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REVIEW ARTICLE

Peripartum Cardiomyopathy: A Review Article

Cardiomyopathie du Peripartum : Un Article de Synthèse

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ABSTRACT

Peripartum cardiomyopathy (PPCM) is an important cause of heart failure (HF) in northern Nigeria and many other regions of the world. Although the aetiology is unknown, several aetiopathogenic mechanisms have been proposed, including myocarditis, vasculo-hormonal (16-kDa prolactin and Cathepsin D), genetic susceptibility and selenium deficiency hypotheses. The peripartum cardiomyopathy in Nigeria (PEACE) registry has revealed that three socioeconomic factors (lack of formal education, unemployment, underweight status), pre-eclampsia and selenium deficiency were independently associated with higher risk for PPCM. However the customary postpartum practices previously implicated in the aetiopathogenesis of postpartum cardiac failure, comprising regular hot baths and pap enriched with dried lake salt, were not associated with PPCM. Maternal age <20 years, tachycardia, hypotension and ejection fraction <25% independently increased the risk for mortality. Regular use of beta-blockers and obesity were independently associated with higher survival, and selenium supplementation is a promising treatment strategy for PPCM. **WAJM 2023; 40(1): 104–113.**

Keywords: Peripartum cardiomyopathy, Risk factors, Aetiology, Outcomes.

RÉSUMÉ

La cardiomyopathie du péripartum (PPCM) est une cause importante d'insuffisance cardiaque (IC) dans le nord du Nigeria et dans de nombreuses autres régions du monde. Bien que l'étiologie soit inconnue, plusieurs mécanismes étiopathogéniques ont été proposés, notamment les hypothèses de myocardite, vasculo-hormonale (prolactine 16-kDa et cathepsine D), de susceptibilité génétique et de carence en sélénium. Le registre PEACE (peripartum cardiomyopathy in Nigeria) a révélé que trois facteurs socio-économiques (absence d'éducation formelle, chômage, insuffisance pondérale), la pré-éclampsie et la carence en sélénium étaient indépendamment associés à un risque plus élevé de PPCM. Cependant, les pratiques post-partum habituelles, précédemment impliquées dans l'étiopathogénie de l'insuffisance cardiaque post-partum, comprenant des bains chauds réguliers et des bouillies enrichies de sel de lac séché, n'étaient pas associées au PPCM. L'âge maternel <20 ans, la tachycardie, l'hypotension et la fraction d'éjection <25% augmentaient indépendamment le risque de mortalité. L'utilisation régulière de bêta-bloquants et l'obésité étaient indépendamment associées à une survie plus élevée, et la supplémentation en sélénium est une stratégie de traitement prometteuse pour le PPCM. . **WAJM 2023; 40(1): 104–113.**

Mots clés: Cardiomyopathie du péripartum; Facteurs de risque; Étiologie; résultats.

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INTRODUCTION

Peripartum cardiomyopathy (PPCM) was defined by the PPCM Working Group of European Heart Failure (HF) Association in 2007, as "an idiopathic cardiomyopathy presenting with HF secondary to left ventricular (LV) systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of HF is found. It is a diagnosis of exclusion. The LV may not be dilated but the LV ejection fraction (LVEF) is reduced below 45%".[1] However the first description of PPCM dates back to 1880, when Virchow and Porak in two separate studies established an association between cardiac failure and the puerperium.[2,3] In 1937, Gouley et al established the syndrome of peripartum HF as a distinct clinical entity by describing the clinical and pathological features of a severe and fatal type of HF in seven pregnant women.[4] These women had dilated hearts in the last months of pregnancy, which persisted after delivery. An autopsy on four out of the seven patients who died demonstrated enlarged hearts with distinct widespread severe focal areas of necrosis and fibrosis.[4] In 1938, Hull and Hidden then described eighty patients with this condition in New Orleans, and called it 'postpartal HF'.[5] In 1971 and for the first time, Demakis and colleagues defined and described the diagnostic criteria of PPCM, as the development of HF within the last month of pregnancy or first five months postpartum, in the absence of any identifiable cause for the HF, and any recognisable heart disease before the last month of pregnancy.[6]

