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Thrombocytopenia and Anaemia Status of Pregnant Nigerian Women with Malaria Infection

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ABSTRACT

Thrombocytopenia indicated by low platelet (PLT) counts and anaemia, low haemoglobin (Hb) levels, are the major commonest complications in severe malaria infection. *Plasmodium falciparum* malaria can cause thrombocytopenia, where there is an abnormally low number of platelets, and activation of the coagulation cascade. Nitric oxide is also a key mediator of platelet homeostasis. The results of this study revealed significantly ($p < 0.05$) low PLT counts and Hb levels ($188.16\pm7.03 \times 10^3$ U/L and 8.88 ± 0.15 g/dl) in the infected pregnant women when compared to the control subjects ($241.17\pm9.80 \times 10^3$ U/L and 12.11 ± 0.27 g/dl respectively).Degree of parasitaemia, gestational period, gravidae and age are inversely correlated with anaemia status and are statistically significant when compared to the control subjects. The platelet counts were found to decrease with severity of parasitaemia ($163.17 \pm 15.20 \times 10^3$ U/L). Thus, severe malaria and anaemia can lead to thrombocytopenia complication with fatal consequences both to the mother and foetus.
Key words: Malaria, pregnant women, anaemia, thrombocytopenia.

INTRODUCTION

Malaria is the most important parasitic infection in humans and is common in tropical Africa. Each year, more than 30 million African women in malaria-endemic areas become pregnant and are at risk of infection with *Plasmodium falciparum*[1]. Prevention of malaria in pregnancy, which can have serious consequences for both the mother and her unborn child, is a major public health challenge [2].Malaria during pregnancy is a major public health concern and an important contributor to maternal and infant morbidity and mortality in malaria-endemic countries [3]. Pregnant women are particularly susceptible to malaria,

and in high transmissionsettings they have a greater risk of severe *P. falciparum* malaria. *Plasmodium falciparum* infected red cells sequester in the placenta, disrupting nutritional exchange between mother and fetus and causing intrauterine growth retardation[4].

Malaria is associated with an increased risk of abortion, stillbirth, and low birth weight [5].One of the detrimental effects of malaria in pregnancy is the risk of becoming anaemic [6]. In Africa, 5-10% of pregnant women suffer from severe anaemia, with 26% of these cases being attributable to malaria [7]Van Den Bro. Anaemia in pregnant women is a more crucial public health problem. The most at risk groups of pregnant women are those who are pregnant for the first time and women of young maternal age [8]. Another stage of pregnancy that is at high risk of being infected with malaria is the first and second trimester of pregnancy [9].During pregnancy there are a number of changes that happen that put the mother at risk of infection. This risk is made worse by the ability of infected erythrocytes generated by the malaria infection to target the placenta [10].

Anaemia occurs during the erythrocytic stage of malaria. During this stage red blood cells are digested by the parasite and as a result of this, remove iron from the blood [11]. If this continues, it develops into maternal anaemia [12]. Maternal malaria can have health impacts on the child as it grows. There is the risk that infants whose mothers have suffered from malaria may also suffer from increased risk of malaria infection [13]. Effects may also be seen in the infant in their mental growth and development [14]. Increased risk to metabolic diseases may also occur. Other problems that can also occur when apregnant mother contracts malaria is complications during the pregnancy [15]. Anaemia could be caused by hemolysis, increased splenic clearance of infected and uninfected red blood cells, cytokine-induced dyserythropoiesis, iron deficiency and malaria [16].

Thrombocytopenia is a condition whereby the blood has a lower than normal number of blood cells (platelets) which is as a result of peripheral destruction and consumption[17]. The aetiology of malaria-related thrombocytopenia is thought to include coagulation disturbances, splenomegaly, oxidative stress, bone marrow alterations, alterations in splenic functions, a direct interaction between *Plasmodium* and platelets, sequestration and pooling of the platelets in the spleen, immune-mediated destruction of circulating platelets, and platelets mediated clumping of *P. falciparum* - infected erythrocytes resulting in pseudo-thrombocytopenia [18][19].

