Rossi EG, Grinberg M, Mady C, et al. Pregnancy and peripartum cardiomyopathy. A comparative and prospective study. Arq Bras Cardiol. 2002; 79(5):484-93.
58. Sliwa K, Forster O, Zhanje F, Candy G, Kachope J, Essop R. Outcome of subsequent pregnancy in patients with documented peripartum cardiomyopathy. Am J Cardiol. 2004; 93(11):1441-3, a10.
59. Chapa JB, Heiberger HB, Weinert L, Decara J, Lang RM, Hibbard JU. Prognostic value of echocardiography in peripartum cardiomyopathy. Obstet Gynecol. 2005; 105(6):1303-8.
60. Fett JD, Christie LG, Murphy JG. Brief communication: Outcomes of subsequent pregnancy after peripartum cardiomyopathy: a case series from Haiti. Ann Intern Med. 2006; 145(1):30-4.
61. Habli M, O'Brien T, Nowack E, Khoury S, Barton JR, Sibai B. Peripartum cardiomyopathy: prognostic factors for long-term maternal outcome. Am J Obstet Gynecol. 2008; 199(4):415.e1-5.

62. Modi KA, Illum S, Jariatul K, Caldito G, Reddy PC. Poor outcome of indigent patients with peripartum cardiomyopathy in the United States. Am J Oster Gynecol. 2009; 201(2):171.e1-5.

63. Fett JD, Fristoe KL, Welsh SN. Risk of heart failure relapse in subsequent pregnancy among peripartum cardiomyopathy mothers. Int J Gynaecol Obstet. 2010;109(1):34-6.

64. Mandal D, Mandal S, Mukherjee D, Biswas SC, Maiti TK, Chattopadhaya N, et al. Pregnancy and subsequent pregnancy outcomes in peripartum cardiomyopathy. J Obstet Gynaecol Res. 2011; 37(3):222-7.