Studies dating back to the early 1970s have shown that peripartum HF was common in Northern Nigeria. Investigators working in the northern Nigerian City of Zaria described a common and rapidly developing type of congestive HF among women shortly after delivery, with an incidence as high as 1:100 deliveries, and termed it "postpartum cardiac failure" (PPCF).[7] The investigators attributed the syndrome to certain local postpartum customs, mainly in the form of taking twice daily hot baths by new mothers, regular ingestion of a gruel made of millet and enriched with dry lake salt ('Kunun Kanwa' in Hausa Language), and lying on beds made of baked clay that were heated with firewood from beneath. These postpartum customs were started shortly after giving birth and continued for about three months.[7] The local people believed that the rituals improve the health of new mothers from the rigours of pregnancy and childbirth. The earlier studies were carried out before the availability of echocardiography in the region. However, when echocardiography became available in Zaria in the late 1970s, Sanderson *et al* reported that PPCF was mainly a "high-output HF with well-preserved ventricular function", and not a cardiomyopathy.[8]

Significant progress has been made in the literature of PPCM over the years. In this paper we aimed to review the literature on epidemiology and management of PPCM, with a focus on local data.

Epidemiology

Incidence

PPCM has world-wide distribution, but with a significant geographical variability within and between countries.[1] PPCM is common in some parts of Africa but its true incidence is still unknown. This is largely because to date there is no population-based study on PPCM in Africa, and very few such studies have been conducted elsewhere. Recent studies have consistently shown that PPCM tends to be common in some parts of the world while its rare in others.[9–16] Recent population-based studies carried out in non-African countries have estimated incidence of PPCM as 1 in 1,741 deliveries in South Korea, 1 in 3,790 deliveries in Taiwan, 1 in 10,149 deliveries in Denmark, 1 in 3,189 live births in the United States of America and 1 in 20,000 deliveries in Japan.[9–13] Hospital-based studies in Africa have also estimated varying incidence of PPCM in Africa as 1 in 1000 live births in South Africa, 1 in 3,800 live births in Burkina Faso, and as high as 1:96 live births in northern Nigeria.[14–16] Data from the Peripartum Cardiomyopathy in Nigeria (PEACE) registry has clearly illustrated that the epidemiology of PPCM may vary widely even within the same country.[16] In the PEACE registry, in which patients were consecutively recruited, 72.3% of the patients were recruited from the North-West zone alone, where an incidence as high as 1 per 96 live births was obtained, while the disease was uncommon (7.6% of all recruited patients) in the Southern zones of Nigeria.[16] The reason for this variation in incidence of PPCM between and within countries remains unknown, but could be due to significant differences in the prevalence of both genetic and non-genetic risk factors.

PPCM Risk Factors

PPCM is most likely a multifactorial disease, and several risk factors have been inconsistently linked with the disease over the years. The suggested risk factors include increased age, high gravidity or parity, African origin, pre-eclampsia, use of tocolytics, twin pregnancy, obesity, poor socioeconomic status, malnutrition, customary birth practices and selenium deficiency.[17] However, data from the PEACE registry, which is the largest prospective study on PPCM in Africa, has shown that in Nigeria, the independent risk factors of PPCM are lack of formal education (Odd's Ratio: (OR) 3.1), unemployment (OR: 3.3), underweight status (OR: 13.4) and pre-eclampsia (OR: 9.0).[16] In addition, selenium deficiency seems to be the risk factor that links malnutrition with PPCM, in northern Nigeria.[18,19] However the customary postpartum practices previously implicated in the aetio-pathogenesis of PPCF, comprising regular hot baths and pap enriched with dried lake salt, and Hausa-Fulani ethnicity, all did not achieve statistical significance as PPCM risk factors.[16,19]

African origin: Although PPCM is not limited to Black women, its incidence is significantly higher among women of African ancestry as compared with other races. Gentry *et al* conducted a case-control study in Augusta, Georgia, and Memphis, and found almost a 16-fold higher incidence of PPCM in African American compared with non–African American women.[20] African ancestry seems to also confer worse prognosis among PPCM patients, likely due to poorer access to medical care and the presence of guanine nucleotide-binding protein β-3 subunit (GNB3) TT genotype,

which is more prevalent in Blacks and associated with worse outcomes.[20] Overall, African American women compared with non-African American women in the United States, were diagnosed with PPCM later in the postpartum period, presented with more severe disease, recovered less frequently, and took longer to recover.[21]

Preeclampsia: It has been suggested that preeclampsia and PPCM share a common pathophysiological mechanism that leads to the clinical syndrome of HF, related to the secretion of antiangiogenic factors, including soluble fms-like tyrosine kinase-1 (sFLT1) from the placenta during pregnancy.[22] PPCM patients with concomitant preeclampsia seem to have worse morbidity and event-free survival, a more concentric than eccentric patterns of LV remodelling and lesser recovery of LV function, when compared with patients with PPCM that is not complicated by preeclampsia.[23] Data from PEACE registry shows that preeclampsia was 7 times more common in PPCM patients than in age- and parity-matched controls, and it independently increased the risk of PPCM by 9-fold.[16]

