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Comparative Study of Total Antioxidant Capacity (TAC) Levels of Pregnant Women on Intermittent Preventive Treatment with Sulphadoxine Pyrimethamine and their Controls in Malaria Endeminicity

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Abstract

Background: The issue of malaria prevention in endemic areas during antenatal periods needs continuous emphasis so as to achieve its desired goals. Its roles in reducing the problems of malaria in pregnancy has been proven. The problems of anaemia in pregnancy, preterm labours, small for gestational age babies have been greatly reduced by adequate practice of Intermittent Preventive Treatment with Sulphadoxine Pyrimethamine (IPT-SP). It is also advocated that optimal levels of antioxidants like Total Antioxidant status (TAC/TAS) is necessary to assist pregnant women enjoy uneventful pregnancies as well as avert other problems associated with pregnancy. Such problems may include preterm births, neonatal anaemias, intrauterine growth retardations (IUGR), increased admissions into special care baby units and even neonatal deaths.

Objectives: We have comparatively studied the plasma Total Antioxidant Capacity / Status levels in parturients who received intermittent preventive treatment with sulphadoxine pyrimethamine (IPT-SP), and their controls during current confinements.

Method: This study was carried out at the Federal Medical Centre (FMC), Owerri Nigeria. Owerri, the capital of Imo state Nigeria and has a typical malaria endemic setting as seen in most parts of Sub-Saharan Africa. Ethical clearance and subsequent certification were obtained from the ethics committee of FMC Owerri enabling the commencement of the longitudinal recruitment of participants. This was after an adequate counseling and informed consent involving both groups. As a laboratory based, cross-sectional descriptive study, it involved 296 participants who clearly satisfied the inclusion criteria for either the study or control groups as allotted longitudinal. Participants were followed up after recruitment through their entire antenatal course till delivery to enable collection of blood samples for the estimation of Total Antioxidant Status/Capacity which was done using the Ferric Reducing Ability of Plasma, FRAP; by **(Benzie and Strain, 1996)**. The methodology principle is based on the fact that at low pH, antioxidant power causes the reduction of ferric tripyridyl triazine (Fe III TPTZ) complex to ferrous form (which has an intense blue colour) that can be monitored by measuring the change in absorption at 593nm. FRAP values are obtained by comparing the absorbance change at 593 nm in mixture (test), with those containing ferrous ion in known concentration (Standard).

Data analysis: The data obtained was analysis using the computer Software Package for Social Science (SPSS) version 20.0 (SPSS, Inc, 2007, Chicago) while the descriptive statistics (mean, standard deviation, range, percentages etc) were determined for continuous variables. P-value less than (<0.05) at 95% confidence interval was considered statistically significant.

Result: The mean serum level of total antioxidant status (TAS) in the study group was 846.55 umol/l while the minimum and maximum serum Total antioxidant status were 706 and 991 umol/l respectively. For their controls, the mean serum level of Total

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antioxidant status was 833.70 umol/l. However, the minimum and maximum serum Total antioxidant statuses were 291 and 1065 umol/l respectively. The difference was not statistically significant (p= 0.167) with odds ratio 1.00 (CI of 95% 0.997-1.006).

Keywords: Anaemia in pregnancy, Antenatal course, Ferric Reducing Ability of Plasma (FRAP), Malaria endeminicity, Sulphadoxine-Pyrimethamine, Total Antioxidant Capacity.

I. Introduction

Malaria is an infectious disease caused by a protozoa organism of the genus, **plasmodium**. Plasmodium has about five identified disease-causing species namely: **plasmodium falciparum, p**. **vivax, p**. **ovale, p**. **malariae** and **p**. **knowlesi.** In Nigeria **98%** of all cases of malaria are due to plasmodium falciparum. This is the specie that is responsible for resistance and the severe forms of the disease that may lead to coma and death. Almost all complicated forms of malaria disease are attributable to the specie, plasmodium falciparum (Getachew & Tsige, 2016; FMOH, Nigeria, 2005).

