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REVIEW

Epidemiology of peripartum cardiomyopathy in Africa

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Abstract

Peripartum cardiomyopathy (PPCM) is a disease that primarily affects Black African women. The history of peripartum cardiac failure in Africa dates to the 1960s, before the availability of echocardiography. With the availability of echocardiography in the late 1970s, studies on well-characterized PPCM began to be reported. To date, there is no population-based PPCM study in Africa. However, hospital-based studies have reported incidence rates as high as 1:100 deliveries in Nigeria and representing up to 52% of all cardiomyopathies. For reasons that are not yet very clear, there are obvious wide disparities in incidence and prevalence within and between African Countries. Likewise, prevalence of suggested risk factors for the disease such as increased age, gravidity or parity, twin pregnancy, obesity, poor socioeconomic status/malnutrition and selenium deficiency vary widely between studies. However, the disease seems to be more common among the poor rural population. Clinical outcomes are much worse in Africa than in Western Europe and North America. Mortality rates as high as 24.2% at 6 months and 47.4% at 1 year of follow-up had been recorded in Kano, Nigeria, 48.3% over 4 years in Burkina Faso, 11.6% over 6 months in Zimbabwe and 13.0% over 6 months in South Africa. It is hoped that the ongoing peripartum cardiomyopathy in Nigeria (PEACE Registry) and the worldwide EURObservational Research Programme on PPCM will soon shed more light on the epidemiology of PPCM in Africa. The present article aimed to review the epidemiology of the disease in Africa, where the disease is relatively more common.

Key words: peripartum cardiomyopathy, epidemiology, Africa, Nigeria.

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Introduction

Peripartum cardiomyopathy (PPCM) is defined as *an idiopathic cardiomyopathy presenting with heart failure (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 nearly always reduced below 45%.*[1] Although the disease was first described by Gouley *et al.* in 1937, its etiology is still unknown and large scale epidemiologic studies begun only recently.[2-4] However, several case series of HF around the puerperium dating back to 1961, many predating the wide availability of echocardiography and most not confirmed with autopsy, have been reported from Africa (Table 1).[5-9] With the availability of echocardiography in the late 1970s in parts of Africa however, many of those postpartum HF cases were shown not to be due to a cardiomyopathy.[5-9]

Given that African ancestry is believed to be a strong risk factor for PPCM, the present article aimed to review the epidemiology of the disease in Africa, where the disease is relatively more common.[1]

Epidemiology

PPCM is a global disease with epidemiology that varies widely and with multifactorial etiology.

Prevalence/incidence of peripartum cardiomyopathy

The true incidence or prevalence of PPCM in Africa and in some other populations is unknown. This is largely because to date there is no population-based study on PPCM in Africa, and very few such studies were carried out elsewhere. However, from available data, PPCM tends to be rare in some

parts of the world and more common in others.[10-14] For example recent population-based studies suggest an estimated incidence of PPCM of 1 in 1741 deliveries in South Korea, 1 in 3790 deliveries (925 patients in 15 years) in Taiwan, 1 in 10,149 deliveries in Denmark (61 patients in 10 years), 1 in 3189 live births in the United States of America and 1 in 20,000 deliveries in Japan.[10-14] Studies that estimated incidence in Africa used hospital-based data, arriving at values such as 1 in 1000 live births in South Africa, 1 in 100 deliveries in Sokoto, Nigeria, and 1 in 3800 in Burkina Faso.[15-17] Prevalence of PPCM was also estimated in a multicenter study in Kano, Nigeria.[18] It was the most prevalent type of cardiomyopathy in Kano, found in 55 out of 1296 patients (4.2%) referred for echocardiography over a period of 7 months, representing 52.4% of all cardiomyopathies.[18] However, one of the objectives of the ongoing Peripartum Cardiomyopathy in Nigeria (PEACE) registry is to estimate the burden of PPCM in 20 hospitals spread across Nigeria, and the study will be concluded by the end of March 2019.[4] The ongoing worldwide EURObservational Research Programme (EORP) on PPCM has also recruited many patients from South Africa, Nigeria, Egypt, Burkina Faso, Democratic Republic of Congo and Sudan, and will hopefully provide broad overview of epidemiologic data on PPCM in Africa.[3]

The reasons for the variation in incidence between and within countries remain unknown, but probably reflect both environmental and genetic factors.

