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ARTICLE

Rationale and design for the peripartum cardiomyopathy in Nigeria (PEACE) registry

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Abstract

Background: Nigeria probably has the highest burden of peripartum cardiomyopathy (PPCM) in the world. The primary objective is to describe the burden, ventricular remodelling, and outcomes (rehospitalisation rate, cardio-embolic events and survival) of PPCM in Nigeria. In the sub-studies, we aim to describe the relationship between selenium deficiency, oxidative stress and PPCM, the impact of sodium selenite supplementation on cardiac function in PPCM, and the prevalence of selenium deficiency and its relationship with cardiac function in apparently healthy pregnant women.
Methods: The main registry and the first sub-study are prospective longitudinal studies, while the second sub-study is an open-label randomised trial. 36 study centres across Nigeria have been registered and 10 of them are already recruiting subjects. Patients will be recruited from June to December 2017 and followed up till December 2018. Serum selenium and glutathione peroxidase will be assayed at recruitment for consecutive PPCM patients with left ventricular ejection fraction <45% at 6 months postpartum. 200 subjects with selenium deficiency will be randomised into treatment (selenium selenite 200 µg tablets daily for 3 months) and control arms. In the second sub-study, 120 apparently healthy pregnant women will be recruited at 28-38 weeks of gestation and reviewed at 6-8 weeks postpartum, and their serum selenium and glutathione peroxidas levels will be measured at recruitment.
Conclusions: This will be the largest systematic evaluation of PPCM in Nigeria, and it is hoped that the information will assist in developing locally applicable treatment guidelines and policies for the disease.

Key words peripartum cardiomyopathy registry, PEACE, selenium, Nigeria.

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Introduction

The first descriptions of the association between cardiac failure and the puerperium were made by Rudolf Virchow and Charles Porak separately in 1880.[1,2] In 1937, Gouley *et al.* described the clinical and pathological features of a severe and fatal type of heart failure (HF) in seven pregnant women in the last months of pregnancy, which persisted after delivery.[3] Hull and Hidden then described 80 postpartum patients with similar clinical features in New Orleans in 1938, and called it *Postpartal HF*.[4] However, it was in 1971 that Demakis *et al.* first described the diagnostic criteria of the disease and called it peripartum cardiomyopathy (PPCM).[5,6] Since then, the definition of PPCM has undergone several modifications but the most recent was by the HF Association of European Society of Cardiology (ESC) Working Group on PPCM.[7]

Epidemiology

The true incidence or prevalence of PPCM is unknown. However PPCM is rare in some parts of the world and more common in others.[8,9] Recent studies suggest an estimated incidence of 1 case per 299 live births in Haiti, one case per 1000 live births in South Africa, and 1 case per 2289-4000 live births in the USA.[10-13] The reasons for this variation in incidence between and within countries remain unknown, but probably reflect an overestimation of the disorder in earlier studies that relied upon clinical criteria alone for the diagnosis. Northern Nigeria seems to be one of the *hot spots* of PPCM in the world.

The disease was recently described as the most prevalent type of cardiomyopathy in Kano, Nigeria, found in 55 out of 1296 patients (4.2%) referred for echocardiography over a period of 7 months, representing 52.4% of all cardiomyopathies.[14] However, PPCM seems less common among other ethnic groups in Nigeria for reasons that are not yet clear.

