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Antioxidant status and acute phase reactants in pregnant women infected with *Plasmodium falciparum*

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ABSTRACT

INTRODUCTION: Malaria during pregnancy remains a public health issue. The most deadly plasmodium, *Plasmodium falciparum*, kills about 40% of the world's population, especially pregnant women and children under five. In pregnant women infected with *Plasmodium falciparum*, MDA, CAT, H_2O_2, SOD, and GPx were measured as oxidative stress markers and SAA and CRP as acute-phase proteins.

METHODS: A total of 90 subjects were recruited for this study, which were subdivided into 30 pregnant women infected with malaria (PWM), 35 pregnant women not infected with malaria (PWN), and 25 healthy women without pregnancy (WWP) who served as the control groups. 5mls of venous blood was collected and dispensed into appropriate bottles for malaria parasite assessment using a rapid diagnostic test (RDT) and MDA, CAT, H_2O_2, SOD, GPx, SAA, and CRP analysis using conventional laboratory techniques. Statistical analysis was done, and P values under 0.05 were significant.

RESULTS: The PWM and PWN groups had significantly higher MDA and H2O2 values, but SOD, GPx, and CAT values were significantly lower ($p<0.05$). When comparing CRP and SAA levels between PWM, PWN, and control groups, both groups with pregnancy had significantly greater levels ($p<0.05$). A negative correlation ($r = -0.442$, $p<0.05$) was found between MDA and SAA, while positive correlations were seen between CAT and CRP, and SOD and SAA in pregnant women with malaria

CONCLUSION: This study found that malaria during pregnancy increases oxidants and decreases antioxidant enzymes, causing oxidative stress. This study showed that CRP and SAA may indicate malaria infections.

Keywords: Acute Phase Reaction, Inflammation, Anaemia, Amyloid A, *Plasmodium Falciparum*

INTRODUCTION

Malaria continues to be one of the leading causes of maternal mortality in Sub-Saharan Africa. At least 6 million pregnant women worldwide are at risk of malaria infection. Malaria causes at least 10,000

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maternal deaths and at least 200, 000 newborn deaths each year. Malaria is a contributing or etiologic factor in pregnancy complications such as anemia, spontaneous abortion, prematurity, and stillbirth [1,2]. Malaria infection during pregnancy causes an enormous risk to the mother, fetus, and neonates [3,4].

Over the years, there have been concerted worldwide collaboration efforts spearheaded by the World Health Organization (WHO) and including governments and affiliated institutions to combat the scourge of malaria in pregnancy [5]. The primary goals of such initiatives have been to improve the use of insecticide-treated mosquito bed nets (ITN), intermittent preventative treatment of malaria (IPT), and adequate case management of acute malaria attacks in pregnant women [6]. Although malaria during pregnancy may be asymptomatic due to high levels of acquired immunity in mothers living in high transmission areas, it is nonetheless linked to an increased risk of maternal anemia, spontaneous abortion, stillbirth, preterm, and low birth weight [7]. Furthermore, severe maternal anemia raises the mother's mortality risk. Malaria-related anemia is predicted to cause up to 10,000 maternal deaths in Africa each year [7,8].

The term "acute phase reaction" or "response" refers to the multiple systemic, metabolic, behavioral, physiological, and nutritional changes that occur in the body as a result of an inflammatory stimulation [9]. The acute-phase response begins within hours of inflammation [10], lasts around 1 or 2 days, and normalcy is restored in the body 4 to 7 days after the inflammatory stimulus is resolved [11,12]. Acute-phase response can develop as a result of a single or a combination of local or systemic instability caused by chemical infection, neoplasm, surgery or trauma, tissue injury, or immunological diseases [13]. The degree of change in acute-phase protein concentration is influenced by the severity of the inflammatory stimulus and lasts as long as the stimulus exists. These proteins can be used to detect stress and disease [10,14]. C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR) are the most often used acute phase reactants; however, Serum Amyloid A (SAA) may be used as well.