The principal mode of spread is from the bites of an infected female anopheles' mosquito and these bites are more frequent at night. Other uncommon modes of transmission are from blood transfusion, the pregnant mother to her unborn child, sharing of needles in drug users and abusers as well as organ transplantation. (FMOH, Nigeria 2011, 2005).

Malaria is one of the most important infectious diseases in the world. It is said to cause hundreds of millions of illnesses and an estimated one million deaths each year. **Malaria is endemic throughout most of the tropics, but it is most readily** transmitted in sub-Saharan Africa. Nearly all serious illnesses and deaths from malaria are caused by P. falciparum (Thwing, Skarbinski & Newman, 2005; Newman, Praise, Barbar & Steketee, 2004; WHO, 2000).

In areas of high or moderate transmission, most malaria infections in pregnant women are asymptomatic and as such infected women do not present for treatment. In such areas, the World Health Organization (WHO) recommends a combination of interventions to prevent malaria in pregnancy. These interventions include the use of insecticide-treated bed nets (ITNs), intermittent preventive treatment in pregnancy (IPT) and effective case management and treatment of malaria.

(http://www.malariajournal.com/conten or Andrew Vallely, Lisa Vallely John Changalucha, Brain Greenwood & Daniel Chandramohan, 2007; WHO, 2004; Nalen, 2000).

Worthy of note in the fight against malaria is the launching of Roll Back Malaria initiative in **April 25, 2000.** The commitment of African leaders to fight this disease which kills over one million children and pregnant women every year was quite a commendable approach (FMOH Nigeria, 2011). In areas of malaria endemicity, it is known that fetal abortions, premature labor, small-for-date babies and fetal or even maternal deaths remain some of the consequences of malaria parasite invasion of the pregnant placenta. In the course of these invasions, cytokines and some inflammatory cells are released which also aid to further complicate the unfavorable pregnancy outcomes classically associated with malaria parasite sequestration in the placental intervillous spaces around the chondroitin sulphate, A (Falade et al, 2007; Williams, 1996).

Still in the bid to fight and eradicate malaria in pregnancy, Intermittent preventive treatment (IPT-SP) for malaria in pregnancy was later introduced by WHO for the prevention of malaria in pregnancy, which itself is a major public health problem, with substantial risks to the mother, her fetus and the neonate. IPT-SP for malaria in pregnancy is a full therapeutic course of antimalarial regimen for the pregnant women prescribed during routine antenatal visits. The component drugs usually in a fixed dose regimen, is meant to be given regardless of whether the recipient is infected with malaria or not as well as with or without malaria symptoms (WHO, 2012; WHO, 2006).

Sulfadoxine-pyrimethamine, (IPT-SP) is recommended by WHO in all areas with moderate to high malaria transmission in Africa. By October 2012, WHO recommended that this preventive treatment be given to all pregnant women at antenatal care visit starting as early as possible in the second trimester. Each IPT-SP dose should be given at least 1 month apart from the other. IPT-SP is said to reduce maternal malaria episodes, maternal and fetal anaemia, placental parasitaemia, as well as reduce the incidence of low birth weight, and neonatal mortality (WHO, 2017; WHO, 2012).

The pathophysiology of malaria infection has been widely reported to involve oxidative stress especially that of malaria in pregnancy where the natural body defense mechanisms are markedly reduced. Such reports have been accepted by varying researchers with missed feelings. Tiyong and co studied oxidants and antioxidants in Cameroon and suggested an imbalance between oxidants and antioxidants in pregnant women suffering from malaria, a situation that could cause severe damage to the mother, the fetus or both. (Tiyong et al., 2009).

