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Micronutrient deficiencies among pregnant women with *Plasmodium falciparum* infection in Owo, Ondo State, Nigeria

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Abstract

Background: Two important barriers to a successful pregnancy outcome are maternal under nutrition and malaria. This study was conducted to determine some micronutrient deficiencies among pregnant women infected with *Plasmodium falciparum* in Owo, Ondo State, Nigeria

Material and methods: Two hundred and fifty four participants aged 18 to 42 years consisting of 154 pregnant women attending antenatal clinic of the Federal Medical Center, Owo, and 100 apparently healthy non-pregnant women as controls were randomly enrolled in this study. Blood specimen was collected and analyzed for the detection of *P. falciparum* using 10% Giemsa staining technique while micronutrients (calcium, copper, iron and zinc) were analyzed using Atomic Absorption Spectrophotometer (AAS).

Results: Out of 154 pregnant women studied, 91 (59.1%) had micronutrient deficiency (MND) while 5 out of 100 (5.0%) non-pregnant control had micronutrient deficiency ($p < 0.0001$). Forty three (27.9%) of the 154 pregnant women and 3 (3.0%) of 100 non-pregnant control had *P. falciparum* infection ($p < 0.0001$). Forty three of the 91 (47.3%) pregnant women and 3 of the 5 (60%) non-pregnant women with MND had *P. falciparum* infection ($p = 0.6681$). All 43 pregnant women with MND but none of the 63 pregnant women without MND had *P. falciparum* infection ($p < 0.0001$). Similarly, all 3 non-pregnant women with *P. falciparum* infection had MND but none of the 95 non-pregnant women without MND had *P. falciparum* infection ($p < 0.0001$). Multiple micronutrient deficiencies of iron and calcium (65.3%), iron and zinc (16.1%) and iron and copper (18.6%) were observed among pregnant women but none among non-pregnant women. Factors significantly associated with *P. falciparum* infection among pregnant women with MND were age group 23-27 years ($p = 0.0109$), first trimester gestational age ($p = 0.0234$), primiparity ($p = 0.0303$) and wet season ($p < 0.0173$). There was no significant association between anaemia and prevalence of *P. falciparum* infection in pregnant women with MND ($p = 0.1327$) but pregnant women with iron deficiency were more likely to be infected with *P. falciparum* than those with other micronutrient deficiencies ($p = 0.0013$)

Conclusion: This study reported a higher prevalence rate of 27.9% for *P. falciparum* infection in pregnant women compared to 3% in non-pregnant women population, but a much higher rate of 47.3% among pregnant women with micronutrient deficiencies.

Key words: Micronutrient deficiencies, *Plasmodium falciparum*, pregnant women, Owo

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Carences en micronutriments chez les femmes enceintes atteintes d'une infection à *Plasmodium falciparum* à Owo, dans l'État d'Ondo, au Nigéria

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Abstrait

Contexte: La sous-nutrition maternelle et le paludisme sont deux obstacles importants à la réussite de la grossesse. Cette étude avait pour objectif de déterminer certaines carences en micronutriments chez les femmes enceintes infectées par *Plasmodium falciparum* à Owo, dans l'État d'Ondo, au Nigéria

Matériel et méthodes: Deux cent cinquante-quatre participants âgés de 18 à 42 ans, dont 154 femmes enceintes fréquentant la clinique prénatale du Centre médical fédéral d'Owo et 100 femmes apparemment non enceintes et en bonne santé comme témoins ont été inscrits au hasard dans cette étude. Des échantillons de sang ont été prélevés et analysés pour la détection de *P. falciparum* en utilisant une technique de coloration à 10% de Giemsa, tandis que les micronutriments (calcium, cuivre, fer et zinc) ont été analysés à l'aide d'un spectrophotomètre d'absorption atomique (AAS)

