

# Comparative analysis of the safety and tolerability of fixed-dose artesunate/amodiaquine versus artemether/lumefantrine combinations for uncomplicated *falciparum* malaria in pregnancy: a randomized open label study

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**Abstract:** A comparative clinical study was conducted to evaluate the safety and tolerability of two commonly used fixed dose artemisinin-based combinations for the treatment of uncomplicated *Plasmodium falciparum* malaria in the second and third trimester of pregnancy. To achieve this, a total of 155 participants were recruited for the study. Eighty of these were drawn from pregnant women who came for routine antenatal care while 40 nonpregnant participants were recruited from apparently healthy females in the community. Eighty pregnant participants with uncomplicated *P. falciparum* malaria were randomized into artesunate/amodiaquine (AA) and artemether/lumefantrine (AL) treatment arms while 40 nonpregnant and 35 nonmalarious pregnant women were used as control. The interventional groups received standard fixed dose combinations of AA (100/270 mg) daily or AL (20/120 mg) twice daily for 3 days. Blood samples were collected on day 4 and patients were followed-up closely to ascertain the safety of the drugs. The study showed a significant ( $p < 0.0001$ ) elevation of alkaline phosphatase in the AA and AL group compared to the nonpregnant control and a significant ( $p < 0.05$ ) elevation of alanine transaminase and aspartate transaminase level in the AL combination group when compared with the AA group. The elevated hepatic enzymes were within the normal range for pregnancy and were not clinically significant. Adverse event rate was higher in the AA group ( $n=28$  [70%]) when compared to the AL group ( $n=4$  [10%]) although the drugs were well-tolerated in both treatment arms. In conclusion, the use of these combinations is safe in the second and third trimester of pregnancy. However, we recommend active pharmacovigilance and spontaneous drug reporting of the agents in order to continuously monitor safety in the vastly heterogeneous population.

**Keywords:** fixed dose combination, *Plasmodium falciparum* malaria, safety, pregnancy, tolerance, pharmacovigilance

## Introduction

Artemisinin and its derivatives are known to be effective against multidrug resistant *Plasmodium falciparum* malaria with a more rapid clearance of sensitive parasites from the blood than any other antimalarial agent.<sup>1,2</sup> This activity is, generally, attributed to the rapid schizonticidal action of the drugs. The drug is, generally, well-tolerated despite reports of neurotoxicity and embryotoxicity from animal studies.<sup>3,4</sup>

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However, reported cases of adverse reactions include a few case reports of anaphylaxis.<sup>5,6</sup> Currently the recommended antimalarial policy requires the use of combination therapy which includes an artemisinin to delay the emergence of drug resistance as well as improve cure rates. In this treatment, the choice of partner drugs used in combination with artemisinin derivatives depends on the pattern of parasite resistance in the region.<sup>1,5</sup> For example, in Nigeria the combinations commonly used for treatment of uncomplicated *P. falciparum* malaria are artesunate/amodiaquine (AA) and artemether/lumefantrine (AL) combinations. This is based on a research report from the Nigerian Ministry of Health which revealed that the combinations have an acceptable cure rate of >90% in some of the geopolitical zones of the country.<sup>7</sup>

Artemether is a semisynthetic derivative of artemisinin whereas lumefantrine also known as benflumetol is a synthetic product. Both drugs were first developed in China. Artesunate is a hemisuccinate derivative of dihydroartemisinin obtained by the reduction of artemisinin, a sesquiterpene lactone endoperoxide extracted from a plant known as *Artemisia annua*. This is used as traditional herbal preparation in the treatment of malaria.<sup>8</sup> The report that lethal agranulocytosis and severe hepatic impairment is associated with the use of amodiaquine as a chemoprophylactic agent<sup>9</sup> and the fact that the safety of artemisinins still remains a questionable in pregnancy due to insufficient data, forms the rationale for this study.

In malaria endemic regions, malaria infection may occur repeatedly in individuals within months which warrants the use of repeated doses of antimalarials. This situation occurs more prominently in individuals with increased susceptibility such as children, pregnant women and immunocompromised patients.<sup>10,11</sup> Hence, the issue of safety cannot be overemphasized. Also, there is a dearth of safety data on the use of these combinations in the treatment of uncomplicated malaria in pregnancy particularly among Africans. This forms the basis for this study, which aims to comparatively assess the safety of the combinations in the management of uncomplicated *falciparum* malaria in pregnancy.

## Study design

The study is an open label randomized control trial comparing the safety and tolerability of artesunate + amodiaquine and artemether + lumefantrine combinations in a population of pregnant women with uncomplicated *P. falciparum* malaria. The minimum sample size required to determine an inter-group difference of <10% in a population with type 1 error of 5% and a power of 80% was statistically estimated to be 35 per group. A total of 155 participants were recruited

for the study. Eighty participants were drawn from the pool of pregnant women who came for routine antenatal care visits to a busy hospital in Ekpoma, a semi-urban community endemic for malaria. Eligibility for the study was based on the following inclusion criteria:

- age of >18≤35 years,
- positive rapid diagnostic test (RDT) for *P. falciparum* + microscopic confirmation of asexual parasitemia in Giemsa stained thick and thin blood film,
- parasite density ≥1000/μL,
- acute manifestation of malaria (e.g., history of fever in the preceding 24 hours, a temperature of >37.5°C at baseline, malaise, generalized body pains, chills, rigors, etc.),
- ability to tolerate oral therapy,
- second and third trimester of pregnancy (i.e., >12 weeks gestation),
- informed consent.

