Peripartum cardiomyopathy: A review of literature on clinical status and meta-analysis of diagnosis and clinical management

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Abstract
Despite most pregnant women safely tolerating heart diseases, they remain a leading cause of non-obstetric maternal mortality. Peripartum cardiomyopathy (PPCM) is a serious heart muscle disease caused or aggravated by pregnancy. It imposes significant risks for the development of pregnancy-associated heart failure with an elevated risk of fetomaternal morbidity and mortality. Its incidence has significance geographic variations with considerably higher rates in developing countries. With increased efforts to improve fetomaternal health in disadvantaged populations, there is need to improve the understanding of PPCM including its risk factors, diagnosis and clinical management. This review accumulates current evidence on research and clinical status as well as conducts a meta-analysis of diagnosis and clinical management to advance understanding.

Introduction
Cardiac diseases are present in 1-4% of pregnancies and are a leading cause of non-obstetric maternal mortality [1]. Early diagnosis and appropriate management enable majorities of women to tolerate most cardiac diseases and safely come to term. However, some cardiac conditions such as peripartum cardiomyopathy (PPCM) are high-risk and an important cause of fetomaternal mortality [2,3]. Despite the high risk, a complete understanding of risk factors, etiopathogenesis and diagnosis of PPCM remains tenuous. This paper reviews published studies on PPCM with an emphasis on clinical definition, epidemiology, risk factors, clinical presentation, prognosis, etiopathogenesis, differential diagnosis and clinical management. The aim is to advance clinical knowledge and understanding of PPCM to improve diagnostic and therapeutic management.

Description
Historical context
The seminal reference to PPCM in medical literature, described as idiopathic myocardial failure with onset of symptoms in early puerperium, was in 1849 by Ritchie in the article, "Clinical contributions to the pathology, diagnosis, and treatment of certain chronic diseases of the heart" [4]. Later in 1880, Virchow and Porak also described an association between heart failure and early puerperium in the absence of determinable cardiac disease [5]. However, formal recognition of PPCM as a distinct clinical entity was in 1937, when Gouley, et al. [6], and Hull and Hafkesbring [7] described an idiopathic origin of postpartal toxic heart disease in previously healthy women.

In 1971, Demakis and Rahimtoola [8] proposed the terminology peripartum cardiomyopathy in place of postpartum cardiomyopathy, which excluded patients with onset of symptoms antepartum. The duo also proposed three diagnostic criteria for PPCM: (i) has onset of acute heart failure in the last month of pregnancy or within five months postpartum; (ii) has an idiopathic origin; and (iii) develops in the absence of any determinable heart disease [8,9]. Later in 1999, Hibbard, Lindheimer and Lang [10] proposed an additional diagnostic criterion based on echocardiographically defined left ventricular (LV) systolic dysfunction as LV ejection fraction (LVEF) of < 45% and LV enlargement. More recently, Elkayam, et al. [11] described 23 cases of idiopathic dilated cardiomyopathy (DCM) with onset of symptoms earlier than the last gestational month but indistinguishable from classic PPCM (occurring in the last month of pregnancy or early puerperium).

Clinical definition
PPCM has had several clinical definitions. Although all the definition agrees that PPCM occur a few weeks prior to and after pregnancy, they differ in the description of the actual condition. It is a rare form of cardiomyopathy presenting with LV systolic dysfunction and idiopathic heart failure (HF) [12]; acute heart failure in the absence of heart diseases prior to the last month of pregnancy [13]; and idiopathic cardiomyopathy manifesting with HF secondary to LV systolic dysfunction [14] (Table 1).

Despite the definitional variations across regional and national health organizations, there is a unanimous consensus that PPCM is a clinical entity (heart muscle failure) distinct from pre-existing forms of cardiomyopathies, facilitated or aggravated by pregnancy-induced stress and diagnosed primarily through the exclusion of other cardiac diseases [12-14]. Taking together the definitions,
PPCM may be described as an idioicpic myocardial condition with onset of acute heart failure in the third trimester of pregnancy or five months postpartum with echocardiography demonstrated LV systolic dysfunction (LVEF < 45% and enlarged LV).

### Epidemiology

The exact incidence of PPCM remains poorly defined chiefly due to the lack of population-based estimates and universal diagnostic criteria. The existing small-scale population-based studies may also suffer from dependence on the experience of the institution, referral bias or individual practice patterns that could potentially underreport incidence rate but otherwise provide important estimates of incidence of PPCM [3,13]. The reported incidence rates have large temporal and geographic variations ranging between 1 in 1,485 [15] and 1 in 15,000 [16]. The rates are higher in developing countries such as Nigeria 1 in 100 [17] and Haiti 1 in 300 [18] compared to more developed countries such as South Africa at 1 in 1,000 [19] and the U.S. at 1 in 3-4,000 [20]. In support, several studies on incidence of PPCM since 1985 with a sample of more than 25 patients, using either or both clinical tests and echocardiography-defined LV systolic dysfunction as diagnostic criteria indicate incidence of PPCM ranges between 300 and 4,025 per 10,000 persons [18,21-27] (Table 2).

### Risk factors

Several risk factors have been associated with the development of PPCM but many have not been evaluated in epidemiology studies and their contribution to the development of PPCM remains inconclusive [21,28]. Risk factors can be classified as probable, proposed or emerging (Figure 1).