Résultats: Sur 154 femmes enceintes étudiées, 91 (59,1%) avaient un déficit en micronutriments (MND), tandis que 5 sur 100 (5,0%) des témoins non enceintes avaient un déficit en micronutriments ($p < 0,0001$). Quarante-trois (27,9%) des 154 femmes enceintes et 3 (3,0%) des 100 témoins non enceintes avaient une infection à *P. falciparum* ($p < 0,0001$). Quarante-trois des 91 (47,3%) femmes enceintes et 3 des 5 (60%) femmes non enceintes atteintes de MND avaient une infection à *P. falciparum* ($p = 0,6681$). Les 43 femmes enceintes atteintes de MND, mais aucune des 63 femmes enceintes sans MND n'a été infectée par *P. falciparum* ($p < 0,0001$). De même, les 3 femmes non enceintes atteintes de MND, mais aucune des 95 femmes non enceintes sans MND n'a été infectée par *P. falciparum* ($p < 0,0001$). Des carences multiples en micronutriments en fer et en calcium (65,3%), en fer et en zinc (16,1%) et en fer et en cuivre (18,6%) ont été observées chez les femmes enceintes mais aucune chez les femmes non enceintes. Les facteurs significativement associés à l'infection à *P. falciparum* chez les femmes enceintes atteintes de MND étaient les groupes d'âge 23-27 ans ($p = 0,0109$), l'âge gestationnel au premier trimestre ($p = 0,0234$), primiparité ($p = 0,0303$) et saison des pluies ($p < 0,0173$). Il n'y avait pas d'association significative entre l'anémie et la prévalence de l'infection à *P. falciparum* chez les femmes enceintes atteintes de MND ($p = 0,1327$), mais les femmes enceintes présentant une carence en fer étaient plus susceptibles d'être infectées par *P. falciparum* que celles présentant d'autres carences en micronutriments ($p = 0,0013$)

Conclusion: Cette étude a révélé un taux de prévalence plus élevé de 27,9% pour l'infection à *P. falciparum* chez les femmes enceintes, contre 3% chez les femmes non enceintes, mais un taux beaucoup plus élevé de 47,3% chez les femmes enceintes présentant des carences en micronutriments

Mots-clés: carences en micronutriments, *Plasmodium falciparum*, femmes enceintes, Owo

Introduction:

Malaria has been reported to be one of the three killer communicable diseases in Africa (1). An estimated 35,000 children in the Southern region of Nigeria die from malaria infection annually (2). Malaria is one of the main causes of maternal and child mortality with severe consequences on the population, social and economic development of countries

ravaged by this disease (3, 4). It is estimated that each year over 125 million pregnant women living in low-and-middle-income countries are at risk of infection with *P. falciparum* and *P. vivax* (5). It has long been observed that populations residing in malaria endemic areas generally live under conditions that lead to poor nutritional status. Children and pregnant women are the worse hit by

malaria and also affected by poor nutrition (6).

Pregnancy is a period in the life cycle of a woman when additional nutrients are needed to meet the metabolic and psychological demands as well as the increased requirements of the growing fetus and placenta (7). Many anatomic, biochemical and physiologic changes occur during pregnancy to maintain a healthy environment for the growing fetus (8). Maternal nutrition does not only impact the mother in terms of morbidity but also on the growth and development of the fetus (9). The quality of nutrition in the first 1000 days beginning from the mother's pregnancy through her child's second birthday is a critical window when a child's brain and body develop rapidly and good nutrition is essential to lay the foundation for a healthy and productive future (10). Under nutrition is an underlying cause of death and it leaves millions more with lifelong physical and mental impairments (11).

Poor quality diet due to inadequate intake of animal source foods particularly in developing countries has been implicated as the major cause of micronutrient deficiencies. In addition, women who avoid meat and/or milk in developed countries have been reported to have higher risk of micronutrient depletion during pregnancy and lactation (12). Several micronutrient deficiencies have been established to contribute to abnormal prenatal development and/or pregnancy outcome (12). The common micronutrients are vitamins A, B, C, D and E, calcium, zinc, copper, iron, and magnesium (4, 13).