The exclusion criteria for the study were as follows:

- adequate antimalarial treatment within the previous 4 weeks,
- use of hematinics in the last 4 weeks,
- use of herbal medications in the last 4 weeks,
- antibiotic treatment for a concurrent infection,
- mixed plasmodial infection,
- severe malaria,
- severe underlying disease,
- other diseases associated with fever.

The pregnant and nonpregnant control subjects were screened for malaria using RDT and microscopy. They were found to have no clinical or laboratory evidence of malaria and were ascertained to be apparently healthy after evaluation.

Written informed consent was obtained from the participants and approval was granted by the Ethical Review Board of the Edo State Ministry of Health. The study was conducted in accordance with the principles of the Helsinki Declaration and its Hong Kong amendment and according to the principles of good clinical practice. Recruited participants with malaria were randomly assigned in a 1:1 ratio to either AA or AL treatment arm. On day 0 the treatment groups were placed on oral doses of fixed dose combination of AA (100/270 mg) and AL (20/120 mg), respectively. The drugs were administered orally for 3 days (AA 3 tablets once daily and AL 4 tablets twice daily). Dosing was based on the recommended WHO schedule for uncomplicated malaria in pregnancy.<sup>12</sup> The other comparator groups consisted of 35 pregnant and 40 nonpregnant women who had no malaria and were not on any antimalarial drug.

Patients on treatment were followed-up consecutively on days 1–3, 7, 14, 21 and 28. At each visit, patients were clinically evaluated and adverse events were monitored and documented. Venous blood samples were taken on study day 4 to determine the hemoglobin level, hematocrit, differential white blood cell count and some biochemical parameters such as total and conjugated bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and serum lipid profile. Dried thick blood smears were stained with 10% Giemsa solutions at pH 7.2 for 10 minutes. Thin blood smears were also made. Parasite species were identified using standard morphological characteristics, and the presence of asexual parasitemia was confirmed accordingly. Parasite density was evaluated using standard procedure in which parasites were counted per 200 white blood cells (WBC) multiplied by leukocytes count/ $\mu\text{L}$ . Statistical analyses of the data were performed using graph pad prism 6.0. Student's *t*-test and one way analysis of variance were used to compare the mean of the laboratory data between groups. This was followed by Tukey's post hoc test for multiple comparisons. The statistical significance level was set at 95% confidence interval and *p* value <0.05 was considered significant. A flow chart was developed for the study based on the CONSORT 2010 statement for the reporting of clinical trials.<sup>13</sup>

## Results

The baseline characteristics of the study population (Table 1) showed that most of the recruited pregnant patients were multiparous with body mass index and blood pressures within normal range (body mass index [BMI]: AA;  $21.76 \pm 0.21 \text{ kg/m}^2$ , AL;  $20.98 \pm 0.56 \text{ kg/m}^2$ ). The mean systolic and diastolic blood pressures in the AA and AL group were  $106.81 \pm 0.91/68.76 \pm 1.21 \text{ mmHg}$  and  $112.13 \pm 0.86/69.83 \pm 0.45 \text{ mmHg}$ , respectively. Of the 80 participants assigned into both treatment arms, five (AA,  $n=3$  [3.75%]; AL,  $n=2$  [2.5%]) were lost to follow-up on day 14 (Figure 1).

In addition, there was a consistent reduction (Figures 2, 3) in mean temperature (AA,  $38.08^\circ\text{C} \pm 0.10^\circ\text{C}$ ; AL,  $38.51^\circ\text{C} \pm 0.12^\circ\text{C}$ ) and parasite density (AA,  $3634 \pm 537/\mu\text{L}$ ; AL,  $4884 \pm 386.59/\mu\text{L}$ ) after day 0 of treatment. However, the late parasitological failure observed on day 14 (AA,  $n=1$  [2.63%]; AL,  $n=2$  [5.41%]) in both treatment arms may be due to a reinfection because this was not polymerase chain reaction-corrected to rule out recrudescence. Clinical response was adequate throughout the follow-up period.