#### Probable/Independent

Probable risk factors for the development of PPCM include extreme maternal age greater than 30 years, multiparous women, multiple gestations, presence of pre-eclampsia or prolonged tocolytic therapy [11,13,29]. In a systematic review and meta-analysis of 22 studies (N=979), Bello, et al. [30] find the prevalence of both pre-eclampsia and multiparity in PPCM women is significantly higher than that found in the general population strongly suggesting shared pathogenesis. The study also finds hypertension and multiple gestations are strong risk factors for developing PPCM. In a case-series epidemiology study in Northern California delivery hospitals, Gunderson, et al. [27] supports that maternal age greater than 25 years, multiparity, multiple gestation and hypertensive disorders are independent risk factors for the development of PPCM. However, in a recent U.S study, Elkayam, et al. [11] showed statistically insignificant association between multiparity and the development of PPCM where 40% of PPCM incidence occurred in the first pregnancy and greater than 50% in the second pregnancy.

#### Proposed/Emerging

Proposed risk factors for PPCM include smoking, hypertension, malnutrition, ethnicity (mainly African descent), cocaine abuse and socio-economic status. They are proposed because they require additional studies to determine whether they have an independent effect or derive their effect from interaction between race, hypertension and low socio-economic status. Genetics and obesity are emerging risk factors whose contribution to the development of PPCM is still under investigation [28]. In a study of 115 German cohort of PPCM women, Haghikia, et al. [31] found a positive family history of cardiomyopathy in 16.5% but did not suggest it has an independent effect on the development of PPCM. Additional systematic studies on genetic basis of PPCM would provide important insight into the role of genetics in the development of PPCM. In another case-controlled study in Georgia, U.S., Gentry, et al. [32] found African-American women are 15.7 more likely to develop PPCM compared to non-African American, which could not be explained by other factors. However, Elkayam, et al. [11] showed a weak association between race (African American) and the development of PPCM. Additional large-scale studies or meta-analysis studies are warranted to determine whether the presence of genetic or environmental factors in African women could underlie or explain the higher risk. Clearly identifying risk factors for the development of PPCM has important clinical implications in developing recommendations for screening high-risk population [33].

### Clinical presentation

#### Onset of symptoms

The onset of clinical symptoms in PPCM patients varies significantly but a majority (78%) develop symptoms in the first four
Table 2. Summary of Studies on Incidence of PPCM.

| First Author [Ref #] | Study Period       | Country  | Type   | Design | Incidence | Mean Age |
|----------------------|--------------------|----------|--------|--------|-----------|----------|
| Mielniczuk, et al. [22] | 1990-2002          | U.S.     | PB     | R      | 1:3,189   | 30       |
| Brar, et al. [23]     | 1996-2005          | U.S.     | PB     | R      | 1:4,025   | 33       |
| Fett, et al. [18]     | 2000-2005          | Haiti    | CS     | P      | 1:300     | 32       |
| Chapa, et al. [24]    | 1988-2001          | U.S.     | CS     | P      | 1:1,149   | 27       |
| Desai, et al. [25]    | 1986-1989          | S. Africa| CS    | P      | 1:1,000   | 29       |
| Witlin, et al. [26]   | 1986-1994          | U.S.     | CS     | R      | 1:2,406   | --       |
| Gunderson, et al. [27] | 1995-2004          | U.S.     | CS     | R      | 1:2,066   | --       |

PB: Population-based study; CS: Case Series single center study; R: Retrospective study; P: Prospective study

Figure 2. Differential Diagnostic Workup of PPCM [28].

Diagnostic work-up of PPCM begins with examining patient history to find the onset of HF symptoms, then a confirmation of systolic HF using clinical examination and LV dysfunction using echocardiography imaging. Additional tests such as chest X-ray excludes other etiologies of HF symptoms including severe anemia, thyroid or liver disease; laboratory tests in select cases to exclude other etiologies; and ECG to exclude other etiologies such as CAD or thrombosis. Alternative diagnosis such as cardiac MRI are useful when echocardiography is non-conclusive and RV biopsy for patients with ventricular tachycardia or refractory to treatment.

Signs and symptoms

The initial signs and symptoms of PPCM mimic those of normal physiology in pregnancy such as pedal edema, dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, and persistent cough [14] (Table 3).

These symptoms are also indistinguishable to those of heart failure in the setting of idiopathic dilated cardiomyopathy [21]. The similarity of symptoms could delay or even miss the diagnosis of PPCM potentially leading to the development of preventable major adverse cardiac events requiring cardiac transplantation or in rare cases culminating in cardiac death. PPCM patients also frequently present with cough, chest pain and abdominal pain, which complicates initial clinical assessment [28].

Prognosis

Recovery (or normalization) of LV function is defined as LVEF ≥ 50% or an improvement > 20% [3]. Unlike other forms of non-ischemic cardiomyopathies, a majority of PPCM patients have a spontaneous recovery of LV function [34]. Several studies have reported 23% to 54% of PPCM patients recover between three and six months postpartum and over 70% by 12 months postpartum [11,18,34-36]. About 10% take up to 48 months to recover while fewer (with treatment) have months postpartum, 9% in the last gestational month and 13% either one month prior to delivery or more than four months after delivery [15]. In a few countries such as South Africa, some patients have the onset of PPCM symptoms later than five months after delivery but have not been included in any study because they do not fall within the accepted clinical definition of PPCM [14].
a good LV function in the range 30-49% and 2% may require heart transplantation [37]. Even after full recovery, PPCM patients have a high risk of recurrence in subsequent pregnancies with a marked decline of LVEF [38]. In a U.S. study of 44 PPCM patients with subsequent pregnancies, LVEF dysfunction was more severe in those with partial recovery (44%) compared to those with complete recovery (21%) [39]. More patients with a baseline LVEF < 55% have PPCM recurrence in subsequent pregnancies than those with LVEF ≥ 55% (17%) [40]. Whereas exercise stress echocardiography can uncover subtle residual LV dysfunction that subsequent pregnancy can exacerbate [40], current guidelines recommend against future pregnancies [14].