In the case of *P. falciparum*, immune reaction and complement activation are presumed to be the initiating steps leading to anemia and thrombocytopenia [20]. Platelets play a critical role in the pathogenesis of malaria infection [21]. Platelets act by stabilising and strengthening bridges between RBCs and endothelial cells, which is considered the cornerstone of*falciparum* malaria [19]. This study therefore was carried out to evaluate thrombocytopenia and anaemia status of pregnant Nigerian women with malaria in Benin – City, Nigeria.

MATERIALS AND METHODS

Study Location

This study was conducted at the Central Hospital, Benin - City, Edo State, Nigeria. The study subjects are pregnant women suffering from malaria infection. Infected non – pregnant women were also recruited for the study. Healthy non – malaria (non – pregnant) subjects were used as the controls. The study was approved by the Edo State Ministry of Health Ethical Committee (HA.577/VOL.11/80) before its commencement.

Study group

A total of one hundred and twelve (112) pregnant women were recruited and screened for malaria parasite; 44 (39.29%) pregnant women were positive for malaria parasite and 68 (60.71%) pregnant women were negative for malaria parasite. A total of fifty – four (54) non pregnant women were used as the control subjects.These pregnant women visited the ante - natal clinic at Central Hospital, Benin City, Edo State, Nigeria, forroutine medical check-up. All the patients in this study were infected with the specie *P.falciparum.* Other clinical history such as gestational period, parity, age were obtained from their clinical records.

Blood collection

About 10ml of venous blood was drawn by venipuncture from each woman and immediately transferred into a bottle containing ethylenediamine tetra acetic acid (EDTA). The blood samples were centrifuged at 3000 r.p.mfor 10 minutes and the plasma separated and stored at -4˚ until assayed.

Determination of parasitaemia

Parasitaemia was determined by the use of thick and thin blood films using Geimsa stain. The thick blood film was used to attain a qualitative diagnose for malarial infection and the thin blood film was used to identify the *Plasmodium* specie present. The thick and thin films were viewed for the number of parasites per 200 blood cells. Patients were labelled as malaria negative only if three consecutive smears were

negative.The degree of parasitaemia was expressed as mild (+), moderate (++) and severe (+++).

Haematological analysis

The following were analysed:Red blood cells (RBC), white blood cells (WBC), packed cell volume (PVC), haemoglobin (Hb), platelet counts, mean corpuscular volume (MCV), mean corpuscular haemglobin (MCH)andmean corpuscular haemoglobin concentration (MCHC), using an automated haematological analyser (Erma Inc Erma, Tokyo Japan);

STATISTICAL ANALYSIS

The data obtained were subjected to statistical analysis using automated package SPSS (version 21.0) and were expressed as mean ±SEM. One way ANOVA and Duncan multiple range comparison tests were used to compare the means and to test for levels of significance at 95%confidence.

RESULTS

Table1: Haematological status of pregnant Nigerianwomen with malaria from Benin - City, Nigeria.

	Control	INPW	UIPW	IPW
WBC (× 10^3/UL)	5.13±0.43^b	3.35±0.39^a	5.06±0.33^b	4.23±0.41^a
RBC (× 10^6/UL)	4.27±0.05^a	4.02±0.09^a	4.03±0.05^a	3.72±0.07^a
Hb (g/dl)	11.11±0.27^c	7.19±0.52^a	9.53±0.09^b	8.88±0.15^a
HCT (%)	31.39±0.30^b	23.26±2.79^a	30.48±0.44^b	28.46±0.59^{ab}
MCV (fl)	76.44±0.88^b	52.41±3.77^a	75.49±1.29^b	77.92±0.96^b
MCH (pg)	23.63±0.53^a	26.32±0.64^b	24.05±0.33^a	23.81±0.36^a
MCHC (g/dl)	31.74±0.38^b	29.76±0.82^a	30.84±0.31^a	30.69±0.39^a
PLT COUNT (× 10^3/UL)	214.76±7.03^b	183.20±4.94^a	231.39±8.39^c	188.16±7.03^{ab}

All values are represented as mean ± SEM. Values in the same row with different alphabets differ significantly ($p < 0.05$).