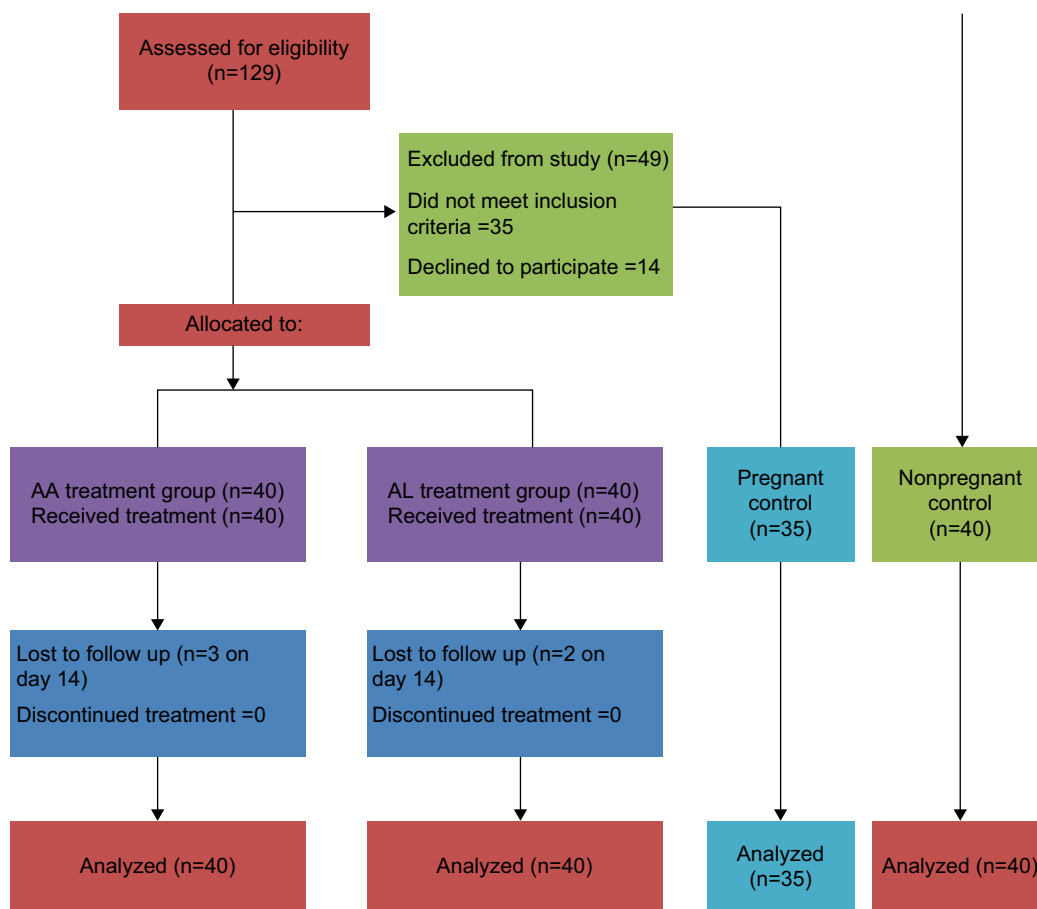
There was no significant change ( $p > 0.05$ ) in ALP levels (Figure 3A) between treatment groups and pregnant control.

**Table 1** Baseline characteristics of the study population

Group	Age (years)	P	G	G	Wt (kg)	Ht (m)	Ges (week)	SBP (mmHg)	DBP (mmHg)	FHR/min	SFH (cm)	ABG (cm)	BMI ( $\text{kg/m}^2$ )
Pregnant control (n=35)	$28.74 \pm 0.86$	$3.21 \pm 0.41$	$4.32 \pm 0.38$	$4.32 \pm 0.38$	$72.08 \pm 2.07$	$1.68 \pm 0.03$	$28.21 \pm 0.15$	$110.24 \pm 1.41$	$70.12 \pm 0.81$	$118.54 \pm 0.92$	$27.64 \pm 0.51$	$101.23 \pm 1.22$	$22.67 \pm 0.41$
AA (n=40)	$27.21 \pm 0.51$	$2.91 \pm 0.12$	$3.71 \pm 0.10$	$3.71 \pm 0.10$	$68.97 \pm 0.87$	$1.58 \pm 0.06$	$31.32 \pm 0.04$	$106.81 \pm 0.91$	$68.76 \pm 1.21$	$121.42 \pm 0.76$	$29.87 \pm 0.91$	$118.31 \pm 0.51$	$21.76 \pm 0.21$
AL (n=40)	$31.02 \pm 0.47$	$3.42 \pm 0.73$	$4.25 \pm 0.64$	$4.25 \pm 0.64$	$68.23 \pm 0.25$	$1.61 \pm 0.28$	$27.87 \pm 0.34$	$112.13 \pm 0.86$	$69.83 \pm 0.45$	$124.01 \pm 0.05$	$28.21 \pm 0.34$	$121.23 \pm 0.36$	$20.98 \pm 0.56$