Predictors of LV recovery

Echocardiographically defined LV functional properties are the most frequently researched predictors of recovery in PPCM patients. Baseline LV ejection fraction (LVEF) > 30% has been shown to predict favorable prognosis [11]. In a study of South African women diagnosed with PPCM, multiple regression analysis reveals after adjustment of New York Heart Association (NYHA) functional class, ethnicity (African American), LVEF and LV end-diastolic dimension (LVEDD), smaller LV end-systolic dimension (LVESD) (Odds Ratio: OR 1.08, 95% CI 1.01-1.17) and older age (OR 0.92, 95% CI 0.86-0.98) are independent predictors of favorable prognosis [41]. Patients with baseline LVEF ≥ 30% are five times more likely to completely recover LV function compared to those with LVEF < 30% [42]. Other studies reveal LVEDD [26,43], higher LVEF [35,44], higher fractional shortening [42] and the absence of thrombus [26] may predict better LV recovery. On the other hand, high troponin levels and LVEDD > 5.6 cm, late diagnosis > one week, high NYHA functional class, African American, multiparity and co-existing illnesses predict poor LV recovery [11,32,42,45]. Patient with low-level recovery often require heart transplantation [40].

Predictors of mortality

Race, especially African women, have been suggested to be an independent predictor of mortality. Blauwet, et al. [41] find 13% mortality rate among African women diagnosed with PPCM. In two other studies [35,36], univariate analysis reveals the main predictors of PPCM-related mortality were the extent of LV enlargement and higher NYHA functional class at baseline. Other emerging predictors of mortality were younger age at diagnosis and lower body mass index (BMI). However, the low number of deaths was insufficient to conduct multiple regression and thus studies recruiting a large sample are warranted to validate whether race, LV enlargement, NYHA functional class, young age and lower BMI are predictors of mortality in PPCM patients [41].

Etiopathogenesis

The exact etiopathogenesis of PPCM remains incompletely understood but several hypotheses have been advanced to explain etiologic or pathologic processes underlying PPCM. These include stress-activated cytokines, unbalanced oxidative stress, myocardial inflammation, pathological maternal autoimmune response, genetics factors and pathological response to pregnancy-associated hemodynamic stress.

Stress activated cytokines

Sliwa, et al. [46] discovered high concentration of serum markers of inflammation including cytokines such as tumor necrosis factor alpha (TNFα), interferon gamma, interleukin-6 (IL-6), C-reactive protein (CRP) and apoptosis antigen 1 to suggest inflammatory processes underlie pathophysiological development of PPCM [47]. However, it is not known whether the high concentration of cytokines is reactive or causative [28].

Unbalanced oxidative stress

Pregnancy normally induces pathophysiologic changes characterized with increases in maternal antioxidant defense mechanism [47]. However, PPCM patients have higher levels of oxidative stress evident in elevated (unbalanced) concentration of oxidized low-density lipoprotein [48]. Unbalanced oxidative stress mediates the cleavage of prolactin hormone into 16kDa increasing its antiangiogenic and pro-apoptotic properties that destroys cardiovascular tissues [48]. This finding forms the basis of the suggestion that blocking the splitting of prolactin hormone may confer a therapeutic value for PPCM [21].

Myocardial inflammation

Reports of a majority of PPCM patients having viral or antigen-induced myocardial inflammation contributed to the hypothesis that it may contribute to pathophysiological mechanisms of PPCM. However, the link between PPCM and myocardial inflammation has remained inconclusive [3]. The incidence of myocarditis in PPCM patients ranges between 29% and 100% [49]. The explanation for the wide variation remains unknown but Rizq, et al. [50] theorizes that the cause could be endomyocardial biopsy only detects myocarditis when performed at or closer to the onset of PPCM, performed at the wrong site or misdiagnosis of another form of heart failure.

Pathological autoimmune response

Maternal immune system usually destroys fetal microchimeric cells escaping into the maternal circulation system [51]. However, due to a weakened maternal immune system during pregnancy, some of the fetal microchimeric cells may evade destruction and accumulate in the maternal heart. During puerperium, the maternal immune system normalizes and triggers a pathological immune response to fetal microchimeric cells deposited on the heart [52]. Ansari, et al. [51] report high concentration of antibodies directed at cardiac myosin heavy chains in the serum of PPCM patients but absent in idiopathic DCM patients or in healthy individuals [51]. However, a causal relationship between the high concentration of antibodies and PPCM has not been established [3].

Genetic factors

Few data, largely case studies, have been published to evaluate genetic basis of PPCM. High incidences in certain geographical regions supports the hypothesis that genetic predisposition may have
an important role in the pathophysiology of PPCM [29]. Further, accumulating research evidence indicate a subset of PPCM patients have mothers or sisters also with PPCM [53-57] or have genetic mutations – MYBPC3, MYH6, MYH7, SCN5A, TNNC1 and TNNT2 – associated with dilated cardiomyopathy, suggesting overlapping clinical spectrum of the two cardiomyopathy phenotypes [57-59]. However, additional randomized controlled trials are warranted to establish the genetic basis of PPCM, which will pave way for genetic screening of PPCM patients.

**Pathological response to hemodynamic stress**

Hemodynamic changes during pregnancy leads to an exaggerated decrease in LV systolic function. Plasma volumes go up by 50% and the mass of red cells increases by 20%, decreased blood pressure and increased heart rate, decreased pulmonary/systemic resistances and increased cardiac output [60]. These hemodynamic changes peak during the second and third trimester of pregnancy and fully resolves around three months postpartum [28]. Echocardiography findings in normal pregnancy reveal LVED volume increases by 10% resulting into transient LV wall thickening and reversible LV systolic dysfunction from the second and third trimester and early puerperium [28].

