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Prevalence of left ventricular dysfunction and relationship with serum selenium in apparently healthy pregnant women: results from the PEACE registry

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Abstract

Background: Peripartum cardiomyopathy (PPCM) is common in North-West Nigeria and many affected patients have selenium deficiency. It is not known whether asymptomatic cardiac dysfunction related to selenium deficiency commonly starts during pregnancy in the region. The study aimed to determine the prevalence of left ventricular (LV) systolic and diastolic dysfunction in apparently healthy pregnant women and if there is relationship with serum selenium, in a society with high prevalence of PPCM.

Methods: This was a prospective longitudinal study carried out in 3 centers in Kano, Nigeria. 108 apparently healthy pregnant women were consecutively recruited between the 28th and 38th weeks of gestation and re-evaluated at the 6th to 8th weeks postpartum. Serum selenium was measured at enrolment during pregnancy. LV systolic dysfunction was defined as LV ejection fraction (LVEF) below 50% and LV diastolic dysfunction was defined and graded according to the recommendations of the American Society of Echocardiography.

Results: LV systolic dysfunction and diastolic dysfunction were found in 6 subjects (5.6%) and 20 subjects (18.5%) during pregnancy, and in 9 subjects (10.2%; $p=0.340$) and 14 (15.9%; $p=0.631$) of them after delivery, respectively. Mean LVEF was $62.2\pm 6.9\%$ and $60.6\pm 8.2\%$ ($p=0.108$) during pregnancy and after delivery respectively. Mean LV end-diastolic dimension measured during pregnancy (48.6 ± 4.9 mm) was not significantly difference with what was obtained after delivery (47.2 ± 6.9 mm) ($p=0.099$). Mean left atrial size (37.0 ± 4.8 mm vs. 35.2 ± 4.8 mm; $p<0.001$) and mitral septal E/e' ratio (8.4 ± 2.8 vs. 1.3 ± 0.5 ; $p<0.001$) were higher during pregnancy than after delivery, respectively. Selenium deficiency (<70 $\mu\text{g/L}$) was found in only 2.8% of subjects, and serum selenium did not significantly correlate with indices for LVEF or diastolic (mitral E/e' ratio) functions both during pregnancy and after delivery.

Conclusions: LV systolic and diastolic dysfunction and selenium deficiency were uncommon during apparently healthy pregnancy and early puerperium, and serum selenium did not correlate with indices for LV function, in a population with high prevalence of PPCM.

Key words: left ventricular dysfunction; pregnancy; selenium; peripartum cardiomyopathy; PEACE registry.

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Introduction

Several hemodynamic changes such as peripheral vasodilatation and increases in blood volume and cardiac output occur during pregnancy, and these seem to affect cardiac structure and function, even if the pregnancy is uneventful.¹ It has been recently reported that by the end of uneventful pregnancies, 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.² In addition, there was full recovery of the cardiac dysfunction at one year postpartum.³

Peripartum cardiomyopathy (PPCM) is a disease of multifactorial origin that has a global spread, but with higher prevalence among women of African ancestry.⁴ Hemodynamic burden of pregnancy and delivery had been postulated to be among the potential mechanisms of PPCM, but factors that modify those stresses, including cesarean delivery, did not appear to modify the risk of developing it.⁴ However, it is not known whether asymptomatic cardiac dysfunction commonly starts during pregnancy in societies with high PPCM prevalence.

Although it is a global disease, PPCM has important inter- and intra-regional variations in geographical spread. Northern Nigeria seems to be one of the regions of the world with high prevalence of PPCM, and mortality rate and prevalence of selenium deficiency had been found to be high among affected patients.^{5,6} To the best of our knowledge, the impact of hemodynamic burden of pregnancy on cardiac function and its relationship with serum selenium in a society with high burden of PPCM has not been previously described. Thus, in this study we aimed to determine the prevalence of LV systolic and diastolic dysfunction in apparently healthy pregnant women, and if there is relationship with serum selenium, in a society with high prevalence of PPCM.

Materials and Methods

Peripartum cardiomyopathy in Nigeria (PEACE) Registry is a prospective longitudinal study that was conducted in 22 centers spread across Nigeria. However, this sub-study was carried out in 3 centers [Aminu Kano Teaching Hospital (AKTH), Murtala Mohammed Specialist Hospital (MMSH) and Mohammed Abdullahi Wase Specialist Hospital (MAWSH)] in Kano, Nigeria, between June 2017 and February 2018.