CRP is a pentametric, ring-shaped protein present in the blood whose circulating levels rise in response to inflammation. It is an acute-phase protein with a hepatic origin that rises when macrophages and T cells secrete interleukin-6. CRP, on the other hand, has been examined and proposed as a biomarker for a variety of acute and chronic disorders [15,16], and it has to be observed whether its significance is seen in pregnant women with or without malaria. Another APP that has recently been studied is SAA. It is vital in the inflammatory process and can increase neutrophil IL-8 secretion. Previous studies to evaluate the levels of SAA in some illness conditions found that SAA levels were higher than CRP levels [16,17]. As a result, both proteins are fundamental in the diagnosis of certain diseases. Similarly, acute-phase reactants such as CRP or SAA have been used to assess antibiotic therapy response [18]. SAA must also be examined further to see whether it is important in pregnant women with or without malaria.

Pregnancy is usually associated with many changes in a woman, which can be physiologic or pathologic. It is characterized by both anti-inflammatory and pro-inflammatory reactions; the immune system reacts differently depending on the type of the microbe and the stage of pregnancy, and so is modulated [13]. Several antioxidants and oxidants have been linked to malaria in pregnancy, including malondialdehyde (MDA), catalase (CAT), glutathione peroxidase (GPx), hydrogen peroxide (H2O2), and superoxide dismutase (SOD). During a *Plasmodium falciparum* malaria infection, maternal MDA levels have been shown to rise together with those of the other oxidants indicated above [19,20]. The goal of this study was to investigate if assessing antioxidant status and acute phase reactants instead of cytokine concentrations would be effective in managing the health of pregnant women with malaria (especially *Plasmodium falciparum*).

METHODS

Study Design

This is a case-control study. The study was carried out between January and August of 2022. A total of 90 subjects were recruited for this study, which were subdivided into 30 pregnant women infected with malaria (PWM), 35 pregnant women not infected with malaria (PWN), and 25 healthy women without pregnancy (WWP) served as the control groups. *Plasmodium falciparum* malaria in this study was determined by a rapid diagnostic

kit based on antigens malaria detection in the patients' blood as described by WPRO [21].

Subjects participating in this study were fully briefed on the research protocols in the clinic, after which they were required to sign a written consent. Ethical clearance with reference number FMC/OW/380/VOL.CLI/28 was obtained from the Federal Medical Center, Owo Ethical Review Committee.

Eligibility Criteria

The study enrolled pregnant women aged 18 to 50 with or without malaria. The control group included apparently healthy women who were not pregnant.

Participants with known comorbidities, such as hypertension, HIV, hepatitis, cancer, oral anticoagulant treatment, bleeding tendencies, and so on, as well as breastfeeding mothers, were excluded from the study. The controls were subjected to the same exclusion criteria as the subjects. Those who did not fall within the age range and did not give their consent were excluded from the study.

Data Collection

Five milliliters (5mls) of venous blood was collected from each subject and dispensed into an appropriate bottle for the detection of *plasmodium falciparum* parasite and determination of Malondialdehyde (MDA), Hydrogen peroxide (H2O2), C- reactive protein (CRP), Serum Amyloid A (SAA), the serum enzymatic activity of Superoxide dismutase (SOD), Catalase (CAT), Glutathione peroxidase (GPx). Each sample was spun at 4000rpm for 5 minutes to obtain serum, which was then stored at-200C until analysis.

Data Analyis

CareStartTM, Access Bio, Inc., USA, an in vitro rapid diagnostic kit based on antigens, was carried out on aliquots of whole blood in duplicates as described by WPRO [21]. Serum levels of Malondialdehyde (MDA) and Hydrogen peroxide (H2O2) were determined using standard spectrophotometric techniques, while C-reactive protein (CRP) and Serum Amyloid A (SAA) were estimated using ELISA kits obtained from Melsin Medical Company, USA. Serum enzyme activity of Superoxide dismutase (SOD), Glutathione peroxidase (GPx), and Catalase (CAT) were also determined using spectrophotometric techniques as described by Atere et al. [22].

For the suitable data analysis, a statistical package for social sciences version 25.0 (SPSS Inc, Chicago, IL) was used. One-way analysis of variance (ANOVA) was used to compare the groups. Correlation was also applied to examine the relationship between variables. The 95% confidence interval was used as the level of significance, and a P value less than 0.05 was considered significant.