**Diagnosis**

**Diagnosis pathway**

The American Heart Association (AHA) statement on current diagnostic and treatment strategies for specific dilated cardiomyopathies recommend confirmatory diagnosis of PPCM should involve several methods including full patient history, physical examination and diagnostic testing to exclude previous history of cardiac disease and other cardiomyopathies. The initial clue for PPCM diagnosis is patient history confirming the onset of HF began in the last months of pregnancy or months after pregnancy, and cardiac evaluation should confirm LV dysfunction. The usual laboratory assessment for cardiomyopathies such as chest radiograph, ECG and assessment for cardiac biomarkers [12].

Diagnosis pathway for PPCM begins with patient history to identify symptoms of heart failure in the third trimester or the first few weeks postpartum. Initial clinical examination usually excludes hypertension then considers echocardiographic tests for LV dysfunction defined by LVEF ≤ 45% [12]. Additional tests including chest x-ray, electrocardiography and lab tests could assist to confirm PPCM diagnosis. Other tests such as cardiac MRI are useful when echo findings are non-diagnostic while biopsy are useful for patients with ventricular tachycardia or high-grade heart failure, or patient’s refractory to optimal medical therapy [28] (Figure 2).

If initial tests (clinical examination and echocardiography) do not provide a confirmatory diagnosis of abnormalities in cardiac functions, differential diagnosis should be considered to exclude other cardiac and non-cardiac conditions that share similar symptoms with PPCM. Frequently encountered heart etiologies for differential diagnosis should be considered to exclude other cardiac and non-cardiac conditions mimicking PPCM, the relevant clinical tests and results to underpin the need for differential diagnosis.

**Differential diagnosis**

**Biomarkers for diagnosis**

PPCM symptoms may overlap with those of heart failure and of normal pregnancy to delay a definitive differential diagnosis. These symptoms include exertional shortness of breath, nocturnal dyspnea, palpitations, fatigue, cough and pedal edema. In addition, specialists other than cardiologists usually see PPCM patients, which further complicates diagnosis [61,62]. Despite these complications, biomarkers provide important information that raise the suspicion of PPCM and inform referrals to expert physicians for additional diagnostic evaluation. Table 5 provides a summary of the major biomarkers screened of PPCM patients and their relevance in the diagnosis of PPCM.

**Electrocardiogram**

Electrocardiogram (ECG) should be performed when symptoms of heart failure are present or suspected to identify and rule out pulmonary embolism or acute ischemic event [3]. Although pathognomonic ECG patterns have not been identified for PPCM patients, wide ranges of ECG abnormalities are common in PPCM patients [63]. The most frequently encountered ECG abnormalities are LV hypertrophy and

### Table 4. Differential Diagnosis of PPCM [14].

| Condition | Diagnostic Tests | Findings |
|-----------|------------------|----------|
| Pre-existing idiopathic DCM unmasked by pregnancy | History, electrocardiography, BNP and echocardiography. | PPCM presents postpartum while DCM in the second trimester. |
| Pre-existing familial DCM unmasked by pregnancy | Patient history, family screening, electrocardiography, echocardiography and genetic testing. | PPCM presents postpartum while familial DCM in the second trimester. |
| Cardiomyopathy due to HIV/AIDS | HIV test | HIV cardiomyopathy presents with non-dilated ventricles. |
| Pre-existing valvular heart disease unmasked by pregnancy | Patient history, physical examination, ECG and Echo. | PPCM presents postpartum while valvular disease in the second trimester. |
| Hypertensive heart disease | -- | Exclude hypertension presenting before delivery. |
| Pre-existing idiopathic congenital heart disease | Patient history, ECG and Echo. | PPCM presents postpartum while congenital heart disease in the second trimester. |
| Pregnancy-associated myocardial infarction | History, ECG, BNP, coronary angiography and Echo | Patient history |
| Pulmonary embolus | History, ECG, echo, perfusion scan, CT and pulmonary angiography. | Patient history |

### Table 5. Biomarkers Raising Suspicion of PPCM [62].

| Biomarker | Relevance for PPCM |
|-----------|--------------------|
| NT-proBNP | Commercial marker for screening of PPCM but non-specific – also elevated in preeclampsia, pulmonary embolism and heart failure. |
| 16-kDa Prolactin | Pathophysiological factor for PPCM but diagnostic accuracy requires confirmation |
| Interferon Alpha | Elevated plasma levels in PPCM patients but diagnostic accuracy requires further evaluation |
| Asymmetric Dimethylarginine | Marker for endothelial dysfunction and cardiac risk. |
| Cathepsin D | Elevated activity in plasma of PPCM patients |
| Soluble fms-like tyrosine kinase-1 | Elevated activity in plasma of PPCM patients |
| MicroRNA-146a | Pathophysiological factor for PPCM but diagnostic accuracy requires further evaluation |
ST-T wave abnormalities [8]. A small subset of PPCM patients may also have intraventricular conductance abnormalities such as left bundle branch block (LBBB). Other cardiac complications such as atrial fibrillation, atrial flutter, prolonged PR, and QRS intervals may be detected in some PPCM patients [3].

Cardiac protein assays

The use of cardiac protein assays in the diagnosis of PPCM requires further clinical evaluation. However, it shows promising results for determining diagnosis and prognosis of PCM [3]. B-type Natriuretic peptide (BNP) tests for systolic dysfunction. In PPCM patients, systolic dysfunction causes an elevated LV-end diastolic pressure leading to increased plasma levels of BNP or N-terminal pro-BNP (NT-proBNP) [64]. In analysis of 38 PPCM patients, Sliwa, et al. [14] find all had elevated NT-proBNP (mean = 1727.2 fmol/mL) compared to 21 healthy women (mean = 339.5 fmol/mL).

Echocardiography

Whereas diagnosis of PPCM is by exclusion, echocardiography is the current gold standard for diagnostic confirmation and prognostication of PPCM. The modality assesses and monitors regional and global ventricular function based on onset of HF, no pre-existing heart condition, idiopathic and echocardiography findings (LVEDD > 2.7 cm/m³, LVEF < 45% and M-mode fractional shortening < 30%) (Table 6).