The study protocol for PEACE Registry has already been published.⁷ We consecutively enrolled into the study apparently healthy pregnant women attending the antenatal clinics of the study centers after obtaining written informed consent. Subjects were recruited between the 28th and 38th weeks of gestation. Subjects with known medical conditions or unlikely to attend follow-up were excluded. A pretested questionnaire was used to collect demographic, clinical and laboratory data of the subjects. Electrocardiography (ECG), echocardiography, and assay for serum selenium, were carried out on each subject, using

standard criteria and methods, as previously described.⁷⁻⁹

Subjects were followed-up and re-evaluated between the 6th and 8th week after delivery. Data collected included history of survival of childbirth, other aspects of clinical history, and physical examination and trans-thoracic-echocardiogram findings. Low serum selenium was defined as $<70 \mu\text{g/L}$.⁷ For the purpose of this study, LV systolic dysfunction was defined as LV ejection fraction (LVEF) of less than 50%. LV diastolic function was defined and graded using trans-mitral flow and LV myocardial tissue Doppler imaging velocities at the mitral (septal) annular level as follows:⁸

- Normal LV diastolic function: E:A ratio 1-2, deceleration time (DT) 160-230 milliseconds (ms) and $E/e' < 8$.
- Grade I LV diastolic dysfunction (DD) (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 $E/e' > 15.0$.

Ethical approval for the study was obtained from the Ethical Research Committees of all the participating centers before the commencement of the study, and the study conformed to the ethical guidelines of the Declaration of Helsinki on the principles for medical research involving human subjects.¹⁰

Data analysis

Continuous variables were explored for the presence of skewness. Proportions, medians with interquartile ranges and means with standard deviations were used to summarize subjects' characteristics, as appropriate. Chi-square, Fisher's exact, Student's t and Mann-Whitney tests were used to compare categorical and continuous variables, as appropriate. Relationships between serum selenium and variables of interest were determined using Spearman's correlation coefficient. Two-sided p-value < 0.05 was used as minimum level of statistical significance. The statistical analysis was carried out using SPSS version 23.0 software.

Results

A total of 108 apparently healthy pregnant subjects were consecutively recruited from the 3 study sites, at a rate of about 10 subjects/week, between June and December 2017; 58 (53.7%) from AKTH and 25 (23.2%) each from MMSH and MAWSH. They were recruited between the 28th and 38th weeks of gestation and reviewed again between the 6th and 8th weeks postpartum. The subjects' baseline characteristics are presented in Table 1, and they were compared with the postpartum variables in Table 2 and Figure 1. All the subjects were Nigerians and 88.9% of them were of Hausa-Fulani ethnic group. The majority of them (90.7%) had at least 6 years of basic primary school education, while 41.7% had tertiary-level education. Regarding their occupation, 52.8% were unemployed housewives, while 16 (14.8%) were petty traders and 11 (10.2%) were civil servants. All the subjects were residing within the vicinity of Kano City, Nigeria.

LV systolic dysfunction and diastolic dysfunction were found in 6 subjects (5.6%) and 20 subjects (18.5%) during pregnancy respectively, and in 9 subjects (10.2%) ($p=0.340$) and 14 (15.9%) ($p=0.631$) of them after delivery respectively. Mean LVEF was $62.2\pm 6.9\%$ and $60.6\pm 8.2\%$ ($p=0.108$) during pregnancy and after delivery respectively. Mean LV end-diastolic dimension was within normal limits both during pregnancy (48.6 ± 4.9 mm) and after delivery (47.2 ± 6.9 mm) ($p=0.099$). Mean left atrial size (37.0 ± 4.8 mm vs. 35.2 ± 4.8 mm; $p<0.001$) and mitral septal E/e' ratio (8.4 ± 2.8 vs. 1.3 ± 0.5 ; $p<0.001$) were higher during pregnancy than after delivery, respectively. Selenium deficiency ($<70\mu\text{g/L}$) was found in only 2.8% of subjects, and serum selenium did not correlate significantly with LVEF ($p=0.339$ during pregnancy, $p=0.648$ postpartum), E:A waves ratio of mitral filling

velocities ($p=0.751$ during pregnancy, $p=0.872$ postpartum) or mitral septal E/e' ratio ($p=0.838$ during pregnancy, $p=0.101$ postpartum).

The ECG variables are presented in Table 2, and it shows that there were no significant differences between the groups.

Of the 108 subjects, echocardiography could not be repeated for twenty (18.5%) of them after their delivery for various reasons (relocation to other cities, $n=5$; various other reasons including cultural, $n=15$). However, they were all contacted by telephone during the follow-up period and confirmed to be alive and healthy.

Discussion

In the present study we showed that the prevalence of LV systolic and diastolic dysfunction and of selenium deficiency in apparently healthy pregnant women were low. We also showed that serum selenium was not associated with indices for LV function in the studied population.

Previous studies had suggested that regions of northern Nigeria and southern Niger Republic have high prevalence of PPCM, which presents predominantly in the early puerperium, and selenium deficiency was relevant in its aetiopathogenesis.^{5,11} Prior to this study, it was not clear whether LV dysfunction was common during apparently healthy pregnancy and puerperium in a society with high PPCM prevalence. We therefore enrolled subjects into this study towards the end of pregnancy (28th-38th weeks of gestation) to screen for asymptomatic cases of LV dysfunction, which could later on progress into PPCM.