As stated above, a lot of discrepancies exist in the studies of the relationships between malaria infection pathogenesis and oxidative stress and oxidants. While some authors think oxidative stress may have a protective role in malaria infection others suggest a relation to the physiopathology of malaria infection (Sandro et al., 2012; Sohail, Kaul, Raziuddin, & Adak, 2007). Part of the duty of this study is to further elucidate the actual relationships between malaria infection pathogenesis and oxidative stress whether protective, aiding malaria pathogenesis or both. This is one knowledge gap that is existing in research.

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Malaria, Total Antioxidant Status (TAS) and Antioxidation

The need to investigate Oxidative Stress (OS) and antioxidant status/capacity of pregnant women may be related to the facts stated above. In oxidative stress, there exist an imbalance in the production of reactive oxygen species and the capacity of antioxidant defenses (Claudio et al., 2011). In oxidative stress, the generation of free radicals (substances with one or more unpaired electrons) exceeds the capacity of antioxidant defense mechanisms (processes meant to protect against the harmful effects of free radicals). It is worthy of note that, free radical induced damage to cells, lipids and proteins have been linked to the aetiology of a number of disease states, amongst them are miscarriages and pre-eclampsia in pregnancy (Poston and Raijmakes, 2004).

In a study that evaluated the oxido-reductive state of mothers and their newborns immediately after delivery and in the first few days after birth, it was found that values of oxidative stress markers were elevated in mothers and their newborns immediately after birth and increased further during the first few days of neonatal life. Breast milk was the only nutritional substance with high antioxidant activity. At the same time, thiobarbituric acid reactive substances (TBARS) levels in breast milk decreased, which might indicate its protective role in reducing oxidative stress in newborns (Wilinska et al. 2015). It is also noted that the antioxidant status of newborns reveals low concentrations of glutathione peroxidase, superoxide dismutase, ß-carotene, riboflavin, α-proteinase, vitamin E, selenium, copper, zinc, transferrin and other plasmatic factors while the maternal milk contain considerable antioxidative status/capacity, which might have protective roles on the breastfed infant (Buonocore and Groenendaal, 2007; Wilinska et al. 2015). The balance between oxidative stress (oxidants) and the neutralizing systems (antioxidants) represents the total antioxidant status (capacity). The oxidants are mainly reactive oxygen species and their derivatives e.g. peroxynitrite anion. In contrast, homeostasis against the effects of reactive oxygen species and their derivatives are maintained by antioxidants such as catalase, super oxide dismutase, beta-carotene, vitamin C, vitamin E, glutathione peroxides, ceruloplasmin and transferrin. These agents are thought to intercept, modify or destroy the reactive free radicals (Idogun, Odiegwu, Momak & Okonofua, 2008). In another study that assessed the total antioxidant status of normal pregnancies during the 3rd trimester, it was found that low levels of total antioxidant status exist in Nigerian pregnant women with normal pregnancy. Although most other studies reported low levels of certain antioxidants in pregnancy some studies have demonstrated a global reduction in total antioxidant capacity during normal pregnancy (Jonathan et al., 1998; Uchenna and Fidelis, 2005; Idogun et al. 2008). In another study to assess the total antioxidant activity in normal pregnancy, Adiga and Adiga demonstrated a significant reduction in total antioxidant status in pregnancy ($P< 0.001$). They concluded that the reduction in total antioxidant activity indicated a disturbance in the antioxidant system, which could be due to diminished individual antioxidants though previous literatures contain varying reports (Adiga and Adiga, 2009). In a study on Free Radicals and Antioxidant Enzyme Status in Normal Pregnant Women, Shrivastava and co showed that during normal pregnancy, lipoperoxidation is increased when compared with healthy, non-pregnant women. As the total antioxidant capacity (enzymatic and non-enzymatic) increased, a compensatory balance of the injury/defense ratio is maintained. Therefore, oxidative equilibrium persists throughout a normal pregnancy (Shrivastava, Kumar & Shrivastava, 2015). Falciparum malaria infection produces reactive oxygen species (ROS) leading to serum lipid peroxidation. This can overwhelm the body's antioxidant defenses. An imbalance between reactive oxygen species and antioxidant defense mechanisms of a cell leads to **oxidative stresses.** The interplay between these factors and IPT-SP following ingestion of SP for the prevention of malaria in pregnancy (SP) has remained a virgin area for clinical research before this study especially in Owerri, a heavy malaria endemic area (Chukwu Leo Clinton, Ph. D Research Thesis, 2019). The inconclusive status of most reports and studies on oxidative stress and activities of the entire antioxidant machinery has informed the need for further research in this body of science. Hence, the dare need for this our study.