Echocardiography tests should be performed in all suspected cases of PPCM. It obviates the need for invasive procedures such as cardiac catheterization and endomyocardial biopsy [3] but in some rare cases, invasive procedures may be required to obtain additional information about ischemic causes of heart failure [62,65]. The Heart Failure Association of the European Society of Cardiology Working Group on periartum cardiomyopathy recommends repeat echocardiography at 6 weeks and 6 months to obtain prognostic information.

Chest X-Ray

Chest x-ray visualizes cardiomegaly in the setting of LV enlargement and/or pericardial effusion. Chest x-ray may be useful to assess and exclude other etiologies for heart failure symptoms such as pneumonia and pneumothorax [28].

Cardiac MRI

Cardiac Magnetic Resonance Imaging (MRI) is usually indicated for women having symptoms of heart failure to determine diagnosis, and in the case of PPCM, to provide prognostic information [14]. Cardiac MRI provides more detailed information than echocardiography about myocardial morphology and RV function [66]. Cardiac MRI T2-weighted spin echo sequence helps in the precise diagnosis of myocardial inflammation, cell necrosis, the presence of LV thrombus and provides accurate quantification of ventricular volumes [62]. Cardiac MRI also assists in the identification of sites for endomyocardial biopsy. However, the European Society of Radiology contraindicates contrast-enhanced cardiac MRI during prepartum because it crosses the placenta and may harm the developing fetus [3].

Meta-analysis of diagnostic/Prognostic methods

Search Strategy

Studies investigating diagnosis and prognosis of PPCM were searched from three electronic databases (PubMed, Embase, and Cochrane) and Google Scholar. Broad search terms, "periartum cardiomyopathy” OR “pregnancy associated cardiomyopathy” AND “diagnosis” OR “prognosis” were used to ensure all relevant studies were identified. Studies were included if they were (a) prospective or retrospective; (b) relied on echocardiography-defined LV dysfunction for diagnosis; (c) had a follow-up period of at least 6 months; and (d) had at least one outcome assessing predictors of prognosis (recovery of LV function), mortality, heart transplantation and predictors of mortality. Studies were excluded if (a) only abstract was available (difficult to extract data); (b) were conference papers (they are not final since they may be subjected to revision) and (c) were case series (studies one or a few cases of PPCM and thus insufficient for statistical analysis).

Additional studies were included from a review of bibliographies of included studies. Each study included in the meta-analysis was read and data extracted on a Microsoft Excel Worksheet. The extracted data was name of first author, study period, number of patients, diagnosis criteria used, LV recovery (%), predictors of LV recovery, mortality rate, heart transplantation rate and predictors of mortality (Table 7). [67-74].

Study characteristics

Seventeen (17) studies investigating diagnosis and prognosis of PPCM meeting the inclusion criteria were included in the present meta-analysis [18,23,24,25,32,35,36,42-44,75-81]. In total the recruited patient population in the 17 studies was (N=1,329). The patients were followed for a period of six months or above. One of the common diagnostic criterion in 16 studies was echocardiography-defined LVEF while one study [24] used echocardiography-defined fractional shortening (FS) and LV end diastolic dimension (LVEDD). The main prognostic information assessed were predictors of LV recovery in 10 studies [18,24,32,35,36,42-44,76,79], mortality in 13 studies [18,23,25,35,36,43,44,75-79,81], heart transplantation in five studies [24,35,43,76,81] and predictors of mortality in two studies [36,76].

Study outcomes

Diagnosis of the 1,329 PPCM patients was through exclusion of other cardiac and non-cardiac condition but confirmation was through echocardiography-defined LV dysfunction, considered the gold standard of PPCM diagnosis. Whereas LVEF < 45% is considered one of the criterion for PPCM diagnosis, three studies used different LVEF criteria of < 30% [74], < 40% [36] and < 50% [23] suggesting the lack of a universal LVEF criteria. Only one study [24] used fractional shortening and LV end diastolic dimension for PPCM diagnosis. Echocardiography assessed LV dysfunction provided valuable prognostic information for PPCM status and clinical outcomes. Slightly less than half (40%) of the 1,320 patients recovered LV function (defined as LVEF > 50%) within the first six months postpartum. The major predictors of LV recovery were baseline LVEF ≥ 30% indicated by 52% of the studies, baseline LVEDD ≥ 5.5 cm indicated by 24% of the studies, fractional shortening ≥ 20% indicated by 12%
of the studies, and non-African American ancestry indicated by 12% of the studies. Other predictors were no LV thrombus, younger age, gestational hypertension, postpartum diagnosis indicated by 6% (1) of the reviewed studies. Mortality rate was low (7.7%) predicted by Fas/Apo-1 plasma levels and NYHA functional class [36], and age > 30yrs, LVEF ≤ 25% and delayed diagnosis ≥ 1wk [76].

Discussion

According to AHA practice guidelines, the cornerstone of the diagnosis of PPCM is the onset of symptomatic HF a few months pre-partum or post-partum complemented with clinical evidence of LV systolic dysfunction [12]. Similarly, the present meta-analysis reveals that, following the initial clinical suspicion of PPCM based on the onset of HF symptoms, echocardiography is the most preferred imaging modality for identifying and characterizing LV dysfunction. However, the accuracy of echocardiography-based diagnosis is limited by the lack of a standardized definition of LV dysfunction. The greater majority of the studies (84%) defined LV dysfunction as LVEF < 45% while the remaining two studies used LVEF < 30% [75] and LVEF < 50% [23]. The variation in the definition of LVEF arises due the lack of published standardized LV parameters to define LV dysfunction in PPCM patients. The lack of standardization has implications on the accuracy of diagnosis and on the determination of the precise prevalence of PPCM in expectant or post-partum mothers [13]. In addition to LVEF, one study demonstrated that LV dysfunction in PPCM patients could be quantified using LV fractional shortening and/or LV end-diastolic dimension (LVEDD). However, additional studies are warranted to provide demonstrable evidence of the value of LV fractional shortening and LVEDD in quantifying LV dysfunction in PPCM women.