Key: WBC: White blood cells; RBC: Red blood cells; Hb: Haemoglobin; HCT: Haematocrit; MCV: Mean corpuscular volume; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular haemoglobin concentration; PLT: Platelet; INPW: Infected non – pregnant women; UIPW: Uninfected pregnant women; IPW: Infected pregnant women.

Table 1shows a significant ($p < 0.05$) decrease inRBC: Red blood cells; WBCs, Hb, HCT, MCV, MCHC and PLT count levels in infected pregnant women when compared to the control subjects. There was significant difference in ($p < 0.05$) MCH in infected non - pregnant women when compared to the controls.

Table 2: Effect of gestational period, parity and age on platelet counts of pregnant women from Benin City, Nigeria.

GESTATION PERIOD		PARITY	AGE (Years)	
FT	175.53±7.60^{a}	P	182.25±5.13^{ab}	18 – 27	163.17±15.20^{a}
ST	175.77±4.00^{a}	S	169.40±6.05^{a}	28 – 37	174.82±13.90^{ab}
TT	177.92± 4.70^{b}	M	204.53± 6.7^{b}	38 – 47	187.03±7.77^{b}

All values are represented as mean ± SEM. Values in the same column with different alphabets differ significantly ($p < 0.05$).

Key: FT: First trimester; ST: Second trimester; TT: Third trimester; P: Primigravidae;S: Secundigravidae; M: Multigravidae, Gestational period, parity and age of infected pregnant women were found to be positively correlated with platelet counts when compared to the control subjects (Table 2)

Table 3: Effect of parasitaemia on haematological indices ofpregnant women with malaria from Benin City, Nigeria.

	INPW				IPW		
	DEGREE OF PARASITAEMIA				DEGREE OF PARASITAEMIA		
	CONTROL	MILD (+)	MODERATE (++)	SEVERE (+++)	MILD (+)	MODERATE (++)	SEVERE (+++)
WBC($\times10^3$/UL)	5.13±0.43^a	5.97±0.41^a	6.13±0.68^a	6.00±0.50^a	4.99±0.40^a	4.80±0.84^a	5.14±0.70^a
RBC ($\times10^6$/UL)	4.27 ± 0.50^b	3.90±0.09^a	3.68±0.12^a	3.50±0.40^a	3.82±0.09^a	3. 69±0.12^a	3.18±0.19^a
Hb (g/dl)	11.11 ± 0.27^c	9.91±0.25^b	9.62±0.20^b	8.75±0.65^b	8.56±0.20^b	9.10±0.27^b	7.98±0.40^a
HCT (%)	31.29 ± 0.30^{ab}	28.50±0.47^a	30.96±0.17^{ab}	27.80±3.00^a	31.27±0.59^{ab}	33.36±0.71^b	32.73±0.60^b
MCV (fl)	76.44 ± 0.88^b	78.22±1.30^b	74.76±2.0^{ab}	60.85±3.00^a	76.52±1.08^{ab}	78.05±1.83^b	72.27±3.23^{ab}
MCH (pg)	23.63 ± 0.53^a	30.59±0.50^{ab}	33.50±1.18^b	33.55±0.05^b	32.23±0.41^{ab}	32.17±0.40^{ab}	34.35±0.29^b
MCHC (g/dl)	31.74 ± 0.38^b	23.45±0.42^a	23.92±0.96^a	24.15±0.85^a	26.48±1.74^{ab}	26.49±0.69^{ab}	22.49±1.77^a
PLT ($\times10^3$/UL)	241.76±9.80^c	177.77±6.95^{ab}	191.08±16.07^b	153.50±20.50^a	187.03±7.77^{ab}	174.82±13.9^{ab}	163.17±15.2^{ab}

All values are represented as mean ± SEM. Values in the same row with different alphabets differ significantly ($p < 0.05$).