RESULTS

Table 1 shows a total of 90 subjects who were recruited for this study, which further subdivided into 30 pregnant women who had malaria (PWM), 35 pregnant women without malaria (PWN), and 25 healthy women without pregnancy (WWP) served as the (control group). The mean ages were 30.97 ± 6.65 years, 27.69 ± 8.35 years, and 30.72 ± 5.23 years in PWM, PWN, and control groups, respectively. The majority of the pregnant women (42.2%) in this study are in their first trimester.

The mean values of MDA and H2O2 were

Table 1: Demographics of the study participants (N = 90)

Variables	PWM (n = 30)	PWN (n = 35)	WWP (n = 25)	*P*-value
Age	30.97 ± 6.65	27.69 ± 8.35	30.72 ± 5.23	0.120
Gestational age	14.43 ± 7.33	12.06 ± 7.49	NA	
Trimester				
First trimester	16 (53.3)	22 (62.8)	NA	
Second trimester	11 (36.7)	10 (28.6)		
Third trimester	3 (10.0)	3 (8.6)		

*Values were expressed as mean ± standard deviation. Figure in parenthesis denoted percentage. *Significant at p <0.05. PWM = Pregnant women with malaria, PWN = Pregnant women without malaria, WWP = Women without pregnancy, N= Total number of subjects, n = number of subjects, NA = Not applicable.*

significantly higher in both naive PWM and PWN groups, while SOD, GPx, and CAT were significantly lower (p<0.05). When multiple comparisons were performed using the post hoc test, the same pattern was observed, with a significant difference in the mean values of SOD, MDA, GPx, CAT, and H2O2 among PWM, PWN, and WWP (p<0.001) (Table 2). When the mean age and acute phase reactants (CRP and SAA) of RMP, RMN, and control were compared using a standard error bar chart, the mean CRP and SAA were significantly higher in both groups of subjects with pregnancy (p<0.05) (Figures 1–2).

In Table 3, a negative correlation was observed between MDA and SAA (r =-0.442, p<0.05), while a positive correlation was observed between CAT and CRP and SOD and SAA, even though they are not statistically significant. A negative correlation was also observed between H2O2 and CRP when acute phase reactants (CRP and SOD) were correlated with oxidative stress biomarkers among pregnant women without malaria (r = -0.334, p<0.05) (Table 4).

Table 2: Comparison of antioxidant status and free radicals among pregnant women

Parameter	PWM (n = 30)	PWN (n = 35)	WWP (n = 25)	*p*-value
SOD (U/ml)	1.96 ± 0.49[a]	2.48 ± 0.51[b]	3.22 ± 0.63[c]	0.001*
MDA (µmol/L)	3.15 ± 0.67[a]	2.41 ± 0.43[b]	1.77 ± 0.28[c]	0.000*
GPX (U/ml)	2.06 ± 0.35[a]	2.39 ± 0.29[b]	3.48 ± 0.35[c]	0.000*
CAT (U/L)	38.11 ± 1.12[a]	43.87 ± 2.04[b]	53.29 ± 3.16[c]	0.000*
H_2O_2 (µmol/L)	3.72 ± 0.64[a]	3.17 ± 0.43[b]	2.30 ± 0.44[c]	0.000*

*Values were expressed as mean ± standard deviation. *Significant at p <0.05.*
Where: a = Pregnant women with malaria; b = Pregnant women without malaria; c = Non-pregnant women.
PWM = Pregnant women with malaria, PWN = Pregnant women without malaria, WWP = Women without pregnancy,