Peripartum cardiomyopathy risk factors

PPCM has been associated with several risk factors over the years, but there is significant inconsistency between studies of their association with the disease. The suggested risk factors include increased age, gravidity or parity, African origin, pre-eclampsia, use of tocolytics, twin pregnancy, obesity, poor socioeconomic status/malnutrition, customary birth practices and selenium deficiency.[19-21]

Increased age

Although PPCM is thought to be more prevalent in the upper and lower extremes of childbearing age, and in older women of high parity, it is important to note that the disease could affect such women regardless of their age or parity.[19-22] In our recent series comprising of 54 PPCM patients in Kano, Nigeria, the age of the patients ranged from 18 to 45 years with a mean of 26.6±6.7 years, and 35.2% were between 18 and 20 years, and only 20.4% were older than 30 years.[21] In compar-

Table 1. Some pioneer studies on peripartum heart failure in Africa.

Study	Country	N.	Echo?	Main findings
Seftel & Susser, 1961[5]	South Africa (Johannesburg)	23	No	The commonest type of idiopathic myocardial failure in Johannesburg in African women before themenopause. Two-thirds developed symptoms within first 10 weeks postpartum. A significant relationship is shown between incidence on the one hand and high parity, high childbearing age, and twinning on the other. Poor prognosis is significantly related to high age and parity; prolonged lactation after presentation and presence of cardiomegaly or LVH on ECG. Early onset followed by prompt medical attention is associated with a favorable outcome.
Brockington, 1971[6]	Nigeria (Ibadan)	50	No	The clinical findings are of biventricular myocardial failure with mild transitory hypertension. Clinical syndrome is more compatible with a hypertensive origin than with intrinsic myocardial disease.
Davidson *et al.*, 1974[7]	Nigeria (Zaria)	224	No	PPCF patients recruited from 1969-1972. 96% were Hausa or Fulani in origin, compared with 70% for women admitted to the medical wards (Controls). 58% of the patients lived in rural areas, compared with only 37% of controls. Incidence of PPCF in Zaria about 1% of Hausa deliveries, with a peak in July. Only 1% of Hausa PPCF patients did not take postpartum baths, 3% did not lie on hot beds, and 6% took no "Kanwa" at all. Authors believed that the customs of Hausa women in Zaria were important in the pathogenesis of PPCF, although they may not be wholly responsible for the syndrome.
Davidson *et al.*, 1978[8]	Nigeria (Zaria)	224	No	Results of 2-5-year follow-up. Post-partum hypertension was found in 87% of PPCF patients and 61% of Controls. Digoxin and diuretics were rapidly effective, causing a mean weight loss of 29% in 15 days, resolution of hypertension, and a fall in the cardio-thoracic ratio (CTR). During the 1st year after diagnosis, the CTR became normal in 82% of patients, and the ECG in 60%. PPCF recurred, again with the same seasonal variation, after 19 per cent of subsequent pregnancies. During follow up for 2 to 5 years, 22% of the patients became hypertensive, and 11% died. The prognosis was worst in those with an arrhythmia, hypertension, sustained cardiomegaly or aged 30 or more.
Sanderson *et al.*, 1979[9] ,	Nigeria (Zaria)	43	Yes	Left ventricular function and systolic time intervals were relatively good. Estimated cardiac output were high. Findings not compatible with a severe heart muscle disorder or cardiomyopathy.

ECG, electrocardiogram; LVH, left ventricular hypertrophy; PPCF, peripartum cardiac failure; CTR, cardiothoracic ratio.

ison to controls who were lactating mothers from the same locality as the patients, increased age was not a risk factor for the disease.[23]

Gravidity/parity

Although several studies have suggested that high parity is an important risk factor for PPCM, it is important to note that 24-37% of cases may occur in young primigravid/primiparous patients.[1,3,19-23] Of the 43 patients studied in Harare, Zimbabwe, 34.9% were primiparous, and 16.3% had parity of 4 or more.[24] The average parity among PPCM patients was 2 in South Africa and Burkina Faso, but 4 to 5 in Nigeria and up to one-third was primiparous.[16,17,20,21] In comparison, PPCM patients in the PPCM EORP recruited from European countries had a median parity of 2 and only 18.6% were primiparous, while those from non-European countries had median parity of 3 and 12.1% were primiparous.[3] In our cohort, multiparity was also not associated with PPCM because it was even more common in the control (84%) than PPCM (74.4%) groups (p=0.296).[23]