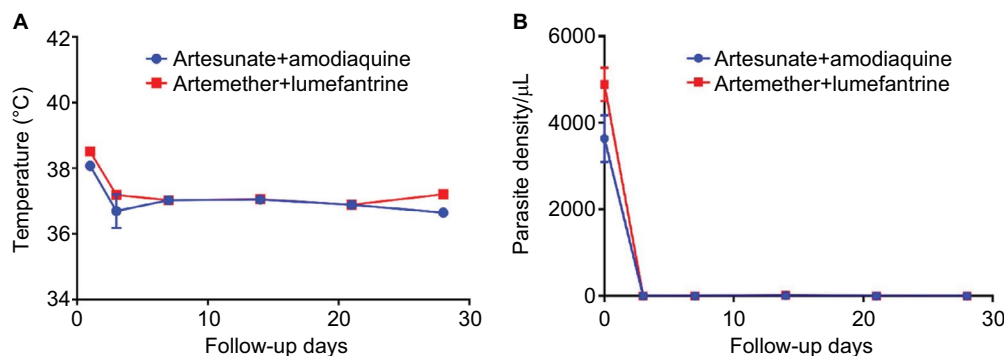
Note: Data presented as mean  $\pm$  standard deviation.

Abbreviations: AA, artesunate/amodiaquine; ABG, abdominal girth; AL, artemether/lumefantrine; BMI, body mass index; DBP, diastolic blood pressure; FHR, fetal heart rate; Ges, gestation; Ht, height; P, parity; SBP, systolic blood pressure; SFH, symphysiofundal height; Wt, weight.



**Figure 1** Study flow chart.

**Abbreviations:** AA, artesunate/amodiaquine; AL, artemether/lumefantrine.



**Figure 2** Temperature and parasite density following intervention in AA and AL treatment arm.

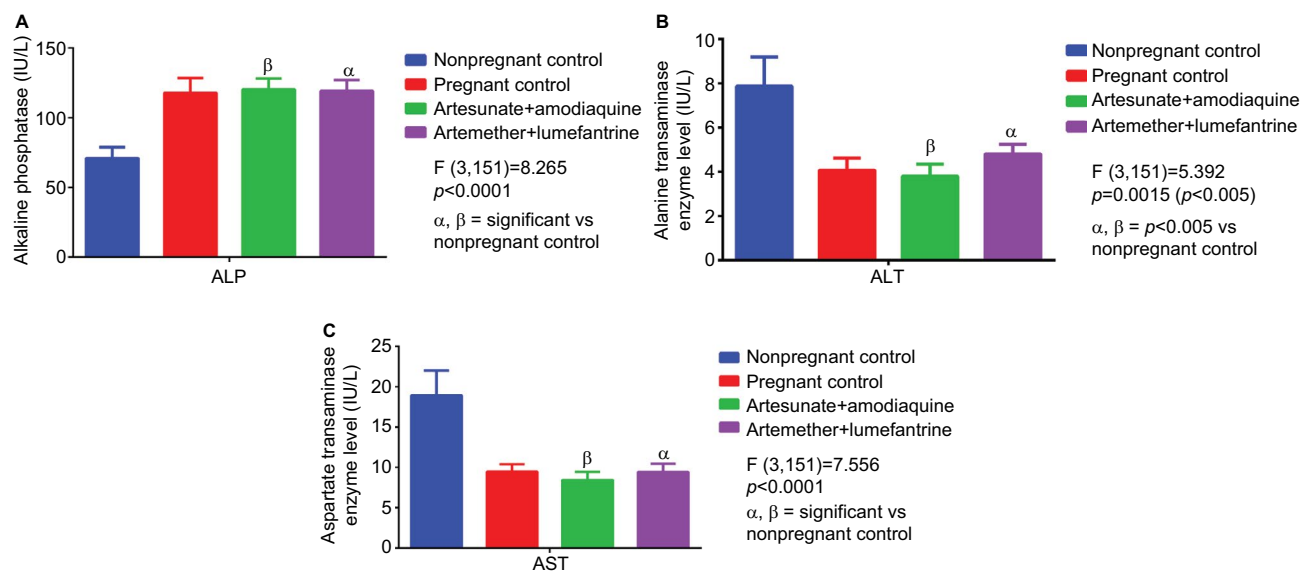
**Notes:** (A) Temperature profile from days 0 to 28. (B) Parasite density from days 0 to 28.

**Abbreviations:** AA, artesunate/amodiaquine; AL, artemether/lumefantrine.

Although ALP values were within normal reference range in the test groups (AA,  $120.27 \pm 7.81$  IU/L; AL,  $119.27 \pm 7.81$  IU/L) they were significantly ( $p < 0.0001$ ) different from the nonpregnant control ( $70.97 \pm 7.87$  IU/L). In addition, the serum levels of ALT and AST (Figure 3B, C) though significantly higher ( $p < 0.05$ ) in AL ( $4.85 \pm 0.44$  and  $9.47 \pm 1.01$  IU/L) compared to the AA ( $3.80 \pm 0.54$  and  $8.43 \pm 1.02$  IU/L) group, were within normal range in pregnancy. Also, the

serum transaminase levels though normal in the treated groups were significantly different from the nonpregnant control.