In addition to diagnosis, echocardiography imaging provides valuable prognostic information on PPCM. Generally, PPCM has a favorable prognosis with slightly over half of the patients having a spontaneous recovering of LV function six months post-partum [34-36]. Consistent with these previous studies, the present findings reveal 40% of the patients recovered their LV function six months after giving birth. The main predictors of LV recovery were LVEF ≥ 30%, LVEDD ≥ 5.6 cm; LV fractional shortening ≥ 20% at presentation (baseline). In addition to LV recovery, a lower mortality rate (7.7%) indicated a favorable prognosis. However, delayed diagnosis, Fas/Apo-1 plasma levels, NYHA functional class and baseline LVEF ≤ 25% indicated a higher risk for mortality. Consistent with previous studies [11,43] LV functional parameters defined using echocardiography imaging modality is an accurate predictor of PPCM prognosis. Higher LVEF > 30%, LV fractional shortening, LVEDD and LVESD have a statistically significant correlation with subsequent improvement in LV function [42,43]. Although in general PPCM has a low mortality rate, patients African ancestry, very low LVEF < 30%, and higher NYHA functional class suggests a greater risk of death [35,36,41].

In summary, the diagnosis of PPCM is HF symptoms, which appear in the last month of pregnancy or within five months postpartum in the setting of clinically significant LV dysfunction. Cardiac imaging

Table 7. Major Studies on Diagnosis and Prognosis of PPCM at 6 Months Follow-up.

| 1st Author [Ref. #] | Study Period | No. of Patients | Diagnosis Criteria | LV Recovery (LVEF > 50%) (%) | Predictors of LV Recovery | Mortality (%) | Heart Transplantation (%) | Predictors of Mortality |
|---------------------|--------------|-----------------|--------------------|-------------------------------|--------------------------|--------------|--------------------------|-------------------------|
| Fett, et al. [18]   | 2000-2005    | 92              | LVEF < 45%         | 32                            | LVEF ≥ 30%; FS ≥ 20%     | 15.3         | --                       | --                      |
| Brar, et al. [23]   | 1996-2005    | 60              | LVEF < 50%         | --                            | --                       | 3.3          | --                       | --                      |
| Chapa, et al. [24]  | 1988-2001    | 32              | FS < 30%; LVEDD ≥ 4.8 cm | 41                            | LVEDD ≥ 6cm; FS ≥ 20%    | 9.6          | 6.5                      | --                      |
| Desai, et al. [25]  | 1986-1999    | 99              | LVEF < 45%         |                              |                          |              | --                       | --                      |
| Gentry, et al. [32] | 2003-2008    | 28              | LVEF < 45%         | 28                            | Non-African American      |              | --                       | --                      |
| Duran, et al. [35]  | 1995-2007    | 33              | LVEF < 45%         | 24                            | LVEF ≥ 27%; LVEDD ≥ 5.5 cm | 10.0         | 6                        | --                      |
| Sliva, et al. [36]  | 2003-2005    | 100             | LVEF < 40%         | 23                            | LVEF ≥ 30%, LVEDD         | 15.0         | --                       | Fas/Apo-1; NYHA FC      |
| Goland, et al. [42] | 1994-2004    | 187             | LVEF < 45%         | 61                            | LVEF ≥ 30%                | --           | --                       | --                      |
| Amos, et al. [43]   | 1990-2003    | 55              | LVEF < 45%         | 45                            | LVEDD > 5.6 cm; LVEF ≥ 30% No LV thrombus | 0.0          | 10                       | --                      |
| Modi, et al. [44]   | 1992-2003    | 44              | LVEF < 45%         | 35                            | LVEF ≥ 30%                | 15.9         | --                       | --                      |
| Sliva, et al. [75]  | 2005-2006    | 80              | LVEF < 30%         | --                            | LVEF ≥ 30%                | 10.0         | --                       | --                      |
| Goland, et al. [76] | 2009-2011    | 182             | LVEF < 45%         | 49                            | LVEF ≥ 25%                | 7.1          | 4.9                      | Age > 30yrs; LVEF ≥ 25% Delayed diagnosis ≥ 1wk |
| Felker, et al. [77] | 1982-1977    | 51              | LVEF < 45%         | --                            | --                       | 7.0          | --                       | --                      |
| Mielniczuk, et al. [78] | 1990-2002    | 171             | --                 | --                            | Younger age, non- African American | 1.4          | --                       | --                      |
| Hanan, et al. [79]  | 2003-2007    | 32              | LVEF < 45%         | 63                            | --                       | 9.3          | --                       | --                      |
| Safirstein, et al. [80] | 2005-2007    | 55              | LVEF < 45%         | --                            | LVEF ≥ 35%; gHTN, breastfeeding; postpartum diagnosis | --           | --                       | --                      |
| Witlin, et al. [81] | 1986-1994    | 28              | LVEF < 45%         | --                            | --                       | 18.0         | 11                       | --                      |
| Total/ Mean         |              | 1329            | 40                 | 9.7                           | 7.7                      |              | --                       | --                      |

**LVEDD**: Left Ventricular End Diastolic Dimension; **FS**: Fractional Shortening; **gHTN**: Gestational Hypertension
by echocardiography is able to characterize LV dysfunction but confirmatory diagnosis is usually obtained by additional tests including chest X-ray, ECG and laboratory examination to exclude other potential etiologies such as severe anemia, thyroid disease, liver disease, coronary artery disease (CAD) or thrombosis. Cardiac MRI is an alternative diagnostic method when echocardiography is inconclusive as well as provides additional prognostic information.