Key: WBC: White blood cells; NO: Nitric oxide: RBC: Red blood cells; HGB: Haemoglobin; HCT: Haematocrit; MCV: Mean corpuscular volume; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular haemoglobin concentration; PLT: Platelets; (+): Mild, (++): Moderate, (+++): Severe parasitaemia; INPW: Infected non - pregnant women; IPW: Infected pregnant women.

There was significant difference ($p < 0.05$) in the levels of WBC, HCT, MCV and PLT in the infected pregnant women in relation to degree of parasitaemiawhen compared to the control subjects. There was a significant ($p < 0.05$) increase in MCH in relation to degree of parasitaemiain the infected pregnant women (34.35±0.29 pg) when compared to the control subjects(23.63±0.53pg) (Table 3).

Table 4: Anaemia status of pregnant women from Benin City, Nigeria.

	INPW			IPW			
	DEGREE OF PARASITAEMIA				DEGREE OF PARASITAEMIA		
	CONTROL	MILD (+)	MODERATE (++)	SEVERE (+++)	MILD (+)	MODERATE (++)	SEVERE (+++)
Hb (g/dl)	I2.67±0.27^{c}	9.91±0.25^{ab}	9.62±0.20^{ab}	8.75±0.65^{a}	8.56±0.20^{a}	9.10±0.27^{ab}	7.98±0.40^{a}

All values are represented as mean ± SEM. Values in the same row with different alphabets differ significantly ($p < 0.05$).

Key: Hb: Haemoglobin; INPW: Infected non - pregnant; IPW: Infected pregnant women

The results in Table 4 show significant decreases($p < 0.05$) in the Hb levels of the infected pregnant women when compared with that of the control subjects. This decrease was dependent on the degree of parasitaemia and itsinversely correlated.

Table 5: Effect of gestation on anaemia status of pregnant women from Benin City, Nigeria.

	INPW		IPW					
	DEGREE OF PARASITAEMIA		DEGREE OF PARASITAEMIA					
GP	C	NP	MILD(+)	MODERATE(++)	SEVERE(+++)	MILD(+)	MODERATE(++)	SEVERE(+++)
FT	13.57±3.66^{c}	32	10.36±1.42^{b}	7.25±0.32^{ab}	8.22±0.32^{ab}	8.22±0.92^{ab}	7.01±2.08^{ab}	4.73±6.11^{a}
ST	11.74±0.18^{c}	20	9.89±0.09^{b}	8.12±0.21^{b}	8.90±0.11^{b}	9.41±1.44^{b}	6.89±4.01^{a}	5.29±1.90^{a}
TT	12.40±0.51^{c}	16	11.62±0.24^{c}	10.23±0.10^{b}	9.58±0.00^{b}	9.09±3.19^{b}	5.65±0.26^{a}	5.88±2.71^{a}

All values are represented as mean ± SEM. Values in the same row with different alphabets differ significantly ($p < 0.05$).

Key: FT: First trimester; ST: Second trimester; TT: Third trimester; INPW: Uninfected non - pregnant women; IPW: Infected pregnant women; GP: Gestation period; C: Control; NP: Number of patients.

Table 5 shows that there was a significant ($p < 0.05$) decrease in the Hb levels across the three trimesters, with the first trimester having mostsevere anaemia with the least Hb concentration when compared to the control subjects.

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Table 6: Effect of parity on anaemia status of pregnant women from Benin City, Nigeria.