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, toxaemia or hypertension of pregnancy, use of tocolytics, twin pregnancy, obesity and low socioeconomic status.[15-20]

The aetiology and pathogenesis of PPCM are unknown, but several hypotheses have been proposed over the years. Although possible role of genetic susceptibility has been suggested, its role in the aetiology of PPCM is still weak.[21] In a small study in Kano, sisters of PPCM patients were systematically screened with echocardiogram for possible cardiac abnormalities to support the familial theory of the disease, but none was found.[22] Most of the hypotheses were on non-genetic factors such as selenium deficiency, myocarditis, autoimmunity, vasculo-hormonal abnormalities and increased hemodynamic burden of pregnancy.[7]

Selenium deficiency hypothesis

In Kano, it was observed that among women referred for echocardiography, PPCM almost always occurred in women with low income.[17] The most plausible explanation for this observation would be poor nutrition predisposing the poor women to the disease, although the confounding effect of other risk/aetiological factors associated with poverty, such as increased tendency to infections, cannot be dismissed. Malnutrition had been suspected to play an important role in the aetiopathogenesis of PPCM, but the occurrence of the disease in well-nourished patients had put this theory to doubt.[23] Cenac *et al.* had reported selenium deficiency in 35 women with PPCM in Niger Republic.[9] However, a similar study among 18 PPCM patients in Haiti didn't corroborate the findings.[9,11] A more recent study in Kano, Nigeria, Karaye *et al.* reported significantly lower serum selenium in PPCM patients than in controls, and patients had higher prevalence (76.9%) of critically low serum selenium (<70 μg/L) than controls (22.0%) ($p<0.001$).[20]

Epidemiologic studies showed that low selenium levels in the soil and in local foodstuffs correlated with low selenium levels in whole-blood and hair samples, and treatment with sodium selenite prevented Keshan disease and mitigated the clinical manifestations in patients with the disease.[19,24] 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.[25,26] Therefore in spite of the observations by Fett *et al*., it is still conceivable that selenium deficiency is related to PPCM, at least in some parts of the world, such as the Sahel regions of Africa.[20,27] Although selenium supplementation has been used safely in Keshan disease and for other indications in pregnant women with beneficial effects, it has not been previously systematically used to treat PPCM.[19,28,29]

Hemodynamic burden of pregnancy hypothesis

Several hemodynamic changes such as peripheral vasodilatation, increase in blood volume and cardiac output occur between the 1st and 2nd trimesters of pregnancy, and patients with known pre-existing structural cardiac diseases typically present with clinical HF at this time.[30,31] In striking contrast, PPCM overwhelmingly presents during the postpartum period, and factors that modify the stresses of vaginal delivery such as caesarean section do not appear to modify the risk of developing the disease.[31]

Pregnancy seems to affect cardiac structure and function, even if uneventful. Melchiorre *et al*. found that by the end of uneventful pregnancy, significant left ventricular (LV) diastolic dysfunction and impaired myocardial relaxation were evident in 17.9% and 28.4% of women, respectively, whereas myocardial contractility was preserved.[32] There was full recovery of the cardiac dysfunction at 1 year postpartum.[32]

Outcomes

LV function recovery and mortality rates for PPCM vary widely across the globe due to several reasons; likely a reflection of the standard of medical care in various countries.[33-37] Mortality rates as high as 24.2% at 6 months and 47.4% at 1 year of follow-up have been reported in Kano, Nigeria, but much lower rates of 13.0% over 6 months in South Africa, 15.3% over 2 years in Haiti and 28.0% over 5 years in USA, have also been reported.[33-37] In addition, majority of the deaths seem to occur within 6 months of PPCM diagnosis.[33-37] 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.[33-37]

LV reverse remodelling (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.[36-38] In our cohort, 47.1% satisfied the criteria for LVRR while 29.4% recovered LV systolic function at 1 year follow-up.[36] 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.[33] In addition, *electrical remodelling* in the form of shortening of previously broad QRS duration, which is suggestive of improved LV function, has also been reported among PPCM patients.[39]

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.[37,40,41] Karaye *et al*. recently reported a prevalence of RVSD of 71.1% of the patients at baseline, which fell to 36.4% at 6

months and 18.8% at 1 year.[37] Karaye *et al*. also found RVDD in 69.8%, and combined RVSD and RVDD in 58.1% of PPCM patients.[42] In this study, selenium deficiency was the only variable that significantly determined RVDD, being related to impaired RV relaxation in late diastole.[42]

Hypotheses

The aetiology of PPCM is multifactorial, and we hypothesised that in our setting, the impact of selenium deficiency on hemodynamic effects of pregnancy on cardiac function is probably of significant importance. We also hypothesised that selenium supplementation using oral Sodium Selenite 200 µg/day for 3 months, will be safe, and could correct the selenium deficiency in affected subjects and improve the LV systolic function.