Also, there is dearth of scholarly works assessing Total Antioxidant Status (TAS) levels and their interactions with Intermittent Preventive Treatment with Sulphadoxine Pyrimethamine in Parturients who Received Intermittent Preventive Treatment with Sulphadoxine Pyrimethamine in pregnancy. Hence, this study was conducted to ascertain a comparative assessment of the Plasma TAS Levels in Parturients who Received Intermittent Preventive Treatment with Sulphadoxine Pyrimethamine (IPT-SP), and their Controls during their Current Confinements. It is believed that the results of this study will guide policy makers and stakeholders in obstetrics and gynecological practice in adopting strategies that will ensure better pregnancy outcomes for our women. The research question is: Does the levels of Total Antioxidant Status affect pregnancy outcomes in malaria endemic areas of the world?

II. Materials and Methods

Study Setting and Center

The study was carried out at the Federal Medical Center (FMC) Owerri which is domiciled in the Owerri Municipal Local Government Area of Imo State Nigeria. Owerri is densely populated and known for its malaria endemicity. Most patients come for consultation for malaria treatment. Situated at 5.49^0 North Latitude and 7.03^0 East Longitude, Owerri is located at 159 meters' elevation above sea level. Owerri is a big town in Nigeria having about 215038 inhabitants (www.maps-

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streetview.com/nigeria/owerri 2011). The hospital (FMC) is a tertiary hospital located in the state capital of Imo. It offers quality health services in specialist and general medical practices, comprehensive maternity care, emergency obstetric care, safe motherhood and others. Parturients from far and wide in the state and other towns in neighboring states are attracted to the hospital because of their quality health services.

Study Population

The study population comprised of pregnant women that attended antenatal care at the Federal Medical Center, Owerri during the period of the study. Booked antenatal pregnant women without any known sign of malaria infection nor parasitological diagnosis of malaria were among those considered for recruitment.

Inclusion Criteria

The pregnant women recruited did consent to the study as well as satisfied the inclusion criteria which included: Parturients whose place of residence could afford them antenatal follow up as well as the readiness to have their delivery at the FMC, Owerri. Also included were antenatal patients of the hospital with ancillary body temperature of < 37.5 ^{o}C. Such patients must be without any symptom, sign nor laboratory diagnosis of malaria. (c). Their readiness to take the IPT-SP as DOTS (Directly observed therapy) as well as to have had no prior history of allergies to SP was equally a criterion. Recruited parturients were not to have ingested any form of antimalarial drug at least ≥ 2 weeks to the at time of recruitment.

The Control Group

On the other hand, the control group consisted of gravid women either presenting for delivery **(unbooked)** but met other criteria for inclusion or those who presented late for antenatal care **(late booking)** in the last month of pregnancy. At FMC Owerri, pregnant women receive only 2 doses (3 doses for HIV/AIDS OR SCD patients) of IPT-SP per confinement. The women are not given SP in their last month of pregnancy.

Exlusion Criteria

The following pregnant women were excluded from the study: Those gravid women with symptoms and signs of severe malaria as well as their counterparts with serious underlying ailments (examples are known diabetics, hypertensives, or those suffering from congestive heart failure, nephrosis, HIV/AIDS, SCD or other conditions thought to affect the study outcome). All Haemoglobin AS women were also excluded from the study. Those who have had prior allergies to any component of the drug, SP were equally excluded, these parturient were then included among those who did not receive any IPT-SP **(the control group).** Also excluded were women who had ingested any antimalarial drug in the 2 weeks prior to recruitment as well as women who live far away from the study base as to discourage effective follow-up.