African origin

There seems to be a strong relationship between African ancestry and PPCM, although Elkayam *et al*. clearly showed that PPCM in the United States is not limited to black women.[25] However, there was a significantly higher incidence in African American women as compared with other races.[26] 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.[26] Furthermore, African ancestry seems to confer worse prognosis among PPCM patients, likely due to poorer access to medical care and the presence of guanine nucleotide-binding proteins β-3 subunit (GNB3) TT genotype, which is more prevalent in blacks and associated with worse outcomes.[27] In subset analysis by race, black women with the GNB3 TT genotype had a significantly lower mean LVEF at entry compared to C allele carriers (0.28±0.09 *vs*. 0.35± 0.08; p=0.04).[27] The ongoing worldwide PPCM EORP aims to delineate the impact of socioeconomic factors *vs*. ethnicity on a number of management and outcome parameters.[3]

Preeclampsia

It has been suggested that preeclampsia and PPCM share a common pathophysiological mechanism that leads to the clinical syndrome of HF, and both are possibly related to the secretion of antiangiogenic factors, including soluble fms-like tyrosine kinase-1 (sFLT1) from the placenta in pregnancy.[28,29] Although epidemiologic studies have reported a strong association between preeclampsia and PPCM, with a prevalence of preeclampsia in patients with PPCM of about 20%, previous studies from Africa have not reported such an association.[16,20-24,30] It is hoped that the ongoing PEACE Registry in Nigeria will shed more light on this.[4] In itself, preeclampsia occurs in 10% of pregnancies in Africa, which is significantly higher than the global average of approximately 2%.[31]

Systemic hypertension

A review by ElKayam described hypertension as a strong *associated condition*, and not an etiologic factor of PPCM.[32] However, in societies where both PPCM and sustained hypertension are common in women, differentiating PPCM from hypertensive heart disease could be difficult if high blood pressure (BP) is considered a clinical feature of PPCM. In support of this point, we found eccentric left ventricular hypertrophy, irrespective of gender, to be the most common type of abnormal LV geometry in hypertensive subjects in Kano, Nigeria.[33] These patients tend to present in HF with similar clinical and echocardiographic features to PPCM, except for the high BP or history of hypertension.[33] Some PPCM registries have shown that high BP in PPCM is rare, as reported by Sliwa *et al*. from South Africa (2%) and Fett *et al.* from Haiti (4%).[34,35] In contrast, we recently found hypertension among 41% of untreated PPCM patients and 28% of controls (p=0.197).[23] A retrospective study in Japan similarly reported the incidence of hypertension in PPCM as 41%, which is substantially higher than in the overall pregnant population.[14,36] Moreover, Kamiya *et al.* revealed that the hypertension is independently associated with a shorter hospital stay and higher LVEF.[14,36] However, hypertensive patients with and without PPCM had the same LV size and systolic dysfunction at diagnosis and discharge. In addition, parameters such as LV systolic diameter, fractional shortening, and LVEF showed greater improvement in the hypertensive patients. Thus, they concluded that the hypertensive state is not causative in the development of PPCM and might be a subset of PPCM that is characterized by relatively swift recovery, except in fatal cases.[14] Similarly, Ntusi *et al.* showed different modes of recovery in patients presenting with PPCM *versus* those with hypertensive disorders of pregnancy presenting with LV dysfunction and HF in a South African cohort.[37] In addition to important differences in the ages, time of onset of HF, clinical, ECG and echocardiographic features, 5 of the 30 PPCM patients died over 3.5 years as against none of the 53 hypertensive patients over 6 years of follow-up.[37] In a retrospective analysis of data from 6 States in the USA, Kao *et al*. also reported a significantly higher prevalence of hypertension among PPCM patients (46.9%) than Controls (6.4%), and considered it a strong PPCM risk factor.[38] Similarly in the Investigations of Pregnancy-Associated Cardiomyopathy (IPAC) study, hypertension was found in 45% of the PPCM patients and was commoner in Blacks (70% *vs*. 34%) but not associated with worse outcomes.[39] Placental ischemia seems to be the main pathogenic mechanism of pregnancy-induced hypertension. This is followed by the placental release of vasopressor substances that are involved both in generalized endotheliosis that characterizes the disease, and in hypertension.[40] From the foregoing, it clear that the relationship between hypertension and PPCM needs further research.