The primary aim of the present study is to describe the burden and demographic, social and clinical characteristics, and ventricular remodelling and outcomes (rehospitalisation rate, cardio-embolic events and survival) of PPCM in Nigeria. In the first sub-study, we aim to describe the prevalence of selenium deficiency and its relationship with cardiac function in apparently healthy pregnant women in Nigeria. In the second sub-study, we aim to determine the relationship between selenium deficiency, oxidative stress and PPCM, and the impact of sodium selenite supplementation on cardiac function in an open-label randomised trial.

Materials and Methods

Study design

The main registry is a prospective, national, multicentre longitudinal study, being conducted in centres in Nigeria. It is expected that PPCM subjects will be recruited in 36 registered tertiary and secondary level healthcare centres in Nigeria that have Doppler echocardiography facility. Ten centres have started recruiting patients on 5th June 2017, and the remaining 26 centres are expected to join soon.

The sub-studies are being carried out in only 4 centres in 2 cities (Kano and Ile-Ife) in Nigeria, because of the logistics of biomarker assays. The first sub-study is also a longitudinal study in which apparently healthy pregnant women at 28-38 weeks of gestation and attending antenatal clinic (ANC) are being recruited, evaluated and followed up till 6-8 weeks postpartum.

The second sub-study is an open-label randomised trial in which oral sodium selenite (by NaturesWay®) 200 µg/day for 3 months will be offered to PPCM patients with selenium deficiency and LVEF<45% at 6 months postpartum. The randomisation is being carried out by simple balloting at the laboratories of the participating centres by the lead chemical pathologist who is blinded to the patients' identities and clinical characteristics, after measuring the biomarkers of the patients and confirming their selenium deficiency status.

Sample size estimation for the sub-study

The minimum sample size for the sub-study was estimated at 32, using 2-sided significance level of 95%, power of 80% and prevalence of selenium deficiency among apparently healthy postpartum women of 22% and among untreated PPCM patients of 76.9%.[20] However, we shall recruit into the sub-studies 200 PPCM subjects and randomise them to treatment and control groups, and 120 apparently healthy pregnant subjects who have satisfied the inclusion criteria.

Inclusion criteria

Inclusion criteria are as follows:

i. Confirmed diagnosis of PPCM;
ii. PPCM patients with HF symptoms at the time of recruitment (for new patients only);
iii. Asymptomatic pregnant women attending ANC;
iv. Sub-study: open-label randomised trial: non-pregnant PPCM patients with all of the following: LVEF <45% at 6 months postpartum AND selenium deficiency
v. Written informed consent.

Exclusion criteria

Exclusion criteria are as follows:

i. Asymptomatic PPCM patients at the time of recruitment (for new patients only);
ii. PPCM patients who are not expected to survive at least 6 months from recruitment;
iii. Pregnant women with any medical condition other than PPCM;
iv. Subjects who are considered not likely to attend follow up reviews regularly, because of lack of patient's and close relative's phone numbers, or long distance from the study centre, etc;
v. Refusal or withdrawal of consent.

PPCM subjects that are being followed up by the centres are to be recruited regardless of the presence of symptoms.