Firstly, this study has confirmed the previously described hemo-

Table 1. Baseline characteristics of subjects.

Variables	Pregnant subjects (N=108)
Age, years	29.1 \pm 5.4
Estimated gestational age, weeks	32.0 \pm 5.0
Gravidity, median (interquartile range)	3 (1-5)
Hausa/Fulani ethnicity, N. (%)	96 (88.9)
No formal education, N. (%)	10 (9.3)
Unemployed, N. (%)	57 (52.8)
Hemoglobin, g/dL	13.0 \pm 1.5
Selenium, $\mu\text{g/L}$	120.6 \pm 27.9
Selenium $<70\mu\text{g/L}$, N. (%)	3 (2.8)

Values are presented as the mean \pm standard deviation or as median with the interquartile range or as proportions.

Table 2. Comparison of clinical characteristics of subjects during pregnancy and after delivery.

Variables	Pregnancy (N=108)	Postpartum (N=88)	p-value
Systolic BP, mmHg	118 \pm 14	119 \pm 15	0.495
Diastolic BP, mmHg	74 \pm 8	77 \pm 10	0.025*
Heart rate/min	91 \pm 13	81 \pm 10	<0.001 *
Echocardiogram			
Left Atrium, mm	37.0 \pm 4.8	35.2 \pm 4.8	<0.001 *
LVEDD, mm	48.6 \pm 4.9	47.2 \pm 6.9	0.099
LVESD, mm	32.4 \pm 4.4	31.6 \pm 5.3	0.250
LV ejection fraction, %	62.2 \pm 6.9	60.6 \pm 8.2	0.108
LV Ejection Fraction $<45\%$	1 (0.9%)	3(3.4%)	0.229
IVSD, mm	7.3 \pm 2.0	7.5 \pm 2.0	0.210
LVPWD, mm	7.2 \pm 2.3	7.3 \pm 2.2	0.573
Mitral filling E/e'	8.4 \pm 2.8	1.3 \pm 0.5	<0.001 *
PASP, mmHg	19.4 \pm 3.7	18.1 \pm 8.0	0.650
LV diastolic dysfunction	20 (18.5%)	14 (15.9%)	0.631
Electrocardiogram			
PR interval, ms	146.4 \pm 19.7	151.2 \pm 20.1	0.177
QRS duration, ms	74.6 \pm 9.0	77.6 \pm 11.1	0.288
QTc interval, ms	430.4 \pm 29.8	422.6 \pm 14.8	0.321

LVEDD and LVESD, left ventricular end-diastolic and end-systolic dimensions respectively; IVSD, interventricular septal thickness at end-diastole; LVPWD, LV posterior wall end-diastolic dimension; PASP, pulmonary artery systolic pressure.

*p-value statistically significant. Values are presented as the mean \pm standard deviation or as median with the interquartile range or as proportions.

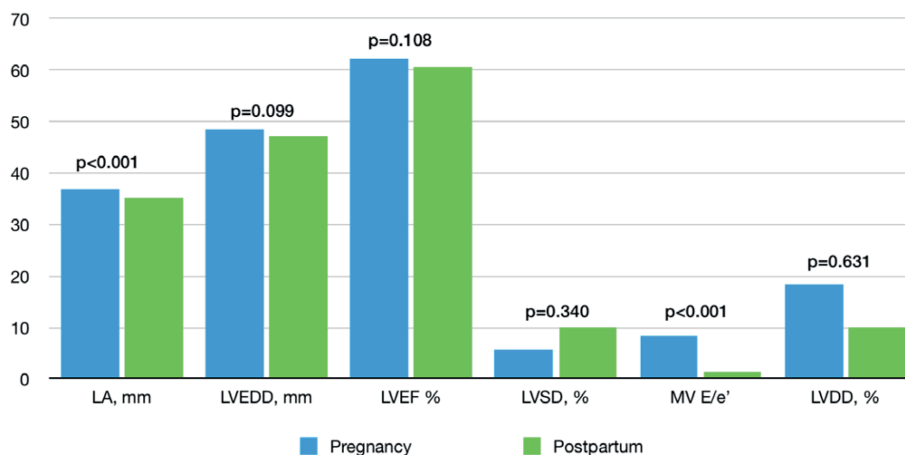


Illustration of echocardiogram variables for subjects obtained during pregnancy and after delivery. The bars representing the means and the p-values of the comparisons are presented.

LA, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVSD, LV systolic dysfunction (LVEF <50%); LVDD, LV diastolic dysfunction.