Poor socio-economic status/malnutrition

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.[5,8] In Kano (Nigeria), it was also observed that among women referred for echocardiography, PPCM almost always occurred in women with low income (7.3% *vs* 0%).[41] The most plausible explanations for this observation could be poor nutrition and poor medical care. However, the occurrence of the disease in well-nourished patients had put this theory to doubt. A more recent study in Kano has further questioned the theory of poor socioeconomic status as a risk factor for PPCM by finding no significant differences in income and educational level between PPCM patients and controls.[23]

Customary birth practices

About 4 decades ago in Zaria (northern Nigeria), women of the Hausa tribe appeared to have a high incidence (1:100) of a form of HF within the time frame of PPCM, termed postpartum cardiac failure (PPCF).[9,42] This was believed to be related to some local Hausa postpartum customary practices, mainly twice daily hot baths by new mothers, regular ingestion of a thick drink made from millet and rich in dry lake salt, *Kunun Kanwa* (in Hausa Language), and lying on heated mud beds, starting from shortly after giving birth and continuing for about 3 months.[9,42] Although these practices were intended to stimulate breastmilk production, protect from the harmful effects of *cold* and improve the general wellbeing of the new mother, they were also believed to cause significant volume overload and vasodilatation, resulting in PPCF.[8,9,42] When echocardiography became available in Zaria in the late 1970s, Sanderson *et al.* confirmed that PPCF was mainly a *high-output HF with well-preserved ventricular function,* and not a cardiomyopathy.[9] For this reason therefore, PPCF is an entity different from what we know today as PPCM, going by the current definition.[1]

Among a well-characterized cohort of 21 PPCM patients, Danbauchi reported from Zaria that all of them practiced the postpartum customs, while Isezuo *et al.* reported from Sokoto (northern Nigeria) that up to 81.5% of PPCM patients practiced the hot baths for at least 30 days.[16,43] When compared with apparently healthy controls however, the practices were found to be even more common among them than the PPCM patients (hot baths, 82% *vs* 35.1%; Kunun Kanwa, 78% *vs* 23.1%; p<0.001; respectively), clearly implying that the practices were simply common cultural habits among the Hausas that are not related to PPCM (Figure 1).[23] It is important to note that traditional customary birth practices are not limited