Population Size And Recruitment

The study protocol used recommended that booked pregnant women who came for antenatal services were recruited longitudinally. These women must have witnessed quickening from 16 weeks but not beyond 28 weeks' gestation. Selected candidates who default at any stage of the study were discarded.

Sampling Size Determination

Sample size was calculated using he formulae: $n = \frac{z^2pq}{d^2}$

Where: the desired sample size (n) =n.

the standard normal deviate (z), usually set at 1.96 (or more simply 2.0) =z.

This corresponds to the 95% confidence level.

incidence of malaria (p) in pregnancy in Owerri by Ogbusu et al = 11 %

q= 1.0-p =p

degree of accuracy (d) desired, usually set at 0.05 or occasionally 0.02 =d.

From: $n = \frac{z^2pq}{d^2}$

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$$n = \frac{(1.96)^2 (0.11) (1-0.11)}{(0.05)^2}$$

= 148. Approximated to 150 to account for minimal attrition **(Araoye, 2004; Ogbosu et al, 2004).**

Following the above, a sample size of 150 subjects for each group who meet the inclusion criteria and consented to the study (both verbally and in writing) as well as used the above hospitals for antenatal care were recruited longitudinally.

Study Duration

The study was carried out between November, 2015 and June, 2016 (8 months).

Exclusion Tests for Chronic Illnesses:
Screening tests for chronic diseases did include among others:
Blood pressure measurements for hypertension and urinalysis tests for diabetes and nephrosis;
Pulse recording for heart failure and Genotype screening for sickle cell disease (SCD) were equally done.

Estimation of Total Antioxidant Capacity

Total antioxidant activity was estimated by **Ferric Reducing Ability of Plasma (FRAP) method by Benzie and Strain, 1996.**

At low pH, Antioxidant power causes the reduction of ferric tripyridyl triazine (Fe III TPTZ) complex to ferrous form (which has an intense blue colour) that can be monitored by measuring the change in absorption at 593nm. FRAP values are obtained by comparing the absorbance change at 593 nm in mixture (test), with those containing ferrous ion in known concentration (Standard).

Procedure:

Initially, a working reagent comprising acetate buffer (pH 3.6), ferric chloride and tripyridyltriazine in the ratio of 10:1:1 respectively was prepared. To 60 µl of sample or standard or blank in a clean test tube, 1.8 ml of working reagent was added. The reaction mixture was mixed thoroughly, and incubated at 37 °C for 10 minutes. The resulting blue coloured solution developed was then read at 593 nm. The blank was treated the same way except that 60 ul of distilled water was added instead of plasma. The standard solution contains 1000 µmol/l of ferrous sulphate.

Calculation:

$$\text{Total Antioxidant Capacity (µmol/l)} = \frac{OD_{TEST}}{OD_{STD}} \times \text{standard concentration (1000).}$$

(Benzie and Strain, 1996).

Data Analysis and Presentation

At the end of the bench work, the data gotten was computed and analyzed using the computer Software Package for Social Science (SPSS) version 22 (SPSS, Inc., 2013, Chicago). The data collected from all the above has been presented in the sessions below as tables and figures (see below). Where necessary, Student's t- test was used to analyze continuous variables.

Descriptive statistics (mean, standard deviation, range, percentages were determined for continuous variables. The results were presented using tables. P-value <0.05 at 95% confidence interval was considered statistically significant.

III. Results

A total of 456 antenatal women were assessed for eligibility. With the initial exclusion of 56 women from the study, only 296 of the recruited women finally completed the study. This number comprised of equal numbers (148) each of study (case) and control groups.