Deficiencies in maternal micro nutrient status may be a product of poor quality diets, high fertility rates, repeated pregnancies, short inter pregnancy intervals and increased physiological needs. All of these factors may be aggravated by inadequate healthcare systems with poor capacity, poverty and inequities, and socio-cultural factors such as early marriage, adolescent pregnancies and traditional dietary practices (14, 15, 16, 17, 18). The two important barriers to

a successful pregnancy outcome are maternal undernutrition which contributes an estimated 800,000 neonatal mortality annually and malaria, estimated to cause about 900,000 low birth weight deliveries and over 100,000 infant deaths yearly (19, 20, 21). Foetal exposure to under nutrition is associated with congenital anomalies, intrauterine growth restriction, low birth weight, stunting in childhood, shorter adult height, lower educational attainment, and reduced economic activity (22).

Adequate intakes of micronutrients are needed for the development of efficient immune system (23). There is a growing body of reports linking micronutrient deficiencies and malaria caused by *P. falciparum* in developing countries where certain micronutrient deficiencies may be predisposing factors (24, 25, 26, 27). There is paucity of data on micronutrient deficiencies among pregnant women with *P. falciparum* infection in Owo, Ondo State. Against this background, this study was conducted to determine the micronutrient deficiencies among *P. falciparum* infected pregnant women in Owo, Ondo State.

Materials and methods:

Study area

This study was carried out at the Federal Medical Center, Owo, Ondo State. The hospital is a tertiary health institution with a referral status to Primary Health Care Centers, Maternity and Antenatal Clinics around Owo town.

Study population

This study was conducted between January and June, 2018 at the Federal Medical Center, Owo, Ondo State. Two hundred and fifty four participants consisting of 154 pregnant women attending antenatal clinics at the Federal Medical Center, and 100 apparently healthy, age matched non pregnant women as controls were enrolled in this study by simple random sampling technique. The participants' age ranged from 18-42 years.

Participants who refused informed

consent, pregnant women on treatment plan for trace elements (supplements) and those on antimalarial agents were excluded from the study. A well structured questionnaire was administered to collect demographic information from participants whereas informed consent was sought from participants before specimen collection. Information obtained through the questionnaire includes age, marital status, gestational age and parity amongst others. The Ethics and Research Committee of the Federal Medical Center, Owo, Ondo State approved the protocol for this study.

Collection of blood specimen

About 10 ml of venous blood was collected from each participant, 5 ml of which was dispensed into ethylene diamine tetra acetic acid (EDTA) container and properly mixed. The remaining 5 ml was dispensed into a plain tube and allowed to clot for the serum to separate.

Processing of specimen

Thick and thin blood films from each blood specimen were made, allowed to air-dry and stained in 10% Giemsa stain solution for 30 min. The stained smears were rinsed in buffer solution and allowed to air-dry. The stained thick films were examined under bright field light microscope for estimation of malaria parasite density while the thin films were examined for species of *Plasmodium*. A total of 200 fields per film were examined (28).

Haemoglobin concentration was determined using the automated analyzer-Sysmex Kx-21 (Sysmex Cooperation,

Kobe, Japan). According to the WHO cutoff, anaemia was determined as haemoglobin concentration less than 11 g/dl for pregnant women and less than 12 g/dl for non-pregnant women (29, 30).

The micronutrients assayed for were calcium, copper, iron and zinc using Atomic Absorption Spectrophotometer (Buck Scientific 210 VGP, East Norwalk, CT). Briefly, for each element, the AAS was auto-zeroed using the flame from the lowest to the highest calibration. The corresponding absorbance was obtained and the graph of absorbance against concentration of the trace elements present being displayed in parts per million (ppm) (31).

Statistical analysis

The frequency data were analyzed by Chi-square test while the potential risk factors were analyzed using odd ratios. The statistical software used in the data analyses was INSTAT® (GraphPad Software Inc, La Jolla, CA, USA).

Results:

The micronutrients assayed in this study were calcium, copper, iron and zinc. Out of 154 pregnant women studied, 91 (59.1%) had micronutrient (iron) deficiency while 5 out of 100 (5.0%) non-pregnant control had micronutrient (iron) deficiency (OR 27.44, $p < 0.0001$). This trend was similar for copper, calcium and zinc (Table 1) which showed that pregnancy status was significantly associated with reduction in all micronutrients assayed with iron having the greatest reduction.