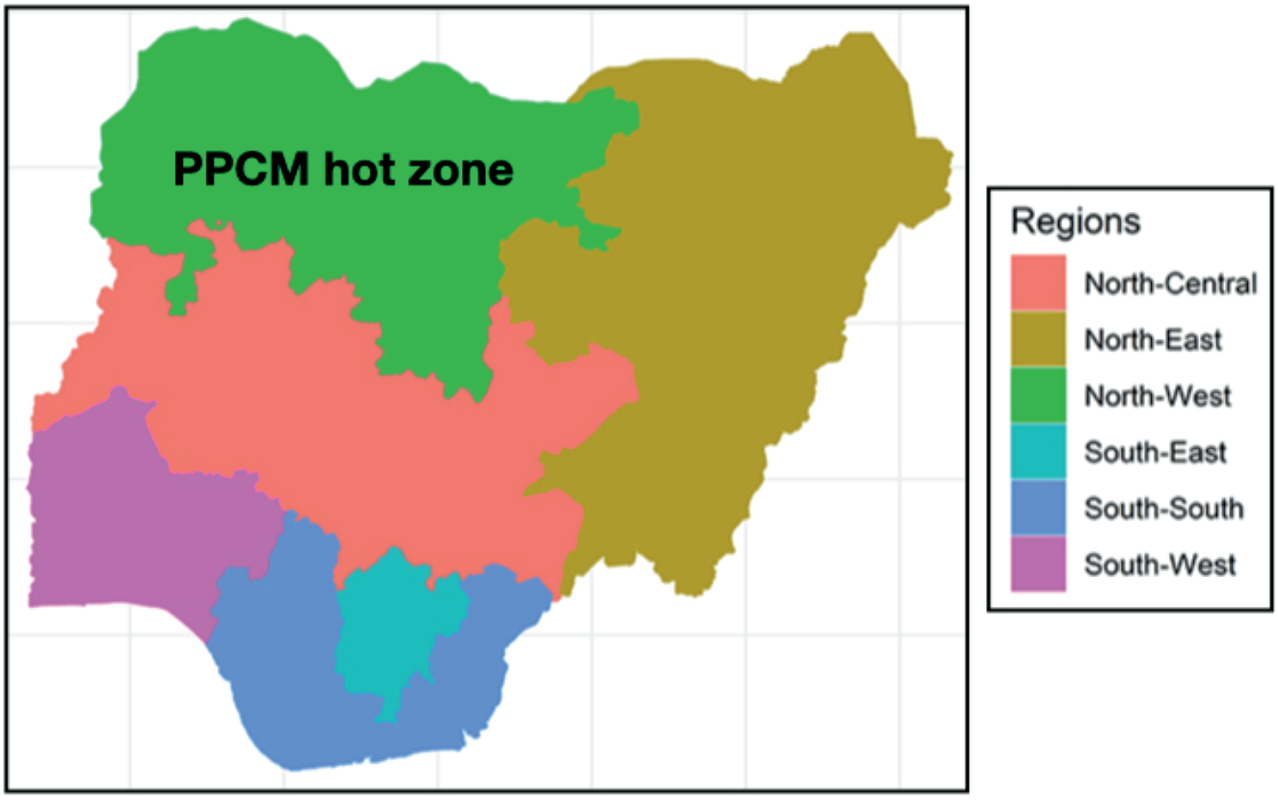

Figure 1. Map of Nigeria showing the peripartum cardiomyopathy "hot zone" in green.

to the Hausas or Fulanis in Nigeria. Okeke *et al*. reported that in the immediate postpartum period, 25.2% of 420 women in Enugu, South Eastern Nigeria drank various forms of alcoholic beverages to induce lactation while 80.2% of them applied hot compresses on the lower abdomen to aid lochia drainage and involution of the uterus, 75% of them sat in hot salt water solution (sitz bath) in the immediate postpartum to aid lochia drainage, aid perineal wound healing and improve vaginal tone.[44] Although the results of PEACE Registry are still being awaited, it is common knowledge that PPCM is relatively more common in northern than other regions of Nigeria, and the relevance of the traditional birth practices in PPCM would be clarified.[4,7-9]

Selenium deficiency

Selenium is a naturally occurring element found in soil, rocks and water.[37] The selenium content in foods principally depends on the concentration and physico-chemical forms existing in the soil.[45] However, levels of serum selenium are determined by many factors, including its availability in foods, absorption, cooking, lactation, alcohol, chronic illnesses, etc.[37,41] Cenac *et al.* reported for the first time from Niger Republic, where PPCM is an endemic disease, that selenium deficiency may be an important problem in Sahelian African patients with PPCM, akin to what was described for Keshan disease.[47,48] In support of the PPCM selenium theory by Cenac *et al*., our results have shown critically low selenium levels among 76.9% of the studied PPCM patients.[23,47] Further analysis of our data (unpublished) shows that selenium levels increase the odds of having PPCM to 1.08 (95% confidence interval: 1.043-1.118; p<0.001).[23] North-western Nigeria shares a long border, geography and customs with Niger republic, hence the common food types and dietary habits, which are the sources of selenium. Our results have shown that PPCM patients had significantly lower serum selenium levels and significantly higher prevalence of rural residency than controls despite similar income and educational levels. In addition, rural residency significantly increased the odds of having critically low serum selenium levels. Our observation of high prevalence of rural residency among PPCM patients was similarly made for PPCF decades ago in Zaria and Johannesburg.[5,7,8,23] It is well known that in Nigeria, most rural residents are subsistence farmers who tend to consume the locally produced foods and grown animals. Urban residents on the other hand are more exposed to imported foods and animals, from regions where there is no selenium deficient soil and animals. Therefore, it is reasonable to hypothesize that most women in Kano (and the Sahel region) develop PPCM if they depend on locally produced foods and animals. The serum selenium levels among PPCM patients in Kano (61.7±14.9 µg/L) and Niamey (48.0±25 µg/L) were similar, most likely because of their geographical and cultural similarities which explains the heavy burden of the disease in the region, in comparison with respective values in Haiti of 110 µg/L (range 67-145 µg/L).[23,47,49] It is hoped that the ongoing PEACE Registry will further clarify the relationship between PPCM and selenium deficiency. This study aims to describe the relationship between selenium deficiency, oxidative stress and PPCM, the impact of sodium selenite supplementation on LV reverse remodeling, change in New York Heart Association (NYHA) functional class and survival in PPCM, and the prevalence of selenium deficiency and its relationship with cardiac function in apparently healthy pregnant women.[4]

Clinical outcomes

LV function recovery and mortality rates for PPCM vary widely across the globe due to various reasons. Mortality rates as high as 24.2% at 6 months and 47.4% at 1 year of follow-up had been recorded in Kano, Nigeria, 48.3% over 4 years in Burkina Faso, 11.6% over 6 months in Zimbabwe and 13.0% over 6 months in South Africa (Table 2).[17,20,21,24] In comparison, mortality rates were much lower in the United States (4.1% over 1 year); 2.4% at one month post-hospital discharge in the EORP study, in-hospital mortality of 1% in South Korea, and 0% at 6 months in Germany; possibly a reflection of the higher standard of health care.[3,10,39,50] Although some researchers didn't identify any predictors of mortality, others inconsistently reported younger age at diagnosis, lower body mass index and some echocardiographic variables as independent predictors of mortality.[20,21,34] Whitehead *et al.* reported that mortality in-

Table 2. Pattern of mortality and left ventricular reverse remodeling among peripartum cardiomyopathy patients.