Influence of TAS/TAC in the study and control groups:

Table 1 below, showed the summary of mothers Total Antioxidant Status (TAC) parameters studied. The average Total Antioxidant Status (TAS) of the mothers was 846.6 ± 61.8 for the study group and 833.7 ± 92.6 for the control.

The comparative Box plot below, represented the total antioxidant (TAS/TAC) status in both the study group and the control. The mean values were close to each other in the study/case and control groups.

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In an addition to the box plot, **the histogram below** indicated similar result for the two groups. **Table 2 below equally,** showed that the mean value was slightly higher in the case group (846.55) umol/l compared to the control group (833.7) umol/l, with a difference of 12.85, which was not found to be statistically significant with p value= 0.165; 95% CI =0.997 – 1.005 (see table 2 below).

Results From TAS / TAC Studies

Table 1: Summary of mothers Biochemical Parameters studied

	Study					Control				
Measure	**n**	**min**	**max**	**mean**	**Std.dev**	**n**	**Min**	**Max**	**Mean**	**Std.dev**
TAS (umol/l)	148	706	991	846.55	61.781	148	291	1065	833.70	92.638

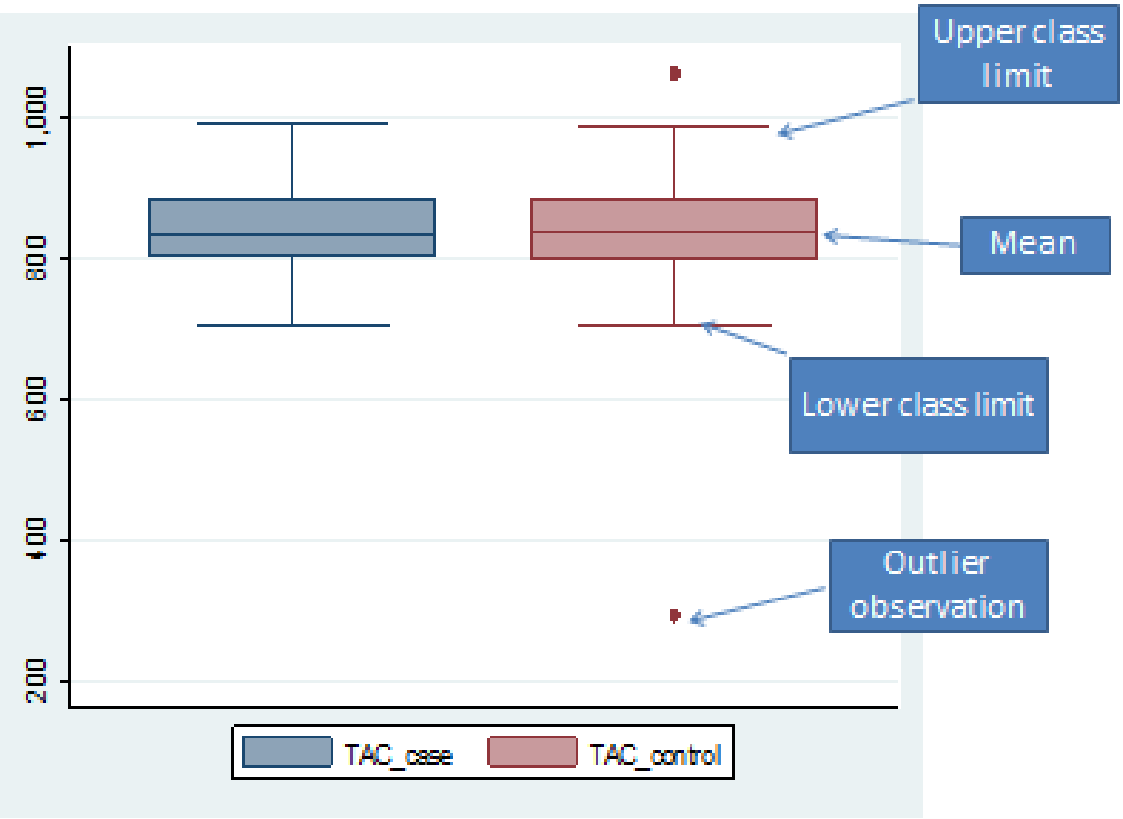

Figure 1 (Box plot 1): Serum levels of Total Antioxidant Status (TAS/TAC) in case and control groups.

