



## **Possible Impact of Select Trace Mineral Deficiency in HIV Seropositive Pregnant Women with/without Malaria Co-infection in NAUTH, Nnewi, Nigeria**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. Author NRU conceptualized and designed the study. Authors IUC, ISO, VOA and OBOI managed the literature searches and performed the experiment. Authors IUC, VOA, JCA and FAE analyzed and interpreted the data. Authors IUC and NRU wrote the original manuscript. All authors read and approved the final manuscript.*

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### **ABSTRACT**

**Aims:** To evaluate the impact of HIV and malaria on serum Zinc (zn), Selenium (se) and Magnesium (mg) in HIV seropositive pregnant women in Nnewi, Nigeria.

**Study Design:** This is a case-control study.

**Place and Duration of Study:** Prevention of Mother to Child transmission (PMTCT) of HIV Clinic of Nnamdi Azikiwe University Teaching Hospital, Nnewi, (NAUTH), Nigeria, between December, 2017 and April, 2018.

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**Methodology:** We included 122 consented female participants; 32 HIV seropositive pregnant women with malaria parasitaemia, 30 HIV seropositive pregnant women without malaria parasitaemia, 30 Malaria infected pregnant women, 30 pregnant women without HIV or malaria parasitaemia, aged between 18 and 42 years. Screening for HIV antibodies and malaria parasite was double screened using National algorithm, rapid detection technique (RDT) and Giemsa staining microscopy technique respectively. Micronutrient levels were determined using atomic absorption spectrophotometry (AAS).

**Results:** When the mean zn, sel and mg levels were compared between the test and control groups, significant decreases in serum zn ( $37.34 \pm 6.7$ ,  $36.70 \pm 4.39$ ), sel ( $29.93 \pm 6.02$ ,  $28.00 \pm 5.04$ ) and mg ( $2.41 \pm 0.46$ ,  $2.33 \pm 0.14$ ) were observed in HIV seropositive pregnant participants with/without malaria co-infection when compared with their corresponding controls Zn ( $45.1 \pm 7.83$ ,  $50.36 \pm 8.73$ ); Sel ( $31.46 \pm 6.19$ ,  $31.96 \pm 6.81$ ); Mg ( $2.62 \pm 0.30$ ) and ( $P < .05$  respectively). Body mass index (BMI) was significantly decreased while diastolic blood pressure (DBP) and systolic blood pressure (SBP) were significantly increased in HIV seropositive pregnant women with malaria compared with their seronegative counterparts ( $P < .05$  respectively).

**Conclusion:** The significant loss in BMI with derangement in serum zn, sel and mg levels in HIV seropositive pregnant women with/without malaria co-infection indicates high degree of malnutrition while the increased blood pressure suggests high blood pressure which might predispose the pregnant mothers to pre-eclampsia if not properly managed. Adequate micronutrient supplementation and effective anti malaria agent is strictly advocated in the routine management of HIV infected mothers during pregnancy to reduce the severity of the co-infection and adverse pregnancy complications especially in areas of malaria endemic transmissions.

*Keywords: HIV/malaria; co-infection; trace minerals; pregnancy.*

## 1. INTRODUCTION

Human immune deficiency virus and malaria infection remain a major public health issue in Nigeria health care system. Both infections pose great challenges in diagnosis and therapy specifically during pregnancy with detrimental outcomes that may affect both the mother and fetus [1]. It has been shown that HIV and malaria infections have a reciprocal effect on each other with a consequent increase in mortality rate [2]. HIV-infected pregnant women have been reported to be at greater risk of placental malaria infection [3]. Ayisi and colleagues has reported that malaria infection during pregnancy may increase the risk of mother-to-child transmission of HIV [4].

Trace elements deficiencies and HIV disease however, are thought to interact with each other [5]. The authors have shown that micronutrient deficiencies in HIV infected pregnant mothers could lead to disease progression and may contribute to an increased risk of placental malaria and adverse pregnancy outcomes [5]. The implications of these findings in malaria endemic region such as Nigeria form the bases for the present study.