Table 1: Micronutrient deficiency status of pregnant and non-pregnant women population

MND status	Pregnant (%) n=154	Non-pregnant (%) n=100	Total (%) n=254	OR	95% CI	P value
Iron	91 (59.1)	5 (5)	96 (37.8)	27.44	10.559-71.332	< 0.0001
Copper	38 (24.7)	2 (2)	40 (15.7)	16.052	3.775-68.052	< 0.0001
Zinc	29 (18.8)	0 (0)	29 (11.4)	47.247	2.850-783.34	< 0.0001
Calcium	24 (15.6)	1 (1)	25 (9.8)	18.277	2.430-137.49	< 0.0001

MND = Micronutrient Deficiency

Table 2: Risk factors associated with MND and *P. falciparum* infection among studied population

Risk factors	No of pregnant women with MND (%)	No infected with <i>P. falciparum</i> (%)	OR	95% CI	P value
1. Age group					
18-22	26	9 (32.1)			0.0109
23-27	25	18 (72.0)			
28-32	15	8 (53.3)			
33-37	20	6 (30.0)			
38-42	5	2 (40.0)			
2. Marital status					
Single	19	7 (36.8)			0.5933
Married	62	31 (50.0)			
Widowed	10	5 (50.0)			
3. Gestational age					
1 st trimester	28	19 (67.9)			0.0234
2 nd trimester	38	16 (42.1)			
3 rd trimester	25	8 (32.0)			
4. Parity					
Primiparous	35	22 (62.9)	2.821	1.177-6.757	0.0303
Multiparous	56	21 (37.5)			
5. Seasonal variation					
Dry season	33	10 (30.3)	0.3294	0.1331-0.8185	0.0173
Wet season	58	33 (56.9)			
6. Pregnancy status in relation to MND and <i>P. falciparum</i> infection					
Pregnancy status	No of women with MND	No infected with <i>P. falciparum</i>	OR	95% CI	P value
Pregnant	91	43 (47.3)	0.5972	0.09519-3.747	0.6681
Not pregnant	5	3 (60.0)			

MND = Micronutrient Deficiency

Forty three (27.9%) of the 154 pregnant women and 3 (3.0%) of 100 non-pregnant control had *P. falciparum* infection (OR 12.526, $p < 0.0001$) indicating that pregnancy is a significant risk factor for acquisition of *P. falciparum* infection (Table 2). Forty three of the 91 (47.3%) pregnant women and 3 of the 5 (60%) non-pregnant women with MND had *P. falciparum* infection, indicating that MND is an independent risk factor for *P. falciparum* infection in both pregnant and non-pregnant subjects (OR 0.5972, $p = 0.6681$) (Table 2).

MND as a significant risk factor for *P. falciparum* infection among the studied population is further highlighted by the fact that all 43 pregnant women with MND but none of the 63 pregnant women without MND had *P. falciparum* infection (OR 113.9110, $p < 0.0001$). Similarly, all

3 non-pregnant women with *P. falciparum* infection had MND but none of the 95 non-pregnant women without MND had *P. falciparum* infection (OR 267.40, $p < 0.0001$) (Table 3).

Table 3: MND and *P. falciparum* infections in pregnant and non-pregnant women population

(a)					
MND status	No with pregnancy	No with <i>P. falciparum</i> infection	OR	95% CI	P value
MND positive	91	43	113.9110	6.835-1898.3	< 0.0001
MND negative	63	0			
(b)					
MND status	No without pregnancy	No with <i>P. falciparum</i> infection	OR	95% CI	P value
MND positive	3	2	267.40	10.694-6686.3	< 0.0001
MND negative	0	95			

MND = Micronutrient Deficiency

Multiple micronutrient deficiencies of iron and calcium (65.3%), iron and zinc (16.1%) and iron and copper (18.6%) were observed among pregnant women (Table 4) but no multiple micronutrient deficiency was observed among non-pregnant women.