Poor Socio-economic Status: It was observed more than 40 years ago that peripartum cardiac failure is a disease that predominates among the poor, living in poor social conditions.[7,24] In Kano (Nigeria), we also observed that among women referred for echocardiography, PPCM almost always occurred in women with low income (7.3% Vs 0%).[25] A recent study in the United States reported that Black race and neighbourhood concentrated disadvantage index (NDI) were independently associated with adverse outcomes in PPCM patients.[26] Neighbourhood low education, a component of NDI, was most strongly associated with clinical outcome, as it increased the risk for sustained cardiac dysfunction by 49% and partially explained differences in race.[26] Results of PEACE registry have shown that lack of formal education and unemployment each independently increased the risk of PPCM by 3-fold.[16] Therefore socioeconomic deprivation is a powerful risk factor for PPCM and HF development in general, and worsens clinical outcomes. Socioeconomic deprivation seems to impact the development of cardiovascular risk factors and disease, health behaviours, treatment patterns, and clinical outcomes in complex ways. However, the precise mechanisms accounting for this risk remain elusive.

Aetiology of PPCM

The aetiology and pathogenesis of PPCM is unknown, but several hypotheses have been proposed over the years. These include the myocarditis, vasculo-hormonal (16-kDa prolactin and Cathepsin D), autoimmune, apoptosis, abnormal response to increased hemodynamic burden of pregnancy, genetic susceptibility and selenium deficiency hypotheses.[17,19,27] It is now widely believed that PPCM is a multifactorial disease, and genetic susceptibility may a play an important role in the development of the disease in some patients ('multiple hit' model of PPCM) (Figure 1).

Genetic Predisposition: It is widely believed that the pathophysiologic mechanisms leading to PPCM may include a genetic predisposition in about 15–20% of the patients, the significance of which is "unmasked" by environmental (non-genetic) factors such as low serum selenium levels, viral infections, stress-activated cytokines, inflammation, autoimmune reaction, pathological response to haemodynamic stress, unbalanced oxidative stress and induction of antiangiogenic factors (Figure 1).[27–29] The genetic predisposition is based on data from Western countries, but a previous attempt to detect signals of familial predisposition by echo-cardiographic screening of apparently healthy sisters of PPCM patients in Nigeria yielded negative results.[30] Mutations in the sarcomeric gene titin (TTN) appears to be the most notable, found in 10–15% of a PPCM cohort, which was also found in 17% of patients with idiopathic dilated cardiomyopathy (DCM).[31] In a sub-study of the