## 2. MATERIALS AND METHODS

### 2.1 Study Design

This is a case-control study designed to assess the levels of trace elements (Zinc, Selenium, and Magnesium) in naive HIV seropositive subjects with malaria co-infection attending the ante-natal clinic at Nnamdi Azikiwe University Teaching Hospital in Nnewi (NAUTH). One hundred and twenty two (122) consented female participants aged between 18 and 42 years were randomly selected including: HIV seropositive pregnant women with malaria parasitaemia (32), HIV seropositive pregnant women without malaria parasitaemia (30), Malaria infected pregnant women without HIV infection (30), pregnant women without HIV or malaria parasitaemia (30) as control. All HIV seropositive pregnant women were yet to commence anti-retroviral therapy (naive). All subjects were screened for HIV seropositivity and malaria parasitaemia. Screening for HIV antibodies was done using Determine and Stat-Pak kit and confirmed with Unigold HIV kit. Pregnancy testing was done using human chorionic gonadotropin (HCG) one step pregnancy test strip. Peripheral malaria was double screened using Rapid Detection Technique (RDT) (2SD) and Giemsa stain thin and thick blood smears microscopy technique.

A well-structured questionnaire was administered to each participant to obtain their reproductive history and other biodata. Levels of trace elements zinc, selenium and magnesium were determined using atomic absorption spectrophotometry.

## 2.2 Study Site

The study was conducted in Nnamdi Azikiwe University Teaching Hospital (NAUTH) in Nnewi, Anambra State, Nigeria. It is popularly known as NAUTH is located at the south eastern part of Nigeria. It is one of the oldest and most prestigious teaching hospitals in Nigeria and serves as a referral center for the nearby towns and states in the south eastern part of the country. Laboratory analysis of trace elements was done at Biotechnology Research Center, Nnamdi Azikiwe University, Awka.

## 2.3 Subject Recruitment

Purposive sampling technique was employed. The subjects were pregnant women visiting PMCT clinic at NAUTH between December, 2017 and April, 2018 who voluntarily agreed to participate and were subsequently enrolled in the study.

## 2.4 Inclusion and Exclusion Criteria

Pregnant participants between 18 and 42 years of age with HIV/or malaria infection were included in the study. Non-Pregnant participants seronegative to HIV with or without malaria infection were also included. Pregnant women less than 18 and above 42 years were excluded from the study. Participants who are active smokers, alcoholics, hypertensive and diabetic were excluded. Participant using zinc, selenium and magnesium supplement were also excluded.

## 2.5 Sample Collection

Five milliliters (5ml) of venous blood were collected from each of the participants and dispensed 2.5ml each into a well labeled plain container and an EDTA container. The plain bottle sample was allowed to clot and centrifugation was performed at 1500 rpm for 5 minutes using bench centrifuge and serum separated for analysis of trace elements.

## 2.6 Laboratory Analyses

Determination of HIV-1/2 antibodies was done according to the National algorithm.

Malaria parasite screening was done using rapid detection test for *Plasmodium falciparum* malaria antigen as described by Murray and Gresser [6] and Giemsa stained thick and thin blood film for microscopic detection of *P. falciparum* parasites as described by WHO [7].

Determination of serum zinc, selenium and magnesium was done using atomic absorption spectrophotometry (AAS) as described by PerkinElmer [8].

## 2.6.1 Anthropometric data collection

A well-structured questionnaire was administered to all the participants to ascertain their medical history. The height and weight of the participants were measured. Height was measured to the nearest 0.1 cm using a tape rule, and weight measured to the nearest 0.1 kg using calibrated platform scales. The body mass index (BMI) was calculated by the formula of weight (kg)/height (m<sup>2</sup>). Obesity was assessed using body mass index (BMI) and waist circumference (WC). Three separate blood pressure (BP) readings were obtained per participants from the non-dominant arm using accoson sphygmomanometer with appropriate cuff size in sitting position at 2 min interval after an initial rest of 5–10 min with arm supported at heart level. The average of the past two readings was recorded for both systolic blood pressure and diastolic blood pressures (SBP and DBP) of each student. The cutoff value for hypertension was taken as SBP reading  $\geq 130$  mmHg and/or DBP of  $\geq 85$  mmHg.