Country	Patients at follow up	Mortality, %	LVRR, %
Nigeria (1 year)[16]	33	47.4	29.4
South Africa (6 months)[15]	141	13	21
Burkina Faso (6 months)[12]	29	48.3	44.8
Zimbabwe (6 months)[19]	35	13	22.9
United States (1 year)[42]	100	4	71
EORP (1 month)[3]	411	2.4	-
Haiti (2 years)[29]	98	15.3	28
South Korea (in-hospital)[5]	795	1	
Germany (6 months)[48]	45	0	51.1

LVRR, left ventricular reverse remodeling; EORP, EURObservational Research Programme on peripartum cardiomyopathy.

creased with maternal age, in women with parity of more than 4, and in black women, who were 6.4 times more likely to die compared with whites.[51] In the IPAC study, 30% of patients were Black, and clinical outcomes were significantly worse in Black women as only 59% achieved a final LVEF >50% *versus* 77% of whites or others, whereas 26% of black women had either an event or a final LVEF <35% *versus* only 8% of whites or others (p=0.03).[39] However, in the EORP program, 106 (25.8%) patients were Black Africans, but mortality rate at one month post discharge did not differ between patients from ESC and non-ESC countries (p=0.216).[3]

LV reverse remodeling (LVRR) was recently shown to involve both LV systolic and diastolic functions, and maximum improvement seems to occur within the first 6 months of PPCM diagnosis.[20,21,23,39] In our cohort, 47.1% satisfied the criteria for LVRR while 29.4% recovered LV systolic function at 1 year follow-up; somewhat similar to the prevalence of LVRR of 28% over 2 years reported from Haiti and of 21% in South Africa over 6 months (Table 2).[20,21,34] Blauwet *et al.* found older age and smaller LV end-systolic dimension (LVESD) to be significant predictors of LV recovery among PPCM patients in South Africa.[20] In addition, *electrical remodeling* in the form of shortening of previously broader QRS duration, which is suggestive of improved LV function, has also been reported among PPCM patients.[53]

Right ventricular (RV) systolic and diastolic dysfunction (RVSD and RVDD respectively) have been recently studied in PPCM, suggesting that the disease is bi-ventricular in nature.[54-57] Karaye *et al.* recently reported a prevalence of RVSD (defined using tricuspid annular plane systolic excursion) of 71.1% of the patients at baseline, which reduced to 36.4% at 6 months and 18.8% at 1 year.[55] Karaye *et al*. also found RVDD in 69.8%, and combined RVSD and RVDD in 58.1% of PPCM patients.[56] In this study, Selenium deficiency was the only variable that significantly determined RVDD, being related to impaired RV relaxation in late diastole.[56] In the IPAC study however, results showed that RVSD (defined using RV fractional area change) was present in only one-third of PPCM patients at baseline, and was an independent predictor of subsequent lack of recovery of LV function and clinical outcomes including death.[57]

Conclusions

The history of peripartum cardiac failure in Africa dates to the 1960s and early mid 1970s, before the availability of echocardiography. To date, there is no population-based PPCM study in Africa to the best of our knowledge. However, hospital-based studies have reported incidence rates as high as 1:100 deliveries in Nigeria and representing up to 52% of all cardiomyopathies. For reasons that are not very clear, there are wide disparities in the epidemiology of PPCM within and between African Countries. However, the disease seems to be more common among the poor rural population. With the availability of echocardiography and other investigation tools, well characterized PPCM patients have been studied in Africa. One of the first studies on RV function in PPCM had come from Nigeria, and subsequent studies elsewhere have further described the bi-ventricular nature of the disease. Clinical outcomes are much worse in Africa than in Western Europe and North America. It is hoped that the ongoing peripartum cardiomyopathy in Nigeria (PEACE) Registry and the worldwide EURObservational Research Programme (EORP) on PPCM will soon shed more light on the epidemiology of PPCM in Africa.

Contributions

The authors contributed equally.

Conflict of interest

The authors declare no potential conflict of interest.

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