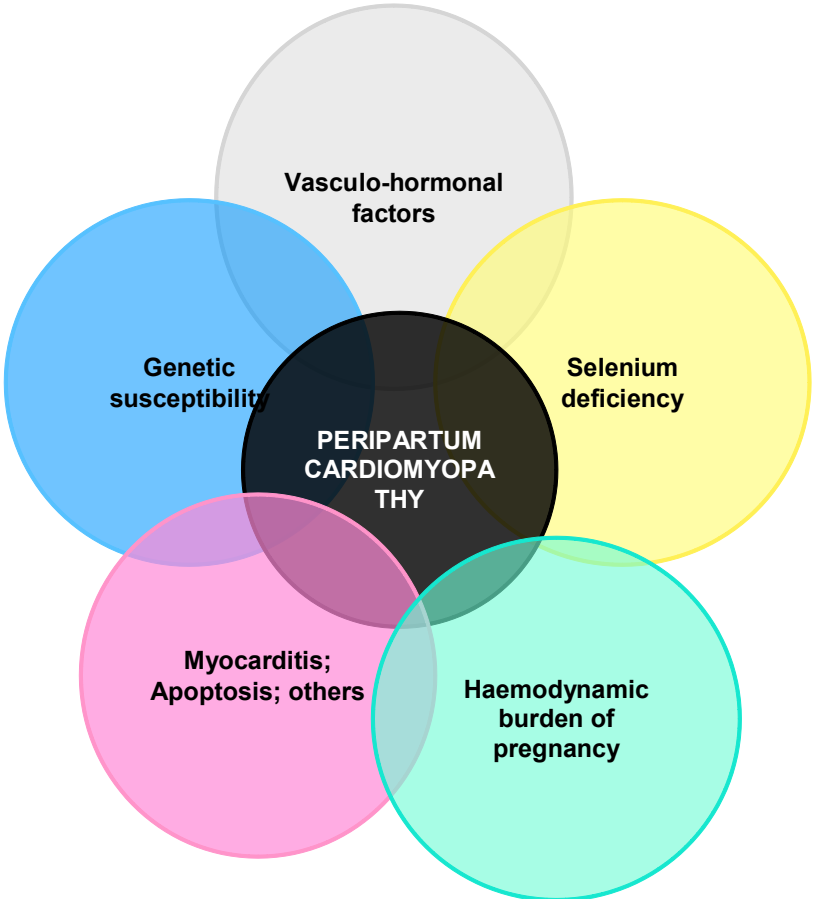

Fig 1: Putative Multifactorial Pathophysiologic Mechanisms of PPCM

Investigations of Pregnancy-Associated Cardiomyopathy (IPAC) study, GNB3 TT genotype was shown to be more prevalent in Black women with PPCM and associated with poorer outcomes.[32] Further, frequency of angiotensin converting enzyme (ACE)-DD genotype (and of the whole D allele) was significantly higher in patients with PPCM than in controls, and is associated with worse echocardiographic systolic performance indices.[33] It is recommended that genetic testing may be considered for prognostication and family screening of cases of PPCM with a familial aggregation of HF or cardiomyopathies.[28]

Vasculo-hormonal Hypothesis

Prolactin, 16 kDa prolactin and Cathepsin D hypothesis: Experimental work suggested a novel and specific pathogenic mechanism by demonstrating the development of PPCM in female mice with a cardiomyocyte-specific deletion of the transcription factor, signal transducer and activator of transcription 3 (STAT3) protein.[33] Absence of cardiomyocyte STAT3 in the postpartum heart blunts the induction of the antioxidant enzyme manganese superoxide dismutase, resulting in increased oxidative stress. This then leads to increased expression and proteolytic activity of cardiac cathepsin D, which causes cleavage of the nursing hormone prolactin into an antiangiogenic and proapoptotic 16-kDa form of the prolactin. The latter has a detrimental effect on the myocardial microvasculature resulting in myocardial hypoxemia and apoptosis, and the development of PPCM.[33] This would imply that PPCM is a microvascular disease. A pilot study on a limited number of patients with PPCM had shown a favourable effect of bromocriptine, a pharmacological inhibitor of prolactin, in support of this hypothesis of PPCM.[34]

Further studies have shown that 16-kDa prolactin induces endothelial cells to package micro RNA (miR)-146a into small lipid-encapsulated particles (exosomes), which are then secreted and taken up by cardiomyocytes.[36,37] The miR-146a in the cardiomyocytes then promotes cardiomyocyte apoptosis. Interestingly, blood levels of miR-146a are high in women with PPCM and can be suppressed by bromocriptine treatment, implying that prolactin is the driver for miR-146a secretion.[38] Thus it has been suggested that MiR-146a may be a specific biomarker of PPCM that can be specifically inhibited clinically.

Soluble Fms-Like Tyrosine Kinase 1 (sFlt1): Animal model studies have shown that in mammals, the placenta in late pregnancy secretes into the maternal circulation numerous hormones, including a soluble variant of vascular endothelial growth factor (VEGF) receptor 1, sFlt1, which inactivates most free VEGF in the maternal circulation.[22,39,40] In normal circumstances, the heart and other organs neutralise this insult partly by locally producing sufficient quantity of VEGF, which is proangiogenic. However it is believed that this defensive mechanism is diminished and ineffective in patients predisposed to PPCM.

Therefore, evidence suggests that sFlt1 and 16-kDa prolactin are two potentially vasculotoxic hormones of late gestation that can cause PPCM in sensitised hosts.[38]

Selenium Deficiency: Malnutrition was thought to play an important role in the aetiopathogenesis of PPCM, but the occurrence of the disease in well-nourished patients questioned this theory. However, high frequency of selenium deficiency was reported among PPCM patients in Nigeria (in 84.9% of PPCM patients Vs 2.8% of controls in Kano) and Niger Republic (in 74.3% of PPCM patients Vs 33.3% of controls in Niamey), which share a common land border (Table 1).[19,41-43] In these cohorts, selenium deficiency increased the odds of PPCM by an average of 29-fold, which might be considered high enough to suggest a signal for a cause-effect relationship, that needs to be explored further.