Diagnosis of peripartum cardiomyopathy

PPCM will be defined according to the recommendations of the HF Association of ESC Working Group on PPCM.[7] The LV may not be dilated but the LVEF should be <45%. It is a diagnosis of exclusion. HF will be defined as a syndrome in which patients have the following features: symptoms of HF, typically shortness of breath at rest or during exertion, and/or fatigue; signs of fluid retention such as pulmonary congestion or ankle swelling; and objective evidence of an abnormality of the structure or function of the heart at rest.[43]

Data collection

E-mails were sent to the e-mail group of the Nigerian Cardiac Society to invite all centres to join the Registry. Centres that

have facilities to assay the biomarkers for the sub-study were invited to join it. A study protocol was provided to each of the sites to guide investigators to consistently complete the CRFs and send to the Registry Coordinator through the site's Principal Investigator (PI). At the study sites, physicians and obstetricians are being approached and requested to consecutively refer all patients with suspected PPCM to the investigators, for further evaluation. In addition, apparently healthy pregnant women attending the antenatal clinic are being consecutively referred to the investigators for evaluation and follow up at no cost. The study would be explained to the subjects, and then interviewed, clinically evaluated and recruited consecutively after applying the inclusion and exclusion criteria. Demographic data, relevant aspects of history and physical signs, results of investigations, medications, co-morbid conditions, and complications would be recorded in a detailed questionnaire.

Results

Enrolment visit

At this visit, each subject will have a 12-lead ECG and transthoracic echocardiogram at rest at the study centres according to standard recommendations.[44,45] Other baseline investigations recommended for the management of patients with PPCM would be carried out at the laboratories of the study centres, including complete blood counts and serum urea, electrolytes and creatinine.[7] For the study centres that have facilities to join the sub-study, the serum selenium and glutathione peroxidise (GPO) will be assayed according to standard criteria.[46-48] Abnormal values of the biomarkers will be defined as serum selenium <70 µg/L and GPO >470 U/L.

Follow-up visits

Patients will be reviewed every 3 months for 18 months, and investigations will be repeated every 6 months. Data will be recorded in the study questionnaire.

Subjects in the treatment arm of the randomised open-label trial will be given sodium selenite 200 µg tablets to take daily for 3 months. One month supply of the drug will be supplied to each patient at a time, and all the patients in the sub-study will be reviewed monthly for the 3 months and then every 3 months. Both arms will continue to receive best medical treatment according standard recommendations.[7,43] The biomarkers will be reassessed at the completion of the study, while ECG and echocardiography will be carried out at baseline, and then every 6 months till the completion of the study, at 12-18 months of follow up. All adverse events relating to the supplementation will be recorded and sent to the Registry Coordinator for forwarding to the appropriate local authority. The following details will be expected for each patient reporting an adverse event following the selenium supplementation: name, age, hospital number, address, type of adverse event, date and time of the event, the intervention needed to treat the event, and the outcome of the intervention. The patients' journey from enrolment to the end of the study is summarised in Figure 1.

Cardiac function assessment

Standard echocardiographic recordings would be obtained, and LVRR would be defined as the presence of both absolute increase in LVEF ≥10.0% and decrease in LV end-diastolic dimension indexed to body surface area (LVEDDi) ≤33.0 mm/m^2, while recovered LV systolic function as LVEF ≥55%, during the follow-up.[38,44]

LVDD would be defined and graded using trans-mitral flow and LV myocardial TDI velocities at the mitral (septal) annular level as follows:[44]

Normal LV diastolic function: E:A ratio 1-2, deceleration time (DT) 160-230 milliseconds (ms) and E/e' <8.

Grade I LVDD (impaired myocardial relaxation): E:A <1.0 and DT >240 ms.

Grade II LVDD (pseudonormalised pattern): E:A 1-1.5, DT 160-230 ms, e' <7 cm/s and E/e' >15.0.

Grade III LVDD (restrictive filling): E:A >2.0, DT <160 ms, e' <7 cm/s and E/e' >15.0.