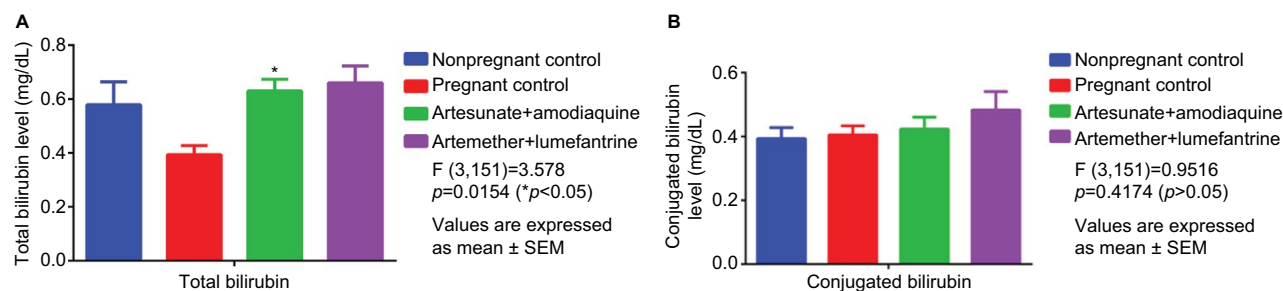
Although, total bilirubin level (Figure 4A) was significantly ( $p < 0.05$ ) higher in AA and AL groups when compared with pregnant control there was no significant change ( $p > 0.05$ ) between the treatment groups (AA,  $0.66 \pm 0.06$  mg/dL; AL,  $0.63 \pm 0.04$  mg/dL). In addition, there



**Figure 3** Alkaline phosphatase and transaminase profile in treated and control groups.

**Notes:** (A) Alkaline phosphatase level in treated groups and control. (B) Serum alanine transaminase level in treated groups and control. (C) Serum aspartate level in treated groups and control.

**Abbreviations:** ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase.



**Figure 4** Comparative serum bilirubin levels in treated vs control groups.

**Notes:** (A) Comparative total bilirubin level in patients treated with artesunate + amodiaquine and artemether + lumefantrine combinations. (B) Comparative conjugated bilirubin level in patients treated with artesunate + amodiaquine and artemether + lumefantrine combinations.

**Abbreviation:** SEM, standard error of mean.

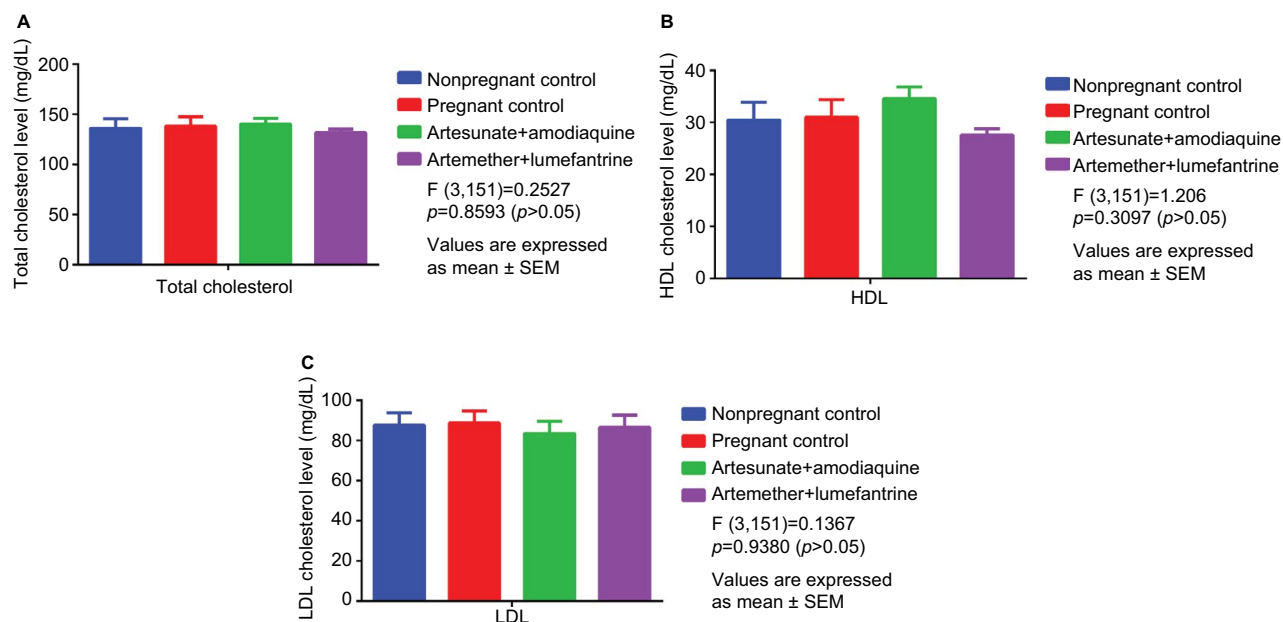
was no significant change (Figure 4B) in conjugated bilirubin level between the treatment groups and control groups.