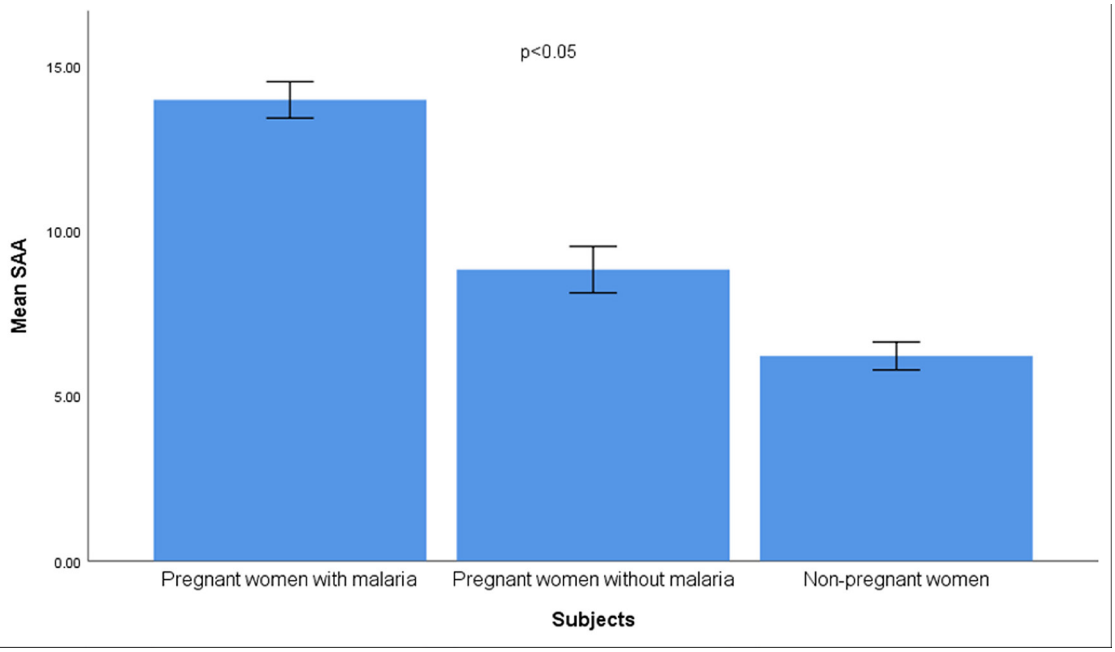

Figure 1: A standard error bar chart showing the mean distribution of serum amyloid A (SAA) among the study participants.

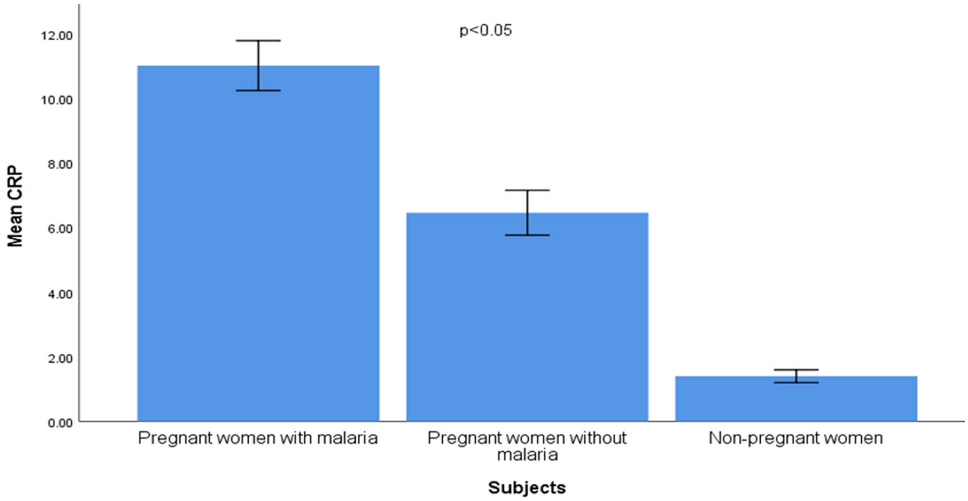

Figure 2: A standard error bar chart showing Mean distribution of C-reactive protein (CRP) among the study participants

Table 3: Correlation of Acute Phase Reactants (CRP and SAA) with Oxidative Stress Biomarkers among Pregnant Women with Malaria

Parameter	CRP		SAA	
	R	p-value	R	p-value
SOD	-0.040	0.834	0.222	0.238
MDA	-0.208	0.271	-0.442	0.015*
GPX	-0.032	0.866	-0.105	0.579
CAT	0.105	0.580	-0.182	0.335
H_2O_2	0.148	0.434	-0.070	0.712