Specimen collection and processing

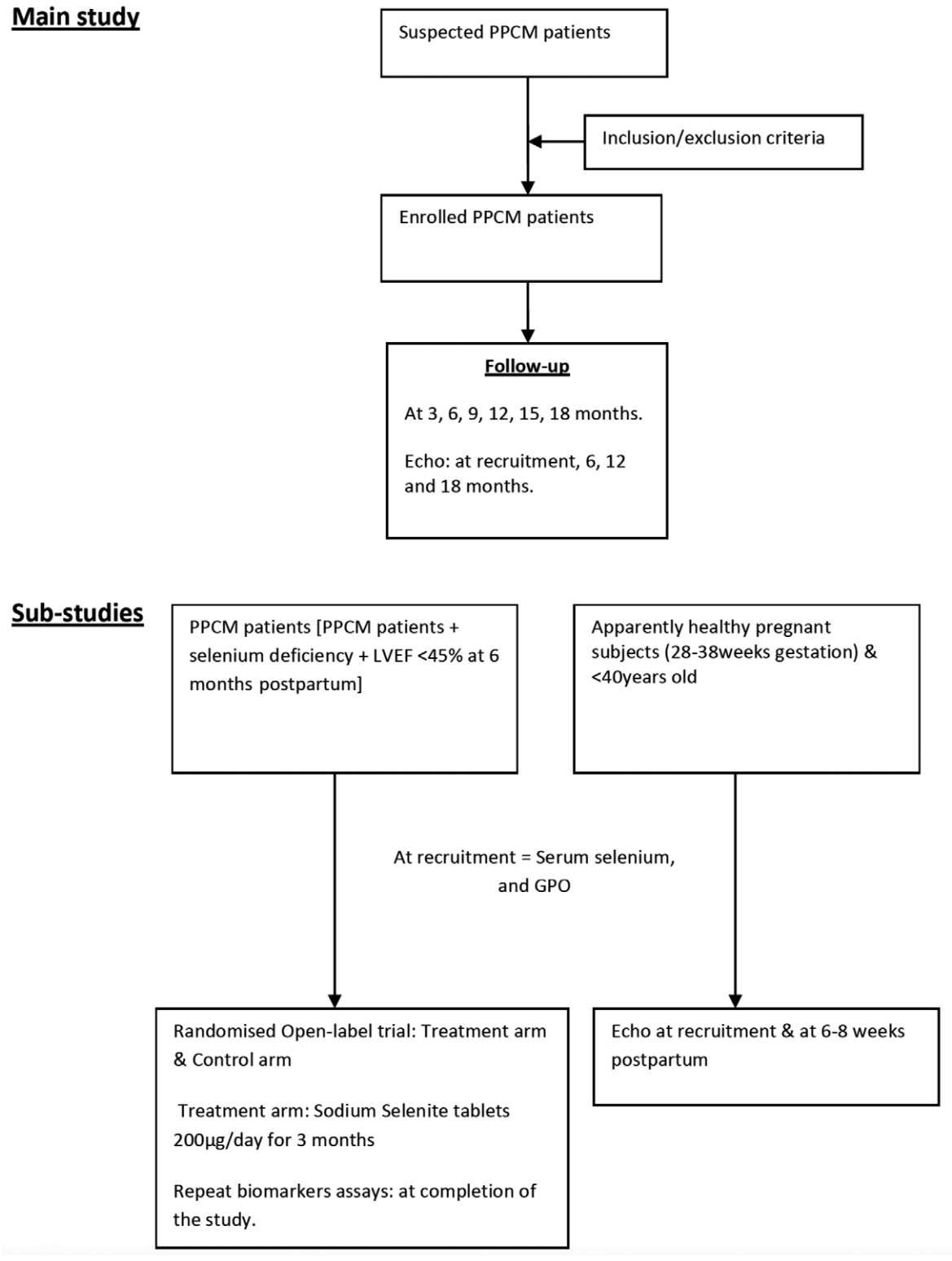
Five millilitres (5 mL) of blood are being collected from the study participants for the biomarkers assays. Blood specimen will be obtained using a prominent vein (antecubital fossa is the preferred site), and minimal tourniquet time is recommended (<2 mins). Skin is cleansed with alcohol swab and the site allowed to dry before venepuncture. Serum separator tube (clot and gel) bottles are used for all samples. Blood is allowed to clot for 30 minutes at 25°C, centrifuged at 3000 rpm for 15 minutes, and then the serum transferred into a plain tube and frozen until analysis. Avoid repeated freeze-thaw cycles and ensure prompt separation of cells from serum. The labelled serum samples are sent to the laboratory immediately and analysis is recommended as soon as possible although the serum is stable for one month at -80°C. GPO will be assayed using the Sandwich ELISA technique while Serum selenium would be measured using the Inductive Coupled Plasma Mass Spectrometry method.