A comparative serum lipid assessment (Figure 5A–C) showed a nonsignificant ( $p>0.05$ ) reduction of low-density lipoprotein (LDL) cholesterol in the AA group when compared with the control and AL combination groups. In addition, high-density lipoprotein (HDL) cholesterol level was nonsignificantly ( $p>0.05$ ) increased in the AA combination group ( $34.60\pm 3.20$  mg/dL) when compared with the control groups ( $31.00\pm 3.39$  and  $30.45\pm 3.37$  mg/dL) and AL ( $27.60\pm 1.20$  mg/dL) groups.

Packed cell volume (PCV) and hemoglobin concentration (Table 2) was markedly and significantly ( $p<0.01$ ) reduced in the AA ( $30.44\%\pm 0.12\%$ ;  $10.12\pm 0.21$  g/dL) and AL ( $31.33\%\pm 0.23\%$ ;  $10.87\pm 0.17$  g/dL) treatment groups when compared with nonpregnant control ( $35.81\%\pm 0.21\%$ ;  $12.21\pm 0.15$  g/dL). This was not significantly ( $p>0.05$ ) different from the

pregnant control group. WBC count was significantly ( $p<0.01$ ) increased in the AA ( $6072.31\pm 224.32/\text{mm}^3$ ) group when compared with the pregnant control ( $5436.00\pm 121.24/\text{mm}^3$ ) which also showed a significant ( $p<0.01$ ) decrease in WBC compared to the nonpregnant control ( $6890.00\pm 213.21/\text{mm}^3$ ). However, the values were well within the range of normal ( $4000$ – $8000/\text{mm}^3$ ) in the environment under consideration.<sup>14</sup> Eosinophil, monocyte and basophil differential count was significantly ( $p<0.01$ ) increased in the AA group when compared with nonpregnant control. There was a significant ( $p<0.01$ ) reduction in the monocyte and basophil differential counts in the AL group when compared with the AA group. The neutrophil and basophil count in the pregnant control were also significantly ( $p<0.01$ ) increased compared to the nonpregnant control.

The adverse event rate was higher in the AA group ( $n=28$  [70%]) when compared to the AL group ( $n=4$  [10%]).



**Figure 5** Comparative lipid profile in treated versus control groups.

**Notes:** (A) Total cholesterol level in pregnant women treated with artesunate + amodiaquine and artemether + lumefantrine combinations. (B) HDL cholesterol level in patients treated with artesunate + amodiaquine and artemether + lumefantrine combination. (C) Comparative LDL cholesterol level in pregnant women treated with artesunate + amodiaquine and artemether + lumefantrine combinations.

**Abbreviations:** HDL, high density lipoprotein; LDL, low density lipoprotein; SEM, standard error of mean.

**Table 2** Hematological profile of pregnant women on artesunate + amodiaquine and artemether + lumefantrine combination for uncomplicated malaria

Group	PCV (%)	Hb (g/dL)	WBC/mm <sup>3</sup>	Lymph (%)	Neutro (%)	Eosino (%)	Mono (%)	Baso (%)
Nonpregnant control, N=40	35.81 $\pm$ 0.21	12.21 $\pm$ 0.15	6890.00 $\pm$ 213.21	58.31 $\pm$ 2.32	40.02 $\pm$ 2.13	0.10 $\pm$ 0.12	0.30 $\pm$ 0.10	0.15 $\pm$ 0.10
Pregnant control, N=35	31.76 $\pm$ 0.32	10.54 $\pm$ 0.10	5436.00 $\pm$ 121.24 <sup>a</sup>	55.45 $\pm$ 1.87 <sup>a</sup>	43.72 $\pm$ 2.01 <sup>a</sup>	0.08 $\pm$ 0.02	0.27 $\pm$ 0.09 <sup>a</sup>	0.21 $\pm$ 0.12 <sup>a</sup>
AA, N=40	30.44 $\pm$ 0.12 <sup>a</sup>	10.12 $\pm$ 0.21 <sup>a</sup>	6072.31 $\pm$ 224.32 <sup>b</sup>	56.57 $\pm$ 2.12	42.98 $\pm$ 3.02	0.18 $\pm$ 0.01 <sup>b</sup>	0.40 $\pm$ 0.02 <sup>b</sup>	0.20 $\pm$ 0.10
AL, N=40	31.33 $\pm$ 0.23 <sup>a</sup>	10.87 $\pm$ 0.17 <sup>a</sup>	5340.67 $\pm$ 108.95	54.95 $\pm$ 1.59	44.35 $\pm$ 1.98	0.22 $\pm$ 0.10 <sup>b</sup>	0.12 $\pm$ 0.04 <sup>b</sup>	0.17 $\pm$ 0.06 <sup>b</sup>

**Notes:** <sup>a</sup> $p<0.05$  is significant vs nonpregnant control; <sup>b</sup> $p<0.05$  is significant vs pregnant control. Data presented as mean  $\pm$  SEM.

**Abbreviations:** AA, artesunate/amodiaquine; AL, artemether/lumefantrine; Baso, basophil; Eosino, eosinophil; Hb, hemoglobin; Lymph, lymphocytes; Mono, monocyte; Neutro, neutrophil; PCV, packed cell volume; SEM, standard error of mean; WBC, white blood cells.