Figure 1. Comparison of echocardiogram variables of subjects during pregnancy and after delivery.

dynamic and cardiac changes that occur during uneventful pregnancy.^{1,2,12,13} Although LV systolic dysfunction was uncommon in most subjects (5.6%) during pregnancy, the prevalence doubled though insignificantly at eight weeks postpartum (10.2%). The prevalence of LV diastolic dysfunction was however higher and only changed minimally (18.9% vs. 15.9%) during pregnancy as compared with after delivery respectively, but subjects had significantly higher mean LA size and LV filling pressure (mitral E/e') during pregnancy than at postpartum. Our study design did not allow us to predict the outcome of these subjects with left heart dysfunction by the end of the puerperium or subsequent pregnancies, but the subjects were to be further evaluated and followed-up for potential future cardiovascular outcomes by their physicians. Melchiorre *et al.* described a higher prevalence of LV diastolic dysfunction of 46.3% among nulliparous apparently healthy pregnant women in London.² In the latter study, there was full recovery of cardiac function at one year postpartum, in contrast to our observation of insignificant changes in the prevalence of LV systolic and diastolic dysfunction at 6-8 weeks postpartum; perhaps a mere reflection of a shorter follow up period.² It is thus conceivable that a longer follow-up of our cohort might show similar observations. The reported reversal of the cardiac structural and functional abnormalities of pregnancy could be explained by the findings of a study in mice that suggested that the temporary cardiac remodeling of pregnancy, associated with volume overload and ventricular hypertrophy is accompanied by upregulation of vascular endothelial growth factor and increased myocardial angiogenesis, but with no increase in cardiac fibrosis.¹⁴

Thus, our results suggest that cardiac function in apparently healthy pregnant women in the society with high PPCM prevalence were not significantly different from what has been reported from elsewhere with lower PPCM prevalence.^{1,2,12,13} Secondly, we found that selenium deficiency was uncommon in

the present study and did not correlate with indices for LV systolic and diastolic function. It is of note that the studied population were mainly city dwellers who had some basic education and who received antenatal care, while majority of the previously studied PPCM subjects with selenium deficiency in the region came from rural areas.⁵ Our findings should therefore be interpreted with caution as it might not be applicable to the rural populace. The subjects were consecutively recruited from the same study sites where we recently recruited majority of the PPCM patients in PEACE registry, which is the largest study on PPCM in Africa.⁶ The mean selenium concentration in the present study was 120.6 ± 27.9 $\mu\text{g/L}$, which was lower than the levels reported from south-eastern Nigeria (169.8 ± 40.3 $\mu\text{g/L}$ or 1.01 ± 0.24 $\mu\text{mol/L}$) among healthy pregnant women where PPCM is rare.¹⁵ The lower value was in spite of the fact that regions in Nigeria prone to erosion such as South-Eastern Nigeria tend to have inadequate soil selenium concentrations which might lead to low availability of the mineral in the locally-produced foods.¹⁶ However, it could be speculated that the relatively low selenium levels in Kano could be due to the commonly known low consumption of sea foods which tend to be richer in selenium than plant materials.¹⁷

The specific impact of selenium deficiency on cardiac structure and function among apparently healthy pregnant women would need a different strategy that is outside the scope of the PEACE Registry at present. It is however important to point out that PPCM is a multifactorial disease that may not be caused by any single factor, but the interaction of several factors that could include genetic predisposition, selenium deficiency or other nutritional factors, deleterious effects of 16kDa form of prolactin, *etc.*^{3-5,11} Even for Keshan disease caused by selenium deficiency, more recent studies suggest that coxsackievirus B3 could be a contributing factor, and that selenium deficiency had additional wide-ranging effects.^{18,19}

Limitations

This study has some limitations. Firstly, 18.5% of the subjects were not re-evaluated with echocardiography after delivery, although they were all confirmed to be alive and asymptomatic on telephone. African researchers conducting longitudinal studies have been bedeviled by this high default rate from follow-up for several decades. Davidson *et al.* described this well in 1974 as a *major hindrance to the study of disease in the developing countries of Africa*, and is caused by many socio-cultural factors that are difficult to overcome.²⁰ Secondly, this is a hospital-based study involving women who were city dwellers and receiving the full complement of orthodox medical care. Therefore, our results may not be generalizable to sub-populations where many women do not attend antenatal care, such as the rural areas, where majority of PPCM patients have been reported to reside.⁵

Conclusions

In this study, we have reported that LV systolic and diastolic dysfunction and selenium deficiency were uncommon during apparently healthy pregnancy and early puerperium, in a population with high prevalence of PPCM. The results also showed that serum selenium was not associated with indices for LV function in the studied population. These findings therefore suggest that cardiac function in apparently healthy pregnant women, who were city dwellers in a region with high PPCM prevalence, was not significantly different from what has been reported from elsewhere with lower prevalence.

Conflict of interest

The authors declare no potential conflict of interest.

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