On the contrary, a prospective study in Haiti found selenium deficiency in only 1 out of 18 PPCM patients.[43] The differences in serum levels of selenium between PPCM patients in the two neighbouring West African nations and Haiti, may be related to the levels of selenium in the soil. Epidemiologic studies have shown that low selenium levels in the soil and in local foodstuffs correlate with low selenium levels in whole-blood and hair samples.[44] Selenium is a critical component of central antioxidant enzymes, including glutathione peroxidases.[45] Owing to the importance of many selenoproteins in attenuating oxidant stress in a variety of cellular compartments, one can readily conclude that selenium deficiency promotes oxidant stress and injury, which may also potentiate the oxidant injury of other contributing pathogenic factors, including viral and other infections.[45,46] Therefore in spite of the observation in Haiti, it is still conceivable that selenium deficiency is related to PPCM as illustrated in Figure 2, at least in some parts of the world.

Clinical Features and Diagnosis of PPCM

The diagnosis of PPCM is based on the development of symptoms and signs

Table 1: Selenium Deficiency as a Risk Factor of PPCM

Studies	PPCM Patients		Controls		OR (95%CI)
	Selenium Deficiency	Normal Selenium	Selenium Deficiency	Normal Selenium	
Cenac *et al,* 1992,42	26	9	12	24	5.8 (2.1–16.1)
Karaye *et al,* 201519	30	9	11	39	11.8 (4.3–32.2)
Karaye *et al,* 2017,18,41	135	24	3	105	196.9 (57.7–671.6)
Total	**191**	**42**	**26**	**168**	**29.4 (17.3–50.0)**

PPCM, Peripartum Cardiomyopathy; OR, odds Ratio; CI, Confidence Interval.

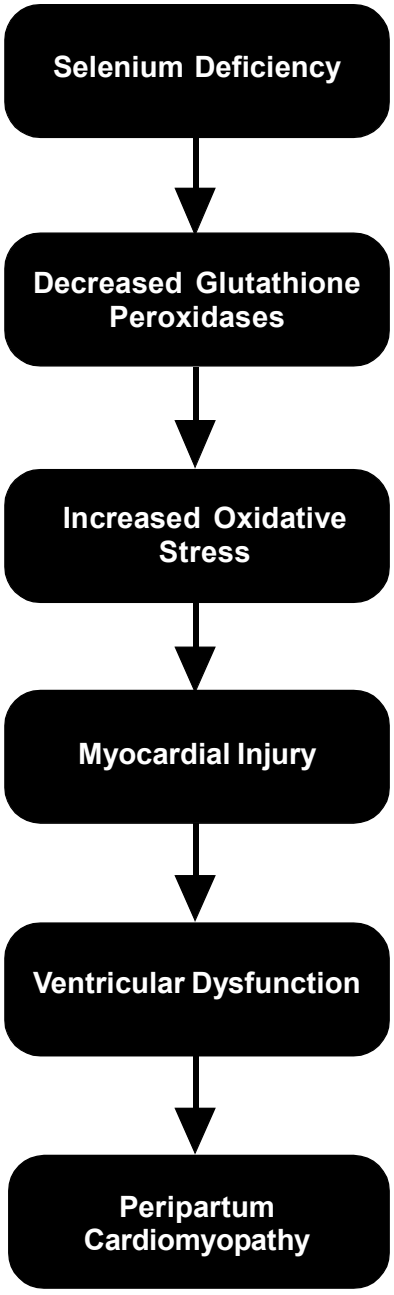

Fig 2: Mechanisms from Selenium Deficiency to PPCM

of HF and echocardiographic identification of new LV systolic dysfunction towards the end of pregnancy and within the first five months postpartum, after excluding other potential causes. This presents a challenge because many women experience dyspnoea, fatigue and pedal oedema towards the end of a normal pregnancy; symptoms identical to those of congestive HF. PPCM may therefore go unrecognised, leading to underestimation of its burden.[1,27]

Symptoms and signs that should raise the suspicion of HF include paroxysmal nocturnal dyspnoea, cough, raised jugular venous pressure, new murmurs consistent with mitral or tricuspid valve (TV) regurgitation, and pulmonary basal crackles. Data from the ongoing worldwide PPCM registry has revealed that clinical features of PPCM are remarkably similar across the globe despite huge differences in socio-demographic factors.[47] At the time of presentation in this registry, 36.6% of the PPCM patients were in NYHA functional class III and 32.2% were in class IV, and two-thirds of them presented after delivery (mostly within the first month postpartum) while one-third presented prepartum.[47] In the PEACE registry however, 37.9% of the PPCM patients were in NYHA class II, 17.5% were in class III and 16.0% were in class IV at enrolment, and all of them presented postpartum.[16,48] Evidence of fluid retention was evident, with pedal oedema found in 44.6%, raised jugular venous pressure in 39.9%, ascites in 43.6% and hepatomegaly in 45.1% of the patients. In addition, 7.4% of the patients had pneumonia, but other co-morbidities were rare.[16,48]