## 2.7 Statistical Analysis

Statistical package for social sciences (SPSS) version 22 was used for the statistical analysis. The data generated was analyzed using Analysis of variance (ANOVA) to compare more than two independent variables and student's t-test for two independent variables. Pearson correlation was used to correlate different parameters. Values were considered statistically significant if  $p$  value  $\leq .05$ .

## 3. RESULTS

### 3.1 Anthropometric Data

When the BMI value was compared between the test and control groups, BMI value was significantly lower in HIV seropositive pregnant women with/without malaria co-infection ( $26.18 \pm 2.59$ ,  $26.85 \pm 3.10$ ) compared with HIV

seronegative pregnant women with/without malaria parasitaemia (28.59 ± 3.70, 27.21 ± 3.41) ( $P = .001$  respectively).

When the mean DBP was compared between the test and control groups, DBP value was significantly higher in HIV seropositive pregnant women with malaria co-infection (85.53 ± 9.90), HIV seronegative pregnant women with malaria parasitaemia (82.96 ± 9.86) compared with HIV seropositive pregnant women without malaria parasitaemia (79.83 ± 9.30) and HIV seronegative pregnant women without malaria parasitaemia (77.60 ± 5.75) ( $P \leq .001$  respectively). The between group comparison showed that DBP value was significantly higher in HIV seronegative pregnant women with malaria parasitaemia (82.96 ± 9.86) compared with HIV seronegative pregnant women without malaria parasitaemia (77.60 ± 5.75) ( $P = .012$ ).

When the mean SBP value was compared between the test and control groups, SBP value was significantly higher in HIV seropositive pregnant women with/without malaria parasitaemia (133.18 ± 8.18, 125.4 ± 6.71) compared with HIV seronegative pregnant women with/without malaria parasitaemia (127.56 ± 7.14, 120.43 ± 4.21) ( $P = .001$  respectively) (Table 1).

### 3.2 Serum Zinc, Selenium and Magnesium Levels

When the mean zinc level was compared between the test and control groups, the mean zinc level was significantly lower in HIV seropositive pregnant women with/without malaria co-infection (37.34 ± 6.7, 36.70 ± 4.39) compared with HIV seronegative pregnant women with/without malaria parasitaemia (45.1 ± 7.83, 50.36 ± 8.73) ( $P = .001$  respectively).

The mean level of selenium was compared between the test and control groups, selenium level was significantly lower in HIV seropositive pregnant women with/without malaria co-infection (29.93 ± 6.02, 28.00 ± 5.04) compared with HIV seronegative pregnant women with/without malaria parasitaemia (31.46 ± 6.19, 31.96 ± 6.81) ( $P = .044$ ). The between group comparison showed that the mean level of selenium was significantly lower in HIV seropositive pregnant women without malaria parasitaemia (28.00 ± 5.04) compared with HIV seronegative pregnant women with/without

malaria parasitaemia (31.46 ± 6.19, 31.96 ± 6.81) ( $P = .033, .015$  respectively).

When the mean serum magnesium level was compared between the test and control participants, magnesium level was significantly lower in HIV seropositive pregnant women without malaria co-infection (2.33 ± 0.15) and HIV seronegative pregnant women with malaria parasitaemia (2.27 ± 0.14) compared with HIV seronegative pregnant women without malaria infection (2.52 ± 0.30) ( $P = .001$ ). The between group comparison showed that magnesium level was significantly lower in HIV seronegative pregnant women with malaria co-infection (2.27 ± 0.14) compared with HIV seropositive women with malaria parasitaemia (2.33 ± 0.15) ( $P = .002$ ). Also, the mean magnesium level was significantly lower in HIV seronegative pregnant women with malaria parasitaemia (2.27 ± 0.15) compared with HIV seronegative women without malaria parasitaemia (2.52 ± 0.30) ( $P = .002$ ) (Table 2).