	INPW		IPW					
	DEGREE OF PARASITAEMIA		DEGREE OF PARASITAEMIA					
P	C	NP	MILD(+)	MODERATE(++)	SEVERE(+++)	MILD(+)	MODERATE(++)	SEVERE(+++)
P	11.09±2.27^{b}	17	10.18±0.50^{b}	11.90±0.53^{b}	9.94±0.17^{ab}	8.22±0.15^{ab}	7.02±2.30^{a}	6.00±0.10^{a}
S	12.64±0.99^{c}	19	10.25±0.28^{b}	9.83 ± 0.25^{ab}	10.57±0.29^{b}	10.18±4.01^{b}	8.43±2.21^{ab}	5.68±2 .45^{a}
M	11.83±1.06^{c}	32	8.99±0.11^{b}	11.00±0.31^{c}	10.22±0.26^{b}	9.59±0.33^{b}	8.02±1.43^{b}	4.79±0.08^{a}

All values are represented as mean ± SEM. Values in the same row with different alphabets differ significantly ($p < 0.05$).

Key: P: Primigravidae;S: Secundigravidae; M: Multigravidae; INPW: Infected non - pregnant women; IPW: Infected pregnant women; GP: Gestation period; C: Control; NP: Number of patients.

There was a significant ($p < 0.05$) decrease in Hb level in the infected pregnant women when compared to the control subjects. This effect was dependent on the degree of parasitaemia and its inversely correlated.

Table 7: Effect of age on anaemia status of pregnant women from Benin City, Nigeria.

	INPW					IPW		
	DEGREE OF PARASITAEMIA					DEGREE OF PARASITAEMIA		
AGE	C	NP	MILD(+)	MODERATE(++)	SEVERE(+++)	MILD(+)	MODERATE(++)	SEVERE(+++)
18-27	11.09±2.27^{b}	32	11.56±1.42^{b}	7.25±0.32^{ab}	8.22±0.32^{ab}	9.99±3.04^{b}	7.04±0.53^{ab}	4.81±0.07^{a}
28-37	12.64±0.99^{c}	21	9.90±0.09^{b}	11.0.7±0.21^{c}	8.90±0.11^{b}	8.75±0.62^{b}	6.99±3.04^{a}	5.03±1.11^{a}
38-47	11.83±1.06^{b}	15	11.09±0.24^{b}	10.00±0.10^{b}	9.58±0.00^{b}	7.95±0.45^{ab}	7.11±0.53^{ab}	5.66±0.06^{a}

All values are represented as mean ± SEM. Values in the same row with different alphabets differ significantly ($p < 0.05$).

Key: C: Control; NP: Number of patients; Infected non - pregnant women; IPW: Infected pregnant women.

There was a significant ($p < 0.05$) decrease in theHb levels of the infected pregnant women when compared to the control subjects. When the anaemia status of the infected pregnant women were compared, those that fell under 18 – 27 years had the highest occurrence of anaemia, followed by those under 28 – 37 of age and lastly those under 38 – 47 of age when compared to the control subjects. The result showed that 18 - 27 of age had the highest prevalence of anaemia in relation to the degree ofparasitaemia when compared to other pregnant women.

Table 8: Thrombocytopenia status of *Plasmodium falciparum*infected pregnant Nigeria women.

	INPW				IPW		
	DEGREE OF PARASITAEMIA				DEGREE OF PARASITAEMIA		
	CONTROL	MILD(+)	MODERATE(++)	SEVERE(+++)	MILD(+)	MODERATE(++)	SEVERE(+++)
PLT($x10^3$/UL)	241.76±9.8^{c}	177.77±6.95^{ab}	191.08±16.07^{bc}	153.50±20.50^{a}	187.03±7.77^{bc}	174.82±13.90^{b}	163.17±15.20^{ab}

All values are represented as mean ± SEM. Values in the same row with different alphabets differ significantly ($p < 0.05$).