The diagnosis of PPCM requires excluding other causes of HF and is confirmed by standard echocardiographic assessment of LVEF below 45%. An electrocardiogram (ECG) is recommended for all PPCM patients, and presence of any two of the following three ECG disturbances (heart rate >100 beats/minute, ST–T-wave abnormalities in all leads excepting aVR, V1 and V2, and QRS duration >110ms) have been shown to predict PPCM in postpartum women, with a sensitivity of 85.2%, specificity of 64.9%, negative predictive value of 86.2% and an area under the curve of 83.8%.[49]

Novel echocardiographic techniques have provided additional insight into the pathophysiology of PPCM.[50,51] In PPCM patients with complete LV functional recovery on 2D echocardiogram, studies using 3D speckle tracking echocardiography have shown that subclinical myocardial damage may indeed persist.[50] The lowest values for global longitudinal strain (GLS) were in the basal and mid regions of anterior, anteroseptal and lateral walls of the PPCM patients. Thus 3D Speckle Tracking Strain analysis is a useful method for detecting subtle myocardial dysfunction that would indicate continuation of guideline-directed medical therapy (GDMT). Furthermore, abnormal GLS and global circumferential strain (GCS) in patients with PPCM at presentation were associated with subsequent clinical outcomes, including death, LV assist device implantation, and evidence of persistent LV dysfunction, after adjusting for LVEF.[51] Therefore strain measures may add prognostic information over LVEF for risk stratification.

Though longitudinally directed fibres situated mainly in the subepicardial and subendocardial regions of the LV and RV free walls and the papillary muscles comprise only a small proportion of the total ventricular myocardial mass, they play a major role in the maintenance of normal EF and in determining atrioventricular interactions.[53,54] Not surprisingly therefore, loss of longitudinal fibre function leads to characteristic ventricular systolic disturbances. The amplitude of atrioventricular ring motion, the "tricuspid annular plane systolic excursion" (TAPSE) provides a simple method of assessing RV function.[52] In a seminal paper, RV systolic dysfunction in PPCM was reported to be common, and worse than in idiopathic DCM.[55] Further studies showed that unlike in DCM, RV reverse remodelling in PPCM occurs in more than 50% of patients at 6 months post diagnosis, and likely related to the recovery of the pulmonary circulation status, rather than to the effects of medications.[56–58] This claim is supported by the modest relationship we previously found between TAPSE and mean pulmonary artery pressure at 6 months follow-up.[57] Therefore RV function recovery in PPCM seems to be related to right ventricular-pulmonary circulation coupling, which appears to be different from the pathophysiologic mechanism in DCM.[58] RV diastolic dysfunction tends to co-exist with RV systolic dysfunction in most PPCM patients, and appears to be mainly determined by pulmonary hypertension due to the LV disease, and probably to selenium deficiency.[57]

Cardiac magnetic resonance imaging (CMR) is a technique used in a limited number of PPCM patients for the assessment of cardiac function and detection of intracardiac thrombus. CMR studies have revealed biventricular systolic dysfunction with diffuse myocardial oedema in PPCM patients, and the myocardial oedema and LGE (which accurately identifies myocardial scarring) may have prognostic value for LVEF recovery.[59,60]

CMR imaging is generally considered safe during pregnancy, but the effect of gadolinium-based contrast agent administration on the foetus is not well established, thus it should be avoided, especially during the first trimester. However, gadolinium-based contrast agents are considered safe during breastfeeding.[60]