## 4. DISCUSSION

Malaria infection seems to accelerate the degree of reduction in micronutrients status during pregnancy [9]. This condition can be worsened by combined effects of HIV infection as observed in the present study [10]. Zinc level was significantly decreased in HIV seropositive pregnant women with malaria co-infection when compared with control participants. This could be attributed to poor nutritional status and reduction in trace mineral levels among pregnant women. The finding was in agreement with previous report [11]. Hypozincemia has also been reported in patients with acute illnesses [12]. The reduction in zinc level observed in pregnant women has been implicated in many adverse pregnancy outcomes as a result of malaria infection [9]. Because of the role of zinc in immune modulation [13], it can be deduced that the significant reduction in zinc level in this study, is an indication of response to the challenges of oxidative stress caused by the triple effects of malaria parasites, possible inflammation as a result of HIV infection [14] as well as negative effect of pregnancy on the element.

The significant decrease in zinc level in HIV seronegative pregnant women without malaria parasitaemia compared with the non-pregnant HIV seronegative women without malaria parasitaemia confirmed the increased utilization of zinc in pregnancy for growth of the fetus.

**Table 1. Values of some anthropometric parameters in HIV seropositive pregnant women with/without malaria co-infection and control group**

	<b>BMI(kg/m<sup>2</sup>) (mean± SD)</b>	<b>DBP(mmHg) (mean + SD)</b>	<b>SBP(mmHg) (mean + SD)</b>
HIV seropositive pregnant women with mp (A) n=32	26.18±2.59	85.53±9.90	133.18±8.18
HIV sero-positive pregnant women without mp (B) n=30	26.85±3.10	79.83±9.30	125.4±6.71
HIV seronegative pregnant women with mp (C) n=30	28.59±3.70	82.96±9.86	127.56±7.14
HIV seronegative Pregnant women without mp (Control) (D) n=30	27.21±3.41	73.60±5.75	120.43±4.21
F- Value	7.105	9.68	17.02
P- Value type	0.001	0.001	0.001
A VS B	0.374	0.007	0.001
A VS C	0.002	0.216	0.005
A VS D	0.173	0.001	0.001
B VS C	0.024	0.137	0.277
B VS D	0.638	0.289	0.014
C VS D	0.074	0.012	0.001

*P was considered statistically significant if ≤ .05*

**Table 2. Serum Levels of zinc, selenium and magnesium in HIV seropositive pregnant women with/without malaria co-infection and control groups**

	<b>Zinc (ug/dl) (mean + SD)</b>	<b>Selenium(ng/ml) (mean + SD)</b>	<b>Magnesium (mg/dl) (mean + SD)</b>
HIV seropositive pregnant women with mp (A) n=32	37.34±6.27	29.93±6.02	2.41±0.16
HIV seropositive pregnant women without mp (B) n=30	36.70±4.39	28.00±5.04	2.33±0.15
HIV seronegative pregnant women with mp (C) n=30	45.10±7.83	31.46±6.19	2.27 ±0.14
HIV seronegative Pregnant women without mp. (Control) (D) n=30	50.36±8.73	31.96±6.81	2.52 ± 0.30
F- Value	38.48	2.52	6.61
P- Value type	0.001	0.044	0.001
A VS B	0.747	0.224	0.283
A VS C	0.001	0.336	0.065
A VS D	0.001	0.203	0.186
B VS C	0.001	0.033	0.444
B VS D	0.001	0.015	0.019
C VS D	0.010	0.757	0.002

