



The Effect of Artemisinin-based Combination Therapy (ACT) Antimalaria Drugs on Liver Enzymes in Pregnancy

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Authors' contributions

This work was carried out in collaboration between both authors. Author AOO designed the study, performed the statistical analysis, and wrote the first draft of the manuscript. Author AAS managed the literature searches and wrote the final manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: Artemisinin-based Combination Therapies (ACTs) are employed as first-line agents in malaria chemotherapy. This study is aimed at assessing the effects of ACTs on renal function of pregnant women.

Study Design: Comparative study.

Place and Duration of Study: Pregnant women aged 18 to 50 years were recruited from antenatal clinic of Obstetrics and Gynecology Department of Ekiti State Hospital, Ado Ekiti, Nigeria between 2016 and 2018

Methodology: One hundred and eighty pregnant women were grouped into three which include: Sixty pregnant women with malaria parasite on ACT drugs (Group A), sixty pregnant women with malaria parasite not on ACT drugs (Group B), sixty pregnant women without malaria parasite (Group C/control). Plasma Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), Alanine

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Transaminase (ALT) and Lactate Dehydrogenase (LDH) activities were evaluated by standard methods. The data collected were analyzed using one-way analysis of variance (ANOVA) and Student's t test to compare the data between the test groups and control.

Results: Results showed there was a significant decrease ($P=.05$) in Body Mass Index in the pregnant women with malaria on ACT and those that were not on ACT when compared with control (24.1 ± 0.32 versus (25 ± 2.30 vs 27 ± 1.62). A significant increase ($P=.05$) occurred in the levels of ALP,AST, ALT and LDH in pregnant women with malaria not on ACT drugs when compared the control (168.45 ± 0.19 , 10.0 ± 0.27 , 8.19 ± 0.25 , 4.5 ± 0.21) versus (143.20 ± 0.12 , 8.71 ± 0.30 , 5.99 ± 0.21 , 2.08 ± 0.19), while no significant difference occurred in the levels of ALP,AST, ALT and LDH in pregnant women with malaria on ACT when compared with control (141.60 ± 0.78 , 8.02 ± 0.32 , 6.10 ± 0.30 , 2.75 ± 0.20) vs (143.20 ± 0.12 , 8.71 ± 0.30 , 5.99 ± 0.21 , 2.08 ± 0.19).

Conclusion: Normal therapeutic dose of ACT has no harmful effect on the liver in pregnancy.

Keywords: Artemisinin-based Combination Therapies (ACTs); malaria; pregnancy; Aspartate Aminotransferase (AST); Alkaline Phosphatase (ALP); Alanine Transaminase (ALT); Lactate Dehydrogenase (LDH).

1. INTRODUCTION

Malaria is a vector-borne infectious disease caused by different strains of the protozoan parasites of the genus plasmodium [1]. Malaria still remains one of the deadliest infections in the tropical and subtropical regions of the world despite various control programs [1]. The WHO African Region carries a disproportionately high share of the global malaria burden. In 2017, nearly half of the world's population was at risk of malaria. Most malaria cases and deaths occur in sub-Saharan Africa. [2]. Malaria infection in pregnant women is associated with high risk of both maternal and perinatal morbidity and mortality. Pregnant women have reduced immune response and therefore less effectively clear malaria infections [3]. Malaria infection during pregnancy can lead to miscarriage, premature delivery, low birth weight, congenital malaria infection and perinatal death [4], because the malaria parasites sequester and replicate in the placenta [5]. Artemisinin-based combination therapies (ACTs) are the recommended first-line treatment for uncomplicated malaria in most countries [6]. ACT prevents the development of gametophyte in *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* and the early stage of *Plasmodium falciparum*. Due to their rapid onset of action and quick elimination, artemisinin derivatives are very effective in reducing parasite load [7,8]. In Nigeria, the combinations commonly used for treatment of uncomplicated *P. falciparum* malaria are artesunate/amodiaquine and artemether/lumefantrine combinations. Aspartate Transaminase (AST) is associated with liver parenchymal cells, found predominantly in the liver, heart (cardiac muscle), skeletal muscle,