Table 4: Micronutrient deficiency combinations in pregnant women

Micronutrient deficiency	Frequency
Iron + calcium	77 (65.3)
Iron + zinc	19 (16.1)
Iron + copper	22 (18.6)
Total	118

Age significantly affected the prevalence of *P. falciparum* infection among pregnant women with MND ($p = 0.0109$) with the 23-27 years age group having the highest prevalence (46.2%). Marital status did not affect the prevalence of *P. falciparum* infection among pregnant women with MND ($p = 0.5933$). Gestational age affected significantly the prevalence of *P. falciparum* infection in pregnant women with MND ($p = 0.0234$) with those in the 1st trimester having the highest prevalence of *P. falciparum* infection (67.9%). Primiparous women with MND were significantly more prone to *P. falciparum* infection ($p = 0.0303$), with a 1 to 6-fold risk of acquisition.

The prevalence of *P. falciparum* infection among pregnant women with MND was higher in rainy season (56.9%) than in dry season (30.3%) ($p < 0.0173$) (Table 2). There was no significant association between anaemia and prevalence of *P. falciparum* infection in pregnant women with MND ($p = 0.1327$) (Table 5). The three cases of *P. falciparum* infection in non-pregnant women with MND were also seen in those without anaemia. Pregnant women with iron deficiency are more likely to be infected with *P. falciparum* than those with other

micronutrient deficiencies ($p = 0.0013$) (Table 6).

Table 5: Relationship between anaemia and prevalence of *P. falciparum* infection in pregnant women with MND

Pregnant women	No with MND	No infected with <i>P. falciparum</i>	OR	95% CI	P value
Anaemia	78	34 (43.6)	0.3434	0.0974-1.211	0.1327
No anaemia	13	9 (69.2)			

MND=Micronutrient Deficiency

Table 6: Comparison of micronutrient deficiencies among pregnant women infected with *P. falciparum*

Micronutrient	No with MND	No infected with <i>P. falciparum</i> (%)	P value
Iron	46	43 (93.5)	0.00013
Copper	20	12 (60.0)	
Zinc	13	9 (69.2)	
Calcium	12	6 (50.0)	

MND=Micronutrient deficiency

Discussion:

Pregnant women are often deficient in several nutrients particularly micronutrients, which can negatively impact on their well being as well as the health, growth and development of their fetus and infants (32). Micronutrient deficiencies in pregnancy have been associated with adverse health outcomes such as maternal anaemia, maternal and perinatal mortality, low birth weight, pre-term birth, intra-uterine growth retardation, altered immune response and cognitive deficits in the newborn (20, 33-37). Malaria has been associated with malnutrition and micronutrient deficiencies and certain micronutrient deficiencies may predispose to malaria especially among pregnant women (4). To the best of our knowledge, this is the first study to assess some micronutrient deficiencies among pregnant women with *P. falciparum* infection in Owo, Ondo State of Nigeria.

An overall prevalence of 27.9% for *P. falciparum* infection was observed among pregnant women population

studied but 47.3% among pregnant women with MND. The prevalence of 27.9% in this study is similar to 24% rate reported in Ouagadougou, Burkina Faso among pregnant women and 26.7% reported in Yaqshid district, Somalia also among pregnant women (38, 39). Pregnancy has been reported to reduce immunity as a result of general immunosuppression sustained by elevated level of serum cortisol which allows fetal allograft retention but renders the women susceptible to various infectious diseases (40). This may partly explain the reason for the high prevalence of *P. falciparum* in pregnancy in our study compared to the low rate of 3% among non-pregnant age matched control.

In this study, pregnancy was a significant risk factor for micronutrients deficiency for all the micronutrients assayed ($p < 0.0001$), with a 10 to 71-fold increased risk for pregnant women to be micronutrient deficient. Requirement for some micronutrients such as calcium, copper, iron and zinc are known to increase during pregnancy due to greater needs of the mother to increase her body tissue reserves, and to meet the high metabolic demands and development of the placenta and fetus (41, 42).

Micronutrients play an important role during pregnancy and reduction may cause physical abnormalities and diseases which increase the risk of adverse pregnancy outcomes (43). The levels of the four micronutrients assayed in our study were significantly reduced among the pregnant women, with highest reduction in the level of iron. Iron deficiency in pregnancy may cause anaemia which can lead to chronic fetal hypoxia, premature birth and perinatal mortality (44, 45). Pregnant women should therefore be encouraged particularly to consume iron-rich diet in order to forestall these adverse pregnancy outcomes.