*P was considered statistically significant if ≤ .05*

The significant drop in trace element status of HIV seropositive participants with malaria co-infection may be a determinant in ascertaining factors that predisposes or determines severity of the disease in malaria endemic area. A high prevalence of malaria parasitemia among HIV infected individuals has been previously reported in Nigeria [14]. This means that the impact of the interaction of malaria and HIV will be most apparent in areas with HIV epidemic and malaria endemic areas such as Nigeria. Malaria parasite itself has been reported to contain a complete glutathione redox system especially glutathione reductase, which are very essential to their growth and development showing that inhibition of glutathione reductase in the malaria parasite with improved trace element supplementation represents an important approach to anti-malarial drug development [5].

In this study, selenium level was significantly lower among HIV seropositive pregnant women without malaria parasitaemia, compared with HIV seronegative pregnant women without malaria parasitaemia. This decrease is independent of malaria parasitaemia showing the place of selenium in HIV infection as well as in pregnancy. During pregnancy, a lot of stress is experienced physiologically and pathologically. The physiological stress is due to changes resulting from increased demands for nutrients, and changes in plasma volume [15]. These increased demands eventually lead to decrease in micronutrients including selenium levels and this likely increase fetal mortality risk [16]. Several authors have linked selenium deficiency in HIV infection to increased oxidative damage, cardiomyopathy and disease progression [17], indicating beneficial effect of antioxidant selenium in inhibition of HIV disease progression and vertical transmission [5,15].

The significant increase in selenium level in parasitemic pregnant women may be due to increased mobilization of this element to fight inflammation caused by parasites' invasion [18]. Furthermore, immune status and selenium concentration are said to increase as parity increases [19]. Increase selenium concentration has also been reported to have some beneficial effects in the treatment of malaria in children [13]; hence we dare to say that increased selenium concentration in parasitemic pregnant women, which may be an inflammatory response, is beneficial to both the pregnant mother and the unborn child.

In this study, the significant decrease observed in mean level of magnesium in HIV seropositive pregnant women with/without malaria co-infection compared with HIV seronegative participants is an indication of magnesium deficiency disease conditions as well as in pregnancy. This increases the demand for adequate supplementation of micronutrient in disease state and pregnancy. Magnesium is essential for many relevant physiological functions, such as bone growth, heart rhythm, vascular tone, nerve function, muscle contraction and relaxation [20]. Variations in the concentration of Mg may be caused by *P. falciparum* malaria, malnutrition as well as malabsorption [21]. There has been a report of increasing demands of adequate magnesium status during pregnancy especially in those from disadvantaged backgrounds [22]. A previous study has also reported decreased adverse pregnant complications with magnesium supplementation [23].

From this study loss of body mass was very significant among HIV seropositive pregnant women with or without malaria co-infection. Consequently, among HIV infected persons, secondary infections or co-infection are also significant predictors of low gestational weight gain [22], possibly through secretion of pro-inflammatory cytokines. Loss of fat mass due to infection during pregnancy might represent a decrease in available substrate for fetal growth [23]. Furthermore, reduction in weight could be a risk factor for chorioamnionitis through impairment in specific immune responses [24], which increases the risk of pregnancy outcomes [25]. The differences in BMI as observed in this study might be that some of the HIV seropositive pregnant women may have been under stress compounded by their poor nutritional and socioeconomic status.

Significant increase in blood pressure observed in HIV seropositive pregnant women than control pregnant women may be an indication of possible exposure to hypertension and preeclampsia. This was in line with the previous finding [26]. The authors reported higher prevalence of hypertension in HIV infected than in the HIV uninfected population. The increasing blood pressure could also be related to HIV specific factors such as lipodystrophy, atherogenesis and cytokines activity [27]. Infection with the human immunodeficiency virus type 1 in pregnant women represents an independent risk factor for maternal mortality and adverse pregnancy outcome [28]. Previous

report has shown that immune hyperactivity to paternal antigens has been hypothesized to play a role in the development of hypertension in pregnancy, and the immunosuppression caused by HIV could temper the immune response at the placental site and reduce placental vasoconstriction [29]. This potential protection may be a function of the intensity of immunosuppression and may depend on the severity of HIV disease and the use of antiretroviral therapy.