kidneys, brain, and red blood cells. Abnormal levels of Alkaline phosphatase (ALP) in the blood could indicate issues relating to the liver, gall bladder or bones. Kidney tumors, infections as well as malnutrition has also shown abnormal level of alkaline phosphatase in blood [9]. Lactate dehydrogenase (LDH) is an intracellular enzyme, which catalyses the readily reversible reaction involving the oxidation of lactate to pyruvate with nicotinamide adenine dinucleotide (NAD) serving as coenzyme. Generally, high concentrations of LDH are found in the liver, heart, erythrocytes, skeletal muscles and kidneys [10]. Consequently, diseases affecting those organs, such as renal infarction, myocardial infarction and haemolysis, have been reported to be associated with significant elevations in total serum LDH activity. Such elevations have been widely applied as diagnostic indices for kidney, liver, heart and red blood cell dysfunction [11,12]. The life cycle of plasmodium parasite in the human host involves the developmental cycle in red blood cells, and the cycle taking place in the liver cell parenchyma, includes a series of transformations in the host hepatocytes [13]. A review of artemisinin use in pregnancy conducted in 2011 concluded that ACTs have an excellent efficacy profile in the second and third trimester, but researchers also stressed the importance of more research into the safety of ACTs in pregnancy [14]. Moreover, some reports have associated hepatotoxicity with ACT which has been described in animal models [15,16,17], while conflicting reports exists in human studies [18]. There are few data on the effects of ACT on renal function during treatment of malaria in pregnant women in this region. Therefore, this study aim to study the effects of artemisin combination therapy on liver function by

evaluating the activities of ALT, AST, ALP and LDH in pregnancy.

2. MATERIALS AND METHODS

This is a comparative study in which pregnant women were recruited from antenatal clinic of Obstetrics and Gynecology Department of Ekiti State Hospital, Ado Ekiti, Nigeria. Ethical Clearance was given by Ethical Committee of the Ekiti State Hospital, Ado Ekiti, Nigeria. The study population were between the ages of 18-50years at gestational ages of 12weeks to 32weeks randomly grouped into three:

- Group A: 60 Pregnant women with malaria parasite on ACT drugs
- Group B: 60 Pregnant women with malaria parasite not in ACT drugs
- Group C: 60 Pregnant women without malaria parasite

Malaria (P.f./Vivax) WB Rapid Test kit was used to determine the presence of plasmodium parasite in the participants. The ACT used by the pregnant women was artemether/lumefantrine, at a dose of 20 mg/120 mg per tablet. 24 tablets was given over 3 days; a 3-day treatment schedule with total of 6 doses. Anthropometry data were collected, and informed consent form duly signed. 5 mls of venous blood was collected from each participant and dispensed into EDTA bottle, centrifuged and plasma collected for analysis of ALT, ALP, AST and LDH.

2.1 Biochemical Assessment

Aspartate Aminotransferase (AST) activity was assayed spectrophotometrically using enzymatic method as reported by [19].

Alkaline Phosphatase (ALP) activity was quantified spectrophotometrically according to enzymatic method of [20].

Alanine Transaminase (ALT) activity was assessed by using Enzymatic Method on

automated chemistry analyser (LW C100 plus) as described by [19].

Lactate Dehydrogenase (LDH) activity was measured on automated chemistry analyser (LW C100 plus) using the International Federation of Clinical Chemistry recommended procedure as described by [21].

2.2 Statistical Analysis

The data collected were analyzed using one-way analysis of variance (ANOVA) and student's t test to compare the data between the test groups and control.

3. RESULTS

Table 1 shows that there was no statistical difference ($p > 0.05$) in age across the three groups while the Body mass Index was significantly reduced ($p < 0.05$) in pregnant women with malaria on ACT and those not on ACT (Group A and B) when compared with control.

Table 2 shows that there was a significant increase ($P < 0.05$) in the levels of Alkaline Phosphatase Aspartate transaminase (AST), Alanine Transaminase (ALT) and Lactate Dehydrogenase (LDH) in pregnant women with malaria not on ACT drugs when compared the control, while levels in pregnant women on ACT was not statistically different ($p > 0.05$) from control.