There were cases of multiple micronutrient deficiencies observed among pregnant women in this study. In addition, pregnancy caused more reduction of the combination of iron and

calcium levels (50%) when compared with other micronutrient combinations. Individually, deficiencies of any of these micronutrients have been associated with adverse outcomes such as preterm delivery, miscarriage, premature rupture of membranes, foetal nervous system damage, gestational hypertension, worsening of post-partum haemorrhage, maternal and fetal ossification disorders, and anomalies in DNA replication and transcription (46, 47, 48, 49, 50). Multiple micronutrients deficiency is expectedly associated with severe complications in pregnancy, childbirth and fetal development (51, 52). Adequate micronutrient supplementation in pregnancy is advocated to break the vicious circle that undernutrition can engender from pregnancy to the newborn through childhood, adolescence, and pregnancy in the next generation (53).

In this study, age was significantly associated with prevalence of *P. falciparum* infection among pregnant women with MND ($p = 0.0109$) with those in the 23-27 years age group having the highest prevalence (72.0%). The nutritional status of Nigerians has over the last few years been poor particularly with recent economic recession in the country. The National Demographic Health Survey 2013 reports indicated that nutritional status among Nigerian women aged 15-49 years has only minimally improved over a 10 year period, with prevalence of undernutrition of 15% in 2003 reduced to 11% in 2013 (54). This may partly explain our findings in this age group. Marital status was not associated with the prevalence of *P. falciparum* infection among pregnant women with MND ($p = 0.5933$) though the three cases of *P. falciparum* infection in the non-pregnant women were observed only in married subjects.

It has been reported that malaria in early pregnancy increase the risk of adverse pregnancy outcomes after organogenesis and placentation (55). In this study, pregnant women with MND in the first trimester had the highest prevalence of malaria (67.9%) when

compared to other trimesters which imply that majority of the women in our study are at high risk of adverse pregnancy outcome.

Our study revealed that primiparous women with MND had a higher risk (1 to 6-fold increased risk) of acquiring *P. falciparum* infection than multiparous women. This observation may be ascribed to inexperience in the act of pregnancy coupled with the fact that primiparous women have the propensity for not attending antenatal clinic early enough during the period they should have received health talks bothering on nutrition and health status during pregnancy.

P. falciparum infection among pregnant women occurred more frequently in rainy season with high prevalence rate of 46.6% compared to 16.7% during the dry season. Rainy season provides ecological alterations favouring the breeding of the mosquito vector which enhance transmission of malaria. Other possible factors for this include inadequate waste disposal facilities, poor drainage system and poor standards of living (56).

Contrary to the World Health Organization (WHO) report that 25% of the world population has anaemia with highest prevalence among preschool children and pregnant women (57), quite surprisingly, we did not find any association between anaemia and prevalence of *P. falciparum* in pregnant women with MND in our study ($p = 0.1327$). Also, the three non-pregnant women with MND who had *P. falciparum* infection did not have anaemia. The reason for this finding is not clear.

Iron deficiency and malaria have reportedly been described as significant co morbidities in most developing countries, and both maladies disproportionately affect pregnant women and children (58). In our study, pregnant women with iron deficiency were more likely to be infected with *P. falciparum* than those with other micronutrient deficiencies ($p = 0.0013$). Iron is essential for the survival of malaria parasite as an essential cofactor for the

DNA replication enzyme, ribonucleotide reductase, required to fuel the rapid intra-erythrocytic proliferation of the parasite (59) and for pyrimidine and heme biosynthesis (60). This may explain the synergy of iron deficiency in pregnancy and *P. falciparum* infection in our study.

Conclusion:

Our study reported a higher prevalence rate of 27.9% for *P. falciparum* infection in pregnant women compared to 3% in non-pregnant women population, and a much higher rate of 47.3% among pregnant women with micronutrient deficiencies. Emphasis on health education, adequate intake of well balanced diets consisting of the appropriate micronutrients in the right proportion and intake of nutritional supplements are advocated in pregnancy.

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