Prognosis

The prognosis in PPCM varies geographically. Mortality rates as high as 47.4% at 1-year follow-up have been previously reported from Nigeria, while studies from Burkina Faso, South Africa and Zambia reported mortality rates of 48.3% over four years, 13.0% over six months and 7% over six months, respectively.[15,61–63] In contrast, mortality rates as low as 4.1% at 1-year and 1.5% at 5-year follow-up have been reported from the United States and Germany, respectively.[64,65] LV functional recovery as low as 29.4% at 1-year, 21% at 6-month and 28% at two-year follow-up was reported from Nigeria, South Africa and Haiti, respectively, while rates as high as 45% at six-month, 71% at 1-year and 95.5% at 5-year follow-up were reported from the Zambia, United States and Germany, respectively.[61–66] Although some researchers have failed to identify precise correlates of mortality and myocardial recovery, it has been suggested that younger age at diagnosis, lower body mass index, Black race, use of guideline-directed treatments, and some key cardiac parameters measured by echocardiography and cardiac magnetic resonance independently influence such outcomes.[63–65] In the PEACE registry, a high mortality rate of 18.7% was recorded within a median follow-up of 17 months.[48] Of note, most deaths occurred within the first twelve months of follow-up, with a particularly high rate of mortality between the 3rd and 6th months. Maternal age below 20 years, tachycardia, hypotension and an LVEF of less than 25% at baseline independently increased the risk for mortality each by approximately two-fold. On the other hand, regular use of beta-blockers and obesity were independently associated with a reduced risk of mortality.[48] In addition only 22.6% of the patients recovered LV systolic function, which was independently improved by regular use of beta-blockers. However, only 7.4% of the patients were rehospitalised for various reasons during the study, in spite of the relatively high mortality and low rate of LV functional recovery. This is not surprising given that most PPCM patients in Nigeria are unemployed and poor, and therefore unable to cope with the high cost of in-patient care.[16,62,67]

Treatment

Management of Acute Heart Failure (AHF)

PPCM patients who present during pregnancy with AHF would need a multidisciplinary care approach, involving cardiologists, obstetricians and anaesthetists, but the standard principles of managing AHF also apply to cases due to PPCM.[68] In summary, AHF management can be categorised into three stages (pre-hospital, in-hospital, and pre-discharge), having different goals and requiring different approaches. In the pre-hospital stage, where such facilities exist, management of AHF patients should include monitoring of pulse oximetry, blood pressure, heart rate, respiratory rate, and 12-lead or continuous ECG instituted within minutes of contact with the patient.[68] In the hospital, diagnostic workup and appropriate pharmacological and non-pharmacological treatment must be started promptly and in parallel. Rapid treatment is essential, especially when the patient has pulmonary oedema and/or hypoxaemia. Oxygen should be administered in order to achieve an arterial oxygen saturation of $\geq$95%, using, where necessary, non-invasive ventilation with a positive end-expiratory pressure of 5–7.5 cm of water. Intravenous diuretics should be given when there is congestion and volume overload, with an initial bolus of furosemide 20–40 mg. Intravenous nitrate is recommended (e.g. nitroglycerine starting at 10–20 up to 200 mg/min) in patients with a systolic blood pressure (SBP) >110 mmHg and may be used with caution in patients with SBP between 90 and 110 mmHg. Inotropic agents should be considered in patients with a low output state, indicated by signs of hypoperfusion.[27,68] Further care in the form of ventricular mechanical support or cardiac transplantation should be offered to patients when needed according to the recommendations in standard guidelines.[68]

Management of Chronic Heart Failure in PPCM

I: Management during pregnancy: this should involve both cardiologists and obstetricians, and follow standard guidelines.[27,68] The exceptions to general HF management would include avoiding ACE inhibitors (ACE-I), angiotensin receptor blockers (ARB), angiotensin receptor-neprilysin inhibitors (ARNI), ivabradine and mineralocorticoid receptor antagonists (MRAs), which are contraindicated because of concerns of teratogenicity and foetotoxicity. Hydrallazine and long-acting nitrates could be used in combination as substitutes for ACE-I, ARB and ARNI. Spironolactone is thought to have antiandrogenic effects in the first trimester. Because the effects of eplerenone on the human foetus are uncertain, it should also be avoided during pregnancy. Beta blockers(preferably metoprolol-succinate) and diuretics can be used but cautiously, given the latter's effect on placental blood flow. Digoxin has been used in pregnancy for both maternal and foetal indications without causing foetal harm. It is excreted into breast milk, but no adverse effects have been reported, and the drug is compatible with breast-feeding.[27]

II: Management of HF after delivery: this should follow standard

guidelines but with some modifications.[27,68] For patients not breastfeeding, HF should be treated according to standard guidelines on acute and chronic HF, including ACE-I or ARB or ARNI, with beta-blockers and MRAs. During breastfeeding, ARBs, ARNI and Ivabradine should be avoided. However captopril or enalapril, metoprolol-succinate, spironolactone, digoxin and hydrallazine-nitrates combination, can be used with caution.[27]

Delivery

PPCM patients presenting during pregnancy should be closely monitored. However vaginal delivery is always preferable if the patient is haemodynamically stable. It should be noted that there are no absolute obstetric indications for caesarean delivery, and epidural analgesia is preferred. Urgent delivery irrespective of gestational age should be considered in women with advanced HF and haemodynamic instability despite optimal HF treatment, regardless of the cause.[27] In these cases, caesarean section is recommended with central neuraxial anaesthesia, but should be carefully titrated, guided by an expert anaesthetic team.[27]