**: Correlation is significant at the 0.05 level (2-tailed)*

DISCUSSION

Malaria is a serious and, in some unfortunate cases, fatal disease caused by a parasite of the Plasmodium genus. The pathogenesis of malaria is complex and incompletely elucidated [23]. Studies have shown that oxidative stress is common among malaria patients as a result of the activation of the immune responses by the malaria parasite, thereby causing the release of reactive oxygen species (ROS) [24,25]. Oxidative stress can occur when there is an imbalance of free radicals and antioxidants in the body. Malarial infection is associated with increased production of reactive oxygen species by phagocytic cells, and this may be more debilitating in pregnancy [26,27]. In this study, MDA and H2O2 levels were significantly higher in PWM and PWN subjects when compared to the control group, while SOD, GPx, and CAT levels were significantly lower ($p<0.05$) (table 4.2). This observation is consistent with Chandrashekhar et al. [28] findings that enzymatic antioxidants are impaired during malaria in pregnancy. This might be due to hemolysis that sometimes occurs during malaria infection, and it can also be attributed to the counter effects of this antioxidant on free radicals that were generated in pregnancy. The same pattern emerged when multiple comparisons were performed using the post hoc test, with a significant difference between PWM and PWN

Table 4: Correlation of Acute Phase Reactants (CRP and SAA) with Oxidative Stress Biomarkers among Pregnant Women without Malaria

Parameter	CRP		SAA	
	R	*p*-value	R	*p*-value
SOD	0.058	0.739	0.030	0.864
MDA	0.224	0.195	-0.089	0.610
GPX	0.099	0.571	0.185	0.288
CAT	-0.054	0.758	-0.107	0.542
H_2O_2	-0.334	0.050*	0.097	0.580

**: Correlation is significant at the 0.05 level (2-tailed)*

groups (p<0.05). When the antioxidant system is unable to effectively deal with the ROS and free radicals produced in living organisms, oxidative stress occurs. A significant decrease in SOD, CAT, and GPx activity indicated an accumulation of H2O2, which is required to mummify these reactive species [29]. The findings of this study could indicate an increase in the formation of free radicals, which could lead to oxidative damage due to the overwhelming antioxidant activities of all of these enzymes in pregnancy, especially with malaria.

During Plasmodium infections, to avoid tissue damage, large quantities of toxic redox-active by-products such as heme resulting from the high metabolic rate of rapidly multiplying parasites must be effectively neutralized. Concordant with previous reports, [2,28], this study also found lower CAT levels in pregnant women, especially during *Plasmodium falciparum* infections. This supports the hypothesis that, during malarial infections, insufficient levels of host antioxidant defense mechanisms fail to adequately neutralize the increased ROS generated.

In this study, a negative correlation was observed between MDA and SAA (r =-0.442, p<0.05), while a positive correlation was observed between CAT and CRP and SOD and SAA, even though they are not statistically significant. A negative correlation was also observed between H2O2 and CRP when acute phase reactants (CRP and SOD) was correlated with oxidative stress biomarkers among pregnant women without malaria (r = -0.334, p<0.05) (Tables 4.3-4.4). Several biological mechanisms have also been proposed to explain the relationships between CRP, SAA, and their correlates. The significant correlations (p<0.05) buttress the roles played by P. falciparum antigen, Histidine Rich Protein 2, (HRP-2) in the production of CRP as highlighted by previous research [30,31] as P. falciparum activates mononuclear cells which produce cytokines that stimulate the hepatic production of several inflammatory markers including CRP.

CONCLUSION

This study showed that malaria in pregnancy plays a vital role in oxidative stress via increasing oxidants, malondialdehyde and hydrogen peroxide and decreasing antioxidant enzymes: superoxide dismutase, catalase, and glutathione peroxidase. This study also demonstrated the possibility of CRP and SAA as a biomarker of malaria infection. The oxidative stress-induced malaria conditions might lead to obstetric complications such as intrauterine growth restriction, low birth weight, miscarriage, and even stillbirths. Thus, it is important to create awareness among the study population about preventive measures, and free government-sponsored antenatal care services are recommended to reduce pregnancy malaria incidences in this region.

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