Adverse events (Table 3) in the AA group were more predominant in the central nervous system (30%) with effects ranging from headaches, dizziness and drowsiness. This was followed closely by gastrointestinal tract disturbances (20%). Most of the reported adverse effects were mild. AL combination showed a comparatively safe profile with fewer side effects reported by patients on treatment with the combination. Adverse events ranged from GIT disturbances (7.5%), to fatigue and muscle weakness (2.5%) and were mostly mild.

## Discussion

Due to the emergence of resistance to previously used anti-malarials there has been a change in the treatment policy for malaria in Africa. Based on WHO recommendation most African countries have resorted to the use of artemisinin-based combination for the treatment of uncomplicated *P. falciparum* malaria. However, one major challenge has been

the issue of safety and tolerability of the drugs in the second and third trimesters of pregnancy. Despite the scarcity of data about the safe use of these agents in pregnancy, the combination is still in use for the treatment of uncomplicated *P. falciparum* malaria in the second and third trimesters of pregnancy in Nigeria due to its efficacy.<sup>15</sup> This has remained so because clinicians have not been able to pin-point any severe adverse effect based on the clinical experience accrued from the use of the drugs over the years.<sup>16</sup>

Recent preclinical safety data for amodiaquine revealed that there was no significant elevation of liver enzymes in rats exposed to high doses (120 mg/kg) except when co-administered with sulfadoxine-pyrimethamine.<sup>17</sup> Additionally, the drug has also been linked to agranulocytosis and hepatotoxicity following prophylactic use.<sup>18</sup> However, other reports have linked amodiaquine to serious hepatic injury with hepatocellular pattern of liver enzyme elevation often associated

**Table 3** Adverse events profile of pregnant patients on artesunate + amodiaquine and artemeter + lumefantrine for uncomplicated malaria

Group	Organ system	Clinical manifestation	Frequency (%)	Mild	Moderate	Severe
AA	CNS	Headaches, dizziness, drowsiness	12 (30)	+	-	-
	ENT	-	-	-	-	-
	Ocular	-	-	-	-	-
	Respiratory	-	-	-	-	-
	CVS	-	-	-	-	-
	GIT	Nausea, vomiting, abdominal discomfort	8 (20)	-	+	-
	UGS	-	-	-	-	-
	Dermatological	Rash, pruritus	3 (7.5)	+	-	-
	Musculoskeletal	Fatigue, weakness	5 (12.5)	+	-	-
AL	CNS	-	-	-	-	-
	ENT	-	-	-	-	-
	Ocular	-	-	-	-	-
	Respiratory	-	-	-	-	-
	CVS	-	-	-	-	-
	GIT	Nausea, vomiting, abdominal discomfort	3 (7.5)	+	-	-
	UGS	-	-	-	-	-
	Dermatological	-	-	-	-	-
	Musculoskeletal	Fatigue, weakness	1 (2.5)	+	-	-

**Note:** +, presence of clinical manifestation; -, no clinical manifestation of adverse event.

**Abbreviations:** AA, artesunate/amodiaquine; AL, artemether/lumefantrine; CNS, central nervous system; CVS, cardiovascular system; ENT, ear, nose and throat; GIT, gastrointestinal tract; UGS, urogenital system.

with agranulocytosis.<sup>19</sup> In addition, AL use has also been associated with some degree of hepatotoxicity. Recent studies suggest an elevation of AST and ALT levels in patients treated with AL.<sup>20</sup> Other studies have also shown hepatorenal and hepatobiliary toxicity in pregnant albino rats.<sup>21,22</sup>

In this study, AST and ALT levels although within normal range were significantly higher in the AL group compared to the AA group, but not significantly different from the pregnant control group. Similarly, ALP levels were within normal range and the elevation in both AA and AL group is likely to be physiological since it was not significantly different from pregnant control. The outcome of a recent animal study showed that the mean serum concentrations of ALP, ALT and AST were not significantly elevated in animals treated with AL.<sup>23</sup> However, the results from this animal study may be due to the fact that the animals used were not parasitized. Although most data from clinical trials suggest elevation of liver enzymes, none has shown any clinically significant outcome.<sup>1</sup> This study suggests that alteration in hepatic enzyme levels may be influenced by physiological changes in pregnancy and not necessarily because of the hepatotoxic effect of the drug as reported by other researchers.