Notably, just as with the case of HIV seropositive pregnant women without malaria parasitaemia, in this study, there is a significant increase in the diastolic and systolic blood pressure in HIV seronegative pregnant women with malaria parasitaemia when compared with control. This is in line with an earlier work by Ndao and colleagues [30]. It has been established that in areas of stable endemic malarial transmission such as Nigeria, *Plasmodium falciparum* infection during pregnancy is usually asymptomatic [31]. This is characterized by sequestration of parasites in the placenta. Massive sequestration of parasites in the placenta leads to placental ischemia and other fatal complications [32]. However, in normal pregnancy, the earliest stages of development take place in a low oxygen environment- tissue hypoxia [33] and thereby, enhancing the release of reactive oxygen species. This has shown to enhance the release of ROS that are potentially damaging to the cardiovascular system [34]. Pathological stress is mainly due to disease conditions including malaria, HIV and hypertension. The effects of malaria in pregnancy have been well described. It has been documented that malarial infection during pregnancy is a major cause of adverse pregnancy outcomes and maternal complications [28, 31].

Oxidative stress has emerged in recent years as a suspected component in the pathogenesis of HIV disease [35]. Research has shown that even in the earliest stages of infection, a deleterious reductive-oxidative (redox) imbalance may occur [36]. Moreover, in response to malaria, HIV, pregnancy and other infections, phagocytic cells such as polymorphonuclear leucocytes and macrophages usually engage in respiratory burst in their attempt to destroy pathogens as a host cell-mediated immune response, with the depleting effect on CD4+T cells, yielding free radicals that react to yield ROS [37]. This shows that HIV and malaria co-infection causes additional oxidative stress in pregnant women.

Since the immune system is constantly stimulated and free radical production is higher than in healthy individuals, adequate intake of antioxidants such as selenium is therefore, critical in minimizing oxidative stress [18, 35]. It has been noted that HIV seropositive pregnant women have a higher risk of developing severe malaria infection particularly in malaria endemic area with attendant immune dysregulation [31, 38]. This can contribute to the sequestering of infected erythrocytes, adhesion of platelets and mononuclear cells [35]. This mechanism of inflammation and sequestration gives rise to tissue stress and significant rise in diastolic and systolic blood pressure as confirmed in this study in HIV seropositive pregnant women with malaria co-infection compared to controls.

## 5. CONCLUSION

From the findings in this study, HIV and malaria co-infection impact serious significant derangements in micronutrient status (zinc, selenium and magnesium) of HIV seropositive pregnant women with malaria co-infection. There was a significant change in anthropometric parameters (DBP, SBP and BMI) in HIV seropositive pregnant women with malaria co-infection. This could predispose the affected individuals to adverse pregnancy outcomes, pre-eclampsia and hypertension if not adequately managed. It is therefore, strictly recommended that adequate micronutrient supplementations with antioxidant trace minerals be included in routine module for management of HIV seropositive pregnant women with or without malaria co-infection during their antenatal visit especially in regions of malaria endemicity.

## 6. LIMITATION OF STUDY

There was lack of analysis of the participants' food profile due to short duration of the study, Further longitudinal study is advocated for explore the participant food habits, since the concentration of these nutrients is directly associated with food habits; time of HIV infection/diagnosis, and viral load + CD4 T count, as all these points can also be crucial for nutrient reduction, etc.

## CONSENT

All authors declare that 'written informed consent was obtained from the participants for publication of this research work.

## ETHICAL APPROVAL

"All authors hereby declare that all experiments have been examined and approved by the board of human research ethics committee of Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State (NAUTH/CS/66/Vol.10/194/2017/104) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki."

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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