Clinical management

PPCM occurs in the setting of pregnancy and clinical management requires a well-coordinated multi-disciplinary team involving cardiovascular drugs, obstetrics, immunology and pathology [62]. According to AHA, guideline-directed medical therapy known to have beneficial outcomes in treating LV dysfunction and heart failure should be considered. However, medication contra-indicated during pregnancy and/or breastfeeding should be considered [12]. In essence, clinical management of PPCM is similar to that of heart failure: relieves congestive symptoms, optimizes hemodynamics and improves acute to chronic prognosis [21].

Pharmacotherapy

Pharmacotherapy for PPCM follows the European Society of Cardiology (ESC) guidelines for management of heart failure [67]. However, restriction (contra-indication) to the guidelines during pregnancy include angiotensin converting enzyme (ACE) inhibitors and angiotensin-II receptor blockers (ARB) because of increased risk of serious renal and fetal toxicity [68,69]. Table 8 outlines drugs for management of PPCM, and their maternal and fetal precautions during antepartum and postpartum [3,14,28,70].

Currently, pharmacotherapy lacks consensus on the ideal period for managing heart failure and its prophylactic value in subsequent pregnancies. The optimal clinical approach has been to give medication over time while gradually tampering the dose between 6 to 12 months as clinical and echocardiographic findings show favorable prognosis until complete recovery [3]. Other drugs on experiment but with promising results include immunosuppression (intravenous immunoglobulin), pentoxifylline (inhibit production of TNF-α) and bromocriptine (prolactin blocker) [74].

Mechanical circulatory support

Mechanical circulatory support devices have been used as a bridge to recovery or to heart transplantation [71]. Intra-aortic balloon pumps or extracorporeal membrane oxygenation have been used in PPCM patients with cardiogenic shock to restore normal ventricular circulation [3,14]. PPCM patients with deteriorating clinical conditions non-responsive to optimal pharmacotherapy may benefit from left ventricular (LV) assist devices (LVAD) [14]. Since PPCM resolves within six months after delivery, in the case of fulminant PPCM, LVAD could serve as a bridge to recovery [3]. However, when LVEF remains significantly depressed or continues to decline, LVAD may also serve as a bridge to heart transplantation [71]. Recent reports indicate prolonged mechanical circulatory support has decreased PPCM patients seeking heart transplantation from 33% to between 4 and 7% [11].

Implantable cardioverter-defibrillators

PPCM patients with persistent LV dysfunction six months since onset of the condition may benefit from implantable cardioverter-defibrillator (ICD), or together with cardiac resynchronization therapy (CRT) if the patient presents with NYHA functional class III symptoms and QRS duration of 120 ms [14]. Since PPCM resolves within 2-6 months, wearable/subcutaneous ICD is advisable [73,74].

Heart transplantation

Heart transplantation is indicated for PPCM patients with symptoms refractory to both optimal pharmacotherapy and mechanical circulatory support. Clinical outcomes of heart transplantation in PPCM patients is comparable to patients transplanted for other etiologies [28]. Although heart transplantation has been successful in many PPCM patients, there is a risk of organ rejection, infection, allograft vasculopathy and even mortality [74].

Meta-analysis of PPCM Clinical Management

Search strategy

Clinical management for PPCM lacks definitive guidelines. Current guidelines adopt treatment developed for LV dysfunction and heart failure, which does not consider changes brought about by pregnancy or breastfeeding. To improve understanding on clinical management approaches, this meta-analysis combines research findings on treatment methods for PPCM. Electronic search for studies on clinical management of PPCM was conducted in PubMed, Embase and Cochrane online databases, and Google Scholar. The broad-based search terms used were "medication therapy" OR "drug therapy" AND "mechanical support" OR "heart transplantation" OR "cardiac transplantation" AND "peripartum cardiomyopathy".

Inclusion criteria

The inclusion criteria for studies were. (a) A prospective or retrospective study. (b) Included at least one clinical management approach for PPCM (medication, mechanical support or heart transplantation therapy). (c) Had a follow-up period of six months or more since commencement of therapy (because in majority of patients PPCM usually resolves by the sixth month postpartum). (d) Included one quantitative clinical outcome (LV recovery and/or mortality). The exclusion criteria was the study were: (a) the study is a case series; (b) conference paper; or (c) had only abstract available (Table 9).

Study characteristics

Screening of all potential studies against the inclusion criteria yielded 17 studies that were included in this meta-analysis [31,43,64,71,82-94]. The 17 studies spanned a period of three decades, published between 1983 and 2013. They provided accumulated evidence on the development of clinical management approaches for PPCM over time.

Table 8. Drugs for PPCM Management and Their Maternal/Fetal Precaution.

| Drug                          | Maternal Precautions | Fetal Precautions |
|-------------------------------|----------------------|-------------------|
| Loop Diuretic (Furosemide)    | Electrolyte abnormalities, hypotension & azotemia | Insufficient uterine/placental perfusion/inhibit lactation. |
| Beta-Blockers (Carvedilol/ Bisoprolol/ Metoprolol) | Bradycardia | Long-term use could cause bradycardia/hypoglycemia/ low birth weight |
| Peripheral vasodilator (Hydralazine/nitrates) | Hypotension | None |
| Digoxin                       | Arrhythmias          | Serum levels should be monitored to avoid toxicity |
| Inotropes (Dobutamine/ Dopamine/Milrinon) | Arrhythmias | None |
| ACE-Inhibitor/ARBs            | Renal toxicity       | Fetal and renal toxicity antepartum |
| Anticoagulants (Unfractionated heparin/low molecular weight heparin) | Considered for patients LVEF > 35% | Consider fetotoxicity/ teratogenic of Warfarin during pregnancy. |
Medication (drug) therapy was the most studied clinical management methods by 71% (n=12) of the included studies [31,43,64,82-90]. This was followed by wearable cardioverter defibrillator (WCD) by 12% (n=2) of the included studies [91,92], heart transplantation by 12% (n=2) [91,92] and finally mechanical/ventilatory support (which included intra-aortic balloon pump, left ventricular assist devices (LVAD) and extra corporeal membrane oxygenation) by 6% (n=1) [71]. The 17 studies recruited a combined population of 670 PPCM patients with a mean age 25 years. The mean follow up period was 15 months.