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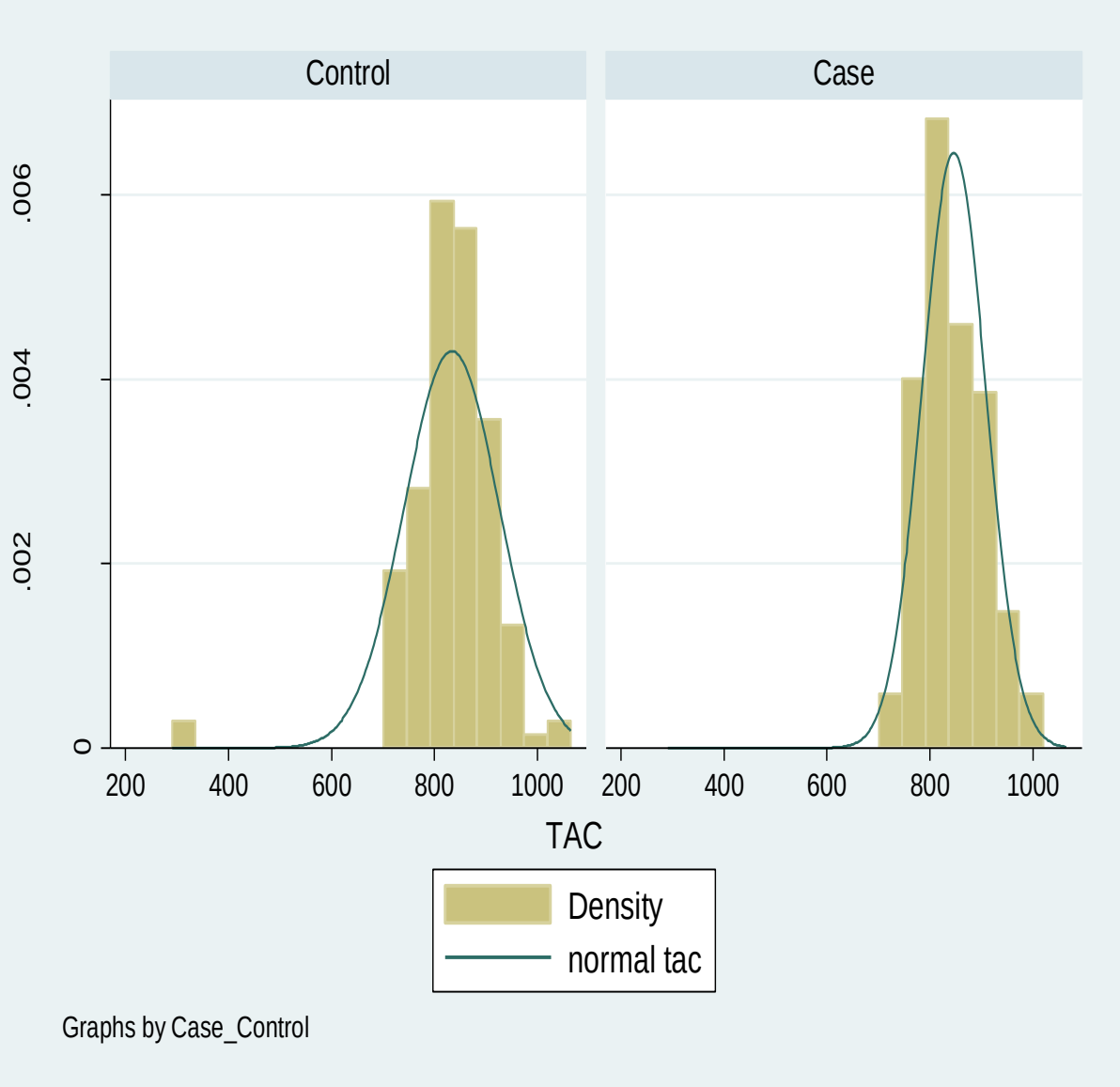