Ethics

Informed consent shall be obtained from all recruited subjects and a consent form signed. Ethical approval for the study has been or is being sought from the Ethical Research Committees of all the participating centres before the commencement of the study, and the research shall conform to the ethical guidelines of the Declaration of Helsinki; on the principles for medical research involving human subjects.[49]

Statistical analysis

Continuous variables would be explored for the presence of skewness. Baseline characteristics will be described using



GPO, glutathione peroxidise; LVEF, left ventricular ejection fraction.

Figure 1. Flow of subjects.

summary statistics, as appropriate. All outcome events will be recorded and summarized individually as proportions, with two-sided confidence intervals calculated. Spearman correlation coefficient and logistic regression models will be used to assess potential associations between LV recovery, LVRR or survival and variables of interest. Kaplan-Meier curves would be obtained for the outcome measures. The statistical analysis will be carried out using SPSS version 16.0 software. Two-sided $p<0.05$ will be considered as minimum level of statistical significance.

Discussion

This will be the largest systematic evaluation of PPCM in Nigeria, which will describe the burden and demographic, social and clinical characteristics and treatment of the disease. The study will also describe the ventricular remodelling and outcomes of PPCM, the relationship between selenium deficiency, oxidative stress and PPCM, the prevalence of selenium deficiency and its relationship with cardiac function in apparently healthy pregnant women, and the impact of sodium selenite supplementation on cardiac function among PPCM patients, in Nigeria. This information will assist in developing locally applicable treatment guidelines, policies and interventions for this seemingly deadly disease.

The available literature on PPCM is limited in several ways. Although Nigeria probably has the highest burden of PPCM in the world, much of the epidemiology of the disease is yet to be described in a comprehensive national study. Secondly, the studies that have described the outcomes of PPCM in Nigeria and elsewhere are still few, and have significant differences in objectives, methodology and follow-up periods. However, the relevance of this information on the management of affected patients and control of the disease cannot be over-emphasised. In addition, the relationship between selenium deficiency and PPCM seems to be relevant, and if proven, could potentially lead to a cure of the disease. However, the 2 studies that suggested the relevance of selenium deficiency in PPCM were single-centred and involved only small number of patients. Therefore, the results need to be further substantiated. Finally, the data on cardiac function during pregnancy in Nigeria is limited, and its relationship with selenium deficiency has not yet been described. The results of this study would be very relevant in preventing and perhaps curing PPCM.

Limitations

The present study has several limitations. Most importantly PEACE Registry has very limited funding in spite of all our efforts. In fact, we are relying on personal funds and donations from philanthropists. The ideal study design for the first sub-study is a randomised double-blind placebo-controlled trial, but our desire for the ideal was barred by the limited funding. We also had to limit the sample size of the sub-study because of the funding challenge. It is our sincere hope that the results of PEACE Registry will open the doors of more funding for us to search for more answers for PPCM.

Conclusions

This will be the largest systematic evaluation of PPCM in Nigeria, and it is hoped that the information will assist in developing locally applicable treatment guidelines and policies for the disease.

Contributions

All the authors made a substantive intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare no potential conflict of interest.

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