4. DISCUSSION

Malaria infection during pregnancy is a major public health problem in tropical and subtropical regions throughout the world [22]. Artemisinin based combination therapy (ACT) is the current standard treatment for uncomplicated malaria caused by Plasmodium falciparum. However this study estimated the levels of ALP, AST, ALT and LDH in pregnant women with malaria administered with ACT drugs and those not on ACT drugs, using the values of pregnant woman without malaria as the control.

Table 1. Anthropometry data of malaria infected pregnant women on ACT drugs, pregnant women with malaria parasite not on ACT drugs and pregnant women without malaria parasite

Parameters	Group A	Group B	Group C
Age (yrs)	30 ± 0.20 ^a	31 ± 0.89 ^a	29 ± 1.70a
BMI (Kg/m ²)	24.1 ± 0.32 ^a	25 ± 2.30 ^a	27 ± 1.62b

Table 2. The levels of some marker enzymes in pregnant women with malaria parasite on ACT drugs, pregnant women with malaria parasite not on ACT drugs and pregnant women without malaria parasite

Parameters	Group A	Group B	Group C
ALP	141.60±0.78 ^a	168.45±0.19 ^b	143.20±0.12 ^a
AST	8.02±0.32 ^a	10.0±0.27 ^b	8.71±0.30 ^a
ALT	6.10±0.30 ^a	8.19±0.27 ^b	5.99±0.21 ^a
LDH	2.75±0.20 ^a	4.51±0.21 ^b	2.08±0.19 ^a

Results were expressed as Mean ± Standard deviation. Statistical significance was defined as P=.05 where superscript a and b indicate significant differences

In this study, levels of ALP, AST, ALT and LDH in pregnant women on ACT was not statistically different from control. This suggests that ACT did not cause hepatocellular damage in pregnant women with malaria since ALT, AST and ALP serve as biomarkers for evaluation of hepatocellular damage, and ALT is the most reliable [23]. Similarly, the work of [24] involving the administration of different ACT to wister rat showed that ALT was not affected by ACTs, while at higher doses there was an increase in the renal markers which resolved completely after ACT was stopped. This shows that at higher doses of ACT there might be hepatocellular damage but at normal doses as taken by subjects in this present work, ACT is considered safe hepatocellularly. A significant increase occurred in ALP, AST and LDH levels in pregnant women with malaria not on ACT drugs when compared with pregnant women without malaria. Our results are consistent with other studies which reported that majority of patients with malaria show elevation in serum activities of AST, ALT and ALP indicating liver damage [13, 25]. This is because the sporozoite form of malaria parasite can infect liver cells and cause organ congestion, and cellular inflammation. These changes in hepatocytes can lead to significant perturbation and leakage of parenchymal and membrane enzymes of the liver into circulation, which increases with higher malaria parasite density [26,27].

The factors involved in hepatic dysfunction in acute *P. falciparum* malaria infection involve a synergy between local circulatory failure and centrilobular cellular damage. Since LDH is found in significant amounts in both the liver and red blood cells, the observed increase in serum LDH activity in pregnant women with *P. falciparum* malaria infection not on ACT in this study can be accounted for by a synergy between the two pathophysiological processes which include the hepatic activity of the invading sporozoites leading to centrilobular liver damage and the destruction of the host red blood cells

consequent to erythrocytic merogony. [28]. The acute liver injury and red blood cell destruction is followed by the release of LDH into the circulation as seen in this study. The normal transaminase value and LDH seen in the women on ACT in this study might be due to the therapeutic effect of the antimalaria therapy in ameliorating the complications associated with acute *P. falciparum* malaria infection.

The reduced BMI in the pregnant women with malaria (Group A and B) observed in this study might be due to the weight loss associated with pathophysiology of malaria [29].

5. CONCLUSION AND RECOMMENDATION

Normal therapeutic dose of ACT has no harmful effect on the liver in pregnancy and as such can be prescribed safely by medical practitioners to pregnant women having malaria. Further studies can be carried out on the effects of ACT on the fetus during pregnancy.

CONSENT

Informed Consent form was issued to all the participants and was duly signed.

ETHICAL APPROVAL

All authors hereby declare that ethical clearance was given by Ekiti State Hospital Ethical committee, Ado Ekiti, Nigeria.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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