Figure 2 (Histogram 1): shows serum levels of Total Antioxidant Status (TAS/TAC) in both the study and control groups

Table 2: The Effects of TAS (TAC) in the study and control groups

										95% C.I.for OR	
Variable	**n**	**Min**	**max**	**mean**	**Std.dev**	**Coef**	**S.e.**	**p-value**	**OR**	**Lower**	**Upper**
Case	148	706	991	846.55	61.78						
Control	148	291	1065	833.70	92.64						
Difference				12.85		0.002	0.002	0.167	1.00	0.997	1.005

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IV. Discussion

The mean serum level of total antioxidant status (TAS) in the study group was 846.55 while in the control, it was 833.70 umol/l. The difference was not statistically significant (p= 0.167) with odds ratio 1.00 (CI of 95% 0.997-1.006). This was also illustrated in the corresponding histogram in the result section above. Intermittent preventive treatment with Sulphadoxine pyrimethamine may have accounted for the slightly higher TAS levels among the study/case group. However, Adiga and Adiga recorded a highly significant decline (P< 0.001) in antioxidant activity in pregnant women with a value of 1.40 ± 0.25 mmol/l compared to the controls, 1.63 ± 0.21 mmol/l. In their study, they concluded that the reductions in TAS/TAC could be due to the fall in individual antioxidant levels. Elevated enzymatic and non-enzymatic antioxidants levels during pregnancy have also been reported in other studies. It should be noted also, that total antioxidant activity was not a simple sum of individual antioxidants, but the dynamic equilibrium between them. So despite the rise in individual antioxidants, total antioxidant activity might be low (Adiga and Adiga, 2009). The higher TAS level among the study participants of this our study might be due **to a compensatory effect of the Intermittent Preventive Therapy with Sulphadoxine-Pyrimethamine (IPT-SP)** administered to the treatment/study group.

Kaya and colleagues considered pregnancy as a state of enhanced oxidative stress. All oxidative stress markers, including total antioxidant status (TAS), were increased in the third trimester. The state of oxidative stress in pregnancy was said to be due to the high metabolic activity of placental mitochondria that generate ROS, and also due to superoxide generation from NADPH oxidase (Kaya, Keskin, Kaya, Ustuner & Avsar, 2013). Increased oxidative stress might occur during the 3rd trimester due to the rapid development of the placenta. The placenta has been associated with an intense cellular activity and was the major source of pro-oxidant agents and oxidative stress in normal human pregnancy. However in the study by Kaya et al, the difference in Antioxidant Status (mM) in post term and term pregnancies was also not significant and did compare with the findings of this very study, p = 0.006 (Kaya et al. 2013; Chukwu L. C, Ph.D Thesis 2019).

V. Conclusion

From the study, we can also deduce that treatment with SP alters the body's enzymatic antioxidant defense profile. This may account for the reported disparity in the serum level of TAS in the mothers and reported as 846.6 ± 61.8 and 833.7 ± 92.6 for the study and control groups respectively.

Research funding:

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Conflict of interest:

In the course of this study till this time of publication, there has been no conflict of interest.

Ethical approval:

Ethical approval and subsequent certification was sought for from the management of Federal Medical Center Owerri (FMC). The study protocol was then approved by the FMC Ethics Committee (No. FMC/OW/HREC/55; May 12, 2016). A written informed consent for study participation was willingly signed by all enrolled mothers. These were all done before the commencement of participant recruitment

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