### Study outcomes

Medication remains the first-line clinical therapy used in the management of PPCM patients diagnosed with mildly severd LV dysfunction (LVEF > 30%) as evident in the majority of studies (71%) examining its use and clinical outcomes. Although medication therapy for PPCM is similar to that of other non-ischemic cardiomyopathies, the studies emphasize on the need to choose medication that are safe in pregnancy and lactation to avoid adverse effects to mother and fetus. Mechanical support for ventilation is an important therapy for patients presenting with symptoms of acute heart failure who require supplemental oxygen. Frequently used mechanical support devices include intra-aortic balloon pump, left ventricular assist devices and extra corporeal membrane oxygenation. Mechanical ventilation has promising recovery rates (33%) within 24 months but suffer from unacceptably high mortality rates (17%) [71]. For PPCM patients refractory to optimal medication therapy and mechanical support with severe LV dysfunction (LVEF < 30%) ICD [91,92] and heart transplantation may be considered [93,94].

### Discussion

The current findings suggest pregnancy and breastfeeding complicate clinical management of PPCM. Current therapeutic approaches adopt guidelines that have proved efficacious in the treatment of LV dysfunction and symptomatic heart failure. Medication remains the frontline therapy for alleviating HF symptoms and treating LV dysfunction in PPCM patients. In the present findings, 71% of the authors report medication was indicated in PPCM patients with mildly severe LV function (LVEF > 30%). Despite its efficacy, the AHA [12] and the ESC [67], caution its use due to potential adverse effects associated with pregnancy (to the mother) or lactation (to the fetus). Its use should be on an individual basis. This is especially true because several current heart failure medications have been contraindicated in pregnant and lactating women, which may reduce the efficacy of medical treatment. In addition, medical therapy for PPCM lacks standardized period for management of heart failure and there is little knowledge on the prophylactic effect of medication on subsequent pregnancies [74].

For PPCM patients diagnosed with significantly depressed LV function (LVEF < 25%) or acute heart failure symptoms and may require supplementary oxygen, mechanical support for circulation is the initially indicated non-pharmacological therapy. Mechanical support is
also considered for patients who are non-responsive to optimal medical therapy. It has promising rates of recovery (33%). Mechanical support such as intra-aortic balloon pumps or extracorporeal membrane oxygenation together with cardiogenic shock are effective in restoring normal LV function as well as a bridge to heart transplantation [14,71]. LV assist devices are indicated as a bridge to recover for acute and severe onset of PPCM. Mechanical circulatory support also reduces the need for heart transplantation in almost a third of PPCM patients but may suffer from high mortality rates. When patients with severely depressed LV function (LVEF > 25%-30%) and are non-responsive to both optimal medical and mechanical circulatory support, heart transplantation is the last medical therapy [93,94]. However, when indicating heart transplantations, complications such as organ rejection, infection and allograft vasculopathy should be considered.

In summary, clinical management of PPCM depends on treatment guidelines developed for LV dysfunction and symptomatic heart failure. Medical therapy is the initial treatment option but potential adverse effect to mother and fetus should be considered. When optimal medical therapy is non-effective, mechanical circulatory support using intra-aortic balloon pumps, extracorporeal membrane oxygenation or LV assist devices should be considered. Heart transplantation is indicated when symptoms are refractory to optimal medical therapy and mechanical circulatory support.

Conclusion
Peripartum cardiomyopathy (PPCM) is a rare form of heart failure associated with pregnancy. It occurs in the setting of LV systolic dysfunction with onset in the third trimester or within six months postpartum in the absence of any demonstrable underlying cardiac condition. It is prevalent in about 1 in 1,500 to 15,000 with higher rates in developing countries. Independent risk factors are maternal age > 30 years, multiparous women, multiple gestation, pre-eclampsia and prolonged tocolytic therapy. Smoking, hypertension, malnutrition, African ancestry cocaine use and socio-economic status are emerging as probable risk factors. Prognosis is favorable with more than half of patients spontaneously recovering their LV function within six months post-partum. Baseline LVEF > 30%, higher LVEDD and fractional shortening predict favorable prognosis. Despite spontaneous recovery, PPCM remains a leading cause of non-obstetric fetomaternal morbidity and mortality. Its etiopathogenesis remains poorly understood but it is hypothesized that stress-activated cytokines, unbalanced oxidative stress, pathological maternal autoimmune response or pathological response to hemodynamic stress may contribute to the development of PPCM. The mainstay of PPCM diagnosis is the onset of heart failure symptoms in the last month of pregnancy or within five months post-partum. Definitive diagnosis is however by exclusion of other probable cardiac and non-cardiac etiologies presenting with similar symptoms using chest X-ray, electrocardiography, laboratory examination and cardiac MRI. Although PPCM lacks definitive treatment, it adopts conventional therapy used for LV dysfunction and heart failure while considering contraindications associated with pregnancy and breastfeeding. Pharmacotherapy remains the main clinical management approach but in the case of persistence LV systolic dysfunction, mechanical circulatory support or ICD may be considered. If conditions remain refractory to both medical therapy and mechanical circulatory support, heart transplantation may be considered but it is rare because of the short duration of the condition (2-6 months) and potential complications.

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