Subsequent pregnancies in women with history of PPCM are associated with a risk for recurrent and persistent cardiac dysfunction and even mortality. The risk is substantially higher in patients with persistent LV dysfunction before subsequent pregnancy. At the same time, however, recovery of LV systolic function does not guarantee an uncomplicated subsequent pregnancy. Therefore, it is strongly recommended that all patients with a previously diagnosed PPCM and their partners should receive careful counselling about the longer-term prognosis and undergo a risk stratification if further pregnancies are considered.[27,28] Advice on contraception should be offered to the patient at the earliest contact. In general, barrier methods are unreliable, ethinyloestradiol-containing contraceptives have the greatest risk of thrombosis, and levonorgestrel-based long-acting reversible contraception implants or intrauterine devices are the safest and most effective contraceptives.[69]

Bromocriptine in the Treatment of PPCM

Bromocriptine, a dopamine 2D agonist which blocks prolactin, may be a novel disease-specific treatment for PPCM. Several case reports and small studies have suggested that the addition of bromocriptine to standard therapy for HF may be beneficial in patients with acute onset of PPCM.[35,70–72] A recent metaanalysis of these studies revealed an 11% higher survival in favour of bromocriptine, but no association with lower composite adverse clinical outcomes or LVEF recovery.[73] Because the drug appears to increase the risk of thromboembolic phenomena including myocardial infarction, anticoagulation therapy is strongly encouraged in PPCM patients taking bromocriptine.[27,70,71] A bromocriptine treatment scheme has been suggested: bromocriptine (2.5 mg once daily) for at least 1week may be considered in uncomplicated cases, whereas prolonged treatment (2.5 mg twice daily for 2weeks, then 2.5 mg once daily for another 6weeks) may be applied in patients with LVEF <25%, RV involvement, intensive care treatment, and/or cardiogenic shock.[71] This scheme may be considered in carefully selected patients as part of a treatment regimen comprising Bromocriptine, Oral heart failure therapies, Anticoagulants, vasoRelaxing agents and Diuretics (BOARD).[72] In addition to the need for anticoagulation during bromocriptine treatment, bromocriptine also suppresses lactation. This is of critical concern because neonates/infants of such patients would be denied breastfeeding with all its devastating consequences. In view of the above-mentioned concerns, many physicians believe that the adverse effects of bromocriptine treatment may significantly outweigh the benefits for the typical poor PPCM patient in Africa. It is hoped that the ongoing "Bromocriptine in the Treatment of Peripartum Cardiomyopathy (BRO-HF)" trial (ClinicalTrials.gov Identifier: NCT02590601) would shed more light on the role of bromocriptine in PPCM management.

Anticoagulation in the treatment of PPCM

In PPCM, anticoagulation is advisable from the time of the diagnosis until LV function improves to an LVEF >35%, or for the treatment of atrial fibrillation, because of the high incidence of thromboembolism associated with the disease.[27,69] Anticoagulation is particularly important during pregnancy and the first 6 to 8 weeks postpartum because of persistent hypercoagulable state.[27] In contrast to warfarin which causes fetotoxicity, both unfractionated heparin and low-molecular-weight heparin (LMWH) do not cross the placenta and are safe throughout pregnancy.[69] However warfarin-induced foetotoxicity is minimal if used during the second and third trimester.[69] LMWH can be used throughout pregnancy but with anti-Xa monitoring and dose adjustment according to peak levels.[69] The use of unfractionated heparin is preferred in the third trimester, towards the end of pregnancy, because of its shorter half-life and reversible effect, in the event of premature labour and a possible need for urgent delivery. Both warfarin and heparin are not secreted into breast milk, and are therefore safe during breastfeeding.[69]

CONCLUSION

PPCM is an important cause of HF in northern Nigeria (which has the highest burden of the disease in the world) and many other regions of the world. Although the aetiology is still unknown, several risk factors and potential aetiopathogenic mechanisms have been proposed, including selenium deficiency. In Nigeria, three socioeconomic factors (lack of formal education, unemployment, underweight status) and pre-eclampsia were independently associated with higher risk for PPCM. In addition, maternal age below 20 years, tachycardia, hypotension and an LVEF of less than 25% independently increased the risk for mortality, each by approximately two-fold. On the other hand, regular use of beta-blockers and obesity were independently associated with a reduced risk of mortality. Selenium supplementation is one of the promising treatment strategies that could improve symptoms and outcomes of PPCM.

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