Key: PLT: Platelet; UIPW: Uninfected pregnant women; IPW: Infected pregnant women.

There was a significant ($p < 0.05$) decrease in the platelet counts of the infected pregnant and non – pregnant women in relationship to parasitaemia when compared to the control subjects, with severe degree of parasitaemia having the least platelet countsin both INPW and IPW respectively(Table 8).

DISCUSSION

Haematological changes like anaemiaand thrombocytopenia are common complications encountered in severe malaria [18].According to WHO, the haemoglobinlevel below which anaemia is likely to occur for a population living at sea level are: 11g/dl for children aged 6 months to six years, 12g/dl for children aged between 6 years and 14 years, 13g/dl for adult males, 12g/dl for adult non – pregnant females and 11g/dl for pregnant adult females [22]. The etiology of anaemia among malaria infected patients is thought to be multifactorial; haemolysis of infected red blood cells, accelerated removal of both infected and non-infected red blood cells, depressed and ineffective erythropoiesis due to tumour necrosis factor alpha, anaemia of chronic disease, and splenic phagocytosis or pooling [23]. Results obtained from this study showed significant ($p < 0.05$) reduction in RBC, haemoglobin and haematocrit levels in the malaria patients when compared to the controls. This is a standard feature in malaria infection.The reduction in haemoglobin is understandably due to haemolytic destruction especially of parasitized red blood cells, suppression of bone marrow activity and ineffective erythropoiesis. The mean haemoglobin (Hb) concentration for the pregnant women in the last trimester in the present study was relatively low (5.88±2.71g/dl) when compared to an earlier study in Ghana with a mean Hb value of 10.70 g/d[24]. It has been reported that anaemia is strongly associated with pregnancy [25]. It is possible that poor nutrition or decreased iron intake may have resulted in anaemia. However, the present study had no information on the diet of participants to evaluate this hypothesis. Profound thrombocytopenia is unusual, and thrombocytopenia is rarely associated with hemorrhagic manifestations or a component of disseminated intravascular coagulation either in non-immune adults or children in endemic areas [3]. Malaria is usually associated with various degrees of thrombocytopenia[14]. Thrombocytopenia has been seen commonly in all forms of malaria [26] and different mechanisms have been proposed as immune mediated mechanisms including immune destruction of circulating platelets, splenic pooling, and reduced platelet lifespan [27]. In this study 59.08% of infected women suffering from malaria showed some degree of thrombocytopenia where they have platelet count of ($188.16±7.03×10^3$/UL) when compared to the control group ($241.76±9.80×10^3$/UL).It is a general consensus that thrombocytopenia is very common in malaria (Akhtar*et al.,* 2005) and this is usually believed to be more common in*Plasmodium falciparum*

malaria, which we observed in this study. When the effects of gestational period, parity and age on the platelet counts were compared among the groups, infected pregnant women in the first trimester had the lowest number of platelet counts when compared to the others. But when gravidae was compared, infected pregnant women insecungravidae had the lowest number of platelet counts when compared to primigravidae and multigravidae. While in age, infected pregnant women between the age of 18 – 27 had the lowest number of platelet counts when compared to the others ages (Table 2).This shows that malaria affects pregnant women of younger age more than their counterparts. These results agree with the reports of [28] and [29]who reported that malaria infection is more in primigravidae and is usually associated with anaemia and thrombocytopenia. Gravidae, parity and age appeared to be the principal influence of malaria prevalence, mostly in teenagers.The results in this study support a role of *P.falciparum* malaria in the development of anaemia and thrombocytopenia in the infected pregnant women.

CONCLUSION

Degree of parasitaemia, gestational period, gravidae and age are inversely correlated with anaemia status and are statistically significant when compared to the control subjects. Thus, severe malaria and anaemia can lead to thrombocytopenia complications with fatal consequences both to the mother and foetus.

CONFLICT OF INTEREST

The authors have no conflict of interest

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