In addition, available facts suggest that many patients show some degree of hepatic impairment following episodes of acute malaria.<sup>24</sup> Therefore, making an inference that the agents are hepatotoxic without correlating it with any clinical

outcome of toxicity makes the finding inconclusive. Hence WHO has recommended that caution should be exercised only in clinical settings that suggest hepatitis, particularly in conditions associated with the development of jaundice and clinical features suggestive of agranulocytosis, such as fever, tonsillitis and mouth ulcers.<sup>14</sup> The marked elevation of total bilirubin in both the AA and AL groups may not be unconnected with increased hemolysis associated with malaria infection.<sup>25,26</sup> This is corroborated by a study conducted in Colombia which showed anemia and elevated bilirubin in patients who received AA.<sup>27</sup> In addition, this study showed a nonsignificant reduction in LDL-cholesterol and a nonsignificant change in HDL-cholesterol in the AA group compared to the AL group. Some studies have shown that AA and AL caused an insignificant decrease in total cholesterol levels when administered at therapeutic doses.<sup>28</sup> However, there are reports that artesunate has significant hypolipidemic effect when coadministered with ursolic acid in rats.<sup>29</sup>

In this study, hematological changes in AA and AL groups were not significantly different from the pregnant control group. However, there was a significant reduction in and hemoglobin concentration in both AA and AL groups and a significant reduction in monocyte and basophil differential count in AL group compared to nonpregnant control. Other studies have shown that administration of AL in Wistar rats caused a significant dose-dependent and reversible decrease

in red blood cells (RBC) and WBC count as well as Hb concentration.<sup>30</sup> In another study, AL did not cause any significant change in hematological parameters when used at recommended doses and duration but only caused significant reduction in RBC count, Hb concentration and PCV when used for a more prolonged period of 7 days.<sup>31</sup> In a recent study conducted in Nigeria, anemia was reported as an adverse event following the administration of AL in children.<sup>32</sup>

In addition, this finding was attributed to be part of the manifestation of malaria rather than an effect caused by the drug. Other reports have also linked maternal anemia to malaria infection in pregnancy<sup>25,26</sup> thus making it difficult to determine the actual effect of the drugs on PCV and Hb indices. This therefore implies that physiological changes in pregnancy and hemolysis associated with malaria infection may have influenced the findings in this study. A Colombian study reported the occurrence of neutropenia and leukopenia. In the study, severe neutropenia developed in 8.3% of subjects who received treatment with AA.<sup>27</sup> However, the findings of this study showed a significant increase in WBC and differential count in the AA and AL groups. In addition, the monocyte and basophil count were significantly decreased in the AL group compared to the AA group. This was not clinically significant as values remained within the normal range for the population.

Also, the adverse event rate was higher in the AA group when compared to the AL group. In the AA group, adverse events involved mainly the central nervous system and the gastrointestinal tract. However, some patients presented with fatigue and muscle weakness and dermatological reactions such as rash and pruritus during follow-up. Gastrointestinal disturbances were the predominant adverse event reported in the AL group. In a similar study, mild to moderate fatigue occurred more frequently in the AA treatment group than the AL group.<sup>33</sup> This corroborates the findings of this study. However, other studies revealed no difference in fatigue between the AA and AL treatment groups.<sup>34-36</sup> In this study, most of the observed adverse effects were mild and well tolerated which is in keeping with other reports. According to Ndiaye et al,<sup>37,38</sup> dizziness and somnolence were the predominant neurological effects reported in the AA group which corroborates our findings. In a systematic review conducted by Manyando et al,<sup>39</sup> AL use in second and third trimester of pregnancy was not associated with adverse pregnancy outcome in 890 clinical studies evaluated. However, this study is limited by the small sample size and the fact that the safety of the drugs was not evaluated in the fetus.

In Nigeria, the practice of pharmacovigilance and adverse drug reporting is low among health personnel in tertiary

health centers.<sup>40</sup> It is therefore important to reawaken the culture of active spontaneous adverse drug reporting in our setting with regards to artemisinin-based combination therapy use in pregnancy. With active monitoring of the safety and tolerability of these agents it will be possible to accumulate data over time that will help to sufficiently address the issue of safety and tolerability of ACTs in pregnancy. Recently, concerted effort was made to monitor the safety of ACTs in the six geopolitical areas of Nigeria. However, challenges that may affect the reliability of data from the project include; dearth of local expertise on pharmacovigilance, the method and approach used in the collection of data, and failure to include researchers with requisite knowledge and skill in the field.<sup>41</sup> The safety of artemisinin-based combination drugs in pregnancy still remains a pressing issue that needs to be addressed in our setting. Also, there is a problem of under-reporting of adverse events by physicians due to difficulty in establishing a causal relationship between the drugs and the suspected reaction.<sup>42</sup> However, there is need to continue to emphasize the adoption of spontaneous adverse drug reporting as a means of creating a reliable platform for the early detection of untoward reactions to ACTs in pregnancy.

## Conclusion

In conclusion, the differences observed in hepatic enzyme levels between treatment groups were not clinically significant though statistically significant. The elevations were within the normal range for the second and third trimesters of pregnancy and no new safety issues were identified with the use of the two ACTs in the treatment of malaria in pregnancy. However, the limitation of the study was the small sample size; hence a large scale multicenter study will have to be conducted in different endemic foci in our region. In addition, a robust pharmacovigilance tool is needed to obtain more safety data in this vulnerable population because we were not able to assess for safety of the ACTs in the fetus.

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## Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.



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